Pharma Science Monitor 5(1), Jan-Mar 2014

PHARMA SCIENCE MONITOR

AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES

Journal home page: http://www.pharmasm.com

APPLICATION OF NATURAL POLYMERS IN THE DEVELOPMENT OF MULTIPARTICULATE SYSTEMS FOR COLON SPECIFIC DRUG DELIVERY

Shailesh U. Ginoya*, Samir A. Atara

Department of Pharmaceutics, School of Pharmacy, RK University, Kasturbadham, Rajkot-360 020

ABSTRACT

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome but also for the potential it holds for the systemic delivery of proteins and therapeutic peptides. To achieve successful colon targeted drug delivery, a drug needs to be protected from degradation, release and/or absorption in the upper portion of the GI tract and then ensure abrupt or controlled release in the proximal colon. The use of biodegradable polymers holds great importance to achieve targeted drug release to the colon. The class of natural polymers has great appeal to drug delivery as it comprises polymers with a large number of derivatizable groups, a wide range of molecular weights, varying chemical compositions, low toxicity and biodegradability yet high stability. Polysaccharidases are bacterial enzymes that are available in sufficient quantity to degrade these natural polysaccharides. This article also discusses some drug delivery systems with polymers used in these systems designed to target a drug to the colon.

KEYWORDS: Colonic drug delivery**,** Biodegradable polymers, Low toxicity, Natural polysaccharides.

INTRODUCTION

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome but also for the potential it holds for the systemic delivery of proteins and therapeutic peptides. The large intestine, though difficult to reach by peroral delivery, is still deemed to be the ideal site for the delivery of agents to cure the local diseases of the colon.[1] The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of the small intestine.[2] In order to develop a reliable colonic drug delivery system, the transit time of dosage forms through the gastrointestinal (GI) tract needs to be understood very well. The transit of perorally administered formulation through the GI tract is highly variable and depends on various factors.[3-6] For example factors like disease state of the lumen (diarrhea, diabetes, peptic ulcer etc), concomitant administration of other drugs (domperidone, cisapride, metoclopromide etc), body posture (vertical or supine) and food type (fat and protein content) can influence the gastric emptying rate.[7] A successful colon drug delivery also requires careful consideration for the number of

factors including the properties of drug, type of delivery systems, and its interaction with healthy or diseased gut.

Criteria for Selection of Drugs for Colon-Specific Drug Delivery Systems:

The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery.[8] The criteria for selection of drugs for CDDS is summarized in Table 2.[9-11] Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule.[12] For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.[8] The polymers used in various colon targeted approaches are given in Table 1.

Table 1: Polymers Used in Different Colon Targeting Approaches [1]

Approaches	Polymers Used
pH dependent	Eudragit L100 and S100 Eudragit L100 and S100 Eudragit L100 and S100 Eudragit S, Eudragit FS, Eudragit P4135 F Eudragit L 30 D-55 and Eudragit FS 30 D
Time dependent	Hydroxy propyl methyl cellulose Hydroxy ethyl cellulose Ethyl cellulose, microcrystalline cellulose Lactose/ Behinic acid Hydroxy propyl methyl cellulose Hydroxy propyl methyl cellulose Acetate succinate
Bacteria dependent/ Polysaccharide based	Chitosan Pectin Guar gum Amylose Alginates

Table 2: Criteria for selection of drugs for CDDS [13]

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amylin, Anti-sense oligonu-cleotide
Drugs poorly absorbed from upper GIT	Antihypertensive and Antianginal drugs	Ibuprofen, Isosorbides, Theophylline	Cyclosporine, Desmopressin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Gluca-gon
Drugs that de-grade in stomach and small intes-tine	Peptides and proteins	Bromophenaramine, 5-Flourouracil, Doxorubi-cin	Gonadoreline, Insulin, Inter-ferons
Drugs that un-dergo extensive first pass metab-olism	Nitroglycerin and Cor-ticosteroids	Bleomycin, Nicotine	Protirelin, Ser-morelin, Saloatonin
Drugs for target-ing	Antiarthritic and Anti-asthamatic drugs	Prednisolone, Hydrocor-tisone, 5-Amino-salicylic acid	Somatropin, Urotoilitin

General Considerations for Design of Colon Delivery Formulations:

Colonic delivery formulation are in general may be designed to provide either for 'burst release' or for sustained/prolonged release once reaching the colon.[14] The proper selection of a formulation approach depends upon several important following factors.[15]

- Pathology and pattern of diseases especially the affected parts of the lower GI tract or physi-ology and physiological compositions of the healthy colon if the formulation is not intended for localized treatment.
- Physicochemical and biopharmaceutical properties of the drug such as solubility, stability, and permeability at the intended site of delivery.
- The desired release profile of the active ingredient. The most common physiological factor con-sidered in the design of delayed release colonic formulations is pH gradient of the GI tract.

Single-unit system for colon targeting:

Single-unit colon-targeted delivery system may suffer from the disadvantage of unintentional disinte-gration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastic changes in patients with inflammatory bowel disease (IBD) than seen in healthy volunteers.

