

Review Article

Polysaccharide: Carrier in colon targeted drug delivery system

Vipin K. Agarwal^a, Amresh Gupta^{b,*}, Shashank Chaturvedi^a, Farheen Khan^a

^a Department of Pharmaceutics, Invertis Institute of Pharmacy, Invertis University, Bareilly, Uttar Pradesh, India.

^b Department of Pharmacognosy, Pharmacy College Saifai, U.P. Rural Institute of Medical Sciences & Research, Saifai, Uttar Pradesh, India.

*Corresponding Author: Tel.: +91 9415520130, E-mail: amreshgupta@gmail.com

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ABSTRACT

Oral delivery has become a widely accepted route of administration of therapeutic drugs. The gastrointestinal tract presents several formidable barriers to drug delivery. The delivery of drugs to the colon has a number of therapeutic implications in the field of drug delivery. The objective of the present study is to develop colon targeted drug delivery system by using polysaccharide as a carrier. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. The various approaches that can be exploited to target the release of drug to colon include prodrug formation, coating with pH sensitive polymers, coating with biodegradable polymers, embedding in biodegradable matrices, hydrogel, timed release systems, osmotic and bioadhesive systems. In this review article we have made an attempt to give an overview on polysaccharide-based colon specific drug delivery system.

1. INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of colonic disorders such as irritable bowel syndrome, crohn's disease such as ulcerative colitis and colon carcinomas. The delivery of drugs to colon is also useful for systemic absorption especially proteins and peptides which are degraded in upper GIT. There were currently a few strategies to achieve colonic specificity, such as use of pH sensitive polymers and pressure-controlled CDDS. The aim of this study was to explore the feasibility of the colonic microorganism to develop CDDS by using polysaccharide as carrier. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. The simplest method for targeting drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layer of conventional enteric coating or extremely slow releasing. Various approaches have been tried for developing

Table 1. Colon targeting disease, drug and site [5,6]

Target Site	Disease Condition	Drugs
Tropical action	Inflammatory Bowel Disease. Crohn's, disease. Irritable bowel disease.	Hydrocortisone, Budesonide, Prednisolone, sulfasalazine, Olsalazine, Mesalazine, Balsalazide
Local Action	Pancreatotomy and cystic fibrosis, Colorectal cancer.	Digestive enzyme supplements. 5-Flourouracil
Systemic action	To prevent gastric irritation. To prevent first pass metabolism orally ingested drug. Oral delivery of peptides. Oral delivery vaccines.	NSAIDS Steroids Insulin Typhoid

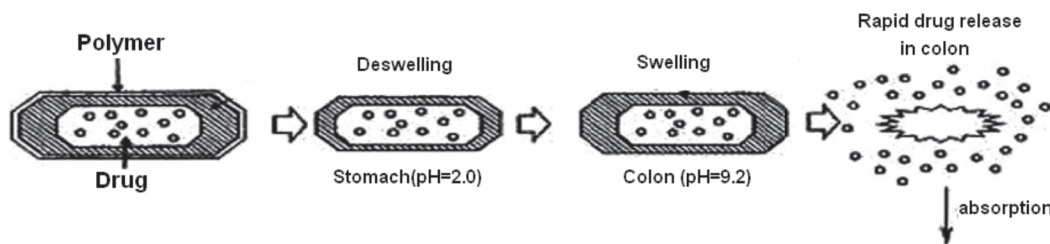


Fig. 1. Diagrammatic representation of colon-specific drug delivery system [7]

formulations with different types of polymers as carriers and systems for successful delivery of the drug at colon site. The present review aims at utilization of polysaccharide as a carrier for colon specific drug delivery. Polysaccharides, the polymer of monosaccharide retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes. Large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, dextrin and locust bean gum have been investigated for their use in colon targeted drug delivery systems. As these polysaccharides are usually soluble in water, they must be made water insoluble by cross linking or hydrophobic derivatisation, very important point is an optimal proportional of the hydrophobic and hydrophilic parts respectively and the number of free hydroxyl groups in the polymeric molecule [1-4].

