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NATURAL POLYMERS BASED DRUG DELIVERY SYSTEMS

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ABSTRACT

Polymers are utilized in drug delivery to provide weight, consistency and in addition, they are multi-functional providing stability, drug release, targeting, enhanced bioavailability and patient acceptability. A polymer is a large molecule (macromolecules) composed of repeating structural units. These subunits are typically connected by covalent chemical bonds. Polymers are broadly classified as natural polymers and synthetic polymers. Natural polymers are materials of large molecular weights from natural origins such as plants, micro-organisms and animals. In comparison to synthetic, natural polymers remain attractive primarily because they are inexpensive, readily available, capable of multitude of chemical modifications and potentially biodegradable and compatible due to their origin. Natural polymers possess wide scope in drug, food and cosmetic industries. Natural polymers are biogenic and their biological properties such as cell recognition and interactions, enzymatic degradability, semblance to the extracellular matrix and their chemical flexibility make them materials of choice for drug delivery. Natural polymers are continually being explored in innovative approaches to drug delivery and personalized medicines. Natural polymers used in various formulations like microspheres, nanoparticles, tablets, gels, implants, niosomes, liposomes etc. have shown the additional effect which is helpful in growing up the property of the system. Increasing application of natural polymers in drug delivery implies increase in demand indicating the need for research and development into new natural polymers for subsequent commercialization.

KEYWORDS: Natural polymers, nanoparticles, niosomes, liposomes, implants.

INTRODUCTION

A polymer is a large molecule (macromolecules) composed of repeating structural units. These subunits are typically connected by covalent chemical bonds. Polymers are generally classified as natural polymers and synthetic polymers. Natural polymers are materials of large molecular weights from natural origins such as plants, micro-organisms and animals. In comparison to synthetic, natural polymers remain attractive primarily because they are inexpensive, readily available, capable of multitude of chemical modifications and potentially biodegradable and compatible due to their origin. Natural polymers possess ample scope in drug, food and cosmetic industries. Natural polymers are biogenic and their biological properties such as cell recognition and interactions, enzymatic degradability, semblance to the extracellular matrix and their chemical flexibility make them materials of choice for drug delivery.

NEED OF NATURAL POLYMERS

1. Biodegradable – Naturally occurring polymers produced by all living organisms. They show no adverse effects on the environment or human being.

2. Biocompatible and non-toxic – Chemically, nearly all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence they are non-toxic.

3. Economic – They are cheaper and their production cost is less than synthetic materials.

4. Safe and devoid of side effects – They are from a natural sources and hence, safe and without side effects.

5. Easy availability – In many countries, they are produced due to their application in many industries. [1]

DISADVANTAGES OF NATURAL POLYMERS

1. Microbial contamination – During production, they are exposed to external environment and hence, there are chances of microbial contamination.

2. Batch to batch variation – Synthetic manufacturing is controlled procedure with fixed quantities of ingredients while production of natural polymers is dependent on environment and various physical factors.

3. The uncontrolled rate of hydration—Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary.

4. Slow Process – As the production rate is depends upon the environment and many other factors, it can't be changed. So natural polymers have a slow rate of production.

5. A "burst effect" or high initial drug release soon after administration is typical of most system.

6. Heavy metal contamination – There are chances of Heavy metal contamination often associated with herbal excipients. [2, 3]

CLASSIFICATION OF NATURAL POLYMERS

1. Plant origin

Rosin, Cellulose, Starch, Pectin, Inulin, Guar gum, Locust bean Gum, Gum Acacia, Karaya gum, Gum tragacanth, Aloe Vera gel.

2. Animal origin

Chitin, Alginates, Carageenans, Psyllium, Xanthum gum. [4]

ROLE OF POLYMERS IN DRUG DELIVERY

1. Immediate release dosage forms

➢ **Tablets:** Microcrystalline cellulose is often used as an alternative to carbohydrates as diluents in tablet formulations of highly potent low-dose drugs. Polymers including polyvinyl-pyrrolidone and hydroxypropyl methylcellulose (HPMC) find uses as binders that aid the formation of granules that improve the flow and compaction properties of tablet formulations prior to tableting.

➢ **Capsules:** Many of the polymeric excipients used to "bulk out" capsule fills are the same as those used in immediate release tablets. Gelatine has been used almost exclusively as a shell material for hard (two-piece) and soft (one-piece) capsules. HPMC has recently been developed and accepted as an alternative material for the manufacture of hard (two-piece) capsules.