In one study involving six patients with ulcerative colitis, the colonic pH of three patients varied from 5.0 to 7.0, whereas in the case of other three patients, very low pH of 2.3, 2.9 and 3.4 were observed. Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single-unit systems because of their potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation, and predictable gastric emptying.[16]

Multiparticulate system for colon targeting:

Multiparticulate approaches include formulations in the form of pellets, granules, beads, microparticles and nanoparticles. Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation, predictable gastric emptying and retained in the ascending colon for a relatively long period of time. Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GI tract easily, leading to less inter and intra-subject variability. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption. Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon.[17]

Nanoparticulate systems:

Nanoparticle size colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting. Orally administered nanoparticles serve as carriers for different types of drugs and have been shown to enhance their solubility, permeability and bioavailability.[18] Nanoparticles have also been investigated for the delivery of protein and peptide drugs.[19]

For colonic pathologies, it was shown that nanoparticles tend to accumulate at the site of inflammation in IBD. This is because in case of colitis, a strong cellular immune response occurs in the inflamed regions due to increased presence of Neutrophils, Natural Killer cells, Macrophages and so on. It has been reported that microspheres and nanoparticles could be efficiently taken up by these macrophages.[20] This results in accumulation of the particulate carrier system resulting in prolonged residence time in the desired area. A study by Lamprecht et al.[21] proved an increased nanoparticle deposition in the inflamed tissue of the colon compared to the healthy control.

However, an important area of concern is to prevent loss of nanoparticle in the early transit through GI tract in order to optimize therapeutic efficacy.[22] Moreover, particle uptake by Payer's patches and/or enzymatic degradation may cause the release of entrapped drug leading to systemic drug absorption and side effects. In order to overcome this problem, drug loaded nanoparticles were entrapped into pH sen-

sitive microspheres, which serve to deliver the incorporated nanoparticle to their site of action, thereby preventing an early drug leakage. The use of Eudragit P-4135F prevented drug release in the upper GI tract and during intestinal passage and permitted selective drug delivery in the colon.

The use of nanoparticles for bioadhesion purposes have also been investigated.[23] Nanoparticles have a large specific surface, which is indicative of high interactive potential with biological surfaces. Since the interaction is of non-specific nature, bioadhesion can be induced by binding nanoparticles with different molecules. For covalent attachment, the nanoparticle surface has to show free functional groups, such as carboxylic or amine residues. In one study, nanoparticles were prepared from gliadin protein isolate from wheat gluten, as these can be readily used for binding ligands to their surface. The gliadin nanoparticles were conjugated with lectins (glycoproteins of non-immune origin which provide specific bioadhesion), fluorescently labeled and evaluated for bioadhesive potential on isolated intestinal segments. It was shown that gliadin nanoparticles have a high capacity of non-specific interaction with intestine and the binding of lectin provided greater specificity for colonic mucosa.

Microsphere:

Microspheres that are biodegradable can be efficiently taken up by macrophages. Therefore, the direct uptake of anti-inflammatory agent-loaded microspheres by macrophages would have a superior immunosuppressive effect and be more useful for treatment of patients with IBD. Hiroshi and co-workers studied incorporation of dexamethasone into poly (dl-lactic acid) microspheres and administered to mice induced with experimental colitis. It was found that serum dexamethasone levels were not increased after oral administration of dexamethasone microspheres, but at the same time the microspheres facilitated mucosal repair of experimental colitis. This strategy could be ideal for the treatment of IBD where local action in colon is needed without systemic drug burden. A new pH-sensitive polymer Eudragit P-4135 F was used to prepare microparticles of an immunosuppressant drug tacrolimus, for colonic delivery. They also used Eudragit P-4135 F in the microencapsulation of 5-fluorouracil for the treatment of colorectal cancer.

The multiparticulate system of chitosan microspheres is coated with Eudragit L100 or S100 for the colonic delivery of metronidazole for the treatment of Amoebiasis.[16]

Beads:

Hydrogel beads were formed by chitosan and tri-poly-phosphate (TPP) for the delivery of protein in the colon. TPP was used as a counter ion to positively charged chitosan to form gel beads. The beads were loaded with bovine serum albumin (BSA), a protein that is liable to degradation in the upper parts of GI tract. The cross-linking of chitosan with TPP resulted in reduced solubility of chitosan thereby resulting in lesser protein release during upper GI transit. At the same time, the cross-linking and reduced solubility did not affect the degradability by microbial flora in the colon as shown by the *in vitro* studies

where the rat caecal contents were able to attack and degrade the cross-linked chitosan.[24]

Importance of Polymer in Designing of Multiparticulate System:

Coating with pH-sensitive polymers:

Human GIT pH increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. Tablets, capsules, or pellets coated with pH-sensitive polymers provide delayed release and protect the active drug from hostile gastric fluid. For colon targeting, polymers used should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine, and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. These processes release the drug throughout the large intestine and thus provide the potential of the CTDS.

Most commonly used pH-dependent coating polymers for peroral delivery are methacrylic acid copolymers, Eudragit L100 and Eudragit S100, which dissolve at pH 6.0 and 7.0 respectively. The combination of these two polymers in various ratios makes it possible to manipulate drug release within 6.0-7.0 pH range. It has been reported earlier that the use of Eudragit S alone is not suitable for colonic delivery.[25] Studies in human volunteers have shown that since the pH drops from 7.0 at terminal ileum to 6.0 of ascending colon, such systems sometimes fail to release the drug.[26] In order to overcome this problem, a proper combination of polymers Eudragit S100 and Eudragit L100 ensures that the release of drug from formulation will occur even when the pH value of the GI tract does not reach more than 6.8.

The various enteric polymers utilized for formulation development with their pH soluble characteristics are shown in Table 3.

