Natural Polysaccharides: An Overview of their Role in the Development of Microparticles for Stomach Targeting

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ABSTRACT

Development of safe and efficacious gastro-retentive dosage forms for stomach specific drug delivery have profound importance in pharmaceutical industry. Different approaches used for gastro retention are discussed with a special focus on the floating drug delivery systems. Natural polymers have great demand in drug delivery as they encompass polymers with many functional groups, wide range of molecular weights, varying chemical composition, for the most part, low toxicity and biodegradability yet high stability. Most of these polymers have been approved by many regulatory bodies all over the globe for their usage as pharmaceutical excipients; hence, their adoptability in formulation and development is hassle free. Natural polysaccharides have been investigated for drug delivery as well as biomedical applications. This review provides an overview of different stomach specific natural polymers used or currently being used specially for controlled drug delivery and the advantages of microparticles for stomach specific drug delivery including their preparation methodologies etc. The review also emphasizes a brief summary of existing challenges associated with microparticles as delivery system for targeting drugs in the stomach and alternative methods/solutions adopted to overcome the same down the years.

Key words: Natural polysaccharides, Stomach specific microparticles, Floating drug delivery system, Gastro-retention, Controlled release, Sustained release.

INTRODUCTION

Despite remarkable advancements in drug delivery systems, the oral route remains the most preferred route for the administration of drugs because of low-cost therapy, ease of administration and great patient compliance. Despite the success, oral controlled drug delivery has faced physiological adversities like acidic environment of stomach or basic environment of intestine, short gastric residence time (GRT) and unpredictable gastric emptying time.¹ By extending the GRT, duration of release of drugs with improvement in bioavailability can be achieved for drugs with short half-life, less soluble at high pH environment with reduction in drug wastage.² Moreover, it is apparent from the recent scientific and patent literature that an increased interest in novel oral control release (CR) dosage forms necessitates the exploration of different strategies to retain drugs in the upper gastrointestinal tract (GIT) for a prolonged and predictable period of time.³

DIFFERENT APPROACHES TO DEVELOP STOMACH SPECIFIC MICROPARTICULATE SYSTEMS

Several techniques are currently being used to formulate successful stomach specific drug delivery systems such as high-density systems where the formulation is retained (sink) in bottom of the stomach,⁴ Polymer based low density floating drug delivery systems that show buoyancy in gastric fluids,⁵ stable super porous hydrogels in low pH environment, floating systems that remain buoyant with the aid of effervescent agents,⁶ raft forming agents in anti-reflux formulations, when react with gastric fluids form gel,⁷ expandable, un-foldable and swellable systems, bio-adhesive or mucoadhesive drug delivery systems, magnetic systems,⁸ and modified shape systems.

CRITERIA FOR SELECTION OF DRUG CANDIDATE FOR STOMACH SPECIFIC MICROPARTICULATE SYSTEMS

Drugs, having shorter half-life,⁹ low oral bio availability,¹⁰ low water solubility,¹¹ dosing several times a day, undesirable fluctuations in gastric fluids,¹² active locally in the stomach, narrow absorption window in GIT, unstable in the intestinal or colonic environment, disturb normal colonic microbes, exhibit low solubility at high pH values¹³ are suitable candidates for formulation of gastro retentive microparticles.

