Review Article

Pectin-based colon-specific drug delivery

Abstract

Colon-specific drug delivery have a great importance in the delivery of drugs for the treatment of local colonic, as well as systemic diseases like Crohn's disease, ulcerative colitis, colorectal cancer, amoebiasis, asthma, arthritis and inflammation which can be achieved by targeted delivery of drug to colon. Specific systemic absorption in the colon gave interesting possibilities for the delivery of protein and peptides. It contains relatively less proteolytic enzyme activities in the colon compared to the upper gastrointestinal tract (GIT). Recommended treatments included the administration of anti-inflammatory drugs, chemotherapeutic agents and antibiotics which must be released in the colon. Pectin is a naturally occurring polysaccharide has in recent years gained increasingly in importance in advance drug delivery. It was employed in pharmaceutical industry, health promotion and treatment. Owing to its gelling properties it has been used potentially as a carrier for drug delivery to the GIT, such as matrix tablets, gel beads, film-coated dose form. This review will discuss the important chemistry and general properties of pectin, its gel formation mechanism properties and its uses in novel drug delivery to the colon.

Key words:
Colon targeting, combination of polymer with other polymers, microflora, pectin

Introduction

Colon-targeted drug delivery system**:** The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of per orally applied, undigested, unchanged and fully active peptide drugs.[1]

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Intestinal Microflora and Metabolic Activity

The human gastrointestinal tract (GIT) consists of a complex ecosystem incorporating aerobic and anerobic micro-organism. In the stomach, due to its lower pH, its bacterial concentration, which is predominantly aerobic in nature, is low (10^2CFU/ML); the number of micro-organism increases gradually on descending along the small intestine. But it rises by several orders of magnitude beyond the ileo-cecal valve. The environment of human colon is anerobic in nature consisting of mainly *Bacteriods*, *Bifidobacteria*, *Eubacteria*, *Clostridium*, *Enterobacteria*, *Lactobacillus*, and anerobic *Enterococci*.[2] Colonic bacterial flora maintaining the cellular function by the fermentation of various substrates. That is left indigested in small intestine. These substrates include di- and tri-saccharides like cellobiose, raffinase, stachyase and lactase and residues of partially digested polysaccharides such as starch and polysaccharides from endogenous sources such as mucopolysaccharides.[3-6] The colonic flora and its nutritional sources remain quantitatively similar from individual to

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another but can change quantitatively from one individual to other. Various factors affecting gastrointestinal microflora are listed below.

Important Factor Which Influencing GIT Microflora

Host factor: Host factor which depends directly or indirectly on following causes like:[7]

- Species, strain and individual difference due to: Acid and alkali secretion, intestinal motility, intestinal structure, level of endogenous nutrients (muci, gut proteins, bile secretions, sloughed mucosal cells), redox potential, bile salts, antibodies.
- Age
- Gastrointestinal disorders

Environmental factors: The following are derived causes of this factor.

- Drug
- Diet
- Xenobiotics

Bacterial factors: Derived causes are:

- Bacterial metabolites (short-chain fatty acid, bacteriocins)
- Bacterial interactions (competition)
- C. pH

Oxygen is a limiting factor for the growth of colonic microflora.[8,9] In addition to mucopolysaccharides, other substrates for fermentation are dietary fibers, which include all the non-α-glucan polymers that originate in the plant cell wall-cellulose hemicelluloses and pectin substances.[10,11] A number of enzymes like β-D-glucocosidase, β-D-galactosidase, β-D-xylosidase. β-D-arabinosidase, azoreductase and nitroreductase are produced by colonic microflora to carry out the process of fermentation.[12]

Chemistry

Pectins are non-starch linear polysaccharides that consist of α-1,4 D galacturonic acid and 1,2 D-rhamnase with D-galactase and D-arabinose side chain having average molecular weight between 50,000 and 150,000.

