

Modified Pectins for Colon-Specific Drug Delivery

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ABSTRACT

Treatment of local diseases such as ulcerative colitis, Crohn's disease, irritable bowel syndrome and colonic cancer by targeting drug to the colon is a viable approach. Due to gastric degradation of drugs, proteins and peptides, only minimum amount of drug gets absorbed when administered orally and shows little therapeutic activity. Hence the strategy of delivering drugs to colon known as colon targeted drug delivery evolved. Pectin a naturally occurring biodegradable polysaccharide has gained importance as a carrier for colon-specific delivery attributed to swelling nature as well as the ability to resist gastric degradation. This review describes the chemistry of pectin, mechanism of action and various novel modified pectin formulations aimed at targeting the colon.

Key words: Colon targeting, Intestinal microflora, Modified pectin forms, Gelling property, biodegradable polysaccharide, Drug delivery.

INTRODUCTION

Overview of colon and diseases

The distal part of the Gastrointestinal Tract (GIT), called the colon is a major site for the absorption of aqueous media and the water-soluble constituents mainly the electrolytes. The colon extending to several centimeters in length when stretched from end to end is characteristically divided into the cecum, ascending, descending and the sigmoid units and the rectum.¹ The epithelial cells that make up the colon have an extreme ability to secrete mucin culminating in a protective covering called the mucus layer. Mucus layer is responsible for protecting the underlying tissues from harsher conditions. The pH of the colonic contents range from almost neutral to slightly alkaline and colon as a whole is recognized for its programmed contractions termed as peristaltic movements.^{1,2} The constant contraction and involuntary movements of the colon not only plays an important role in the absorption of water and essential nutrients, but also is a significant factor governing the absorption of drugs that are administered orally. Particularly, in conditions of diseases

affecting the colon, it is of extreme importance that the drug is allowed to be exposed to the region of interest for a longer time, before being ultimately expelled from the body.

Microflora of the colon

Another factor that usually is well-established in the context of colon includes the descriptions of the microflora residing within it.^{1,2} With more than 300 species of bacteria inhabiting the colon, aids well in the breakdown and absorption of the complex carbohydrates, proteins, bile acids and other substances vital to the human body. A notable influence of the enzymatic reactions brought about by the colonic bacteria is seen during the breakdown of polysaccharides.^{1,2} Thus it is of great interest for formulation scientists to use polysaccharides in delivering the drugs to the colonic regions taking into consideration the bacterial metabolism, in turn aiding the release of the entrapped drug.

Polysaccharide-based approach

Natural polysaccharides originate from plants, microbes or animals and are split

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into simple saccharides by colonic microflora. These polysaccharide-based drug delivery systems protect bioactivity against the harmful conditions of gastric fluid. Bioactive molecules that are entrapped in the polysaccharide networks undergo hydrolysis of the glycosidic linkage on arrival in the colon, which in turn triggers drug delivery resulting in therapeutic action. The saccharolytic species responsible for biodegradation of polysaccharides include *Bacteroides* and *Bifidobacterium*.¹ Colonic regions contain a large number of anaerobic micro-organisms secreting numerous enzymes^{2,3} which metabolize polysaccharides with the drug resulting in polysaccharide degradation followed by the release of drug in the colonic region. The polysaccharides explored for colon targeted drug delivery are chitosan, dextran, pectin, ethyl cellulose and hyaluronic acid. All these polymers are biodegradable and embedded with the drug by various modifications. When administered orally they reach the colon region and release the drug by enzymatic degradation of polysaccharides.

The present review mainly focuses on modified Pectin formulations reported in literature to treat various pathological conditions associated with the colon including inflammatory bowel disease and cancer.