Table 3: Represents various enteric polymers utilized in the development of modified-release formulations for colonic delivery

Enteric polymers	Optimum pH for dissolution
Polyvinyl acetate phthalate (Coateric®[b])	5.0
Cellulose acetate trimellitate	5.5
Hydroxypropyl methylcellulose phthalate	
HP-50	>5.0
HP-55 and HP-55S	>5.5
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	>5.5- >6.8
Methacrylic acid copolymer, Type C (Eudragit® L100-55[a])	
Methacrylic acid copolymer dispersion (Eudragit® L30D-55[b])	5.5
Methacrylic acid copolymer, Type A (EudragitÒ L-100[a] and Eudragit® L12,5)	6.0
Cellulose acetate phthalate (Aquateric®[b])	6.0
Methacrylic acid copolymer, Type B (EudragitÒS-100[a] and Eudragit® S12,5)	7.0
EudragitÒ FS30D[b]	7.0
Shellac (MarCoat 125[c] and 125N[c])	7.0

[a]Suitable for aqueous dispersion; [b]Available as aqueous dispersion; [c]Available as aqueous solution

Coating with biodegradable polymers:

Drugs coated with the biodegradable-type polymers are showing degradability due to the influence of colonic microorganisms that can be exploited in designing drugs for colon targeting. These bacterial degradable polymers especially azo polymers have been explored in order to release an orally administered drug in the colon. Actually, upon passage of the dosage form through the GIT, it remains intact in the stomach and small intestine where very little microbially degradable activity is present that is quiet insufficient for the cleavage of polymer coating. Release of the drugs from azo polymer-coated formulation is supposed to take place after reduction and thus degradation of the azo bonds by the azo reductase enzymes released by the azo bacters present in the colonic microflora.

Embedding in matrices:

The drug molecules are embedded in the polymer matrix. The polymers used for this technique should exhibit degradability in the colon for the liberation of entrapped drug.

Embedding in pH-sensitive matrices:

Extrusion-spheronization and pelletization have been used for the preparation of pH-sensitive matrix pellets for colon-targeted drug delivery.[27] The authors studied the effects of three independent variables (amounts of Eudragit® S, citric acid, and spheronizing time) on pellet size, shape (roundness and aspect ratio), and drug release was studied with central composite design. Nykanen *et al*. used ibuprofen as a model drug and Eudragit® S and Aqoat AS-HF as enteric polymers for developing site-specific systems for release of a drug in the lower part of the small intestine or in the colon. The target of this study was to investigate whether on using organic acids as excipients could influence the drug-release rate from enteric matrix granules. It was concluded that although inclusion of an organic acid in a formulation retarded *in vitro* release of the model drug, no corresponding effect was evident in case of *in vivo* studies.[28]

Embedding in biodegradable matrices and hydrogels:

Polysaccharides, the polymer of monosaccharides, retain their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine, but once they reach in the colon, they are acted upon by the bacterial polysaccharidases and results in degradation of the matrices. A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, and locust bean gum have been investigated for their use in colon-targeted drug delivery systems. The most important fact in the development of polysaccharide derivatives for colon-targeted drug delivery is the selection of a suitable biodegradable polysaccharide. As these polysaccharides are usually soluble in water, they must be made water insoluble by cross-linking or hydrophobic derivatization. The important factor is an optimal proportional of the hydrophobic and

hydrophilic parts, respectively, and the number of free hydroxy groups in the polymeric molecule.

Polymers Importance in Bioadhesive System:

Bioadhesion is a process by which a dosage form remains in contact with a particular organ for an augmented period of time. Their longer residence time of a drug would have high local concentration or improved absorption characteristics in the case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes, and polyethylene oxide-polypropyline oxide copolymers have been investigated as materials for bioadhesive systems.[29]

Natural Polysaccharides for Colon-Specific Drug Delivery:

Polysaccharides are promising agents for obtaining colon-specific drug delivery systems. This article describes the different polysaccharides that have already been used in the initial approaches for colon-specific drug delivery. These natural polymers are strongly appealing to use in a truly colon-specific commercially available drug delivery system. The reasons for this are that they are non-toxic, easy to work with, and will be FDA approved. Also very important is that they are selectively degraded in the colon.

Polysaccharides from plant source:

Starch

It is a polymer which occurs widely in plants. In general, the linear polymer, amylose, makes up about 20% weight of the granule, and the branched polymer, amylopectin, make the rest of the weight. Amylose is crystalline and can have a number average molecular weight as high as 500 000, but it is soluble in boiling water. Amylopectin is insoluble in boiling water, but in their use in foods, both fractions are readily hydrolyzed at the acetal link by enzymes. The α-1, 4-link in both components of starch is attacked by amylases and the α-1; 6-link in amylopectin is attacked by glucosidases.

Cellulose

It has very long molecular chain consisting of one repeating unit (cellobiose), which is a differentiating factor, from other polysaccharides produced by plants. Naturally, it occurs in a crystalline state. From the cell walls, cellulose is isolated from microfibrils by chemical extraction. In all forms, cellulose is a very highly crystalline, high-molecular-weight polymer, which is infusible and insoluble. In anaerobic environments, such as in colon, bacteria secrete both endo- and exo-enzymes, some of which form complexes that act jointly in degrading cellulose to form carbohydrate nutrients, which is utilized by the microorganisms for survival.