Pectin tends to produce lower viscosities than other plant gums. It is refectory to host gastric and small intestinal enzyme but is almost completely degraded by the colonic bacterial enzymes to produce a series of soluble oligolactorunates.[3,13] Pectin is a polygalacturonic acid and the chain molecule is negatively charged at neutral pH. The pKa-value of pectin is approximately 3.5 [Figure 1]. The overall distribution of hydrophilic and hydrophobic groups on the pectin molecule determines the solubility (tendency to gel) of a particular pectin.[14,15]

Depending upon source and preparation, it contains varying degree of methyl ester substituent.[16] It is highly soluble in water but can be reducing the solubility of pectin by forming its calcium salt, calcium pectinate. When the degree of esterification (DE) is less than 50%, pectins form rigid gels by reacting with calcium salts or multivalent cations,[7] which crosslink the galacturonic acids of the main polymer chains. Calcium pectinate is obtained by the formation of an ionic bond between the carboxylic acid groups of the pectin molecules and the calcium ions. The resulting structure has the form of an 'egg box' which is shown in Figure 2.[17] Stable in solutions with a low pH, they swell in solutions that are slightly basic. Calcium pectinate has been studied[10,11,18,19] and has been indexed as a hydrophilic-coating agent which is insoluble when prepared according to the interfacial complexation process.[20] In this case, calcium pectinate prevents the encapsulated drug from being prematurely released. When it is used alone it swells when it comes in contact with aq. fluid of GIT and can causes the release of the entrapped drug through the diffusion, this problem can be manipulated through choice of pectin type or presence of additives.[11,19]

The degree of methylation (the average number of methoxy groups per 100 galacturonic acid units), has an essential influence on the properties of pectin especially on its solubility and its requirement for gelation, which are directly derived from the solubility. Pectin with high degree of methylation is poorly soluble. Pectin with low degree of methylation are more soluble but can be crosslinked by divalent cations most commonly calcium to produce an insoluble pectinate gel.

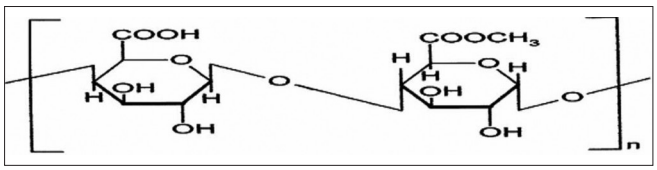

Figure 1: Chemical structure of pectin

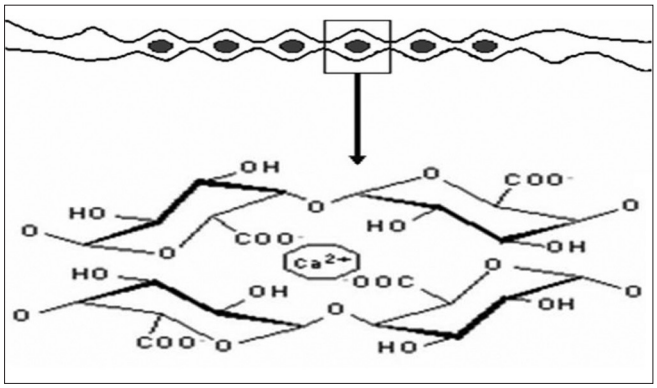

Figure 2: Schematic representation of calcium binding to polygalactoronate sequences: 'egg box' dimer and 'egg box' cavity

Application

Pectin favorably influences cholesterol levels in blood. It has been reported to help reduce blood cholesterol in a wide variety of subjects and experimental conditions as comprehensively reviewed.[21]

Pectin acts as a natural prophylactic substance against poisoning with toxic cations. It has been shown to be effective in removing lead and mercury from the GIT and respiratory organs.[22]

When injected intravenously, pectin shortens the coagulation time of drawn blood, thus being useful in controlling hemorrhage or local bleeding.[23]

Pectin and combinations of pectin with other colloids have been used extensively to treat diarrheal diseases, especially in infants and children.

Owing to its large water-binding capacity, pectin gives a feeling of satiety, thus reducing food consumption.