Pectin and its composition

Pectins are structural polysaccharides of the plant cell wall, consisting mainly of galacturonic acid units, which differ in composition, structure and molecular weight. They are often linked to other cell wall components such as cellulose, hemicellulose and lignin.⁴ In addition to the food industry, pectin has immense potential as a carrier in controlled drug release and, in many other areas like pharmaceuticals and medicine.⁵ The use of pectin has been reported for instance, in nasal, ocular and oral drug delivery⁶ as well as wound healing.⁷

Chemistry of pectin

The three main domains of pectin molecule are the: α -(1 - 4)-linked, irregular, linear homo - galacturonic backbone (HG), with 2 forms of highly - branched regions called the RG - I and the RG - II, which are heterogeneous polysaccharides. Arabinose and galactose side chains replace RG - I. RG - II consists of a well preserved HG backbone, including some rare sugars: 2-O methyl xylose, 2-O methylfucose, apiosis, aceric acid and 2-keto-3-deoxide - d-mano - octulosonic acid and 3-deoxide - d - lyxo-2-heptulosaric acid.⁸ Most of the natural pectins having carboxyl groups exist as ester form.

Sources of pectin

Pectin is present in almost every plant, but the majority of pectin's are produced commercially from citrus fruits like orange, lemons, grapefruit and apples.⁹

Applications of pectin

Pectins are reported to have numerous applications.¹⁰ They include notable prebiotic effect, effect on insulin, in cancer prevention (prostate, colon, breast, pancreatic), anti-proliferative effect and biomedical applications (drug delivery, tissue engineering, wound healing and wound dressing material, and gene delivery).

Pectin for drug delivery

Though a wide range of polysaccharides such as chondroitin sulfate, chitosan, dextran, amylase and inulin are available for colon specific delivery, pectin is most sought and tops the list. Pectin has proven best suited for the supply of colonic medicines because it forms macromolecular additives in the upper portion of GIT and colonized by colonic engraving.¹¹ Pectin is also considered a suitable mode of delivery for the drug because of properties such as biocompatibility, mucoadhesiveness, safety, inertness and ability to gel in acidic environments.^{11,12} However, natural pectin is highly soluble in acidic media and leads to the premature release of the drug.

Modification of pectins

Inherently pectin is water soluble and tend to release the drug prematurely within the initial regions of the GIT, well-before reaching the colon. In order to control the unintended release of the drug, it was reported to form a thick coating of pectin onto the drug core.¹³ Realizing the drawbacks of thick coating, researchers opted for preparing the derivative of pectin that was stable at the various pH conditions but were able to be metabolized by the colonic bacteria.¹⁴ This concept has acquired great relevance in controlled release of drugs directed to the colon, to treat diseases such as colon cancer, irritable bowel disease and Crohn's disease, among others. Diverse studies have been reported in the last decade regarding the use of pectin for drug release.¹⁵

Mechanism of drug release

Pectin a hydrophilic polysaccharide, due to its ability to gel, can alter drug release. The polysaccharide is known to be gastric- and intestinal resistant but is metabolized in the colon by anaerobic bacteria.¹⁴ Colonic drug metabolism may lead to the formation

of pharmacologically active metabolites for the colon-specific drug delivery system.¹⁶ An overview of the drug release and absorption, due to the activity of the resident microflora has been shown in Figure 1.

Various formulations of pectins targeting the colon

Formulations include single unit dosage forms, multi-particulate dosage forms and pectin combined with other polysaccharides. A comprehensive detail on various types of pectin-based formulations have been provided in Table 1 and Table 2. The pectin based systems as microparticles and nanoparticles have been provided in Table 3 and Table 4, respectively.