2. Modified-release dosage form

To achieve gastro retention mucoadhesive and low-density **,** polymers have been evaluated, with little success so far, for their ability to extend gastric residence time by bonding to the mucus lining of the stomach and floating on top of the gastric contents respectively.

3. Extended release dosage forms

Extended and sustained release dosage forms prolong the time that systemic drug levels are within the therapeutic range and thus reduce the number of doses the patient must take to maintain a therapeutic effect thereby increasing compliance**.** The most commonly used water-insoluble polymers for extended-release applications are the ammonium ethacrylate copolymers (Eudragit RS and RL), cellulose derivatives ethylcellulose, and cellulose acetate, and polyvinyl derivative, polyvinyl acetate.

4. Gastroretentive Dosage Forms

Gastroretentive dosage forms offer an alternative strategy for achieving extended release profile, in which the formulation will remain in the stomach for prolonged periods, releasing the drug in situ, which will then dissolve in the liquid contents and slowly pass into the small intestine. [5]

POLYMERS IN PHARMACEUTICAL DRUG DELIVERY SYSTEM

1. Rosin

Rosin, also called colophony or Greek pitch, is a natural non-volatile resinous mass obtained from Pinus palustris. Due to abundant availability and various other characteristics which suggests it to be used as a polymer for different drug delivery systems. Rosin is primarily composed of abietic and pimaric acids and has excellent film-forming properties. Polymerised rosin films containing hydrophobic plasticisers showed excellent potential as coating materials for the preparation of sustained release dosage forms.[6] Rosin can be extensively used in transdermal drug delivery systems due to its significant property to help in skin permeability. [7] Pellets of diclofenac sodium coated with Rosin based polymer showed sustained release effect.[8]

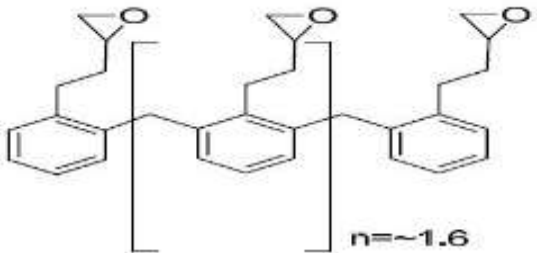

Fig. 1: Chemical Structure of Rosin

2.Locust Bean Gum: Locust bean gum also known as Carob bean gum is derived from the seeds of the leguminous plant *Ceratonia siliqua* Linn (Leguminosae). The brown pods or beans of the locust bean tree are processed by milling the endosperms to form locust bean gum and it is therefore not an extract of the native plant but flour. Locust bean gum is a neutral polymer and its viscosity and solubility are therefore little affected by pH changes within the range of 3-11.[9] Locust bean gum consists of mannose and galactose sugar units at a ratio of 4:1. Like almost all gum solutions, an aqueous solution of this gum displays shear thinning rheology. It shows synergistic effect with xanthan and kappa carrageenan. Venkataraju et al (2007) prepared controlled delivery system for propranolol hydrochloride using the synergistic activity of locust bean gum and xanthan gum to avoid first pass effect.[10] A commercially available tablet system (TIMERx®) developed by Penwest Pharmaceuticals Company consisting of locust bean gum and xanthan gum showed both *in vitro* and *in vivo* controlled release potential. [11]

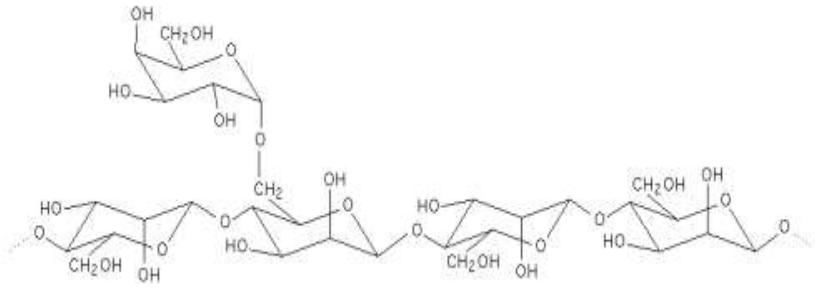

Fig. 2: Chemical Structure of Locust Bean Gum

3. Karaya gum: It is the dried gummy exudate obtained from the tree *Sterculiaurens*Roxb. (Family–Sterculiaceae). It is also known as Sterculia, Karaya, Indian Tragacanth or BassoraTragacanth gum. It is produced in India, Pakistan and to a small extent in Africa. Karaya gum consist of an acetylated, branched heteropolysaccharide with a high component of D-galacturonic acid and D-glucuronic acid residues.HV Gangadharappa et alrecently developed a single unit gastric floating drug delivery system of verapamil hydrochloride using karaya gum and hydroxypropyl methylcellulose (HPMC) as polymers. The feasibility of karaya gum was used for the rate controlling of drug release in the development of floating drug delivery system, evaluating the prepared dosage forms for its sustained release, in vitro buoyancy, swelling index, drug content, and in vitro drug release. The floating matrix tablets were prepared by direct compression technique using a combination of hydroxyl propyl methyl cellulose (HPMC) and karaya gum as polymers and sodium bicarbonate as generating agent. The prepared floating tablets were evaluated for weight variation test,