Pectin hydrogels have been used in tablet formulations as a binding agent,[21] and have been used in controlled-release matrix tablet formulations.[24]

Future prospect

The property of pectin substances is that they act through removing the available toxicity products, which are absorbed by the pectin, due to its colloidal properties. Recently, pectin substances are used on large scale as a delaying agent i.e., they reduce the rate of absorption of various drugs and play the role of a depot.

The proven antitoxin, bactericidal, epithelotonic, delaying and hemostatic activity of pectin can be used for various kinds of pathology in the mouth. The need of complex action is characteristic for the dentist's treatment. The special conditions in the mouth, associated with availability of saliva and developed microflora, also are to be assessed in the use of every local medicinal agent.

The above-listed specific properties of pectin and its hydrophilicity and total safety for the organism, combined with the possibility to form a covering film over the mucosa, lead to the idea of its use as a protective bandage of the damage tissue in mouth and other local placed at stated interval.

Pectin as a carrier for conventional and novel dosage form

Pectin is a non-toxic, biodegradable carrier which is selectively degraded into the colon. Many scientists worked on pectin polymer as a single entity and as in combination with other polysaccharides, which are summarized in Tables 1-3.

Advantages and Disadvantages of Pectin

Gelation of pectins

Low methoxy pectin

Low methoxy pectin (LM) pectins can gel in the presence of divalent cations, usually calcium. In these systems gelation is due to the formation of intermolecular junction zones between homogalacturonic smooth regions of different chains. The structure of such a junction zone is generally ascribed to the so called 'egg box' binding process. Initial

Table 1: Characteristics of various biodegradable polysaccharides for colon-targeted drug delivery[2-5]

Polysaccharides	Chemical name	General properties	Bacterial species that degrade polysaccharide
Amylase	α-1,4D-glucose	Unbranched constituents of starch used as excipient tablet formulation	Bacteroids, Bifidobacterium
Arabinogalactane	β-1,4 and β-1,3D-galactose β-1,6 and β-1,3D-arabinose and D-galactose	Natural pectin, hemicellulose used as thickening agent	Bifidobacterium
Chitosan	Deacetylated β-1,4 N-acetyl-d-glucosamine	Deacetylated chitin used as absorption enhancing agent	Bacteroids
Chondroitin sulfate	β-1,3D-glucuroic acid and N acetyl-D-glucosamine	Mucopolysaccharides contains various amount of sulfate ester group at the 4 or 6 position	Bacteroids
Cyclodextrin	α-1,4D-glucose	Cyclic structures of 6, 7 or 8 units high stability against amylase, used as drug solublising agent and absorption enhancer	Bacteroids
Dextran	α-1,6D-glucose α-1,3D-glucose	Plasma expanders	Bacteroids
Guar gum	α-1,4D-mannose α-1,6-D-galactose	Galactomannan used as thickening agent	Bacteroids Ruminococcus
Pectin	α-1,4D-galacturonic acid and 1,2D rhamnose with D- galactose and D-arabinose side chains	Partial methyl ester, commonly used as thickening agent	Bacteroids Bifidobacterium, Eubacterium
Xylon	β-1,4 D-xylose with β-1,3 L-arabinose side chains	Abundant hemicellulose of plant cell walls	Bacteroids Bifidobacterium

strong association of two polymers into a dimer is followed by the formation of weak interdimer aggregation, mainly governed by electrostatic interations. The gel-forming ability of LM pectins increases with decreasing degree of methylation. LM pectins with a blockwise distribution of free carboxyl groups are very sensitive to low calcium levels. The presence of acetyl groups prevents gel formation with calcium ions but gives the pectin emulsion stabilizing properties.[47-49]

