Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2009; 1(2): 43-46

Review Article ISSN 0975 1556

Natural Polymer in Colon Targeting

Tiwari Akanksha [1*], Shukla Raj Kumar[1, 2]

[1]*School of Pharmaceutical Sciences, Rajiv Gandhi Technological University, Madhya Pradesh-Bhopal-462036, India*
[2]*R&D –NDDS Department, Sun Pharma Industries Ltd., Sun Pharma Advance Research Centre, Tandalja Vadodara-Gujrat, India.*

ABSTRACT
Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. 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 but also for its potential for the delivery of proteins and therapeutic peptides. Targeting of drugs to specific sites of action provides several advantages over non-targeted drugs. These include the prevention of side effects of drugs on healthy tissues and enhancement of drug uptake by targeted cells. Certain plant polysaccharides such as amylose, inulin, pectin and guar gum remains unaffected in the presence of gastrointestinal enzymes and pave the way for the formulation of colon targeted drug delivery systems. This review will cover the use of Natural Polymer for the targeted delivery.

Keywords: Colon; Targeted drug delivery; Natural Polymers.

INTRODUCTION

In recent times, colon targeted drug delivery systems have gained importance for the systemic delivery of protein and peptide drugs. This is because the peptide and protein drugs get destroyed or inactivated in acidic environment of the stomach or by pancreatic enzymes in the small intestine. [1] Drug targeting to colon is also useful when a delay in drug absorption is desired from therapeutic point of view, such as treatment of diseases that have peak symptoms in the early morning like nocturnal asthma, angina or arthritis. [2-3] Among the different approaches to achieve colon specific drug delivery, the use of polymers, specifically biodegraded by colonic bacterial enzymes holds promise. [4-5]

The important bacteria present in the colon such as *Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Lactobacillus, Clostridium* secrete a wide range of reductive and hydrolytic enzymes such as β-glucuronidase, β-xylosidase, β-galactosidase, α-arabinosidase, nitroreductase, azoreductase, deaminase and urea hydroxylase. These enzymes are responsible for degradation of di-, tri- and polysaccharides. [6-7]

Polymers in colon targeting

Natural polysaccharides are extensively used for the development of solid dosage forms. These polymers of monosaccharide (sugars) are inexpensive and available in a variety of structures with a variety of properties. They are highly stable, safe, non-toxic, and hydrophilic and gel forming in nature. Pectin, starch, guar gum, amylase and karaya gum are a few polysaccharides commonly used in dosage forms. Non-starch, linear polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon which make them potentially useful in targeted delivery systems to the colon. [8]

***Corresponding author: Mrs. Akanksha Tiwari**,
School of Pharmaceutical Sciences, Rajiv Gandhi Technological University, Madhya Pradesh-Bhopal-462036, India **Phone:** +919376942854, +919725515969
Email:

Pectin

Pectins are nonstarch linear polysaccharides that consist of α-1, 4 D-galacturonic acid and 1, 2 D-rhamnose with D-galactose and D-arabinose side chains having average molecular weights between 50,000 to 150,000. Pectin tends to produce lower viscosities than other plant gums. It is refractory to host gastric and small intestinal enzymes but is almost completely degraded by the colonic bacterial enzymes to produce a series of soluble oligalactorunates. [9-10] Depending on the plant source and preparation; they contain varying degrees of methyl ester substituents. [11] Micro particulate polymeric delivery systems have been suggested as a possible approach to improve the low bioavailability characteristics shown by standard ophthalmic vehicles (collyria). In this context pectin microspheres of piroxicam were prepared by the spray drying technique. *In vivo* tests in rabbits with dispersions of piroxicam-loaded microspheres also indicated a significant improvement of piroxicam bioavailability in the aqueous humour (2.5-fold) when compared with commercial piroxicam eyedrops. [12-13] *In vivo* gamma scintigraphic studies confirmed the *in vitro* findings. In all the volunteers, the pectin-coated tablets disintegrated in the colon indicating that site-specificity had been achieved

and illustrating the potential of a colonic drug delivery system utilizing pectin. This necessitates the development of such derivatives of pectin, which were less water-soluble but were having the capability to be degraded by the colonic microflora. Calcium pectinate, the insoluble salt of pectin was used for colon targeted drug delivery of indomethacin by Rubeinstein et al. [14].*Musabayane et al*. [15] investigated the suitability of amidated pectin as a matrix patch for transdermal chloroquine delivery in an effort to mask the bitter taste when orally administered. The results suggest that the pectin-chloroquine patch matrix preparation has potential applications for the transdermal delivery of chloroquine and perhaps in the management of malaria. Calcium pectinate nanoparticles to deliver insulin were prepared as a potential colonic delivery system by ionotropic gelation. [16]