Single- and multi-unit dosage forms

Matrix tablets

Due to the high degree of fragmentation, elasticity and plastic deformation, the compatibility of pectin is poor.¹⁷ Hence, the addition of plastic excipients such as EMDEX was employed.¹⁸ Pectin matrix studies on reducing drug release rate in an environment mimicking the gastric and small intestinal environment from the

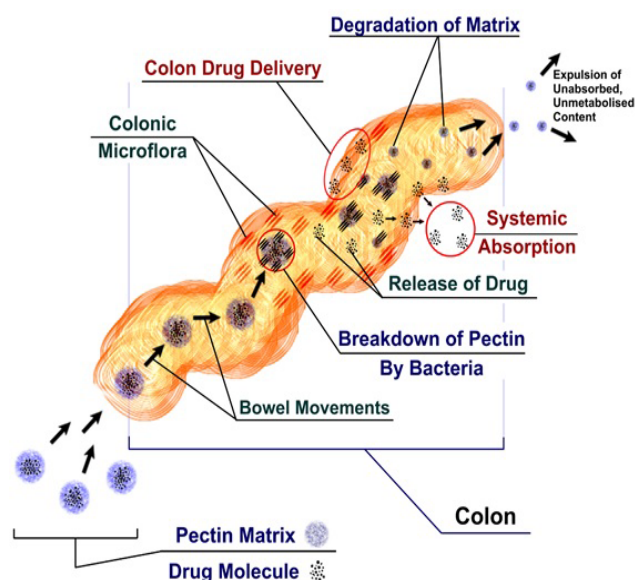


Figure 1: The drug delivery either to the systemic circulation or local colonic tissue using pectin as matrix proceeds with the metabolism of pectin by the resident microflora, thereby slowly eroding the matrix to release the drug. The time of exposure to these microorganisms is limited due to the strong contractions and bowel movements making it a challenge to retain the drug delivery systems at the site of release and action.

Table 1: Various single unit dosage forms of parent and modified pectin, with the entrapped drugs and the respective preparation techniques.

Dosage form	Drug model used	Preparation Method	References
Amidated-pectin Eudragit Matrix tablets	Ropivacaine	Direct compression method	17
Pectin-HPMC compression coated	Calcium sennoside	Wet granulation	39
Enteric coated Pectin Matrix tablets	Theophylline	Direct compression	18
Pectin-Ethyl cellulose Film-coated tablets	Paracetamol	Direct compression followed by fluid bed spray coating	30
Calcium-Pectinate compressed tablets	Indomethacin	Direct compression	40
Calcium-Pectinate capsules	5-Fluorouracil	5-Fu granules prepared by wet granulation and loaded into the capsule	14
Pectin-Chitosan compression coated mini tablets	Indomethacin, Paracetamol	Direct compression followed by coating	33
Modified Pulsincap (pellets were incorporated into capsule shell) Eudragit coated pectin pellets	Metronidazole Aceclofenac	By extrusion spheronization method Twin screw extruder/FB coater	41
Pectin-HPMC-Calcium matrix tablet	Indomethacin	Wet granulation	42
Amidated pectin-Zinc tablet	Ketoprofen	Ionotropic gelation of amidated pectin with zinc ions resulting in microparticles followed by compression of microparticles	23
Eudragit L coated Calcium pectinate tablet	Samarium oxide		43
Pectin-HPMC compression coated tablets	5-Aminosalicylic acid	Wet granulation followed by compression coating	34
Eudragit coated pectin tablets	Levetiracetam	Wet granulation followed by coating with Eudragit polymer by using Fluidized bed coater	44
Chitosan-Pectin polyelectrolyte complex tablets	Vancomycin	Direct compression of microspheres	45

Table 2: Various multiple unit dosage forms of parent and modified pectin, with the entrapped drugs and the respective preparation techniques.