High methoxy pectin

High methoxy pectin (HM) pectins have the ability to form gels with sugar and acid, so-called low water activity gels or sugar-acid-pectin gels. Such a gel is considered a 2-D network of pectin molecules in which the solvent (water) with the cosolutes sugar and acid are immobilized. This results in a system resisting deformation and showing a stress-strain relationship for small deformation. The build-up of the 3-D network is based on the formation of junction zones in which there are chain associations stabilized by hydrogen bonding between undissociated carboxyl and secondary alcohol groups and by hydrophobic interaction between methyl esters. The gelation mechanism of pectins is mainly governed by their DE. For the LM pectins, denoted LMP (DE<50%), gelation results from specific non-covalent ionic interactions between blocks of galacturonic acid residues of

Table 2: Pectin as a carrier for conventional and novel dosage form

Dosage form	Drugs	Outcomes
Pectin as a carrier for novel drug delivery		
5FU-Pectin conjugates[25]	5-Fluorouracil	5-FU-PT conjugate has a good colon-targeting property
Pectin-Ketoprofen prodrug[23]	Ketoprofen	Irritation effect of KP of GI membranes may reduce by the conjugation with PT because of esterification of the KP with PT thus enzyme-dependent PT-KP prodrug with pectin as a carrier
Microsphere[20,26]	Indomethacin	Pectin microsphere degraded by pectinase that is found in the colon and as a result, IND release was increased
Beads[27,28]	Indomethacin	Drug showed very little release (less than 5%) of the drug to the SGF and the rate of release decrease with increase in the concentration of pectin
Microsphere[29]	Indomethacin and tetracycline	Give importance about various parameters like polymer, drug, $CaCl_2$, emulsifier concentration and stirring speed seen as type of polymer and emulsifier
Hydrogel beads[30,31]	Indomethacin or Sulfamethoxa-zole	Amidated pectins are more tolerant to pH variations, which is useful in colonic delivery systems
Pectin as a carrier for conventional drug delivery		
Capsule[32]	Ketoprofen	Zinc pectinate beads showed slower ketoprofen release compared with calcium pectinate beads when enteric hard capsules were used. Thus, the zinc pectinate beads could protect sufficiently drug entrapped from the upper gastrointestinal conditions and drug release will be controlled by pectin degradation with colonic microflora
Matrix tablets[33]	Ropivacaine	Reduce the release of the drug in simulated gastric and intestinal fluids, increase the release in simulated caecal fluid (with pectinolytic enzymes), and improve the poor compactibility of pectins
Matrix tablets[11]	Indomethacin	Better *in vitro* release of water-insoluble drug using calcium salt as cross-linker
Enteric-coated matrix tablets[18]	–	Enteric-coated matrix tablets of pectin arrive intact in the colon where complete disintegration and release occurred compared to the guar gum tablet
Matrix tablets[34]	Paracetamol	*In vitro* trials have confirmed that increasing the coating layer reduced drug release
Compression-coated tablet[34]	Naphthol Green B	NGB rapidly released from the pectin-coated tablet in the presence of enzymes compared with the control
Compression-coated and plain matrix tablet[19]	Indomethacin and insulin	Selective drug targeting to the colon due to presence of pectinolytic enzymes
Compression-coated tablet[15]	Sodium fluorescein	Compression coat of pectin protecting a core tablet in stimulating gastrointestinal environment
Compression-coated tablet[35-37]	Indomethacin	Increasing the degree of cross-linking the drug release was increase drug. Further, drug release was increased in presence of enzymes indicating colon-targeted behavior of the formulation

Table 3: Combination of pectins with polymers (as carriers)