Pectin

Pectin is the methylated ester of polygalacturonic acid. Pectin specifications are given in Table 4. It is commercially extracted from citrus fruits like apple, guava, and gooseberry. Pectins are complex poly-

saccharides present in the walls that surround growing and dividing plant cells. It is also present between xylem and fibre cells in woody tissue.[30] In recent years, pectin has gained increasingly importance. The benefits of natural pectin are also more and more appreciated by scientists and consumer due to its biodegradability. Pectin is a non starch linear polysaccharides that consists of α-1,4-*D*-galactouronic acid and 1,2-*D*-rhamnose, with *D*-galatose, and *D*arabinose side chains having average molecular weight around 50,000-150,000 daltons. The gelling property of the pectin depends upon the molecular size and degree of esterification.[31,32] In recent year's pectin which is a biopolymer, proven very attractive and interesting applications in pharmaceutical and biotechnology industry. It is very well known as a thickening agent, gelling agent, and a colloidal stabilizer polysaccharide in food industry. Pectin is highly soluble in water. When it is used alone, in contact with GIT fluids it swells and the entrapped drug is released through diffusion.[32] This problem was manipulated with chemical modification without affecting favourable biodegradability properties. Pectin can be chemically modified by saponification catalysed by acids, bases, enzymes and salts of weak acids.[33] Calcium salts have reduced the solubility of pectin. Pectin showed very good potential in colon specific drug delivery systems for systemic action or a topical treatment of diseases such as ulcerative colitis, Crohn's disease. Gel forming systems have been widely investigated for sustained drug delivery.[34] Gelling can be induced by mineral acids or by cross-linking with calcium ion or by alginates.[35]

Table 4: Pectin Specification [31, 32]

Parameter	Range
General description	White, yellowish
Taste	Tasteless
Solubility	Soluble in cold and hot water
pH	5 to 7
Moisture content	Max12
Total ash	Max 1%
Acid insoluble	Max 3%

Inulin

Inulin is a natural plant-derived polysaccharide with a diverse range of pharmaceutical and food applications. Inulin specifications are given in Table 5. Inulin are produced by various plants.[36] Inulin belongs to a class of fibers known as fructans. It is used by some plant as a storing energy and is typically found in roots and rhizome. Most of the plants that synthesize Inulin do not contain storing material starch. Plants that contain high content of inulin are found in Dandelion (Taraxacum officinale), wild yam (Discora), chicory (Cinchorium intybus), onion (Allium sativum), and garlic (Allium sativum). Inulin is resistant to digestion in the upper GIT, but it is degraded in colon by colonic microflora specifically by Bifidobacteria.[37,38] Inulin consists of a mixture of oligomers and polymers that belong to the

group of gluco-fructans. α-*D*-glucopyranosyl-[α-*D*-fructofuranosyl] (n-1)-*D*fructofuranoside, commonly referred to as inulin. The inulin molecules contain 2 to 60 or more β-2-1 linked D fructose molecules.[39] Inulin is a natural renewable polysaccharide with a significant number of pharmaceutical and food applications. In the food industry it is used as a fat or sugar replacement and soluble dietary fibre. Since it is soluble in water, inulin with combination of Eudragit films were prepared in order to resist degradation in upper GIT, but were digested in lower intestine by the action of Bifidobacteria and bacteriods.[50] Methylated inulin hydrogels were developed as colon targeted drug delivery systems and investigated for water take up and swelling.[37] The rate of water transport into inulin was quite high and showed anomalous dynamic swelling behaviour. Inulin derivatised with methacrylic anhydride and succinic anhydride produced a pH sensitive hydrogel that exhibited a reduced swelling and low chemical degradation in acidic medium, but had a good swelling and degradation in simulated intestinal fluid in the presence of its specific enzyme, inulinase.[41]

Table 5: Inulin Specifications [39]

Parameter	Range
General description	White to yellowish powder
Taste	Slightly sweet, odourless
Solubility	Soluble in water
pH	6 to 7
Moisture content	Max 9.5%
Total ash	Max 1.5%
Total carbohydrates	Max 98%
Sucrose	Max 3%

Amylose

It is a poly (1-4-α -D-glucopyranose) that consists of D-glucopyranose residues linked by α- (1-4) bonds. Those substances, present naturally in the diet, have the advantages of being safe, nontoxic and easily available. These are resistant to pancreatic α-amylase, but are degraded by colonic bacterial enzyme.[42] Mixed films of amylose and ethyl cellulose as coatings have shown a great potential as colon delivery carriers.[43] Delayed release compositions comprising glassy amylose and an active compound were designed to permit the release when the composition reaches the large intestine. The release of the active compound reported to be delayed in an aqueous environment of pH 1-9 at 37^{o}C.[44] The release was triggered when exposed to an enzyme capable of clearing the amylase. The delivery system can be made into a powder or monolithic form. This composition is useful in the diagnosis and therapy of diseases of the colon. The above composition may also be applied for delivery of anti-arthritic drugs and also for pesticidal delivery.

Guar gum

Guar gum is also known as cluster bean, Guaran, Cyamopsis, Guarina. It is obtained from the seeds endosperm of Cyamompsis tetragaonolobus (Family Leguminoseae) as a storage galactomannan polysaccharide, originated from India and Pakistan and cultivated in United States. It shows delayed gastric emptying.[45] It degrades in the large intestine due to the presence of intestinal microbial flora. It is a linear chain of β 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose, resulting in short chain branches. The mannose to galactose ratio has been estimated as 1.8: 1 to 2: 1. Guar gum is available in different grades based on the colour. Molecular weight is estimated to be in the range of 200,000 to 300,000 Daltons.[46] Mannose: galatose is in the ratio of 2:1. Guar gum is more soluble than locust bean gum, better stabilizer and not self-gelling. When cross linked with borax or calcium gel can be formed. Guar gum is highly soluble in water. As it is non-ionic it is not affected by any pH. It is stable between pH ranges 5-7 and degrades on extreme pH and temperature (3–50˚C). It undergoes hydrolysis when treated with strong acids with viscosity loss. Guar gum gives highly viscous pseudo plastic solutions of generally greater low-shear viscosity when compared to other natural polysaccharides.1% concentration of guar gum exhibits thixotrophy behaviour.[47] Guar gum is used as a protective colloid, binder and disintegrating agent in convectional tablets. Therapeutically used as bulk-forming laxative, appetite depressant and in peptic ulcer therapy. Guar gum is used as an ideal thickening agent in medicated tooth paste, lotions, creams, and ointments. It is also used as emulsifier and stabilizer.[48, 49] Guar gum reduces postprandial glucose and insulin levels in both healthy and diabetic patients and may be useful as adjunct in the treatment of Type II Diabetics. Guar gum is a potential natural polysaccharide to colon controlled drug delivery systems is studied by many researchers. Due to the gelling property of the gum, drug release is retarded from the dosage form and is susceptible to degradation in the colonic environment. Degradation of polysaccharide by intestine micro flora was confirmed by homogenizing and diluting human feces and incubated with guar gum. It resulted in rapid decrease in the viscosity and fall in the pH.[50-54]