NATURAL POLYSACCHARIDES USED FOR THE PREPARATION OF MICROPARTICLES

The drug release and better-floating properties of microparticles mainly depend on the type of polymer, surfactant and solvent used in the preparation.¹⁴ Various types of natural polymers have been reported for their role in formulation of stomach specific floating microparticles. Commonly used natural polymers are polysaccharides (Table 1). More than 90% of the carbohydrate mass in nature is in the form of polysaccharides. These are polymers of monosaccharides with high molecular weight. Polysaccharides are gel-forming agents as well as hydrocolloids (Table 1), when come in contact with gastric fluids form gel and they
<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Polysaccharide</th>
<th>Source</th>
<th>Chemical nature</th>
<th>Solubility</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Chitosan</td>
<td>Partial deacetylation of chitin by chemical method or enzymatic degradation</td>
<td>Linear polysaccharide composed of deacetylated unit of β-(1-4)-linked D-glucosamine and acetylated unit of N-acetyl-D-glucosamine</td>
<td>Insoluble in water. Soluble in dilute acidic solutions such as acetic, formic and lactic acids below pH 6.0</td>
<td>Exhibits anticancer activity by immunomodulatory, anti-angiogenic and anti-inflammatory properties. Use in bacterial, fungal and viral infections. Carrier molecule for anticancer, anti-inflammatory, antibiotic and pulmonary drugs because of its release retardant properties. Chitosan and its derivatives enhance wound healing activity.</td>
</tr>
<tr>
<td>2.</td>
<td>Gellan Gum</td>
<td>Extracellular polysaccharide secreted by <em>Sphingomonas elodea</em></td>
<td>Anionic polysaccharide consists of linear tetrasaccharide units of [(1,3)-β-D-Glcp-(1,4)-β-D-GlcpA-(1,4)-β-D-Glc-(1,4)-α-L-Rha-(1→)], L-rhamnose, D-glucose and D-glucuronate. Two acyl substituents, L-glyceryl and acetyl units are present at the O-3, linked glucose at O-2 and O-6 positions. Based on the degree of acyl substitution, gellan gums are classified into high acyl and low acyl gellan gum.</td>
<td>Insoluble in ethanol and cold water Gets easily dispersed in water</td>
<td>Thickening agent, binding agent, stabilizing agent. Widely used polymer in an ophthalmic formulation, solid dosage forms, <em>in situ</em> gelling systems, tissue engineering, gene transfer, wound healing and bone regeneration.</td>
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<td>3.</td>
<td>Alginate (Sodium or calcium alginate)</td>
<td>Naturally present in cell walls of brown seaweed. Extracted from <em>Macrocystis</em>, <em>Laminaria</em>, <em>Asophyllum</em>, <em>Lessonia</em>, <em>Sargassum</em>, <em>Eclonia</em>, <em>Durvillea</em> species. Alginate is also obtained from bacteria like <em>Pseudomonas</em> and <em>Azotobacter</em>. The structural component of brown microalgae <em>Phaeophyceae</em>. <em>Azotobacter vinelandii</em> a bacterial source for the production of alginate in industry</td>
<td>Linear polysaccharides that are composed of β- D- mannuronic acid and α-1-guluronic acid residues linked via 1→4 glycosidic linkages. In algae, alginate is present in the intracellular matrix in the form of a gel containing ions like sodium, calcium, magnesium, strontium and barium.</td>
<td>Alginate acid: Insoluble in cold/hot water, fats, oils and organic solvents. Sodium alginate: Soluble in cold/hot water, Lye water. Calcium alginate: Insoluble in water, ether, chloroform and ethanol. Soluble in a dilute solution of sodium citrate and sodium bicarbonate.</td>
<td>Thickening agent, gelling agent, film-forming agent, encapsulating material, coating material.</td>
</tr>
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<td>4.</td>
<td>Pectin</td>
<td>Cell wall of a dry substance of higher plants. Apple, plums, quince, oranges, goose berries contain more pectin. Cherries, grapes and strawberries contain less amount of pectin.</td>
<td>High molecular weight complex mixture of polysaccharides. Monomer units of galacturonic acid are linked via α-(1→4)-glycosidic bond which forms a backbone. The substitution of the backbone is present in certain regions of pectin with α-(1→2) rhamnopyranose units. From these units side chains of galactose, mannose, glucose and xylose occur. Galacturonic acid undergoes methyl esterification. Based on methyl esterification, pectin is classified into two types - high methoxyl and low methoxyl pectin.</td>
<td>Soluble in water. Monovalent cation salts of pectinic and pectic acids soluble in water. Di and trivalent cations salts are weakly soluble or insoluble in water.</td>
<td>Mucoadhesive polymer, gelling agent, thickening agent, binding agent, dietary fiber, natural prophylactic agent against poisoning with toxic cations along with carbopol and chitosan, CR formulations, treating polyphagia, site-specific targeting.</td>
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<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>6.</td>
<td>Mucuna gum40,41</td>
<td>Biodegradable polymer Obtained from plant Mucuna flagillepes (Papilionaceae) extracted from the cotyledons Mucuna louni belongs to the family Fabaceae</td>
<td>D-galactose is the major monosaccharide with the D-mannose and D-glucose</td>
<td>Soluble in water</td>
<td>Mucuna gum with Polyethylene glycol has wound-healing activity. Acts as suspending agent, stabilizing agent and also as binding agent in tablet preparation.</td>
</tr>
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<td>7.</td>
<td>Psyllium husk42-45</td>
<td>Obtained from crushed seeds of Plantago ovata, Plantago psyllium, Plantago indica. Psyllium also known as ispaghula seeds obtained from plants of Plantago genus, belongs to the family Plantaginaceae. Psyllium is also obtained from species like Plantago lanceolata, Plantago rugelii and Plantago major.</td>
<td>Contains hemicellulose. Psyllium husk is composed of xylan backbone, which is linked with arabinose, rhamnose and galacturonic acid units.</td>
<td>Soluble in water and can form gels</td>
<td>Reduction in absorption of lithium with co-administration of psyllium. Lowers total cholesterol and Low density lipoproteins levels. Improves dissolution and bioavailability of drugs, super disintegrant.</td>
</tr>
<tr>
<td>8.</td>
<td>Karaya gum46-48</td>
<td>Acetylated polysaccharide dry exudate of tree Sterculia urens and extracts from Sterculia setigera</td>
<td>Acetylated polysaccharide composed of α-D-galacturonic acid and α-L-rhamnose. Acidic groups are glycosylated with β-D-galactose or β-D-glucuronic acid residues, β-D-galactose units as side chains are carried by rhamnose.</td>
<td>Insoluble in water. Soluble in NaOH, KOH and LiOH</td>
<td>Sterculia urens Adhesive, gelling agent, film forming agent, bulk laxative, heals bed sores and acts as rate-controlling polymer. Sterculia setigera Bark: Jaundice and bilharzia. Leaves and bark: Used in the treatment of cough, diarrhea, fever, leprosy, syphilis and acts as diuretic. Boiled leaves: Treatment of Malaria Stem bark decoction: Treatment of asthma, bronchitis, wound, fever, toothache, gingivitis, sore, abscess and diarrhea.</td>
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<td></td>
<td>Xanthan gum49,50</td>
<td>Polysaccharide obtained by aerobic fermentation of bacterium Xanthomonas campestris.</td>
<td>Consists of β-(1-&gt;4) D-glucopyranose glucan backbone with side chains of (3-&gt;1) α-linked D-mannopyranose-(2-&gt;1), β-D-glucuronic acid and (4-&gt;1) β-D-mannopyranose on alternating residues</td>
<td>Soluble in hot and cold water</td>
<td>Rheology modifier, suspending agent, emulsifier, gelling agent.</td>
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<td></td>
<td>Starch51,52</td>
<td>Polysaccharide obtained from grains of maize Zea mays L, rice Oryza sativa L, wheat Triticum aestivum L belonging to family Gramineae, from the tubers of the potato Solarium tuberosum L. belonging to the family Solanaceae</td>
<td>A mixture of two polysaccharides amylpectin (80%), insoluble in water and amylose (20%), soluble in water.</td>
<td>Insoluble in cold water. Soluble in hot water</td>
<td>Used in dusting powder, excipient in tablet preparation, an antidote for iodine poisoning, protective and demulcent.</td>
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</tbody>
</table>
maintain relative integrity of the system by retaining the shape and also bulk density less than the gastric contents enabling buoyancy; in addition, help in maintaining desirable drug delivery properties.