Dosage form	Drugs	Outcomes
Pectin with chitosan (For novel drug delivery)		
Hydrogel beads [36,37]	Indomethacin or sulphamethoxazole	Better protection from upper GIT and selective release release of drug to the colon when chitosan use as a polymer with the combination of pectin
Pellets[38]	Paracetamol	Demonstrate better protection of the drugs in the upper part of the digestive tract when pectin used with chitosan than pectins used alone
Microspheres[39]	Vancomycin	Combination could be capable of achieving a colon-specific delivery of drug due to their pH-dependent swelling ability, mucoadhesion characteristics and enzyme-dependent degradation
Pectin with chitosan (For conventional drug delivery)		
Matrix and multilayer tablets[4,7]	Metronidazole	A high pectin coat:Core ratios 4:1 and 5:1.inclusion of chitosan 3% and 5% w/w in the pectin coat offered better protection at the lowest coat: Core ratio 3:1. Selective delivery of metrinidazole to the colon
Tablets[8,40]	Radiolabelled(^{99m}Tc)	γ-scintigraphy study showed that tablets retain the shape during passage through stomach and small intestine while in the colon liberation of the entrapped material occurred due to degradation of the coat by colonic bacteria
Tablets[41]	Indomethacin and paracetamol	Combination of pectin with chitosan give better *in vitro* release of paracetamol compared with pectin alone
Film coated tablet[1]	Tracer(^{99m}Tc-DTPA)	Combination of polymers restrict the release of radioactive tracer from the labeled tablets in the stomach and the small intestine and give selective targeting to the colon
Pectin with hydroxypropylmethylcellulose (for novel drug delivery)		
Pellets[42]	Curcumin	Pectin:HPMC-coated pellets offer a greater degree of protection from premature drug release in the upper part of GIT than pectin alone
Pectin with hydroxypropylmethylcellulose (for conventional drug delivery)		
Compression-coated core tablets[43]	5-ASA	Better drug release to the colon
Compression-coated core tablets[8]	–	Able to delay drug release before it is completely degraded in the colon
Matrix tablets[44]	tracers	Delay the release of tracers from the tablets in dissolution media
Pectin with eudragit coating (for novel drug delivery)		
Pellets[45]	Aceclofenac	pH-dependent release characteristic of eudragit polymers would not influence the enzymatic degradation of the pectin in SCF. As well as it give better enzymatic degradation by colonic bacteria
Microspheres[44,46]	Metronidazole	Eudragit S-100-coated pectin microspheres bear metronidazole maintain its integrity in the hostile environment of stomach and small intestine and afterward release of drug in colon
Microspheres[47]	5-FU	Reduced the side-effects of the drug caused by its absorption from the upper part of the GIT when given in conventional dosage forms
Pellets[35-37]	Theophylline	Specific delivery of drugs to the colon
Pectin with Eudragit coating (for conventional drug delivery)		
Matrix tablet[48]	Theophylline	Assuring a greater site-specificity of drug release when Eudragit used as a coating material
Matrix tablet[33]	Ropivacaine	Reduced the release of drug in SIF and SGF, increase the release in simulated cecal fluid and improve the poor compatibility of pectins
Pectin with ethyl cellulose aqueous dispersion coatings for various dosage form		
Matrix tablet[8]	–	The coating material produce a satisfactory film with better release
Pellets[34]	Paracetamol	*In vitro* trials have confirmed that increasing the coating layer reduced drug release

the pectin backbone and with divalent ions such as calcium. The affinity of pectin chains towards calcium is known to increase with decreasing DE or ionic strength, and with increasing polymer concentration. Besides the influence of the charge density of the polygalacturonate chain, the distribution pattern of free and esterified carboxyl groups has an important effect on the strength of calcium binding. Molecular weight of pectins can be expected to vary with plant source, raw material and extraction conditions but molecular weight determination is a challenge because of the extra problems of heterogeneity and aggregation which can obscure data gathering.

Interactions of pectin with other hydrocolloids

Interactions between pectins and alginates

Mixtures of pectins with other polysaccharides such as alginate has found that good gels are formed from HM pectin and guluronic-rich alginates. A pH above 4 also hinders the gel formation. This finding, with the added evidence of LM pectin gelation with alginate at very low pH, indicates that the chains must be sufficiently charge neutralized before interaction can occur, and that esterification is required only to reduce electrostatic repulsion. These mixed systems work well with cold setting conditions.