Dosage form	Drug model used	Preparation Method	References
Low methoxy Amidated pectin beads	Indomethacin, Sulphamethoxazole	Beads are prepared from single droplets produced by pumping drug formulations through diameter tube at 1.6mm/min using a peristaltic pump	46
Calcium pectinate beads	Resveratrol	Ionotropic gelation Method	47
Calcium pectinate microbeads	Satranidazole	Ionotropic gelation method	48
Calcium pectinate gel beads	prednisolone	Ionotropic gelation method	49
Pectin bora rice beads	Glipizide	Ionotropic gelation technique	50
Cross-linked alginate-cellulose acetate Acetophalate Gel spheres	Diclofenac sodium	Gel spheres are formed by titrating drug-polymer suspension at 2m/min by using 6-channel peristaltic pump.	22
Calcium pectinate gel beads	Bovine serum albumin	Beads were prepared by extruding pectin solution into calcium chloride solution. On drying matrix beads re produced	51
Silica-coated calcium pectinate gel beads	Theophylline	Calcium pectinate beads were prepared by ionotropic gelation by immersing in a prehydrolysed tetraethoxysilane solution	52
Calcium zinc pectinate gel beads	Mango seed of kernel extract	Ionotropic gelation method	53
Low methoxylated Amidated pectin beads	Benzyl penicillium	Ionotropic gelation method	54
Calcium pectinate beads	Azathioprine	Azathioprine pectin dispersion was added to calcium chloride followed by drying and coating by fluid bed coater	55

Table 3: Various microsphere-based dosage forms of parent and modified pectin, with the entrapped drugs and the respective preparation techniques.

Dosage form	Drug model used	Preparation Method	References
Pectin microspheres	Metronidazole, Tetracycline	Emulsion dehydration technique	28
Low methoxy Amidated pectin microspheres	-	Microfluidic synthesis	56
Pectin microspheres	Vancomycin	Spray dried process	36
Pectin-Alginate microspheres	Metronidazole	Atomization through nozzle spraying	28
Pectin microspheres	Capecitabine	Single emulsification technique	57
Calcium-Pectinate microspheres	Methotrexate, Sulphanilamide, Sulphaguanamide, Sulfathiazole	External gelation using emulsification	58
Zinc-Pectin gel microparticles	Ketoprofen	Ionotropic gelation method	23
Zinc-pectin microparticles reinforced with chitosan	Progesterone	Modified ionotropic gelation technique	59
Pectin microspheres	Prednisolone	Emulsion dehydration technique	60
Eudragit coated Pectin microspheres	5-Fluorouracil	Emulsion dehydration technique	27

Table 4: Various nanoparticle-based dosage forms of parent and modified pectin, with the entrapped drugs and the respective preparation techniques.

Dosage form	Drug model used	Preparation Method	References
Thiolated pectin nanoparticles	Timolol maleate	Ionotropic gelation technique	7
Low methoxy pectin nanoparticles	Bovine beta-lactoglobulin	This method involves preparation of beta-lactoglobulin solution in suitable buffer and addition of this solution to pectin and platinum complex solution prepared by deionized water	61

tablets have been reported.¹⁹ Other approaches include use of calcium pectinates,²⁰ cellulose derivatives such as HPMC, microcrystalline cellulose and more elaborate techniques such as the formation of zinc pectinate beads followed by compression and use of crosslinking agents to pectins have been reported.²¹

Multi-particulate dosage form

Due to more predictable gastric emptying time, multi-particulate dosage forms such as beads are preferred. Hydrogel beads are formulated by the dropwise addition of dissolved pectin solution into a solution containing calcium that results in the formation of insoluble calcium pectinate hydrogel beads due to crosslinking between calcium and pectin.²² However, researchers used zinc acetate as crosslinker that acts superior to calcium.²³ These beads can be used as capsule filling or matrix tablet. There are some patents describing the development of beads in which bioactive substance is loaded in the micro-sponge particles and the openings of those particles are sealed with pectins which act as a further coating to beads.²¹