1.1 Needed of colon targeted drug delivery [8-11]

- ✓ To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- ✓ Colon-specific formulation could also be used to prolong the drug delivery.
- ✓ It should be considered as beneficial in the treatment of colon diseases.
- ✓ The colon is a site where both local or systemic drug delivery could be achieved.
- ✓ Inflammatory conditions are usually treated with glucocorticoids and sulphasalazine and others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- ✓ Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GIT highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

1.2 Advantages of CDDS over conventional drug delivery [12-15]

- ✓ Drugs are available directly at the target site.
- ✓ Side effects can be reduced such as gastric irritation caused by many drugs (e.g. NSAIDs).

- ✓ Utilization of drug is more and lesser amount of dose is required comparatively.
- ✓ The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- ✓ Bypass initial first pass metabolism.
- ✓ Extended daytime or nighttime activity.
- ✓ Improve patient compliance.
- ✓ It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- ✓ It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones,
- ✓ Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.

1.3 Limitations of colon targeting drug delivery system [16-19]

- ✓ Multiple manufacturing steps.
- ✓ The resident micro-flora could also affect colonic performance via metabolic degradation of the drug.
- ✓ Incomplete release of drug.
- ✓ Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- ✓ Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- ✓ Non availability of an appropriate dissolution testing method to evaluate the dosage form *in-vitro*.
- ✓ An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. Normal in patients with ulcerative colitis.

1.4 Selection criteria

1.4.1 Selection of drugs for colon specific drug delivery [20, 21]

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.

Table 2. The criteria for selection of drugs for CDDS

Criteria	Non-peptide Drugs	Peptide Drugs
Drugs used for local effects in colon against GIT diseases	Diclofenac, Metoprolol	Amylin, Calcitonin
Drugs poorly absorbed from upper GIT	Ibuprofen, heophylline, Isosorbides	Cyclosporine, Desmopressin
Drugs for colon cancer	Pseudoephedrine	Glucagon, Epoetin
Drugs that degrade in stomach and small intestine	Bromophenaramine 5-Flourouracil	Gonadorelin, Insulin
Drugs that undergo extensive first pass metabolism	Nimustine, Bleomycin	Sermorelin, Saloatonin
Drugs for targeting	5-Aminosalicylic-acid, Prednisolone	Vasopressin, Urotoilitin

1.4.2 Selection of carriers for colon specific drug delivery [22,23]

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of drug molecule. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems. In this review article we have made an attempt to focus on the polysaccharide based colon delivery systems.

1.5 Factors that influence oral colon specific drug delivery systems [24-26]

1.5.1 Gastric emptying time

This is affected by the state of fed or fast, size and caloric content of the ingested food.

1.5.2 Small intestine transit time

The mean transit time of the dosage form is about 3-4 hours to reach the ileocecal junction and the time period is consistent. It is rich in digestive enzyme, such as esterase, lipase, amylase, protease and glycosidase.

Table 3. Gastrointestinal transit time of contents

Organ	Transit Time (Hrs)
Stomach	<1(fasting), >3(fed)
Small intestine	3-4
Large intestine	20-30

1.5.3 Ileocecal junction (I.C.J.) lag time

Highly variable, and hold up may occur for several hours.

1.5.4 Colonic transit

Show considerable variability between individual can be as high as 2-3 days.

1.6 Gastrointestinal pH profile [24]:

- ✓ Stomach pH 1- 1.5
- ✓ Small intestine pH 5-7.5
- ✓ Ascending colon pH 6.3 ± 0.58
- ✓ Transverse colon pH 6.6 ± 0.83
- ✓ Descending colon pH 7.04 ± 0.67

1.7 Gastrointestinal micro flora:

- ✓ Stomach (<1000 CFU/ml)
- ✓ Small intestine (103-104 CFU/ml)
- ✓ Colon (1011-1012 CFU/ml) 400 species and most of them are anaerobes and bacteroides.