Chitosan
Chitosan is a natural, non-toxic, biocompatible and biodegradable polymer obtained by alkaline deacetylation of chitin. It is soluble in acidic pH due to its cationic nature and possesses an antibacterial property. It forms gel beads with substances possessing multivalent counter-ions such as triply phosphate, alginites by ionotropic gelation method. Drugs like 5-flourouracil, verapamil, metronidazole, atenolol, indomethacin are formulated as the chitosan based CR formulations and glutaraldehyde being the most commonly used cross-linking agent. It has been reported that celecoxib loaded microspheres were prepared to increase its residence time in the stomach by emulsion cross-linking technique using chitosan as a polymer, glutaraldehyde and formaldehyde as cross-linking agents. The authors reported that microspheres cross-linked using glutaraldehyde exhibited delayed drug release than those cross-linked with formaldehyde; whereas the heat cross-linked microspheres showed fastest release. Similarly an attempt has been made to prepare and evaluate trimetazidin dihydrochloride loaded floating microspheres to increase the residence time in the stomach without coming in contact with the mucosa. The microspheres were prepared by the capillary extrusion technique using chitosan as polymer and sodium lauryl sulfate as cross-linking agent. The prepared microspheres demonstrated prolonged drug release and remained buoyant for more than 11 h. The drug release rate was higher in case of microspheres prepared at a higher speed and decreased with an increase in the concentration of the polymer and cross-linking agent; vice-versa is reported in case of microspheres prepared at lower speed. The drug entrapment efficiency was found to increase with increase in polymer to drug ratio. In addition, there are reports on the development and characterization of stomach-specific drug delivery system to increase the efficacy of tetracycline against Helicobacter pylori infection in which chitosan was used as a polymer. The chitosan loaded microspheres were prepared by ionic cross-linking and by precipitation of chitosan with sodium sulphate. Two different methods were adopted to load the drug in microspheres. In the first method, tetracycline was mixed with chitosan solution before the simultaneous cross-linking and precipitation. In the second method, the drug was incubated with pre-formed microspheres for 48 h. It was found that the drug-loaded by the method I was very less i.e., 8% and by method II it was found to be 69%.