hardness, thickness, swelling index, in vitro floating capabilities, floating lag time, compatibility studies, and in vitro drug release. This swellable hydrophilic natural karaya gum was used to control the release of drug. The results showed that the optimized formulation F8 containing 23.3% of karaya gum (70 mg) and 13.3% of HPMC (40 mg) had good floating capability, shorter floating lag time, and sustained drug release for the period of 8 h.[12]

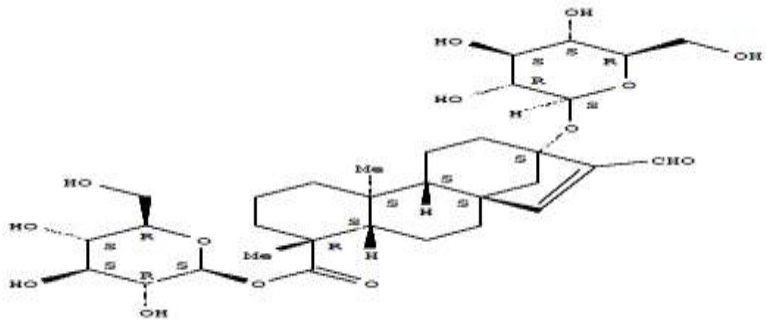

Fig. 3: Chemical Structure of Karaya gum

4. Guar gum: Guar gum (GG) is galactomannan, derived from guar (*cyamopsistetragonolobus*) kernels which belong to family *Leguminosae*. Guar gum is also known as cluster bean, Guaran, Cyamopsis, Guarina, Clusterbean, Calcutta lucern. It is hydrophilic in nature and swells incold water, forming viscous colloidal dispersions or sols. This gelling property retards the release ofthe drug from the dosage form, as well as its susceptibility to degradation in the colonic environment. The bioadhesive and biodegradable property of guar gum make it the first choice for developing controlled and targeting drug delivery systems for colon.[13] Guar gum and its derivatives are used as a binder and disintegrate in tablets to add cohesiveness to drug powder. Guar gum is also used as a controlled release agent for the drug due to high hydration rate. [14] Krishnaveni. G et al, prepared press coated time release tablets of montelukast sodium can be obtained using direct compression technique, it was found that xantham gum and guar gum mixture provided sufficient lag time for timed release of montelukast sodium useful for chronopharmacotherapy of asthma.[15]

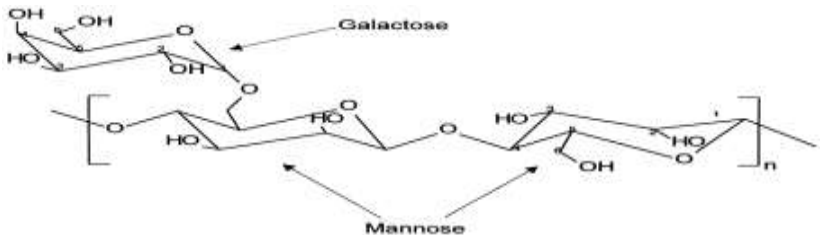

Fig. 4: Chemical structure of guar gum

5. Pectin: Pectins are non-starch, linear polysaccharides present in the walls that surround growing and dividing plant cells. Pectin is widely found in plant tissues where it serves, in combination with cellulose, as intercellular structural substance (membranes, middle lamellae). It is soluble in water, insoluble in ethanol (95%) and other organic solvents. Pectin has been investigated as an excipient in many different types of dosage forms such as film coating of colon-specific drug delivery systems when mixed with ethyl cellulose, microparticulate delivery systems for ophthalmic preparations and matrix type transdermal patches. It has high potential as a hydrophilic polymeric material for controlled release matrix drug delivery systems, but its aqueous solubility contributes to premature and fast release of the drug from these matrices.[16] Mishra et al formulated gastroretentive controlled release system of loratadine to increase the residence time in stomach and to modulate the release behaviour of the drug. Low methoxy polysaccharide, pectin, was employed as one of the polymers in the formulation of oil entrapped floating microbeads. Designed therapeutically efficacious gastroretentive formulation of drug showed an excellent buoyant ability along with suitable drug release pattern.[17] Pectin hydrogels can be used as a binder in tablet formulations.[18,19]