1.8 Enzymatic Activity

Colon lumen contains 80% less enzymatic activity than small

Table 4. Approaches for colonic drug targeting [13]

Colon Targeting Approach	Features
pH sensitive polymers coating	Formulation coated with enteric polymers (methylmethacrylate copolymers) release the drug when formulation reaches down towards the alkaline pH range in the intestine
Biodegradable polymers coating	Degradation of the polymer due to the action of the colonic bacteria releases the drug
Biodegradable matrices and Hydrogels	Drug is released by the swelling and/or erosion of the polymer and by the biodegradable action of the polysaccharide
pH sensitive matrices	Drug released by the degradation of the pH sensitive polymer in the GIT
Bio-adhesive systems	Formulation coated with bio-adhesive polymers that selectively provides adhesion to the colonic mucosa release the drug in the colon
Osmotic controlled drug delivery	Drug releases through semi-permeable membrane after a lag time due to osmotic pressure build up
Timed released systems	Formulation is designed such that the drug releases after a lag time of 3-5 h that is equivalent to small intestinal transit time

intestine. The large intestine is relatively free of peptidases so colon targeted delivery systems will be absorbed after per oral application 25. The activity of the cytochrome P450 3A class is found lower in the mucosa of the colon than the small intestine.

So colon targeted delivery may direct to prominent plasma levels and improved oral bioavailability for drugs which are enzyme substrates. Examples of drugs that are absorbed from the colon include cefimetazole, 5-fluorouracil, cephadrine, riboflavin, L-carnitine, theophylline, naproxen, oxypropolol, nifedipine and indomethacin [26-32].

2. ROLE OF POLYSACCHARIDES IN COLONIC DRUG DELIVERY SYSTEM [3,14]

The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharides are found in abundance, have wide availability are inexpensive and are available in a variety of structures with varied properties. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondroitin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccharides can be broken down by the colonic micro flora to simple saccharides. Therefore, they fall into the category of “generally regarded as safe” (GRAS). A number of polysaccharide-based delivery systems have been outlined in Table 2.

2.1 Classification of polysaccharides [15]

2.1.1 Polysaccharides by source

- ✓ Seaweed extracts: Agars, alginates, carrageenans
- ✓ Higher plant cell walls insoluble: cellulose
- ✓ Higher plant cell wall soluble: pectin
- ✓ Higher plant seeds: cereal starch, guar gum, locust bean gum
- ✓ Higher plant tuber and root: potato starch, tapioca starch
- ✓ Higher plant exudates: gum arabic, gum tragacanth
- ✓ Microorganism: Xanthan gum, Gellan gum
- ✓ Derived: modified starch, carboxy methyl cellulose, propylene glycol alginate

2.2.2 Polysaccharides by structure

- ✓ Linear: amylose, cellulose, pectin, alginates
- ✓ Short branched: guar gum, locust bean gum, Xanthan gum
- ✓ Branch-on-branch: amylopectin, gum arabic, arabinoxylan

2.2.3 Polysaccharides by monomers

- ✓ Homoglycans: starch, cellulose
- ✓ Diheteroglycans: agars, alginate, carrageenans,
- ✓ Triheteroglycans: Xanthan, Gellan, arabinoxylan

Table 5. Characteristics of various biodegradable polysaccharides

Polysaccharide	General Properties	In-vitro/ In-vivo Model Used
Amylose	Unbranched constituents of starch used as excipients in tablets formulation	<i>In-vitro</i>
Arabino galactone	Natural pectin, hemicelluloses used as thickening agents	<i>In-vitro</i>
Chitosan	Deacetylated chitin used as absorption enhancing agents	<i>In-vitro</i>
Chondroitin sulfate	Mucopolysaccharides contains sulphate ester group at 4 or 6 position	<i>In-vitro</i>
Cyclodextran	Cyclic structure of 6, 7 or 8 units, high stability against Amylase, used as drug solubilising agent and absorption enhancer	<i>In-vitro</i>
Dextran	Plasma expanders	<i>In-vitro</i>
Guar gum	Galactomannan used as thickening agents	<i>In-vitro</i>
Pectin	Partial methyl ether commonly used as thickening agents	<i>In-vitro</i>
Xylan	Abundant hemicelluloses of plant cell wall	<i>In-vitro</i>

