



ROLE OF NATURAL POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

Floating drug delivery system is the form of gastro-retentive drug delivery system that controls the kinetic release rate of a drug to a specific site for its pharmacological action. These are achieved by use of various polymeric substance including natural polymers such as Guar Gum, Xanthan Gum, Gellan Gum etc. This delivery system prolongs the retention time of the drug in the stomach as compared to conventional dosage forms. The present article highlights the use of polymers for the formulation of the floating drug delivery system especially with natural polymers.

KEYWORD: Floating Drug Delivery System, Natural Polymer, Floating, Site-Specific drug delivery.

INTRODUCTION

Oral delivery of drug is by-far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. Floating system or hydrodynamically controlled system are low density system that have sufficient buoyancy to float over the gastric contents and tending to keep afloat in the stomach without affecting the gastric emptying rate for a prolonged period of time. Release of ingredients may be controlled by several mechanisms for the delivery of pharmaceuticals and biopharmaceuticals. Gastric retention is an approach for the drug delivery in which desirable for optimizing the therapeutic benefit of drug. The retention of drugs with narrow absorption window in the small intestinal region, longer residence time in stomach and advantageous for local action in the upper part of the small intestine. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system, after release of drug; the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into Non-effervescent and gas-generating system.^{1, 2, 3}

NATURAL POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM

The aim of this work is tried to give a brief overview to the role of natural polymers in the development of floating drug delivery system. The use of natural polymers is valuable based on proven biocompatibility and safety. Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. Polymers are generally employed in floating drug delivery systems so as to target the delivery of drug to a specific region in the gastrointestinal tract i.e. stomach. Moreover, these polymers are safe, nontoxic, and capable of chemical modification and gel forming nature.⁴

ADVANTAGES OF NATURAL POLYMERS: The various advantages of natural plant based materials include.

- **Biodegradable:** Biodegradable is the naturally available; they are produced by all living organisms.
- **Biocompatible and non-toxic:** Basically, all of these plant materials are repeating sugar polysaccharides
- **Low cost:** Cheaper to use as natural sources. the production cost is less compared with the synthetic material. In India and many other developing countries

are dependent on agriculture and they are large amount of money investment on agricultures.

- **Environmental-friendly processing:** There are many types of natural compounds obtained from different plant sources which are widely used in pharmaceutical industry and collected in large quantities due to the simple production processes involved.
- **Local availability (especially in developing countries):** In India and similar developing countries, there is promotion for the production of plants as pharmaceutical excipients being done by government and it also provide the facilities for bulk production, like gum and mucilage's because of their wide applications in industries.
- **They have better patient tolerance as well as public acceptance:** There is less chance of Side and adverse effects with natural materials compared with synthetic one.

LIST OF NATURAL POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM AND THEIR SOURCES

NATURAL POLYMER	BASIC CHAIN	SOURCE
Guar gum	β -D-mannopyranose	Endosperm of the seeds of <i>Cyamopsis tetragonolobus</i>
Pectin	α -(1,4)-linked D-galacturonic acid	Citrus peel, apple pomace, sugar beet pulp etc.
Chitosan	Deacetylated P-1, 4-N-acetyl-1-D-glucosamine	Shell of marine invertebrates
Xanthan gum	β -(1,4)-linked D-glucose	Fermentation of glucose by <i>Xanthomonas campestris</i>
Psyllium husk Starch	β -(1-4)-linked D-xylopyranosyl α -(1,4)-linked D-glucose and α -(1,6)-linked D-glucose	Seed coats of <i>Plantago ovata</i> Storage polysaccharide in plants
Gellan gum	D-glucose, D-glucuronic acid and rhamnose in β -1, 4 linkage	<i>Pseudomonas elodea</i>
Alginates	1-4' linked- β -D-mannuronic acid and α -L-glucuronic acid	<i>Laminaria hyperborea</i> , <i>Ascophyllum nodosum</i> , <i>Macrocystis pyrifera</i> etc