Interactions between pectins and proteins

Understanding interactions between pectins and proteins is thought to be central to developing food texture. Mixtures of proteins and polysaccharides are prone to incompatibility or undesirable complex formation. However, due to the number of interactions possible with pectins, there are many opportunities to explore different systems. One such system sees LM pectin interacting with poly-L-lysine. In pectins with a DE of 36%, strong gels crosslinked by physical bonds with the protein were obtained at pH's close to neutrality. These clear, elastic gels had controlled increase in gel strength with added crosslinker up to an optimum. Excess protein caused increased opacity and eventual network collapse. Poly-L-lysine also serves to control network swelling. As with some hydrocolloids, chain length of the protein was found to have an optimum value, which may correspond to the different regions of the pectin molecule.

Interactions of pectins with gelatin

Gelatin is used almost exclusively in confectionery products, in which long, tough, gum-like textures are desired. For these products a dosage of 7-10% gelatin is required to reach a sufficient firmness. In some gum products even up to 15% gelatin may be necessary to obtain the desired firmness. When using gelatin alone, the low-melting temperature of the products may prove to be a disadvantage. This may be compensated by combining it with pectin. Here a part of the gelatin is replaced by a substantially smaller amount of pectin. The products are more stable at higher temperatures, thus increasing the storage stability of the confectionery products. Texture and chewing behavior of the product can be regulated by the pectin/gelatin ratio. Depending on the ratio of the two gelling agents either the pectin or the gelatin has a greater influence on the texture of the gels. With increasing pectin share the texture of the gum articles becomes more elastic and brittle, with increasing gelatin share the products become more viscous. A further positive effect of adding pectin is the reduction of the setting time compared to a pure gelatin system. With that the residence time in the mogul plant is shorter, resulting in higher production capacity.

Interactions of pectins with starch

One example of a product produced using a combination of pectin and starch, are the so-called "jelly beans". The consumer expects a very special texture of this product and this is regulated with the pectin/starch ratio. Compared with jelly products the texture is long and viscous. Alterations in consistency can be achieved by changing the pectin/starch ratio or by the choice of the pectin or starch used. When selecting the gelling agents, the manufacturers should be consulted.

Combination of pectins with agar-agar

Agar-agar is often used as the classic gelling agent in aerated confectionery products such as marshmallows. In these products a more viscous texture can be achieved by replacing the agar-agar partially or completely with pectin. This enhances the mouth-feel factor and hence provides a more distinctive flavor. The water binding is positively influenced by pectin thus leading to better preservation and longer storage stability.

Interactions with other polymers

Interactions with other hydrocolloids have been studied in depth recently. Gel formation of LM pectins with guar, locust bean gum, oxidized starch, potato maltodextrin and gum arabic have shown there to be specific interactions between polysaccharide complexes. Complex formation between gum arabic and LM pectin (DM 31) was found to be enhanced when there was specific spatial compatibility between the HG areas of the pectin and the gum arabic fibrils. These interactions were found to be non-ionic and were more likely a hydrophobic association and stabilization which resulted in differing gel properties. Branched hydrocolloids caused faster destabilization of calcium induced LM pectin than linear polymers. This takes into account the interactions of branched regions in pectins with other branched regions, interactions that are highly hydrophobic and non-ionic.

Conclusions

The chemistry, biodegradable nature and gel-forming characteristics of pectin have enabled due to this naturally occurring biopolymer to be used in Pharmaceutical industry, health promotion and treatment. Also it has been used potentially in pharmaceutical preparation and drug formulation as a carrier of a wide variety of biologically active agents, not only for sustained release applications but also as a carrier for targeting drugs to the colon for either local treatment or systemic action. The hydrophilic character of

pectin gives wide range for the formulation of hydrophilic drugs. By the selection of appropriate type of pectin, gelation conditions, added excipients and coating agents, the dosage forms of various morphology and characteristics can be fabricated with the combination of other polymer like HPMC, Eudragit, Chitosan, EC, etc. It gives the better result for selective drug release to the colon. As research and development continues with delivery system using pectin, we expect to see many innovative and exciting applications in the future.

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