Expert Opinion

Application of pectin in oral drug delivery

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Introduction: Biopolymers have been used extensively in the pharmaceutical field. Pectin, a biopolymer, has several unique properties that enable it to be used as an excipient or carrier for oral drug delivery systems. Accordingly, several investigators have identified the benefits of pectin-based delivery systems for oral drug administration.
Areas covered: This review first describes the chemical structure, source and production, degree of esterification and gel formation properties of pectin. The application of pectin in various oral drug delivery platforms is also discussed, that is, controlled release systems, gastro-retentive systems, colon-specific delivery systems and mucoadhesive delivery systems.
Expert opinion: Pectin from different sources provides different gelling abilities, due to variations in molecular size and chemical composition. Like other natural polymers, a major problem with pectin is inconsistency in reproducibility between samples, which may result in poor reproducibility in delivery characteristics. Scintigraphic studies and *in vivo* studies, in both animals and human volunteers, demonstrate the successful development of a pectin-based colon-specific drug delivery system. Pectin-based controlled release systems, gastro-retentive systems and mucoadhesive systems present promising approaches for increasing the bioavailability of drugs, but are in their infancy. A lack of direct correlation between *in vitro* release and *in vivo* absorption studies is a major concern with these systems.

Keywords: colonic delivery, controlled release, drug delivery system, floating system, mucoadhesion, pectin

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1. Introduction

1.1 Chemistry of pectin

Pectin is a linear polysaccharide. Structurally, pectin consists mainly of D-galacturonic acid (GalA) units joined in chains by a means of α-(1→4) glycosidic linkage (homopolymer of (1→4) α-D-galactopyranosyluronic acid units with varying degrees of carboxyl groups methylesterified) as shown in **Figure 1A**. In addition to the galacturonan segments, neutral sugars are also present. Rhamnose is a minor component of the pectin backbone and introduces a kink into the straight chain (**Figure 1B**) and other neutral sugars such as arabinose, galactose and xylose occur in the side chains [1,2].

1.2 Source of pectin

Pectin makes up about a third of the cell wall dry substance of higher plants. The highest concentrations of pectin are found in the middle lamella of cell wall [1]. Although pectin occurs commonly in most of the plant tissues, the number of sources that may be used for the commercial manufacture of pectin is limited. The pectin from different sources does not have the same gelling ability due to variations in the molecular size and degree of esterification (DE). Presently, commercial pectins

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Article highlights.

- The most unique and outstanding property of pectin is its ability to form gels. It is the property of pectin that makes it an important ingredient in many food and pharmaceutical products.
- The lack of toxicity and the low production costs of pectin make it of great interest for the formulation of controlled release dosage forms for drugs administered orally.
- In oral controlled release drug delivery system, pectin has been used for the preparation of matrix tablets, gel beads and gel coated pellets.
- Pectin-based floating drug delivery systems present promising approaches for increasing the bioavailability of drugs with absorption windows in the upper small intestine.
- The rationale for using pectin as a carrier for colonic drug delivery is that pectin can be degraded by colonic pectinolytic enzymes.
- Mucoadhesive properties of various pectins have been investigated and the pectin-based mucoadhesive dosage form has been designed and evaluated.

This box summarizes key points contained in the article.

are almost exclusively extracted from apple pomace or peel of citrus fruits (such as orange, lemon and lime), both by-products from juice manufacturing. Apple pomace contains 10 – 15% of pectin on a dry matter basis while citrus peel contains about 20 – 30% [3]. Alternative sources include sugar beet waste from sugar manufacturing, mango waste, sunflower heads, legumes, banana, cabbage, carrots [3] and pomelo peel [4].

From these materials, pectin is extracted by adding hot dilute mineral acid at pH about 2. The pectin extract may be further clarified by filtration through a filter aid. The clarified extract is then concentrated in vacuum and the pectin precipitated by adding ethanol or isopropanol. Treating the initial pectin with dilute acid leads to low-esterified pectins. When this process includes ammonium hydroxide, amidated pectins are obtained. After drying and milling, pectin is usually standardized with sugar and sometimes calcium salts or organic acids to have optimum performance in a particular application [1].