COMMONLY USED NATURAL POLYMER IN THE FLOATING DRUG DELIVERY SYSTEM

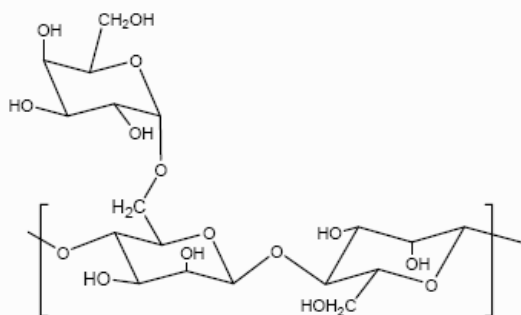
GUAR GUM

Guar also known as cluster bean. Guar gum is a natural non-ionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus* (Family Leguminosae). In pharmaceuticals Guar gum is used in solid dosage forms as a binder,

disintegrant, and as a polymer in the floating drug delivery system.^{5,6}

Chemistry of Guar Gum

Guar Gum mainly consisting of polysaccharides of high molecular weight (50,000-8,000,000) composed of galactomannans, mannose: galactose ratio is about 2:1. The gum may be purified by washing with ethanol or isopropanol or dispersing in boiling water, followed by filtering, evaporation and drying. It consists of linear chains of (1-4)-b-D-mannopyranosyl units with a-D-galactopyranosyl units attached by (1-6) linkages.⁷



Chemical Structure of Guar Gum

Properties of Guar Gum

The most important property of guar gum is its ability to hydrate rapidly in Cold water to attain uniform and very high viscosity at relatively low concentrations. Apart from being the most cost-effective stabilizer and emulsifier it provides texture improvement and water binding, enhances mouth feel and controls crystal formation. The main properties of guar gum are:

- It is soluble in hot & cold water but insoluble in most organic solvents.
- It has strong hydrogen bonding properties.
- It has excellent thickening, emulsion, stabilizing and film forming properties.
- It has excellent ability to control rheology by water phase management.
- The viscosity of guar gum is influenced by temperature, pH, presence of salts and other solids.^{8, 9, 10, 11}

Advantages of guar gum in floating drug delivery system

Srivastava *et al* developed floating matrix tablets of atenolol using polymers such as hydroxypropyl methylcellulose (K4M, K15M), guar gum and sodiumcarboxy methylcellulose to prolong gastric residence time and increase drug bioavailability. It has been reported that polymer swelling plays an important role in pattern and amount of drug release from the formulation. In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant. It was also found that the guar formulations were relatively insensitive to changes in stirring speed during in vitro dissolution testing and that the dissolution profiles were not significantly affected by changes in compaction pressure or by storage under accelerated stress conditions.^{12, 13}

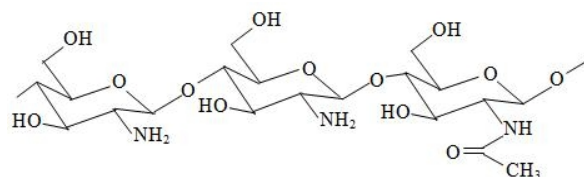
CHITOSAN

Chitosan is a natural and versatile polymer obtained by alkaline deacetylation of chitin. The Deacetylated chitin derivative chitosan is more useful and bioactive polymer .it has many reactive amino side groups, which offer

possibilities of chemical modifications. These properties make chitosan a good candidate for the development of conventional delivery systems. Play important role in the stomach-specific drug delivery, intestinal delivery, and colon-specific drug delivery. The main commercial sources of chitin are the shell wastes of shrimp, lobster, krill, and cra.^{14, 15, 16}

Chemistry of Chitosan

Chitosan has a rigid crystalline structure through inter- and intra-molecular hydrogen bonding. Chitosan [a (1- 4) 2-amino-2-deoxy-b-D-glucan] is obtained by the alkaline deacetylation of chitin. Chitosan molecule is a copolymer of N-acetyl-D- 1 .2 glucosamine and D-glucosamine.^{17, 18, 19}



Chemical structure of chitosan

Properties of Chitosan

Biocompatibility, natural polymer, biodegradable to normal body constituents, safe and non-toxic, haemostatic, bacteriostatic, and fungistatic, spermicidal, Anticancerogen, Anticholesteremic. Chitosan is a high molecular weight polycationic weak base with pKa value of the D-glucosamine residue of about 6.2-7.0 and, therefore, is insoluble at neutral and alkaline pH values. By increasing the chitosan membrane's thickness, the release rate of the drug decreased. Chitosan the second abundant polysaccharide and a cationic polyelectrolyte present in nature. The word chitosan refers to a large number of polymers, which differ in their degree of N- deacetylation (40–98%) and molecular weight is (50,000–2,000,000 Da).²⁰

Chemical properties of Chitosan

The chemical properties of chitosan are as follows:

- Linear polymine.
- Reactive amino group.
- Reactive hydroxyl groups available.
- Chelates many transitional metal ions.