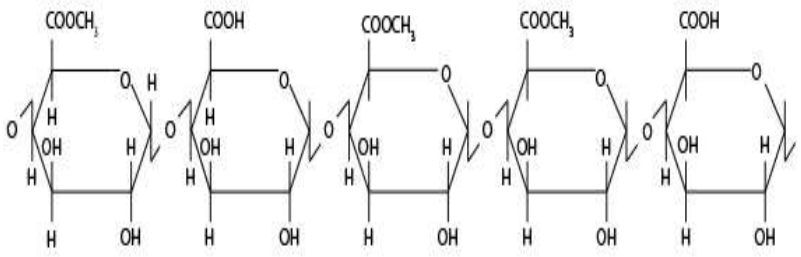

Fig. 5: Chemical structure of pectin

6. Xanthan Gum: Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris*. Xanthan gum and hydroxypropylmethylcellulose were used as hydrophilic matrixing agents for preparing modified release tablets of diltiazem HCl. The amount of hydroxypropylmethylcellulose and xanthan gum exhibited significant effect on drug release from the tablets prepared by direct compression technique. It was concluded that by using a suitable blend of hydroxypropylmethylcellulose and xanthan gum desired modified drug release could be achieved.[20] Muqtader use xanthan gum and guar gum to prepare floating drug delivery systems for famotidine which has higher absorption at low.[21] Subhash Chandra

Bose et al. prepared floating tablets of diltiazem HCl using xanthan gum as carrier. It was found that the formulation with low amount of xanthan gum (40% w/w) showed a low release rate compared to formulation with higher concentration (60% w/w).[22]

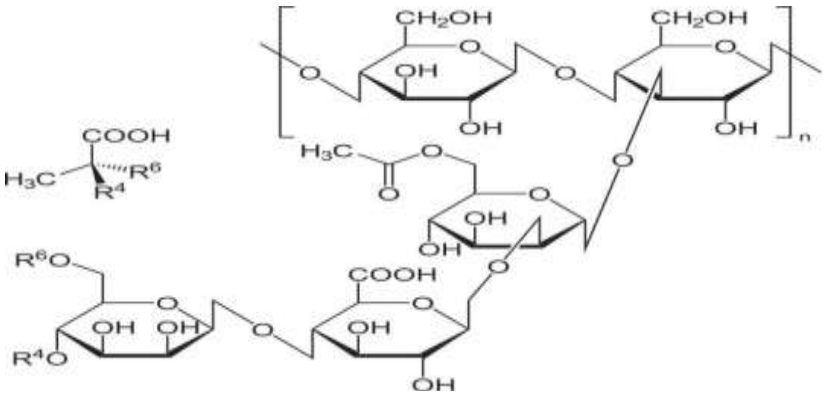

Fig. 6: Chemical structure of xanthan gum.

7. Chitosan: Chitosan is a cationic polymer obtained from chitin comprising copolymers of β(1→4)-glucosamine and N-acetyl-Dglucosamine. Chitin is a natural polysaccharide found particularly in the shell of crustacean, cuticles of insects and cell walls of fungi and is the second most abundant polymerized carbon found in nature. Chitosan, the fully or partially deacetylated form of chitin, due to its properties as attracted much attention in the tissue engineering and drug delivery fields with a wide variety of applications ranging from skin, bone, cartilage and vascular grafts to substrates for mammalian cell culture. It has been proved to be biologically renewable, biodegradable, biocompatible, non-antigenic, non-toxic and biofunctional. [23] They are highly stable, safe, biocompatible, biodegradable, non-toxic, and hydrophilic and gel forming in nature. These properties make chitosan a good candidate for the development of various conventional and novel gastrointestinal dosage forms. The most important property of chitosan with regards to drug delivery is its positive charge under acidic conditions. This positive charge comes from protonation of its free amino groups. Another important feature of using chitosan as drug carrier is its metabolic degradation in the body. Chitosan provides easy elimination process after drug administration, generally by renal clearance; however, this applies for chitosan with suitable molecular weight. For very large molecular weight chitosan, enzyme degradation is required. This rate of degradation depends on the molecular weight and degree of acetylation of the polymer. The possible site of degradation may be liver and kidney. Funkhouser et al. reported the presence of three chitinases enzymes which showed activity of chitosan degradation.[24]