Gellan gum
Gellan gum has a characteristic property of cation induced gelation and it is widely used in CR formulations. An approach to develop and evaluate gellan gum beads containing cephalexin has been described in the literature. Beads were prepared by extruding the dispersion of cephalexin and gellan gum into a solution containing a mixture of calcium and zinc ions. Influence of variables such as pH of the counter ion solution and amount of cephalexin on response variables viz drug entrapment efficiency, release rate, particle size and morphology of beads were studied. The crystalline nature of the drug after its successful entrapment was studied by differential scanning calorimetry and indicated amorphous form of cephalexin loaded polymeric matrix. Fourier transform infrared spectroscopy reports suggested that there was no chemical interaction between drug, polymer and counterions. Light scattering results revealed spherical shaped beads.

Alginate (sodium or calcium alginate)
Alginate is typically extracted from cell walls of brown algae (Phaeophyceae) of Laminaria and Ascophyllum species by treatment with aqueous alkali solution. After the filtration of extract, treatment of filtrate with sodium or calcium chloride results in formation of precipitated alginate. Sodium alginate is known for improving drug entrapment efficiency of floating microparticles. It has been reported that calcium alginate based floating beads of berberine were prepared by suspending octodecanol and berberine in sodium alginate solution. The usage of octodecanol in preparation of microspheres was intended to increase the sustained release properties and floating ability of beads. Likewise, alginate-based microspheres or microbeads have been formulated by coagulation and emulsification methods. In addition, development and evaluation of multi-unit gastro-retentive sustained release dosage form of a water-soluble drug, ranitidine hydrochloride is also mentioned in literature. The method ensured completely aqueous environment avoiding the use of organic solvent in the preparation for the effective treatment of peptic ulcer by releasing the drug in stomach for a prolonged period. Drug entrained micro-beads were prepared using sodium alginate as polymer by an emulsion gelation technique. Sodium alginate alone and sodium alginate along with pectin were used for the formulation. It was found that sodium alginate was not just enough to sustain the drug release in gastric pH. Hence, an appropriate combination of alginate and pectin was used which could provide the sustained release drug release profile. Development of gastro-retentive sustained release alginate beads of diclofenac sodium has been reported as well. Beads were prepared by ionotropic gelation method by dispersing diclofenac sodium together with CaCO3 into a solution of sodium alginate. It was found that increased concentration of polymer has increased the drug entrapment efficiency. Similarly, a study was reported with respect to the formulation of floating dosage form of metformin hydrochloride using sodium alginate as a polymer. Conventional and oil entrapped alginate beads were prepared, former was prepared by ionotropic and later by emulsion gelation method. Different oils of standard pharmaceutical grade like light mineral oil, castor oil, vegetable oil (ground nut oil) and mentha oil were used to formulate and to study the effect of the same on the sustain release property of the formed beads. The oil entrapped calcium alginate gel beads showed better sustained release profile and specifically, liquid paraffin exhibited predominant sustained release action followed by ground nut oil > castor oil > menthol oil, when compared to conventional alginate beads. The results suggested that floating behavior of the beads ascribed to the density of oil used and the amount of oil required was found to be less with oils having less density. In a study, preparation and characterization of cepodoxime proxetil floating beads using sodium alginate as a polymer were described. Floating beads were prepared by precipitation method using calcium carbonate as a gas generating agent. Increasing concentration of sodium alginate had decreased the bead size and increase in concentration of gas forming agent increased the bead size and floating ability. The % Cumulative drug release results of in vitro dissolution study in glycine media for 12h, revealed that the higher concentration of the gas generating agent and lower concentration of sodium alginate provided maximum drug release due the formation of porous beads.