Chitosan

Chitosan is a high molecular weight polycationic polysaccharide derived from naturally occurring chitin by alkaline deacetylation. Chemically, it is a poly (N-glucosamine). Chitosan has favourable biological properties such as nontoxicity, biocompatibility and biodegradability. Similar to other polysaccharides it also undergoes degradation by the action of colonic microflora and hence poses its candidature for colon targeted drug delivery. *Tozaki et al*. [17-18] developed colon-specific insulin delivery with chitosan capsules. A pH-sensitive drug delivery carrier has also been reported for chitosan-based hydrogels. [19-20] Therapeutic effect of R-68070, a new thromboxane synthetase inhibitor on 2,4,6 trinitrobenzene sulfonic acid sodium salt induced ulcerative colitis was studied using chitosan capsules to achieve its colon-specific drug delivery in rats. [21] A multiparticulate system of chitosan hydrogel beads has been investigated for colon-specific drug delivery of macromolecules using fluorescein isothiocanate-labeled bovine serum albumin as a model protein. The hydrogel bead was formed by polyelectrolyte complexation of chitosan with its counter ion, tripolyphosphare. The protein release experiments were carried out *in vitro* under different conditions to simulate the pH and times likely to be encountered during intestinal transit to the colon. The results shown that the hydrogel beads were degraded by rat cecal and colonic enzymes, resulting in a marked acceleration in the release of protein. [22] Chitosan microspheres are used to provide controlled release of many drugs and to improve the bioavailability of degradable substances such as protein, as well as to improve the uptake of hydrophilic substances across the epithelial layers. These microspheres are being investigated both for parenteral and oral drug delivery. [23]

Gums

Gums are translucent and amorphous substances produced by the plants. Usually pathological products, gums are produced when the plant is growing under unfavorable conditions or when injured. Gums are plant hydrocolloids and may be anionic or non ionic polysaccharides. On hydrolysis gums yield sugar and salts of uronic acid. [24]

Guar gums

It is a naturally occurring galactomannan polysaccharide; consists of chiefly high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and shows degradation in the large intestine due the presence of microbial enzymes. [25-28] Guar gum is hydrophilic and swells in cold water, forming viscous colloidal dispersions or sols. This gelling property retards release of the drug from the dosage form, making it more likely that degradation will occur in the colon. Guar gum was found to be a colon-specific drug carrier in the form of matrix and compression-coated tablets as well as microspheres. [29-30] Guar gum-based matrix tablets of rofecoxib were prepared for their intended use in the chemoprevention of colorectal cancer. [31] A colon-specific guar gum–based tablet of 5-FU has also been reported. [32- 33]

Locust Bean Gum

It is also called carob gum, as it is derived from carob (Ceratonia siliqua) seeds. This neutral polymer is only slightly soluble in cold water; it requires heat to achieve full hydration and maximum viscosity. Cross-linked galactomannan however led to water-insoluble film forming product-showing degradation in colonic microflora. [34-35]

Karaya gum

Karaya gum is obtained from *Sterculia urens* (Family sterculiaceae) is a partially acetylated polymer of galactose, rhamnose, and glucuronic acid. [36] Park *et al*. [37] showed that mucoadhesive tablets prepared by karaya gum for buccal delivery, had superior adhesive properties as compared to guar gum and was able to provide zero-order drug release, but concentrations greater than 50 % w/w may be required to provide suitable sustained release.

Albizia gum

Albizia gum is obtained from the incised trunk of the tree Albizia zygia (DC) J. F. Macbr,family *Leguminosae* and is shaped like round elongated tears of variable color ranging from yellow to dark brown. It consists of β-1– 3-linked D-galactose units with some ß1-6-linked Dgalactose units. The genus *Albizzia* containing some twenty-six species is a member of the Mimosacez, a family which also includes the gum-bearing genera *Acacia* and *Prosopis.* Only two species of *Albizia, A. zygia* and *A. sassa,* are however, known to produce gum. Albizia gum has been investigated as a possible substitute for gum Arabic as a naturalemulsifier for food and pharmaceuticals. [38-39] Odeku and Fell [40] used khaya gum, albizia gum and a mixture of both as compressioncoats and evaluated their ability to prevent drug release under conditions mimicking the mouth to colon transit time using indometacin (a water insoluble drug) and paracetamol (a water soluble drug) as model drugs. The susceptibility of the gums to undergo biodegradation in the colon was assessed by conducting drug release studies in the presence of rat caecal contents in phosphatebuffered saline (PBS) at pH 6.8. While Odeku and Fell observed in their work that after 5 h, 21 % of indomethacin and 19 % of paracetamol were released for tablets coated with khaya gum, while tablets coated with albizia gum released less than 4 % of indomethacin and 6 % paracetamol. Tablets containing the khaya/albizia mixture released less than 5 % of indomethacin and 9 % of paracetamol. This suggests that the khaya and albizia gums can effectively control the release of the drugs in the physiological environment of the stomach and small intestine.