2.2.4 Polysaccharides by charge

- ✓ Neutral: amylose, amylopectin, cellulose, guar gum, etc.
- ✓ Anionic: alginates, carrageenans, Gellan, gum arabic, Xanthan
- ✓ Cationic: Chitosan

3. LIST OF POLYMERS

3.1 Agars: [16, 27, 28]

Agars are known as water-soluble, gel-forming polysaccharide extracts from agarophyte members of the Rhodophyta. Agars are usually composed of repeating agarobiose units alternating between 3-linked β -D-galactopyranosyl (G) and 4-linked 3,6-anhydro- α -L-galactopyranosyl (LA) units. This disaccharide regularity may be marked or modified in a number of ways by substitution of hydroxyl groups with sulfate hemiesters and methyl ethers in various combination and more rarely with a cyclic pyruvate ketal as 4,6-O-[(R)-1-carboxyethylidene] acetal and sometimes by additional monosaccharides. Moreover, the pattern of substitution groups depends on the species, various environmental and physiological factors, and the procedures used in extraction and isolating agar. The yield and physical properties of agar such as gel strength, gelling and melting temperature as well as chemical properties, determine its value to the industry. Agar extraction with and without NaOH treatment were carried out.

3.2 Inulin: [17, 18]

Inulin is a naturally occurring storage polysaccharide found in many plants such as onion, garlic, artichoke, and chicory. Chemically, it belongs to the gluco-fructans and consists of a mixture of oligomers and polymers containing 2 to 60 (or more) β -2-1 linked D-fructose molecules. Most of these fructose chains have a glucose unit as the initial moiety. The inulin has been incorporated into Eudragit RS films for preparation of mixed films that resisted degradation in the upper GIT but digested in human fecal medium by the action of Bifido bacteria and Bacteroids. Various inulin hydrogels have been developed that serve as potential carriers for the introduction of drugs into the colon. Vinyl groups were introduced in inulin chains to form hydrogels by free radical polymerization. Inulin was reacted with glycidylmethacrylated in N, N-dimethylformamide in the presence of 4-dimethylaminopyridine as catalyst. Methylated inulin hydrogels were developed as colon targeted drug delivery systems and investigated for water take up and swelling.

Table 6. Specifications of inulin [29]

Parameter	Range
General description	White to yellowish powder
Taste	Slightly sweet, odourless
Solubility	Soluble in water
pH	6 to 7

3.3 Chitosan: [19]

Chitosan are highly basic polysaccharides due to presence of primary amino group in its structure. Chitosan (CS) is modified natural, biodegradable, biocompatible, non-toxic, as well as linear nitrogenous polysaccharides. It acts as a copolymer of varying amounts of N-acetyl glucosamine and N-glucosamine repeated units, the special property that makes CS very useful in pharmaceutical application. CS has an average molecular weight ranging between 3800 and 20,000 Daltons and is 66 to 95% deacetylated. CS is readily soluble in dilute solutions of most of the organic acids such as citric, tartaric acid, while soluble to a limited extent in inorganic acids. It can be modified in to an ester form such as CS glutamate, CS succinate, CS phthalate. The main factors which may affect the CS properties are its molecular weight and degree of deacetylation (DD). The viscosity of CS solution increases with an increase in Chitosan concentration and decreases with increase in temperature. The solubility of Chitosan can be decreased by cross-linking it with covalent bonds using glutaraldehyde. Chitosan is a well-accepted and a promising polymer for drug delivery in colonic part, since it can be biodegraded by the microflora present in the human colon. Kawadkar *et al.* prepared the CS coated microsphere matrix system for the treatment of ulcerative colitis-A, design of microencapsulated chitosan microspheres for colonic drug delivery [40].