Pectin
Pectin is one of the major plant cell wall components and probably the most complex macromolecule in nature as it is composed of 17 different monosaccharides containing more than 20 different linkages. High methoxyl, low methoxyl, amidated and non-amidated pectins (LMP) have been reported for their use in gastro retentive formulations. Rutin, Zinc pectinate beads, metronidazole, metformin, indomethacin
were formulated in the form of microspheres using pectin and its derivatives. A reported method demonstrated the influence of method of preparation of pectin beads on the enhancement of drug loading using atenolol (cationic) and piroxicam (anionic) as model drugs. Pectin beads were prepared by dropping drug-containing pectin solution into calcium chloride solution. The droplets instantaneously turned into gelled spheres by ionotropic gelation. Variables like drug concentration, drying condition and calcium chloride concentration were considered for optimization of prepared beads. Infrared analysis reports suggested that the drug and pectin bound together with hydrogen bonds. In case of atenolol beads, the bead size depended upon the drug concentration and drying method, whereas in piroxicam beads, the bead size was dependent only on drying condition. The encapsulation efficiency for both the drugs was found to depend on calcium chloride and drug concentration. Freeze dried beads of piroxicam showed increased dissolution of drug, whereas freeze dried atenolol beads had no effect.\footnote{19}

Also, as indicated in a study, conventional calcium pectinate gel beads and calcium pectinate gel beads containing edible oils like light mineral oil, olive oil, corn oil, soya bean oil, rice oil, sesame oil, peppermint oil and sunflower oil were prepared by homogenization technique by emulsion gelation method. The oil-entrapped calcium pectinate gel beads showed desirable floating property with enough oil being used when compared with that of conventional pectinate gel beads. Particle size of gel beads depended upon the concentration of oil, as the oil volume increased the particle size also increased. The type and percentage of oil along with the relative density played an important role in controlling the floating behavior of oil-entrapped calcium pectinate gel beads.\footnote{20} Furthermore, it was mentioned that effervescent floating beads containing ketorolac tromethamine was assessed for sustained release property in the stomach with reduction in dose and side effects. Floating beads were prepared by the extrusion congealing method using calcium carbonate as a gas-forming agent, alginate as polymer and hydroxypropyl cellulose, sodium carboxy methyl cellulose, methyl cellulose and pectin as co-polymers. Beads prepared by using only alginate polymer showed low encapsulation efficiency and drug loading, usage of co-polymer along with alginate increased encapsulation efficiency and drug loading by forming two protective layers, which delayed the release of drug. The co-polymer concentration played a major role in the particle size of beads as well as swelling ability. As the concentration of co-polymer increased, the particle size and swelling behavior also increased. Results of analgesic effect studied by tail flick method from hot plate method revealed sustained effect of drug. The inference suggested that sodium alginate beads along with hydroxypropyl cellulose as copolymer showed better drug loading, floating and release profile.\footnote{21} Additionally, an investigation used six pectin derivatives with varying degree of methoxylation to formulate crystal violet encapsulated microspheres in combination with gelatin gum. Based on the morphological characteristics of microspheres, solubility, effect of calcium concentration and viscosity, amidated low methoxyl pectin was selected as a biopolymer. Hydrogel microspheres were prepared by extrusion of biopolymer solution through a 100 μm diameter syringe coupled with a peristaltic pump. Pectin microspheres were stabilized with arabic gum and optimized according to the loading efficiency. Results obtained from optical microscopy showed spheroid shape of microspheres, with homogenous distribution of crystal violet. Crystal violet’s use with biopolymer has shown reduction in viscosity due to molecular interaction between the mas confirmed by FTIR and Raman spectroscopic analysis.\footnote{22}