Biological properties of chitosan:

Following are the biological properties of chitosan:

- ❖ Biocompatible
 - Natural polymer.
 - Biodegradable to normal body constituents.
 - Safe and non-toxic.
- ❖ Bind to mammalian and microbial cells aggressively.
- ❖ Central nervous system depressant.
- ❖ Accelerates bone formation.
- ❖ Immunoadjuvants.

Advantages of Chitosan in floating drug delivery system

Chitosan granules and chitosan-laminated preparations could be helpful in developing drug delivery systems that will reduce the effect of gastrointestinal transit time. Ibrahim El-Gibaly developed novel floating chitosan microcapsules of melatonin by ionic interaction of chitosan with a negatively charged surfactant such as sodium dioctyl sulfosuccinate. Chitosan concentration and drug/ polymer ratio had a remarkable effect on drug entrapment in microcapsules. Most of the hollow microcapsules tended to float over simulated biofluids for more than 12 hrs. Release of drug followed zero

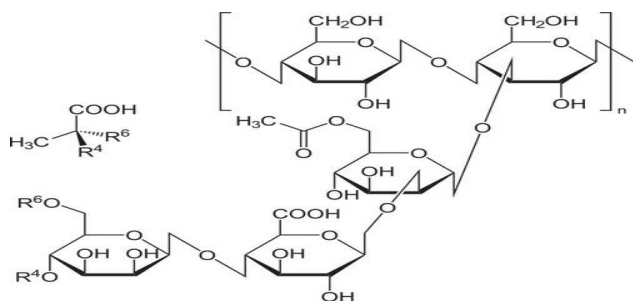
order kinetics and controlled by both diffusion and erosion mechanism. Results indicated that polymer swelling play an important role in pattern and amount of drug release from the formulation.^{21, 22, 23}

XANTHAN GUM

Xanthan is an extracellular hetero-polysaccharide produced by pure culture aerobic fermentation of the carbohydrate with bacterium *Xanthomonas campestris*. Xanthan is a well-known biopolymer. It is an anionic polysaccharide, whose primary structure depends on the bacterial strain and fermentation conditions. Xanthan gum is a natural, biosynthetic, edible gum and an extracellular polysaccharide, xanthan gum consists of glucose, mannose, and glucuronic acid, and is used in different foods as thickener and stabilizer.²⁴

Chemistry of Xanthan Gum

Xanthan is a long chained polysaccharide with large number of trisaccharide side chains. It consists of a β -(1, 4) - D-glucose backbone, which is the same as for cellulose. The side chains are composed of two mannose units and one glucuronic acid unit. The mannose closest to the backbone can carry an acetyl group, and the terminal mannose a pyruvate group. This gum develops a weak structure in water, which creates high viscosity solutions at low concentration. Viscosity remains fairly constant from 0°C to 100°C.²⁵



Chemical structure of xanthan gum

Properties of Xanthan Gum

Xanthan is highly soluble in cold and hot water and this behaviour is related to the polyelectrolyte nature of the xanthan molecule. Xanthan gum is mainly considered to be non-gelling and used for the control of viscosity. It hydrates rapidly in cold water without lumping to give a reliable viscosity, encouraging its use as thickener, stabilizer, emulsifier and foaming agent. Xanthan solutions are highly viscous, even at low concentrations. This property is useful in many industrial applications, especially in the food and cosmetic industries. Anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.

Main characteristics are:

- High stabilising properties
- High viscosity at low concentration
- Soluble in hot and cold water
- High pseudoplasticity (shear-thinning)
- Excellent freeze/thaw stability
- Very resistant to pH variations
- Highly resistant to temperature variations
- Highly resistant to enzymatic degradation
- Very low caloric value
- Compatible with all commercial thickeners and stabilisers.^{26, 27}