Xanthan gum

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris.* The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain. [41] In one of the trials, xanthan gum showed a higher ability to retard the drug release than synthetic

hydroxyproylmethylcellulose. Xanthan gum and hydroxypropylmethylcellulose were used as hydrophilic matrixing agents for preparing modified release tablets of diltiazem HCl. The amount of hydroxypropylmethylcellulose and xanthan gum exhibited significant effect on drug release from the tablets prepared by direct compression technique. It was concluded that by using a suitable blend of hydroxypropylmethylcellulose and xanthan gum desired modified drug release could be achieved. [42]

Starches

It is the principal form of carbohydrate reserve in green plants and especially present in seeds and underground organs. Starch occurs in the form of granules (starch grains), the shape and size of which are characteristic of the species, as is also the ratio of the content of the principal constituents, amylose and amylopectin. A number of starches are recognized for pharmaceutical use. These include maize (*Zea mays*), rice (*Oryza sativa)* , wheat (*Triticum aestivum*), and potato (S *olanum tuberosum*). [43] To deliver proteins or peptidic drugs orally, microcapsules containing a protein and a proteinase inhibitor were prepared. Starch/bovine serum albumin mixed-walled microcapsules were prepared using interfacial cross-linking with terephthaloyl chloride. The microcapsules were loaded with native or amino-protected aprotinin by incorporating protease inhibitors in the aqueous phase during the cross-linking process. The protective effect of microcapsules with aprotinin for bovine serum albumin was revealed *in vitro.* [44]

Alginates

Alginates are linear polymers that have 1-4'linked β-D-mannuronic acid and α-L-guluronic acid residue arranged as blocks of either type of unit or as a random distribution of each type. A Eudragit L-30D–coated calcium alginates bead for colonic delivery of 5-aminosalicylic acid has been reported. [45] Different enteric as well as sustained release polymers were applied as coat on calcium alginate beads. A system was prepared by coating calcium alginate beads with Aquacoat® that is a pH-independent polymer followed by 2 % w/w coating of Eudragit L-30D. Being enteric polymer, Eudragit® resisted the release of drug in acidic media and drug release was triggered at alkaline pH and controlled by thickness of Aquacoat®. When drug-loaded calcium alginate beads swell sufficiently (osmotic gradient) to exceed the strength of outer sustained released coat, the film bursts to release the drug. Such a system delivers drug to the distal intestine with minimal initial leak and provides sustained release in the colon. [46]

Inulin

Inulin is a naturally occurring storage polysaccharide found in many plants such as onion, garlic, artichoke, and chicory. Most of these fructose chains have a glucose unit as the initial moiety. It is not hydrolyzed by the endogenous secretions of the human digestive tract. [47] However, bacteria harboring in the colon and more specifically Bifidobacteria are able to ferment inulin. [48]

CONCLUSION

Today the stress is on patient compliance and to achieve this objective there is a spurt in the development of NDDS. As the Natural Polysaccharides are promising biodegradable materials, these can be chemically compatible with the excipients in drug delivery systems. In addition Natural Polysaccharides are non-toxic, freely available, and less expensive compared to their synthetic counterparts. They have a major role to play in pharmaceutical industry. Therefore, in the years to come, there is going to be continued interest in the natural polysaccharides to have better materials for drug delivery systems.