1.3 Degree of esterification

An important factor characterizing pectin chain is the DE of carboxyl groups with methyl alcohol. In nature, the DE of pectin can vary considerably (from 60 to 90%). DE is intended to mean the ratio of esterified GalA groups to total GalA groups. Pectin is divided into two main categories on the basis of its different gelling properties: high methoxy pectin (HM-pectin), which is characterized by a DE above 50%, and low methoxy pectin (LM-pectin) having a DE below 50%. The LM-pectins are further subdivided into two groups, amidated LM- and conventional LM-pectins [5].

1.4 Gel formation properties of pectin

The most unique and outstanding property of pectin is its ability to form gels. It is the property of pectin that makes it an important ingredient in many food and pharmaceutical products. HM-pectin forms gels with sugar and acid. This can be explained as a partial dehydration of the pectin molecule to a degree where it is in a state between fully dissolved and precipitated. The particular structure of pectin imposes some specific constraints. It has been suggested that hydrogen bonding and hydrophobic interactions are important forces in the aggregation of pectin molecules [2]. In a neutral or only slightly acid dispersion of pectin molecules, most of the unesterified carboxyl groups are present as partially ionized salts which produce a negative charge on the molecule. The repulsive forces between these groups, due to their negative charge, can be sufficiently strong to prevent the formation of a pectin network. In acidic condition, the carboxyl groups are converted to unionized carboxylic acid groups, resulting in a decrease in the number of negative charges. This not only lowers the attraction between pectin and water molecules, but also lowers the repulsive forces between pectin molecules. Sugar further decreases hydration of the pectin by competing for water.

LM-pectin requires the presence of calcium ions (or other multivalent cations) for proper gel formation. It is shown that the divalent cations form gels with the affinity sequence: barium > strontium > calcium, but magnesium does not form gels or dimers [6]. The mechanism of LM-pectin gelation relies on the well-known 'egg-box' model [7]. The mechanism involves junction zones created by the ordered, side-by-side associations of galacturonans, whereby specific sequences of GalA monomer in adjacent chains are linked intermolecularly through electrostatic and ionic bonding of carboxyl groups (**Figure 2A**). However, Braccini and Perez [8] have pointed out that an alginate-like calcium-binding model is not the most favorable state energetically for pectin. Fang *et al.* [9] directly compared the association of calcium ions with pectin and alginate. They observed that LM-pectin appeared to undergo complexation between calcium ions and a single chain followed by dimerization, but did not appear to show the lateral association between the dimerized chains. They suggested that the differences are probably due to the different arrangement of calcium-binding sites, namely, the block pattern in alginate and the random distribution in pectin.

Furthermore, amidation improves the gelling ability of LM-pectin: amidated pectins need less calcium to gel and are less prone to precipitation at high calcium levels [1]. Racape *et al.* [10] suggested that the gelation of amidated pectins could not be explained by the 'egg-box' model alone, as blocks of amide groups along the chain promote association through hydrogen bonding (**Figure 2B**). The presence of small amounts (i.e., 10 – 20%) of sugar tends to decrease syneresis and adds desirable firmness of LM-pectin gels [3]. The amount of calcium required to form gel is also reduced when small amounts of sugar are present. However, high amount of sugar