3.4 Guar gum: [7, 18]

Guar gum is also known as cluster bean, Guaran, Cyamopsis, Guarina. It is obtained from the seeds endosperm of *Cyamopsis*

tetragaonolobus (Family Leguminosae). It shows delayed gastric emptying. 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. 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. 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 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. 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. Three-layer matrix tablets of metoprololtartrate were prepared by using guar gum as a carrier. Matrix tablets of guar gum with dexamethasone, indomethacin and budenoside have been investigated for colon targeted drug delivery. Matrix tablets containing various proportions of guar gum were prepared by wet granulation technique using starch paste as a binder.

3.5 Pectin: [18]

Pectin is the methylated ester of polygalacturonic acid. It is commercially extracted from citrus fruits like apple, guava, and gooseberry. Pectins are complex polysaccharides present in the walls that surround growing and dividing plant cells. It is also present between xylem and fibre cells in woody tissue. Pectin is non starch linear polysaccharides that consists of α -1, 4-D-galactouronic acid and 1, 2-D-rhamnose, with D-galactose, and Darabinose 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. 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. This problem was manipulated with chemical modification without affecting favorable biodegradability properties. Pectin can be chemically modified by saponification catalyzed by acids, bases, enzymes and salts of weak acids. 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. Gelling can be induced by mineral acids or by cross-linking with calcium ion or by alginates.

Table 7. Specification of pectin [30, 31]

Parameter	Range
General description	White, yellowish
Taste	Tasteless
Solubility	Soluble in cold and hot water
Ph	5 to 7
Moisture content	Max12

3.6 Alginates: [7, 17]

Alginates are natural polysaccharide polymers isolated from the brown sea weed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. They are linear polymers consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks in the polymer chain. Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications. Bio-adhesive sodium alginate microspheres of metoprolol tartarate for intranasal systemic delivery were prepared to avoid the first pass effect, as an alternative therapy to injection, and to obtain improved therapeutic efficacy in the treatment of hypertension and angina pectoris. The microspheres were prepared using emulsification-cross linking method. In vivo studies indicated significantly improved therapeutic efficacy of metoprolol from microspheres. There was sustained and controlled inhibition of isoprenaline-induced tachycardia as compared with oral and nasal administration of drug solution. In a comparative study, alginate formulation appeared to be better than the poly-lactide-co-glycoside (PLG) formulation in improving the bioavailability of two clinically important antifungal drugs clotrimazole and econazole. The nanoparticles were prepared by the emulsion-solvent-evaporation technique in case of PLG and by the cation-induced controlled gelling in case of alginate, developed calcium alginate beads as cores with a spray coat of 5-ASA on them. This formulation was evaluated *in vitro* for colon specific drug targeting.

3.7 Cellulose: [32-36]

In higher plants, cellulose is an essential structural component and represents the most abundant organic polymer. Cellulose is a linear un-branched polysaccharide consisting of β -1, 4-linked D-glucose units and many parallel cellulose molecules which form crystalline micro fibrils. The crystalline micro fibrils are mechanically strong and highly resistant to enzymatic attack and are aligned with each other to provide structure to the cell wall. Cellulose is insoluble in water and indigestible by the human body. It is however digested by herbivores and termites. Cellulose obtained from fibrous materials such as wood and cotton can be mechanically disintegrated to produce powdered cellulose which has been used in the pharmaceutical industry as filler in tablets. High quality powdered cellulose when treated with hydrochloric acid produces microcrystalline cellulose which is preferred over powdered cellulose because it is more free-flowing containing non-fibrous particles. It is consequently employed as diluents or

filler/binder in tablets for both granulation and direct compression processes. The formation of derivatives of cellulose is made possible by the hydroxyl moieties on the D-glucopyranose units of the cellulose polymer to give a variety of derivatives. Cellulose derivatives can be made by etherification, esterification, cross linking or graft copolymerization. Etherification yields derivatives such as hydroxyl-propyl-methylcellulose and carboxyl-methyl-cellulose, while esterification results in derivatives which include cellulose nitrate, cellulose acetate and cellulose acetate phthalate. These derivatives have found application in membrane controlled release systems such as enteric coating and the use of semi-permeable membranes in osmotic pump delivery systems. They have also enjoyed wide use and application in monolithic matrix systems. Extensive studies conducted on these derivatives have proven their ability to sustain the release of medicaments and most of these derivatives have been employed for this purpose.