REFERENCES

1. Yang L, James SC, Joseph A. Colon-specific drug delivery: New approaches and *in Vitro/ in vivo* evaluation. Int J Pharm 2002; 235: 1-15.
2. Schacht E, Gevaert A, El Refaie K, Koen M, Verstraete W, Adriaensens P, *et al.* Polymers for colon specific drug delivery. J Control Release 1996; 39: 327-8.
3. Wilding R, Davis SS, Pozzi F, Furlani P, Gazzaniga A. Enteric coated timed release systems for colonic targeting. Int J Pharm 1994; 111: 99-102.
4. Krishnaiah YS, Satyanarayana V, Dinesh Kumar B, Karthikeyan RS. In vitro drug release studies on guar gum-based colon targeted oral drug delivery systems of 5- fluorouracil. Eur J Pharm Sci 2002; 16: 185-92.
5. Sinha VR, Rachna K. Polysaccharides in colon-specific drug delivery. Int J Pharm 2001; 224: 19-38.
6. Sinha VR, Rachna K. Coating polymers for colon specific drug delivery: A comparative *in vitro* evaluation. Acta Pharma 2003; 53: 41-7.
7. Cavalcanti OA, Van den Mooter G, Caramico-Soares I, Kinget R. olysaccharides as excipients for colon-specific coatings, permeability and swelling properties of casted films. Drug Develop Ind Pharm 2002; 28: 157-64.
8. Cummings JH, Southgate DAT, Branch WJ, Wiggins HS, Houston H, enkins DJA, Jirraj T, Hill MJ. The digestion of pectin in human gut and its effect on calcium absorption and large bowel function. Br J Nutr 1979; 41: 477- 485.
9. Englyst HN. Digestion of the polysaccharides of potato in the small intestine of man. Am J Clin Nutr 1987; 45: 423-431.
10. Towle GA, Christensen O. Pectin. In Industrial Gums and Their Derivatives, eds. R. L. Whistler and J. N. BeMiller, New York, Academic Press1973; 429-461.
11. Giunchedi P, Conte U, Chetoni P, Saettone MF. Pectin microspheres as ophthalmic carriers for piroxicam: Evaluation *in vitro* and *in vivo* in albino rabbits. Eur J Pharm Sci 1999; 9: 1-7.
12. Rubinstein A, Radai R, Ezra M, Pathak S, Rokem JM. *In vitro* evaluation of calcium pectinate: A potential colon-specific drug delivery carrier. Pharm Res 1993; 10: 258-263.
13. Musabayane CT, Munjeri O, Matavire TP. Transdermal delivery of chloroquine by amidated pectin hydrogel matrix patch in the rat. Ren Fail 2003; 25: 525-34.
14. Cheng K, Lim LY. Insulin-loaded calcium pectinate nanoparticles: Effects of pectin molecular weight and formulation pH. Drug Develop Ind Pharm 2004; 30: 359-67.
15. Tozaki H, Komoike J, Tada C, Maruyama T, Terabe A, Suzuki T, Yamamoto A, Muranishi S. Chitosan capsules for colon-specific drug delivery: improvement of insulin absorption from the rat colon. J Pharm Sci 1997; 86: 1016-21.
16. Tozaki H, Odoriba T, Okada N, Fujita T, Terabe A, Suzuki T, Okabe S, Murnishi S, Yamamoto A. Chitosan capsules for colon-specific drug delivery: enhanced localization of 5-aminosalicylic acid in the large intestine accelerates healing of TNBS-induced colitis in rats. J Control Res 2002; 82: 51-61.
17. Vandelli MA, Leo E, Forni F, Bernatei MT. *In vitro* evaluation of a potential colonic drug delivery system that releases drug after a controllable lag-time. Eur J Pharm Biopharm 1996; 43: 148-151.
18. Shu XZ, Zhu KJ, Song W. Novel pH-sensitive citrate crosslinked chitosan film for drug controlled release. Int J Pharm 2001; 212: 19-28.
19. Tozaki M, Fujita T, Odoriba T. Colon specific delivery of R68070, a new thromboxane synthetase inhibitor, using chitosan capsules: Therapeutic effects against 2,4,6-trinitrobenzene sulfonic acid-induced ulcerative colitis in rats. Life Sci 1999; 64: 1155-1162.
20. Zhang H, Ibrahim AA, Neau SH. An *in vitro* evaluation of a chitosan-containing multiparticulate system for macromolecule delivery to the colon. Int J Pharm 2002; 239: 197-205.
21. Sinha VR, Singla AK, Wadhawan S, et al. Chitosan microspheres as a potential carrier for drugs. Int J Pharm 2004; 274: 1-33.