Particulate systems with pectin

Lee *et al.* developed micro particles using spray drying technique in which a solution of pectin and drug was spray dried and subsequently crosslinked with calcium. The microparticles produced were in the size range of 3-5 micrometer.²⁴ Literature reports on microencapsulation using pectin are scanty. Chavanpatil and Mishra formulated microcapsules with a polyelectrolyte complex by incorporating drug in a mixture containing alginate,²⁵ pectin and calcium.²⁶ They also reported the preparation of insulin-loaded calcium pectinate nanoparticles by ionotropic gelation method as a promising colonic delivery system and evaluated the influence of pectin molecular weight and formulation pH on nanoparticles. Eudragit-coated pectin microspheres were also found to be an effective carrier for colon targeted drug delivery.²⁷ Pectin microspheres bearing metronidazole coated with Eudragit S100 showed effective treatment for amoebiasis.²⁸ Tinidazole formulated using sodium alginate-pectin polysaccharide coated with Eudragit S 100 for the treatment of amoebic colitis have also been reported.²⁹

Coating of pectins to confer hydrophobicity

In order to overcome the hydrophilicity of pectin as well as the low gastric and intestine pH values, Mura *et al.* coated matrix pectin tablets with Eudragit S100.¹⁸ Fell along with his colleagues worked on pectin as a coating material for colon-specific delivery. Later

it was observed that pectin was unable to provide efficient protection to the tablets. So, they added film formers like ethyl cellulose, chitosan and HPMC in order to enhance formulation stability.³⁰ Pectin-ethyl cellulose mixed film coating system using non aqueous solvent were reported for colon targeting.³¹ Moreover pectin-gelatin film combination were also reported as protective coating for colon delivery.

Compression coating

In order to enhance the efficiency of coating, compression coating has been suggested over film coating. The materials reported for compression coating are methoxylated pectin³² and calcium pectinate with additives like chitosan,³³ HPMC and ethyl cellulose.³⁴

Pectin in combination with other polysaccharides

The main challenge lies in avoiding complete dissolution of pectin formulation *in vivo* until it reaches the colon. Pectin alone is not capable of lasting the 4-6 hrs journey through the upper part of GIT. Hence, formulations of pectin in combination with other polysaccharides or polymers like chitosan, HPMC, Alginates and dextrans have been employed to enhance colon drug delivery.²¹

a) Pectin-HPMC

Ugurlu *et al.* reported different combinations of nisin by using pectin/HPMC formulated into compression coated tablets to attain drug release in the colonic region.³⁵

b) Pectin-chitosan

Bigucci *et al.* reported the improvement of Vancomycin release when designed with pectin-chitosan polysaccharides. Vancomycin was formulated as hydrogel system using pectin-chitosan which limits the drug release in acidic conditions thereby confirming its potential for colonic specific drug delivery.³⁶

c) Amidated pectin-chitosan enteric polymers

Giselle *et al.* formulated Triamcinolone using chitosan and amidated pectin in combination with Cellulose Acetate Phthalate (CAP) and Hydroxypropyl Methylcellulose Phthalate (HPMCP) polymers that resulted in controlled drug release in the colonic region.³⁷

d) Pectin-Eudragit

Jain *et al.* reported dicyclomine micro sponges coated with Eudragit S 100 compressed as tablets, which started drug release at the sixth-hour corresponding to arrival time at colon.³⁸

CONCLUSION

Pectin being natural polysaccharides has various advantages in food and medicinal applications. This article gives information regarding pectin and its various dosage forms targeting colonic site. Biodegradability, gel-forming nature are the characteristic features of this polysaccharide which drives its selection as carrier for colon specific drug delivery. Being highly hydrophilic, it forms a gel when in contact with the intestinal fluid. However, it has a limitation of early release before reaching target site. This has been addressed by modification of pectin by thiolation, amylation, methylation and crosslinking with cations such as calcium and zinc. Coating pectin with polymers like HPMC, Eudragit or combining with other polysaccharides has also found to be effective in delivery of drug to target site rather than pectin alone. As research and development continue with pectin drug delivery, many other formulations targeting colon are expected to emerge.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

ABBREVIATIONS

GIT: Gastro intestinal tract; **CAP:** Cellulose Acetate Phthalate; **HPMCP:** Hydroxy Propyl Methyl Cellulose Phthalate.

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