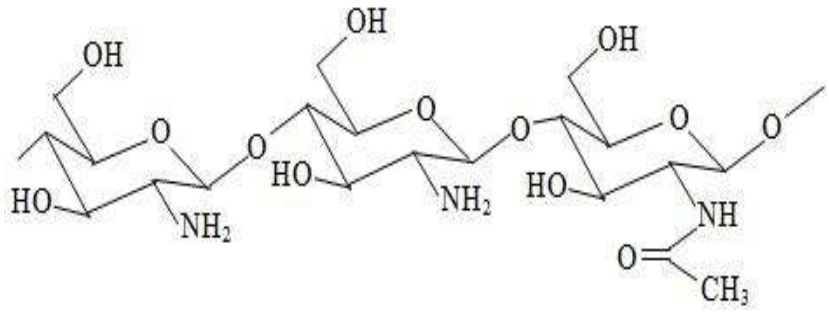

Fig. 7: Chemical structure of chitosan

8. Alginates: Alginates are natural polysaccharide polymers isolated from the brown sea weed (Phaeophyceae) and marine algae such as *Laminaria hyperborea*, *Ascophyllum nodosum and Macrocystis pyrifera*. They are hydrophilic, non toxic, biodegradable, linear polymer consisting of 1-4' linked-ß-D-mannuronic acid and β-L-glucuronic acid residues arranged as blocks of either type of unit or as a random sharing of each type. It is practically insoluble in ethanol (95%), ether, chloroform and slowly soluble in water, forming viscous colloidal solution. Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. The gelling properties of alginate's guluronic residues with polyvalent ions such as calcium oraluminium allow cross-linking with subsequent formationof gels that can be employed to prepare matrices, films, beads, pellets, microparticles and nanoparticles.[25, 26]

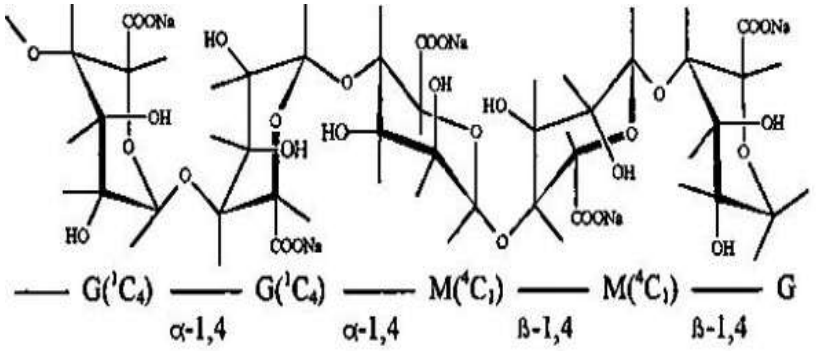

Fig. 8: Chemical structure of alginate.

9. Inulin: Inulin is resistant to digestion in the upper gastrointestinal tract, but is degraded by colonic microflora. Inulin with a high degree of polymerisation was used to prepare biodegradable colon-specific films in combination with Eudragit® RS that could withstand break down by the gastric and intestinal fluids. It was shown in another study where different Eudragits® were formulated into films with inulin that when a combination of Eudragit® RS

and Eudragit® RL was mixed with inulin it exhibited better swelling and permeation properties in colonic medium rather than other gastrointestinal media.[27]

10. Gum tragacanth: Gum tragacanth is the dried gummy exudation obtained from Astragalus gummifer (Leguminosae). Gum tragacanth is a branched, heterogeneous, and anionic carbohydrate which consists of a water-soluble fraction known as tragacanthin (8-10%) and a water swellable fraction known as bassorin (60-70%). Tragacanth when used as the carrier in the formulation of 1- and 3-layer matrices produced satisfactory release prolongation either alone or in combination with other polymers.[28]

CONCLUSION

Natural biodegradable polymers have received much more attention in the last decades due to their applications in the fields related to environmental protection and the maintenance of physical health. From the discussion, it can be concluded that by incorporating drugs in natural polymers, dosage forms that release the drug over a prolong length of time can be prepared in variety of shapes and sizes. Polymers play a vital role in the drug delivery so; the selection of polymer plays an important role in drug manufacturing. But while selecting polymers care has to be taken regarding its toxicity, drug compatibility and degradation pattern. By this review, we can say that natural polymers can be good substitute for the synthetic polymers and many of the side effects of the synthetic polymers can be overcome by using natural polymers.

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