3.8 Starch: [20]

Starch is a polymer, which occurs widely in plants. In general, the linear polymer, amylose, makes up about 20% w/w of the granule, and the branched polymer, amylopectin, the remainder. 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 glucosidase. The hydrophilic nature of the starch due to abundance of hydroxyl group is a major constraint that seriously limits the development of starch-based material for industrial applications. It may be hydroxypropylated, acetylated, carboxymethylated, or succinylated. Starch has been evaluated for colon targeted delivery as enteric-coated capsules. The use of resistant starch was studied for the improvement of gut microflora and to improve clinical conditions related to inflammatory bowel diseases, immune stimulating activities, and protection from colon cancer. The administration of probiotic bacteria with optionally modified resistant starch as a carrier and growth medium to alter the gastrointestinal tract microbial populations has resulted in a number of significant advantages, such as protection, of probiotics, and as a carrier to deliver economically and efficiently to specific sites. Other applications include reducing the incidence of colorectal cancers or colonic atrophy.

3.9 Dextran: [21]

Dextran can be defined as glucose homo-polysaccharides. Dextran and its derivatives are among the main promising candidates for the preparation of networks capable of giving a sustained release of proteins. The dextran derivatives-based hydrogels can therefore be actually considered promising protein delivery systems for tumor immunotherapy. Micro particles of dextran hydroxyethyl methacrylate (HEMA) were also investigated for the potential delivery of macromolecular therapeutics such as proteins and DNA. Dextran microspheres have been also tested as nasal drug delivery systems. The “exploding microgels” used for pulsed drug delivery were micrometer-sized biodegradable gel particles surrounded by a membrane permeable to water but impermeable to both the entrapped drugs and the degradation products of the gel. Dextran polymers have been also evaluated for colon drug

delivery. In particular, some authors have investigated the stability of dextran hydrogels in *in-vitro* models, simulating human small intestinal and colonic environments to evaluate the suitability of dextran matrices as carriers for colonic specific. Dextran has also been evaluated in the form of azodextrans for colon drug delivery. In this case the matrix was degraded both by the reduction of the azo-groups in the crosslinks as well as by enzymatic breakdown of the polysaccharide backbone. Apart from hydrogel approach, prodrug systems have also been found suitable for colon targeting: the drug molecule linked to the polar dextran chain remains intact and unabsorbed in the stomach and in the small intestine but when the prodrug enters into the colonic microflora it is acted upon by dextranase which cleaves the dextran chain randomly and at the terminal linkages releasing the molecules into the colon drug delivery.

3.10 Locust bean gum: [22, 37]

Locust bean gum contains natural polysaccharides which have a molecular weight of 310000. Locust bean gum is also known as ‘Carob gum’ as it is derived from the endosperm of the seed of the ‘Carob’ (*Ceratonia Siliqua Linne*, Fam: Leguminosae). It is irregular shaped molecule with branched β -1, 4-D-galactomannan units. Locust bean contains about 88% D-galacto-D mannoglycan, 4% of pentane, 6% of protein, 1% of cellulose and 1% of ash. Studies on the polysaccharides done by Raghavan *et al.* proved that the combination of locust bean gum and chitosan, as a coating material, is capable of protecting the core tablet containing mesalazine during the condition mimicking mouth to colon transit [39]. The coating was susceptible to the colonic bacterial enzymes which causes the release of drug. It was concluded that the formulation containing locust bean gum and chitosan in the ratio of 4:1 held a better dissolution profile, higher bioavailability and hence a potential carrier for drug targeting to colon.