Advantages of Xanthan Gum in floating drug delivery system

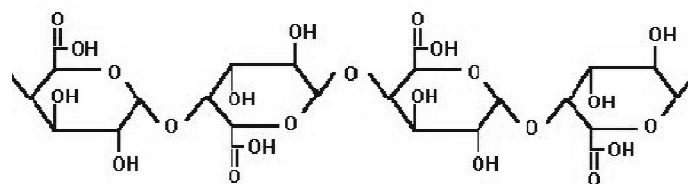
It is used as a tablet excipient to increase or decrease the drug release rate but not much has been reported concerning its use for sustained drug release. Xanthan has the potential advantage of drug release with zero order release kinetics; however its major drawback is that the drug release is influenced by the pH and the presence of ions in the medium. Patel et al investigated Gastroretentive tablets of verapamil hydrochloride using different hydrocolloid polymers including carbopol, hydroxypropyl methylcellulose and xanthan gum by direct compression technique. Selected tablets containing xanthan gum along with citric acid showed buoyancy for more than 24 hrs.²⁸

PECTIN

Pectin's are non-starch, linear polysaccharides present in the walls that surround growing and dividing plant cells. It consists mainly of the partial methyl ester of polygalacturonic acid. Their sodium, potassium, calcium and ammonium salt obtained by extraction in an aqueous of appropriate edible plant material usually citrus or apples.^{29, 30}

Chemistry of Pectin

They are predominantly linear polymers of primarily α -(1,4)-linked D-galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues having an average molecular weight of about 50,000 to about 180,000. Pectin contains from a few hundred to about 1000 saccharide units in a chain-like configuration.³¹



Pectin (polygalacturonic acid)

Properties of Pectin

Pectins have been utilised for their functionality in foods for many years. It is white, yellowish, light greyish or light brownish powder. Pectin used as a gelling agent, thickener, stabilizer, emulsifier agent.³²

Pectins are used as nutritional aspect as:

- Source of dietary fibers.
- Mineral binding.
- Prebiotics effect.
- Cholesterol regulation.
- Anticancer action.

Advantages of Pectin in floating drug delivery system:

Pectin was first isolated in the 1820s and the first commercial production of a liquid pectin extract was recorded in 1908 in Germany. Pectin is widely found in plant tissues where it serves, in combination with cellulose. It is soluble in water, insoluble in ethanol (95%) and other organic solvents. Pectin gel beads have been shown to be an effective medium for controlling the release of a drug within the gastrointestinal tract.

Badve et al developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy. Floating beads obtained were porous and hollow in nature with bulk density less than 1. In vivo studies by gamma scintigraphy determined on rabbits showed gastroretention of beads upto 5 hrs.^{33, 34}

PSYLLIUM HUSK

Psyllium husk obtained from dried seed coats of *Plantago ovata*. Husk and seed of *Plantago ovata* (Plantaginaceae) is commonly referred to as Psyllium. Psyllium is widely used as a fiber supplement for the treatment of constipation.³⁵

Chemistry of Psyllium husk

Psyllium husk contains a high proportion of hemicellulose, composed of a xylan backbone linked with arabinose, rhamnose, and galacturonic acid units (arabinoxylans). The seed consists of 35-percent soluble and 65-percent insoluble polysaccharides (cellulose, hemicellulose, and lignin). The seed contains 5-10% lipids with unsaturated fatty acids, sterols, proteins (15-18%), traces of cyclopentano pyridine-type alkaloids, aucubin and carbohydrates-plantose, a trisaccharide, and 10-12% mucilage of the heteroxylan type.³⁶

Properties of Psyllium husk

Psyllium is classified as a mucilaginous fiber due to its powerful ability to form a gel in water. This ability comes from its role as the endosperm of the *P. ovata* seed, where it functions to retain water in order to prevent the seed from drying out. It is a pale to medium buff-colored powder, having a slight pinkish tinge and a weak characteristic odor. Occasional single and 2-to 4-compound starch granules, the individual grains being spheroidal Plano to angular convex from 2 to 10 μm in diameter, are found embedded in the mucilage.^{37, 38}

Psyllium husk may be used in several diseases such as:

- Constipation.
- Haemorrhoids.
- Fecal incontinence.
- Appetite.
- Hyperlipidaemia.
- Diabetes mellitus.
- Ulcerative colitis.