Table 6: Guar Gum Specifications [55]

Parameter	Range
General description	White to pale yellow free flowing powder
Taste	Tasteless and odourless
Solubility	Soluble in water forms viscous colloidal solution, insoluble in organic solvents
pH	6–7
Moisture content	4%–12%
Total ash	0.4%–1.2%
Acid soluble	2%–5%
Protein	2%–6%
Galactose	0.782
Mannose	0.218

Polysaccharides from animal source:

Hyaluronic acid

Hyaluronic acid also known as Hyaluronan or Hyaluronate is a mucopolysaccharide, a gelatinous material that occurs naturally and extensively in the human body, it also occurs as an extracellular polysaccharide in a variety of bacteria. Hyaluronic acid is concentrated mostly in human cartilage, extra cellular matrix and skin, especially in the tissue spaces, the synovial fluid of joints and the vitreous humour of the eyes. It functions as a binding and protecting agent in tissue hydration and lubrication, by supplementing the natural levels of glycosaminoglycan in the human body, Hyaluronic acid serves as a major ingredient in anti-aging therapies. Hyaluronan is a polymer of disaccharides, composed of *D*-glucuronic acid and *D*-*N*acetylglucosamine, linked together via alternating β-1,4 and β-1,3-glycosidic bonds. Hyaluronan can be 25,000 disaccharide repeats in length. Polymers of Hyaluronan can range in size from 5,000 to 20,000,000 Daltons *in vivo*.[56] Hyaluronic acid is abundantly present in colon tissue, there is some evidence suggests that hyaluronic acid plays an important role in treating colon disorders like inflammatory bowel disorder, ulcerative colitis. Rudzki et.al reported Hyaluronan receptor CD44 are strongly over expressed in tumors compared to colon.[57] Though hyaluronic acid was discovered in 1938, hyaluronic acid still needs to be well investigated compared with other polysaccharides. There is lot of scope to understand its application in controlled drug delivery systems.[58]

Chondroitin sulfate

Chondroitin sulphate soluble mucopolysaccharide belongs to a family of heteropolysaccharides called glycosaminoglycans or GAGs, found in humans in cartilage, bone, cornea, skin and the arterial wall.[59] Chondroitin sulfate B is also known as dermatansulfate. It is abundant in skin and also found in heart valves, tendons and arterial walls. Chondroitin sulfate C is primarily found in fish and shark cartilage. Chondroitin sulfate supplements are usually isomeric mixtures of chondroitin sulfate A and chondroitin sulfate C and from cartilaginous rings of cow trachea and pork by products. Chondroitin sulfate chains are unbranched polysaccharides of variable length containing two alternating monosaccharides: *D*-glucuronic acid (GlcA) and N-acetyl-*D*-galactosamine (GalNAc). Some GlcA residues are epimerized into *L*-iduronic acid (IdoA); the resulting disaccharide is then referred to as dermatan sulfate. Glycosylated serines are often followed by a glycine and have neighbouring acidic residues. Mainly it is to treat osteoarthritis; some investigation has showed chondroitin is a promising excipient for colon targeted drug delivery containing indomethacin, drug release profiles indicated there was a constant degradation in the caecal content.[60] Sintov *et al* 2004, indomethacin tablets were prepared with two cross-linked polymers and their water uptake and drug release characteristics were studied.[61]

Chitosan

It is a functional linear polymer derived from chitin, the most abundant natural polysaccharide next to cellulose, which is not digested in the upper part of the GI tract by human digestive enzymes. Chitosan is a copolymer consisting of 2-amino-2-deoxy- D-glucose units linked with β - (1>4) bonds. It should be susceptible to glycosidic hydrolysis by microbial enzymes in the colon because it possesses glycosidic linkages similar to those of other enzymatically depolymerized polysaccharides.[16]

Polysaccharides from bacterial sources:

Gellan gum

Gellan gum is an anionic microbial polysaccharide produced by fermentation of pure culture of Sphingomonas elodea. The production organism is an aerobic, well characterized, nonpathogenic, and gram-negative bacterium.[62] Gellan gum is available in two types, high and low based on the acyl content. Low acyl gellan products form firm, non-elastic, brittle gels, whereas acyl gellan gum forms soft, very elastic non-brittle gels.The general chemical structure of gellan gum consists of four linked monosaccharides including one molecule of rhamnose, one molecule of glucuronic acid, and two molecules of glucose. In the native form of the polysaccharide, there are approximately one and a half *O*-acyl groups per repeating unit. Originally the *O*-acyl substituent was thought to be *O*-acetyl, resulting in the various forms of gellan gum being referred to as high-and low-acetyl, and so on. Recent studies by Kubo *et al* suggest that gellan gum contains both *O*-acetyl and *O*-*L*-glyceryl substituents on the 3-linked glucose unit; the former tentatively assigned to the 6-position and the latter to the 2-position.Gellan gum is water soluble, off white powder. It has a molecular weight greater than 70,000 daltons. It forms gels when 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 this will result in much stronger physical thermo reversible hydrogels. In the same way, its melting temperature can be modified to either below or above 100˚C. Gellan, the biopolymer gellan is a more recent addition to the family of microbial polysaccharides that is gaining much importance due to its novel property of forming thermo-reversible gels when heated and cooled. It has applications in diverse fields in the food, pharmaceutical and many other industries.[63] Gellan gum is one of the most interesting *in situ* gelling polymers that have been tested since it seems to perform very well in humans.[64]