22. Kokate CK**,** Purohit AP, Gokhale SB, editors. Pharmacognosy, India: Nirali Prakashan 2003; 22 nd ed 133-66.
23. Tomolin J, Taylor JS, Read NW. The effect of mixed faecal bacteria on a selection of viscous polysaccharide *in vitro*. Nutr Rep Int 1989; 39,121–135.
24. Bayliss CE, Houston AP. Degradation of guar gum by faecal bacteria. Appl Environ Microbiol 1986; 48: 626–632.
25. Macfarlane GT, Hay S, Macfarlane S, Gibson GR. Effect of different carbohydrates on growth polysaccharidases and glycosidase production of Bacteroides ovatus in batch and continuous culture. J. Appl. Bacteriol. 1990; 68: 179–187.
26. Chourasia MK, Jain SK. Potential of guar gum microspheres for target specific drug release to colon. Journal of Drug Targeting 2004; 2 (4): 1-8.
27. Ramaprasad YV, Krishaniah YSR, Satyanarayana S. Trends in colonic drug delivery: a review. Indian Drugs 1995; 33: 1-10.
28. Chourasia MK, Jain SK. Potential of guar gum microspheres for target specific drug release to colon. J Drug Target 2004; 12: 435-442.
29. Al-Saidan SM, Krishnaiah YS, Satyanarayana V, Rao GS. *In vitro* and *in vivo evaluation* of guar gum-based matrix tablets of rofecoxib for colonic drug delivery. Curr Drug Deliv 2005; 2: 155-63.
30. Krishnaiah YSR, Satyanarayana V, Kumar DB, 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: 355Y362.
31. Al-Saidan SM, Krishnaiah YS, Patro SS, Satyanaryana V. *In vitro* and *in vivo evaluation* of guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. AAPS PharmSciTech 2005; 6:E14-21.
32. Bauer KH, Kesselhut JF. Novel pharmaceutical excipients for colon targeting. STP Pharm Sci 1995; 5: 54-59.
33. Hirsch S, Binder V, Kolter K, Kesselhut JF, Bauer KH. Lauroyldextran and cross- Linked galactomannan as coating materials for sitespecific drug delivery to the colon. Eur J Pharm Biopharm 1999; 47: 61-71.
34. Amnuaikit C, Ikeuchi I, Ogawara K, Higaki K, Kimura T. Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use. Int J Pharm 2005; 289: 167-78.
35. Park CR, Munday DL. Evaluation of selected polysaccharide excipients in buccoadhesive tablets for sustained release of nicotine. Drug Develop Ind Pharm 2004; 30: 609-17.
36. Ashton WA, Jefferies M, Morley RG, Pass G, Phillips GO, Power DMJ. Physical properties and applications of aqueous solutions of Albizia zygia gum. J Sci Food Agric 1975; 26: 697–704
37. US National Academy of Sciences Tropical legumes. National Academy of Sciences, Washington, DC. 1979.
38. Odeku OA, Fell JT. *In-vitro* evaluation of khaya and albizia gums as compression coatings for drug targeting to the colon. J Pharm Pharmacol 2005; 57: 163-168.
39. BhardwajTR, Kanwar M, Lal R, Gupta A. Natural gums and modified natural gums as sustained-release carriers. Drug Develop Ind Pharm 2000; 26: 1025-38.
40. Gohel MC, Amin AF, Patel KV, Panchal MK. Studies in release behavior of diltiazem HCl from matrix tablets containing (hydroxypropyl) methyl cellulose and xanthan gum. Boll Chim Farm 2002; 141: 21-28.
41. Trease GE, Evans WC editors. Text Book of Pharmacognosy, London: Balliere, Tindall; 2002; 15 th ed.
42. Shun YL, Ayres JW. Calcium alginate beads as core carriers of 5-aminosalicylic acid. Pharm Res 1992; 9: 714Y790.
43. McIntosh M, Stone BA, Stanisich VA. Curdlan and other bacterial (1-3)- beta- D-glucans. Appl Microbiol Biotechnol 2005; 68: 163-173.
44. Dysseler BS, Hoffen MJ. Inulin, an alternative dietary fiber. Properties and quantitative analysis. Eur J Clin Nutr 1995; 49: S145-S152.
45. Keller C, Modler RC, Metabolism of fructooligosaccharides by Biffidobacterium spp. Appl Microbiol Biotechnol 1989; 31: 537-541.
46. Wang X, Gibson GR. Effects of the *in vitro* fermentation of oligofructose and inulin by bacteria growing in the human large intestine. J Appl Bacterol 1993; 75: 373-380.
47. Gibson GR, Roberfroid MR. Dietary modulation of the human colonic microflora, introducing the concept of prebiotics. J Nutr 1995; 125: 1401-1414.
48. Vervoort L, Kinget R. *In vitro* degradation by colonic bacteria of inulin HP incorporated in Eudragit films. Int J Pharm 1996; 129: 185-190.