Table 8. Specifications of gum locust bean [38]

Parameter	Range
General description	White to yellow powder
Taste	Sweet with a flavour similar to that of chocolate
Solubility	Dispersible in cold and hot water, insoluble in organic solvents
pH (1%)	3 to 11
Protein	3%–7%

3.11 Xanthan gum: [20]

Xanthan gum is high molecular weight extracellular polysaccharide secreted by the micro-organism *Xanthomonas campestris*. Xanthan gum is soluble in cold water and solutions exhibit highly pseudoplastic flow. Its viscosity has excellent stability over a wide pH and temperature range and the polysaccharide is resistant to enzymatic degradation. Xanthan gum exhibits a synergistic interaction with the galactomannan guar gum and locust bean gum (LBG) and the glucomannan konjacmannan. This results in enhanced viscosity with guar gum and at low concentrations with

LBG. At higher concentrations soft, elastic, thermally reversible gels are formed with locust bean gum and konjacmannan. Thiruganesh Ramasamy and colleagues described colon targeted drug delivery systems for Aceclofenac using xanthan gum as a carrier. In this study, multilayer coated system that is resistant to gastric and small intestinal conditions but can be easily degraded by colonic bacterial enzymes was designed to achieve effective colon delivery of Aceclofenac. The Eudragit coated system exhibited gastric and small intestinal resistance to the release of Aceclofenac. The rapid increase in release of Aceclofenac in simulated colonic fluid was revealed as due to the degradation of the xanthan gum membrane by bacterial enzymes.

4. EVALUATION TEST [3,7]

4.1 *In-vitro* dissolution test

Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot fully mimic *in vivo* conditions such as those relating to pH, bacterial environment and mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon-specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract have been studied. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileum segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4.

4.2 *In-vivo* test

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS, a novel model has been proposed. In this model, the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which bascularizes within four weeks, matures, and becomes capable of developing of mucosal immune system from the host.

5. CONCLUSION

Polymers traditionally were used as inert substances in pharmaceutical formulations because these are safe, non-toxic, economic and are chemically compatible with the other excipients. Recently they are increasingly included in the various dosage

Table 9. Marketed drug products for the treatment of various diseases of colon [9]

S.No.	Marketed Name	Company Name	Drug	Disease
1.	Mesacol tablet	Sun Pharma,	Mesalamine	Ulcerative colitis
2.	Mesacol enema	Sun Pharma,	Mesalamine	Ulcerative colitis
3.	Asacol	Win-Medicare	Mesalamine	Ulcerative colitis, crohn's disease
4.	SAZO	Wallace	Sulphasalazine	Ulcerative colitis, crohn's disease
5.	Intazide	Intas	Balsalazide	Ulcerative colitis
6.	Lomotil	RPG Life,	Diphenoxylate hcl, atropine sulphate	Mild ulcerative Colitis
7.	Buscopan	German Remedies,	Hyoscine Butylbromide	Colonic motility Disorder
8.	Cyclominol	Neol	Diclomine	Irritable colon Syndrome
9.	Eldicet	Solvay	Pinaverium bromide	Irritable colon syndrome, Spastic colon
10.	Equirex	Jagsonpal Pharmaceutical	Clordiazepoxide	Irritable colon syndrome
11.	Normaxin	Systopic labs	Clidinium bromide	Irritable colon syndrome
12.	Pro-banthine	RPG Life,	Propenthline bromide	Irritable colon syndrome
13.	Entofoam	Cipla	Hydrocortisone acetate	Ulcerative colitis

forms to fulfill specific functions for target drug delivery. Colon targeted drug delivery systems are exploited to selectively target the drug release to the colon. Polysaccharides are concluded to be one of the greater aspects in the field of targeted drug delivery. The polysaccharides based colon specific drug delivery is relatively easy due to the presence of various derivatizable groups, wide range of molecular weights, varying chemical compositions, low toxicity and high stability. As most of the natural polysaccharides are degraded in the colon by intestinal micro flora, natural polysaccharide as a versatile excipient for a controlled drug delivery system is an interesting challenge for future researches and has a wide potential in several pharmaceutical technologies. So polysaccharides appear to be promising agents for obtaining colon-specific drug delivery systems.

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