Curdlan [65]

Curdlan is a high molecular weight polysaccharide consisting of β-1,3-linked glucose units, produced by pure-culture fermentation from a nonpathogenic and non-toxicogenic strain of Agrobacterium biovar. The name curdlan is due to the polymer curdles when heated. Curdlan is used as a thickening and gelling agent in food industry. Gels of various strengthsare formed depending on the temperature. It is registered as a food additive in USA. Investigation has a dietary fibre reveals that curdlan is easily

degraded by intestinal bacteria. Bacterial degradation studies of curdlan as a natural polysaccharide in controlled drug yet to be reported.

Polysaccharides from Algae:

Alginate

Alginates are hydrophilic, nontoxic, biodegradable, linear polymer consisting of 1-4' linked-ß-Dmannuronic acid and β-L-glucuronic acid residues arranged as blocks of either type of unit or as a random sharing of each type. These are unbranched polysaccharides found in brown seaweed and marine algae such as *Laminaria hyperborea*, *Ascophyllum nodosum and Macrocystis pyrifera*. Many different alginate salts and derivatives are also commercially available including sodium alginate, ammonium alginate, calcium alginate, magnesium alginate, potassium alginate etc. Out of these, sodium alginate is most commonly and widely used in floating drug delivery systems. It is practically insoluble in ethanol (95%), ether and chloroform and slowly soluble in water, forming viscous colloidal solution. Favorable properties of alginates have attracted a lot of concern towards the development of different floating dosage forms.[66]

Marine polysaccharides:

Carrageenans

They are marine polysaccharides obtained by the extraction from some members of the class Rhodophyceae. It is named after Irish moss (Chondrus crispus, also known as Carrageen moss. It was originally isolated from alga in 1844. Carrageenans are large, highly flexible molecules that curl forming helical structures, ability to form a variety of different gels at room temperature. They are widely used in the food and other industries as thickening and stabilizing agents. There are three basic types of carrageenans:

1. Kappa (κ) carrageenans mainly used as a gelling agent, Kappa forms strong, rigid gels in the presence of potassium ions, it reacts with dairy proteins and mainly used in bakery products. It is mainly obtained from Eucheuma cottonii. Kappa carrageenans form a brittle gel.
2. Lambda (λ) carrageenans, non gelling agent mainly used as binder and thickener in dairy products obtained from Gigartina from South America.
3. Iota (ι) carrageenans forms soft and brittle gels inpresence of calcium ions obtained from Eucheuma spinosum. Carrageenans are high-molecular weight polysaccharides made up of repeating galactose units and 3,6-anhydrogalactose (3,6-AG), both sulfated and nonsulfated. The units are joined by alternating alpha 1-3 and beta 1-4 glycosidic linkages. The basic structure of carrageenan is disrupted by a more or less ordered distribution of sulphate hemi ester groups.

Table 7: Carrageenans Specifications [67]

Parameter	Range
General description	Yellowish powder
Acid insoluble	Max 1.5%
Solubility	Soluble in hot water.
pH	7 to 10
Moisture content	Max18%
Total ash	Max 15%
Protein	Max 0.5%–0.7%

CONCLUSION

The purpose of designing multiparticulate dosage form is to develop a reliable formulation that comprises all the advantages having in single unit formulations but yet devoid of the danger of alteration in a drug release profile and formulation behaviour due to unit to unit variation, change in gastro-luminal pH and enzyme population. A generally accepted view is that multiparticulate systems perform better *in vivo* than single-unit systems, as they spread out throughout the length of the GI tract causing less irritation, slower transit through the colon, and provide more reproducible drug release. In order to achieve this goal, a wide number of natural polymers are being used by many of workers over past decades and they concluded that polysaccharides appear to be promising agents for obtaining a colon-specific drug. The reasons for this are that they are non-toxic, easy to work with, and will be FDA approved. Also very important is that they are selectively degraded in the colon. So, the challenges in future will be to find a polysaccharide from which one might be able to obtain a non-permeable film or coating and at the same time a high degradability.

REFERENCES

1. Laila Fatima, Ali Asghar and Sajeev Chandran: Multiparticulate Formulation Approach to Colon Specific Drug Delivery: Current Perspectives. J Pharm Pharmaceut Sci. 2006; 9(3): 327-338.
2. Ashford M, Fell JT: Targeting drugs to the colon: delivery systems for oral administration. J Drug Target 1994; 2: 241-258.
3. Devereux JE, Newton JM, Short MB: The influence of density on the gastrointestinal transit of pellets. J Pharm Pharmacol 1990; 42: 500-501.
4. Hunter E, Fell JT, Sharma H: The gastric emptying of pellets contained in hard gelatin capsules. Drug Dev Ind Pharm 1982; 8: 751-757.
5. Meier R, Beglinger C, Dederding JP, et al: Influence of age, gender, hormonal status and smoking habits on colonic transit time. Neurogastroenterol Motil 1995; 7: 235-238.