Moi gum

The gum is obtained from leaves, stems, fruits and most abundant in the bark of the \textit{Lannea coromandelica} (Anacardiaceae). It is yellowish-white while fresh and upon drying becomes dark. Gum ducts are present in leaves, stems and fruits, most abundant in bark of the stem. It is used as microencapsulating agent and release rate controlling material. Moi gum-based microspheres are prepared by solvent evaporation technique and produced microspheres that have acceptable size, morphology and showed sustained release beyond 10 hours in comparison with guar gum but when used in 1:1 ratio showed better sustain release property.\footnote{23,24}

Mucuna gum

Mucuna gum is obtained from \textit{Mucuna flagilipes} (Papilionaceae). It is composed of mainly D-galactose along with D-mannose and D-glucose. A study on suitability of mucuna gum microspheres of glibenclamide for oral delivery was demonstrated; the results showed that the formulation exhibited good \textit{in vitro} release profile and it was also found that the microspheres had good swelling ability in distilled water, suggesting it is suitable for bioadhesive drug delivery system.\footnote{25,26}

Psyllium husk

It is obtained from dried seed coats of \textit{Plantago ovata}.\footnote{27} It contains a high proportion of hemicellulose composed of xylan backbone linked with arabinose, rhamnose and galacturonric acid units.\footnote{28} It can form a gel with water and it is pale to medium buff-colored powder, with a weak characteristic odour.\footnote{29,30} Psyllium husk has release retardant properties. It prolongs the retention time of dosage form in the stomach.\footnote{31}

Karaya or sterculia gum

Karaya gum or Sterculia gum is exuded from the tree \textit{Sterculia urens}, belongs to the family \textit{Sterculiaceae}.\footnote{32} It is naturally occurring polysaccharide constituted from L-rhamnose, D-galactose and D-galacturonic acid.\footnote{33} Sterculia gum has unique features such as high swelling, water retention capacity, high viscosity, inherent anti-microbial activity and abundant availability.\footnote{34,35} It has been used as an emulsifier, stabilizer and thickening agent. It is a strongly acidic polysaccharide and has good stability in acidic preparations.\footnote{36}

The results obtained in an investigation suggested the therapeutic importance of sterculia gum and alginate polymers in controlling the release of pantoprazole from gastro-retentive drug delivery system prepared by ionotropic gelation method.\footnote{37}

Xanthan gum

Xanthan gum (XG) is a high molecular weight natural polysaccharide, due to its exceptional rheological properties acts as an effective stabilizer for water-based systems. XG is produced from a bacterium \textit{Xanthomonas campestris} by fermentation process. It is a heteropolysaccharide with a primary structure consisting of repeated pentasaccharide units formed by two glucose units, two mannose units and one glucuronic acid units.\footnote{38,39} XG is also been used as an effective excipient for sustained-release formulations.\footnote{40} Preparation of floating microspheres with micro-balloons inside using Theophylline as a model drug, XG and gelatin as polymers is been reported in a recent study. Microspheres were prepared by water in oil emulsification method varying the ratio of polymers. It was found that % yield, \textit{in vitro} drug release rate and drug entrapment efficiency reduced with increasing gelatin content.\footnote{41,42}

Starch

Starch is the most commonly used polymer, obtained from jackfruit seeds; these seeds contain a high content of carbohydrate and protein.\footnote{43} The major components of starch are two polysaccharides amylose and amylopectin. Amylose is a predominantly linear polysaccharide consisting of α-1,4 linked D-glucopyranosyl units.\footnote{44} Carboxymethyl starch powder is also been reported for its use in formulation of microspheres.\footnote{45,46} A study proposed an attempt to formulate and characterize starch microspheres...
Table 2: Overview of source, drug, polymer, type of release and uses.