Advantages of Psyllium Husk in floating drug delivery system

Psyllium husk has also release retardant properties. Above discussed characteristics reveal that psyllium husk is most likely to serve as a viable means for Gastroretentive drug delivery system. Various researchers have also focused on the use of this polymer for prolonged retention of dosage form in the stomach. Chavanpatil et al developed sustained release floating tablets of ofloxacin using various combinations of psyllium husk, HPMC K100M and croscopovidone. Formulations were also evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and in vitro drug release profile.³⁹

GELLAN GUM

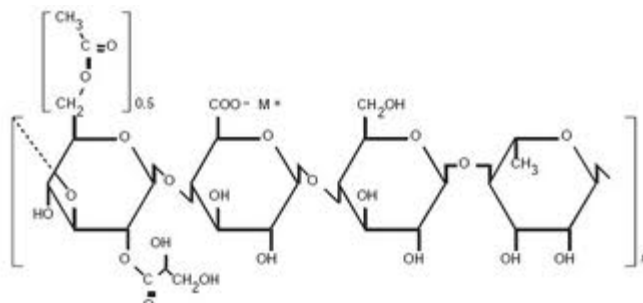
Gellan Gum mainly consists of polysaccharides, obtained from cultured solution of *Pseudomonas* species. Gellan Gum, when dried, contains 85.0–108.0 % of Gellan gum.

Gellan gum produced as a fermentation product by a pure culture of the microbe *Sphingomonas elodea*. The production organism is an aerobic, well characterized, non-pathogenic, gram-negative bacterium.^{40, 41}

Chemistry of Gellan Gum

Gellan gum is an anionic, high molecular weight, deacetylated extracellular linear polysaccharide comprising glucuronic acid, rhamnose and glucose. Its structure consists of four linked monosaccharides (i.e., simple sugars), including one molecule of rhamnose (a sugar found in

various plants), one molecule of glucuronic acid (an oxidized glucose molecule), and two molecules of glucose (a component of sucrose, which is common sugar). The exact molecular formula of Gellan gum may vary slightly (e.g., depending on the degree to which the glucuronic acid is neutralized with various salts.^{42, 43}



Chemical structure of Gellan gum

Properties of Gellan Gum

It is available in two forms (high or low acyl content). This gum has an outstanding flavor release, high gel strength, an excellent stability, process flexibility, high clarity, good film former and thermally reversible gel characteristics. Gellan gum is a water soluble, off-white powder. It has a molecular weight greater than 70,000 daltons with 95 percent above 500,000 daltons. It forms gels when positively charged ions (i.e., cations) are added. Thus, the thickness and texture of gellan gum in various products can be controlled by manipulating the

Addition of potassium, magnesium, calcium, and/or sodium salts. In the same way, its melting temperature can be modified to either be below or above 100° C.

Gellan gum disperses and hydrates easily in either hot or cold deionized water, forming viscous solutions in cold distilled water. It self is chemically inert to most biological growth media additives.^{44, 45}

Specific use of Gellan Gum

Gellan gum is a food additive that acts as a thickening or gelling agent, and can produce gel textures in food products ranging from hard and brittle to fluid. Types of products that typically contain gellan gum include: bakery fillings, confections, dairy products, dessert gels, frostings, icings and glazes, jams and jellies, low-fat spreads.

Action of Gellan Gum

Gellan gum acts as a thickening or gelling agent and can produce textures in the final product that vary from hard, non-elastic, brittle gels to fluid gels. The gel thickness for specific products can be controlled by manipulating the addition of alkali cations (i.e., by adding potassium, magnesium, calcium, and/or sodium salts).

Advantages of Gellan Gum in floating drug delivery system

Gellan gum, also commercially known as Phytigel or Gelrite. It is capable of gelation in the presence of mono- and divalent ions. This gum has an outstanding flavor release, high gel strength, an excellent stability, process flexibility, high clarity, good film former and thermally reversible gel characteristics. This gum has been considered as a potential carrier for different floating dosage forms by various investigators.

Elmowafy et al formulated and examined release mechanisms of single-unit floating matrix tablets of famotidine.

Polysaccharides (kappa-carrageenan, gellan gum, xyloglucan, and pectin) were tried to modulate the release behaviour. In this exploration, floating characteristics, swelling studies, kinetic analysis etc. were also evaluated.⁴⁶

CONCLUSION

Natural polymers have been successfully used by many investigators for various approaches of floating drug delivery technology. After thorough literature survey it had been concluded that natural polymer like guar gum, chitosan, xanthan gum and gellan gum plays vital role in different formulations of floating drug delivery system along with the better utilization and advancement over the synthetic polymers. Natural polymers have been used significantly in designing and synthesis of novel drug delivery system because of its biodegradable, biocompatible, eco-friendly, local availability and patient tolerance capability. Hence these natural polymers will expand the scope of new drug delivery system in the future.

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