6. Price JMC, Davis SS, Sparrow RA, et al: The effect of meal composition on the gastrocolonic response: implications for drug delivery to the colon. Pharm Res 1993; 10: 722-726.
7. Kaus LC, Fell JT, Sharma H, et al: On the intestinal transit of a single non-disintegrating object. Int J Pharm 1984; 14: 143-148.
8. Vyas SP, Khar RK: Gastroretentive systems. In: Vyas SP, Khar RK, editors. Controlled drug delivery: concepts and advances. New Delhi: Vallabh Prakashan, 2005; 218-253.
9. Antonin KH, Rak R, Bieck PR, et al: The absorption of human calcitonin from the transverse colon of man. Int J Pharm 1996; 130(1): 33-39.
10. Fara JW: Novel Drug Delivery and its Therapeutic Application. In: Presscot LF, Nimmo WS, editors. Colonic drug absorption and metabolism. Wiley: Chichester 1989; 103-120.
11. Mackay M, Tomlinson E: Colonic delivery of therapeutic peptides and proteins, In: Biek PR, editors. Colonic drug absorption and metabolism. New York: Marcel Dekker 1993; 159-176.
12. Friend DR, Chang GW: A colon-specific drug delivery system based on drug glycosides and glycosidase of colonic bacteria. J Med Chem 1984; 27: 261-266.
13. Anil K Philip, Betty Philip: Colon Targeted Drug Delivery Systems: A Review on Primary and Novel Approaches. Oman Medical Journal 2010; 25(2): 70-78.
14. Kothawade PD, Gangurde HH, Surawase RK, et al: Conventional and Novel Approaches for Colon Specific Drug Delivery: A Review. e-Journal of Science & Technology 2011; 2(6): 33-56.
15. Brahma NS: Modified-release solid formulations for colonic delivery. Recent Pat Drug Deliv Formul 2007; 1: 53-63.
16. Das S, Jha AK, et al: Role of natural polymers in the development of multiparticulate systems for colon drug targeting. Syst Rev Pharm 2010; 1: 79-85.
17. Jose S, Dhanya K, Cinu TA and Aleykutty NA: Multiparticulate system for colon targeted delivery of ondansetron. Indian J Pharm Sci 2010; 72: 58-64.
18. Kreuter J: Peroral administration of nanoparticles. Adv Drug Deliv Rev 1991; 7: 71-86.
19. Couvreur P, Pursieux F: Nano- and microparticules for the delivery of polypeptides and proteins. Adv Drug Deliv Rev 1993; 10: 141-162.
20. Lamprecht A, Scaffer U and Lehr CM: Size dependent targeting of micro- and nano- particulate carriers to the inflamed colonic mucosa. Pharm Res 2001; 18: 788-793.
21. Lamprecht A, Ubrich N, Yamamoto H, et al: Biodegradable nanoparticles for targeted drug delivery in treatment of inflammatory bowel disease. J P E T 2001; 299: 775-781.

22. Lamprecht A, Yamamoto H, Takeuchi H, Kawashima Y: A pH-sensitive microsphere system for the colonic delivery of tacrolimus containing nanoparticles. J Control Rel 2005; 104: 337-346.
23. Krishnaiah YSR, Satyanarayana V, Kumar BD, Karthikeyan RS, Bhaskar P: In vivo pharmacokinetics in human volunteers: oral administered guar gum- based colon- targeted 5- fluorouracil tablets. Eur J Pharm Sci 2003; 19: 355-362.
24. Healey JN: Gastrointestinal transit and release of mesalazine tablets in patients with inflammatory bowel disease. Scand J Gastroenterol Suppl 1990; 172: 47-51.
25. Watts PJ, Illum L: Colonic drug delivery. Drug Dev Ind Pharm 1997; 23: 893-913.
26. Chu, JS: Advances in colon specific drug delivery system employing the CODESTM, The Drug Delivery Companies Report. Autumn/Winter Pharmaventures Ltd 2003.
27. Krogars K, Heinamaki J, Vesalahti J, Marvola M, Antikainen O, Yliruusi J, et al: Extrusion spheronization of pH-sensitive polymeric matrix pellets for possible colonic drug delivery. Int J Pharm 2000; 199: 187-94.
28. Nykänen P, Krogars K, Säkkinen M, Heinämäki J, Jürjensson H, Veski P, et al: Organic acids as excipients in matrix granules for colon-specific drug delivery. Int J Pharm 1999; 184: 251-61.
29. Lenaert V, Gurny R: Bioadhesive drug delivery systems. Boca Raton: CRC Press; 1990; 25-42.
30. Ridley BL, O'Neill MA and Mohnen D. Pectins: structure, biosynthesis and oligogalacturonide related signalling. Phytochemistry 2001; 57: 929-967.
31. Bhatia MS, Deshmukh R, Choudhari P, et al: Chemical modifications of pectins, characterization and evaluation for drug delivery. Sci Pharm 2008; 76: 775-784.
32. Rubinstein A, Pathak S, Friendman M, et al: In vitro method for drug release analysis for microbiology controlled drug delivery. Proc Int Symp Control Rel Bioact Mater 1990; 17: 466-467.
33. Rubeinstein A, Radai R: Pectin salt as colonic drug delivery systems. Proc Int Symp Control Rel Bioact Mater 1991; 18: 221-222.
34. Liu L, Fishman ML, Kost J, et al: Pectin-based systems for colon-specific drug delivery via oral route. Biomaterials 2003; 24: 3333-3343.
35. Itoh K, Yahaba M, Takahashi A, et al: *In situ* gelling xyloglucan/pectin formulations for oral sustained drug delivery. Int J Pharm 2008; 356: 95-101.
36. Roberfroind. Introducing inulin fructans Br J Nutr 2005; 1: S31-35.
37. Vervoort L, Van den Mooter G, Augustijns P, et al: Inulin hydrogels. I. Dynamic and equilibrium swelling properties. Int J Pharm 1998; 172: 127-135.