<table>
<thead>
<tr>
<th>Source</th>
<th>Drug</th>
<th>Polymer</th>
<th>Type of release</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoki H, Iwao Y, Mizoguchi M,</td>
<td>Clarithromycin</td>
<td>Lubriwax-101</td>
<td>Sustained release</td>
<td>Macrolide antibiotic used to treat bacterial infections.</td>
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<td>Noguchi S, Itai S, 2015.113</td>
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<td>Hooza A, Nanda A, Jain M,</td>
<td>Ranitidine HCl</td>
<td>Chitosan</td>
<td>Controlled release</td>
<td>Histamine H2 receptor antagonist</td>
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<td>Kumar V, Rathee P, 2012.114</td>
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<tr>
<td>Stops F, Fall JT, Collett JH,</td>
<td>Riboflavin</td>
<td>Sodium alginate</td>
<td>Controlled release</td>
<td>Vitamin B2 supplement</td>
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<td>Martini L.G. 2008.115</td>
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<tr>
<td>El-Gibaly I, 2002.116</td>
<td>Melatonin</td>
<td>Chitosan</td>
<td>Controlled release</td>
<td>Treating various circadian rhythm disorders.</td>
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<td>Kumar KV, Choudary PS,</td>
<td>Dopolirone</td>
<td>Pectin</td>
<td>Sustained release</td>
<td>Antiemetic</td>
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<td>Ajaykumar B, 2013.118</td>
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<td>Shailaja T, Ramachandra S,</td>
<td>Diltiazem</td>
<td>Karaya gum, xanthan gum, guar gum, carrageenan, sodium bicarbonate</td>
<td>Sustained release</td>
<td>Calcium channel blocker used for the management of angina pectoris</td>
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<td>Kishore C, Bhushan YS, Lakshmi PK, 2013.120</td>
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<tr>
<td>Mahmoud HA, Melake NA, El-Semary MT, 2012.121</td>
<td>Tetracycline</td>
<td>Chitosan</td>
<td>Controlled release</td>
<td>Against Pseudomonas aeruginosa bacteria</td>
</tr>
<tr>
<td>Pasparalis G, Bouropoulos N, 2006.122</td>
<td>Verapamil</td>
<td>Calcium alginate, calcium alginate-chitosan beads</td>
<td>Controlled drug release (diffusion and swelling controlled)</td>
<td>Treatment of hypertension</td>
</tr>
<tr>
<td>Fathy M, 2006.123</td>
<td>Meloxicam</td>
<td>Calcium alginate</td>
<td>Controlled release profile dependent upon swelling and erosion of beads</td>
<td>Treatment of ulcer, COX-2 inhibitor</td>
</tr>
</tbody>
</table>

ADVANTAGES OF NATURAL POLYSACCHARIDES

- The natural polymers are more superior to the synthetic polymers with respect to their highly organized macroscopic and molecular structure.124
- Low toxicity and excellent biodegradability.124
- Biocompatible and safe.
- Low cost.
- Environment-friendly.
- Better patient tolerance.
- Easily available.125
- Less immunogenicity
- Acts as carrier for drug delivery by complementing the property of drug and other excipients used.126
- Provides controlled drug release
- Capable of chemical modification
- Combination of 2 or more polymers tend to provide better results in case of sustain release formulations

DISADVANTAGES OF NATURAL POLYSACCHARIDES

- Most of the polymers do not undergo enzymatic degradation.127
- Sometimes the degradable polymers exhibit substantial dose dumping.
- A “burst effect” or high initial drug release soon after administration is typical.128
- Variable biocompatibility of polymers
- Due to impurities in the preparation extracts, it is difficult to reproduce some of the properties of polymer.129