38. Akhgari A, Farahmand F, Garekani H, et al: Permeability and swelling studies on free films containing inulin in combination with different polymethacrylates aimed for colonic drug delivery. Eur J Pharm 2006; 28: 307-314.
39. Barday T, Cooper M, Petrosky N: Inulin–a versatile polysaccharide with multiple pharmaceutical and food uses. J Excipients Food Chem 2010; 1: 24-42.
40. Vervoort L, Kinget R: In vitro degradation by colonic bacteria of inulin incorporated in Eudragit films. Int J Pharm 1996; 129: 185-190.
41. Castelli F, Sarpietro MG, Micieli D, et al: Differential scanning colorimetry study on drug release from an inulinbased hydrogel and its interaction with a biomembrane model: pH and loading effect. Eur J Pharm 2008; 35: 76-85.
42. Englyst HN, MacFarlane GT: Breakdown of resistant and readily digestible starch of human gut bacteria. J Sci Food Agric 1986; 37: 699-706.
43. Cummings JH, Milojevic S, Harding M, Coward WA, Gibson GR, Botham RL, et al: In-vivo studies of amylose and ethylcellulose coated 13 C glucose microspheres as a model for drug delivery to the colon. J Control Release 1996; 40: 123-31.
44. Allwood MC, Ring SG, Archer DB, Davies JD, Touitou E, Rubinstein A: Delayed release composition comprising glassy amylase 1989; EP343993-a, A61k-009/22.
45. Richardson PH, Willmer J and Foster TJ: Dilute solution properties of guar and locust bean gum in sucrose solutions. Food Hydrocolloid 1998; 12: 339-348.
46. Englyst HN, Commings JH: Improved method for measurement of dietary fiber as non-starch polysaccharidesin plant foods. J Assoc of Anal Chem 1988; 71: 808-814.
47. Kawamura Y: Guar gum. 69th JECFA 2008; 4(4).
48. Sudhakar Y, Kuotsu K, Bandyopadhyay AK: Buccal bioadhesive drug delivery-a option for orally less efficient drugs. J Control Release 2006; 114: 15-40.
49. Sarmento B, Ribeiro A, Veiga F, et al: Alginate/chitosan nanoparticles are effective for oral insulin delivery. Pharm Res 2007; 24: 2198-2206.
50. Krishnaiah YS, Satyanaryana S and Prasad YV: Studies of guar gum compression coated 5 amino salicylic acid tablets for colon specific drug delivery. Drug Dev Ind Pharm 1999; 25: 651-657.
51. Krishnaiah YS, Satyanaryana S, Prasad YV: A three layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartarate. Int J Pharm 2002; 241: 353-366.
52. Basit AW: Advances in colonic drug delivery drugs. Drugs 2005; 65: 1991-2007.
53. Sinha VR, Kumaria R: Polysaccharides in colon drug delivery. Int J Pharm 2001; 224: 19-38.

54. Friend DR: New oral delivery systems for treatment of inflammatory bowel disease. Adv Dru Del Rev 2005; 57: 247-265.
55. Chu DC, Juneja LR: Chemical and physical properties, safety and application of partially hydrolyzed guar gum as a dietary fibre. J Clin Biochem Nutr 2008; 42: 1-7.
56. Fraser JR, Brown TJ, Laurent TC: Catabolism of hyaluronan. In, Lauret TC, editor. The chemistry, biology, and medicinal applications of hylauronan and its derivatives. Miami FL, Portland Press 1998; 85-92.
57. Rudzki Z, LeDuy L, Jyothy S: Changes in CD44 Expression during carcinogensis of the mouse colon. Exp Mol Pat 1997; 64: 114-125.
58. Jain A, Gupta Y, Jain SK: Perspectives of biodegradable natural polysaccharides for site-specific drug delivery to the colon. J Pharm Sci 2007; 10: 86-126.
59. Wastenson A: Properties of fractional chondroitin sulphate from ox nasal septa. Biochem J 1971; 122: 477-785.
60. Rubinstein A, Nakar D, Sintov A: Chondroitin sulphate, potential prodrug for colon specific drug delivery purposes. Int J Pharm 1992; 9: 276-278.
61. Sintov A, Di-Capua N, Rubinstein A: Crosslinked chondroitin sulphate, characterization for drug delivery purposes. Biomaterials 1995; 16: 473-478.
62. Giarasis I, Harney LM, McNeil B: Gellan gum. Cri Rev Biotechnol 2000; 20: 177-211.
63. Kubo N, Miyazaki S, Attwood D: Oral sustained delivery of paracetamol form in situ gelling gellan and sodium alginate formulation. Int J Pharm 2003; 258: 56-64.
64. Coviello T, Matricard P, Marianecei C, et al: Polysaccharide hydrogels for modified release formulations. J Control Release 2007; 119: 5-24.
65. Shimizu J, Wada M, Takita T: Curdlan and gellan gum bacterial gel-forming polysaccharides, exhibit different effects on lipid metabolism, cacal fermentation and fecal bile acid excretion in rats. J Nutr Sci Vitaminol 1999; 45: 251-262.
66. Kumar Ganesh, Dhyani Archana, Kothiyal Preeti: Natural Polymers in the Development of Floating Drug Delivery Systems: A Review. International Journal of Pharmaceutical and Life Sciences 2013; 2(4): 165-178.
67. G Krishna Mohan, Shobharani Satla and Switi Gaikwad: Natural polysaccharides: versatile excipients for controlled drug delivery systems. Asian Journal of Pharmaceutical Sciences 2011; 6 (6): 275-286.

For Correspondence:
Shailesh U. Ginoya
Email: shailesh.ginoya4224@gmail.com