APPLICATIONS OF NATURAL POLYSACCHARIDES

- Polysaccharides are generally employed in floating drug delivery systems to target the delivery of the drug to a specific region in the GIT.130
- Polysaccharide polymers are used to prepare the gas and gaseous precursor filled microparticles used for magnetic resonance imaging of the stomach.131

ADVANTAGES OF STOMACH SPECIFIC DRUG DELIVERY SYSTEMS

Enhanced GRT: Increased gastric residence can be achieved, when the density of the formulation is less than gastric contents in case of floating systems; muco adhesion because of bioadhesive property of the system; high density system due to its sinking property and formation of hydrated gel layer around the system by making it as superporous hydrogel, modified shape and expansion systems.
**Improved patient compliance:** The chances of missing a dose with a shorter half-life are common in the case of a conventional dosage form which leads to poor patient compliance. This poor patient compliance can be circumvented by using an effective technique using controlled drug delivery systems.

**Desired therapeutic concentration:** Most of the drugs are absorbed from the stomach region, hence the therapeutic concentration of drug in the plasma can be increased by gastro-retention to obtain the desired therapeutic response.

**Increased safety:** Safety margin for high potency drugs can be increased in the body because the plasma level of drugs can be controlled. The drug administered is completely being utilized, by reducing the total amount of drug administered.

**Site-specific delivery of drug:** Slow delivery of drugs at a specific site in the stomach can increase the therapeutic efficacy with the minimal amount of drug, which leads to less drug wastage.

**Economical:** The health care cost is reduced because of improved therapy, shorter treatment period and reduced dosing frequency.

**DISADVANTAGES OF STOMACH SPECIFIC DRUG DELIVERY SYSTEMS**

- Drugs having solubility or stability issues in the stomach environment or gastric fluids are difficult to formulate as stomach specific drug delivery systems.

- Floating drug delivery systems require a high gastric fluid volume to float and show the desired activity.

- Drugs which cause gastric mucosal irritation cannot be formulated as stomach specific drug delivery systems because of poor patient convenience and compliance.

**CONCLUSION**

Natural polysaccharides are widely been used in drug delivery systems because of their advantages over synthetic polymers. These polymers are easily available in nature and they are extracted from plant and animal sources. The selection of polymer plays a major role in the development of particulate drug delivery systems. Polymers can be used either alone or in combination with other polymers to possess better properties. Polymers discussed above influence gastric retention and release profile of drugs. From the research perspective, natural polysaccharides in addition to have gained importance in gastro-retentive drug delivery are extensively being used in cell targeting, nasal drug delivery systems, colon targeting and gene therapy. These polymers seem to be non-reactive with most of the drugs and are highly compatible with other excipients; this makes them to be used more abundantly in the advancement of drug delivery technologies.

Hence forth, the future explorations in the area of stomach specific microparticulate drug delivery using natural polysaccharides subsume, personalized medication approach as patients experience variation in GRT of the formulation affected by physiological factors; use of magnetic and ion exchange resin systems to increase GRT of the drug in the stomach which are not being widely used; reduction of burst effect using smart polymers which has the ability to release the drug at appropriate time and specific site; use of molecular imprinted polymers due to their high stability in gastrointestinal condition; application of artificial intelligence and target fishing to identify the biological targets ensuring accuracy in formulation development. Despite the extensive use of these polymers in research, impo application lacunae in commercially viable drug delivery systems. Thus, above mentioned approaches can be made possible to increase their usage in industries for wide gamut of profits.

**ACKNOWLEDGEMENT**

The authors are indebted to Government College of Pharmacy, Bengaluru and College of Pharmaceutical Sciences, Dayanand Sagar University, Bengaluru for providing necessary support to carry out this literature survey.

**ABBREVIATIONS**

CR: Controlled release; GIT: Gastro intestinal tract; GRT: Gastric residence time; XG: Xanthan gum.

**REFERENCES**


Article History: Submission Date : 08-02-2020; Revised Date : 16-03-2020; Acceptance Date : 14-04-2020.