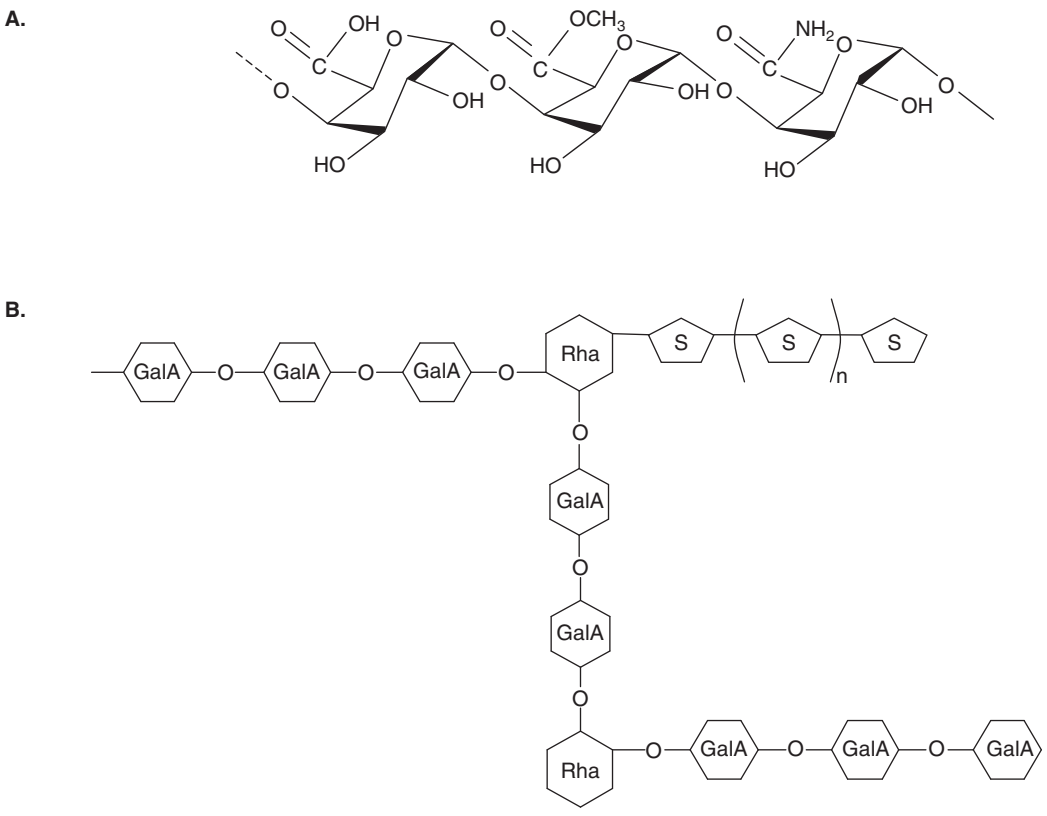

Figure 1. A repeating segment of pectin molecule and functional groups: carboxyl, ester, amide in pectin chain (A) and schematic diagram showing how Rha insertions cause kinking of GalA chain (**B**).
GalA: Galacturonic acid; Rha: Rhamnose; S: Neutral sugars.

(i.e., 60% or higher) interferes with gel formation because the dehydration of the sugar favors hydrogen bonding and decreases crosslinking by divalent ion forces.

2. Pectin for controlled release drug delivery

The oral administration of drug products is the most convenient and commonly employed route of drug delivery. However, it is not always the most suitable route for some active compounds, such as NSAIDs, which cause gastric mucosal damage or for poorly absorbed drugs, such as peptides or proteins. Furthermore, the possibility of controlling drug delivery after oral administration is very limited as it depends on the residence time of the dosage form in the gastrointestinal tract. In fact, the drug will follow the gastric emptying rate, a physiological parameter that is subject to significant inter-individual variability.

For these reasons, researchers have tried new excipients for manufacturing tablets or for developing drug carrier systems capable of controlling drug delivery after oral administration. Recently, many controlled-release formulations based on hydrogels have been developed. Pectin has been one of the successful choices for this purpose. The lack of toxicity and the low production costs of pectin make it of great interest for the formulation of controlled release dosage forms for drugs administered orally. The use of pectin to develop an oral controlled release drug delivery system has been reported by many authors (**Table 1**).

2.1 Matrix tablets

Pectin hydrogels were evaluated as binding agents in tablet formulations [11] and used as controlled-release matrix tablets [12,13]. Sungthongjeen *et al.* [14] investigated HM-pectins for their potential value in controlled-release matrix formulations. The results of the *in vitro* release studies demonstrate that the drug release from pectin matrix tablets can be modified by changing amount of pectin and type of pectin in the matrix tablets. This may be due to a difference in swelling and erosion behaviors of pectin matrix tablets [15]. In general, the pectin matrix tablets form a continuous gel layer while in contact with aqueous medium undergoing a combination of swelling and erosion. Release studies have shown that the swelling and erosion of matrices influenced the drug release.

The modification of drug release has been performed by adding calcium salts in the matrix tablets [16]. When using LM-pectin, the drug release is slower because of the increased binding capacity of pectin to calcium. However,

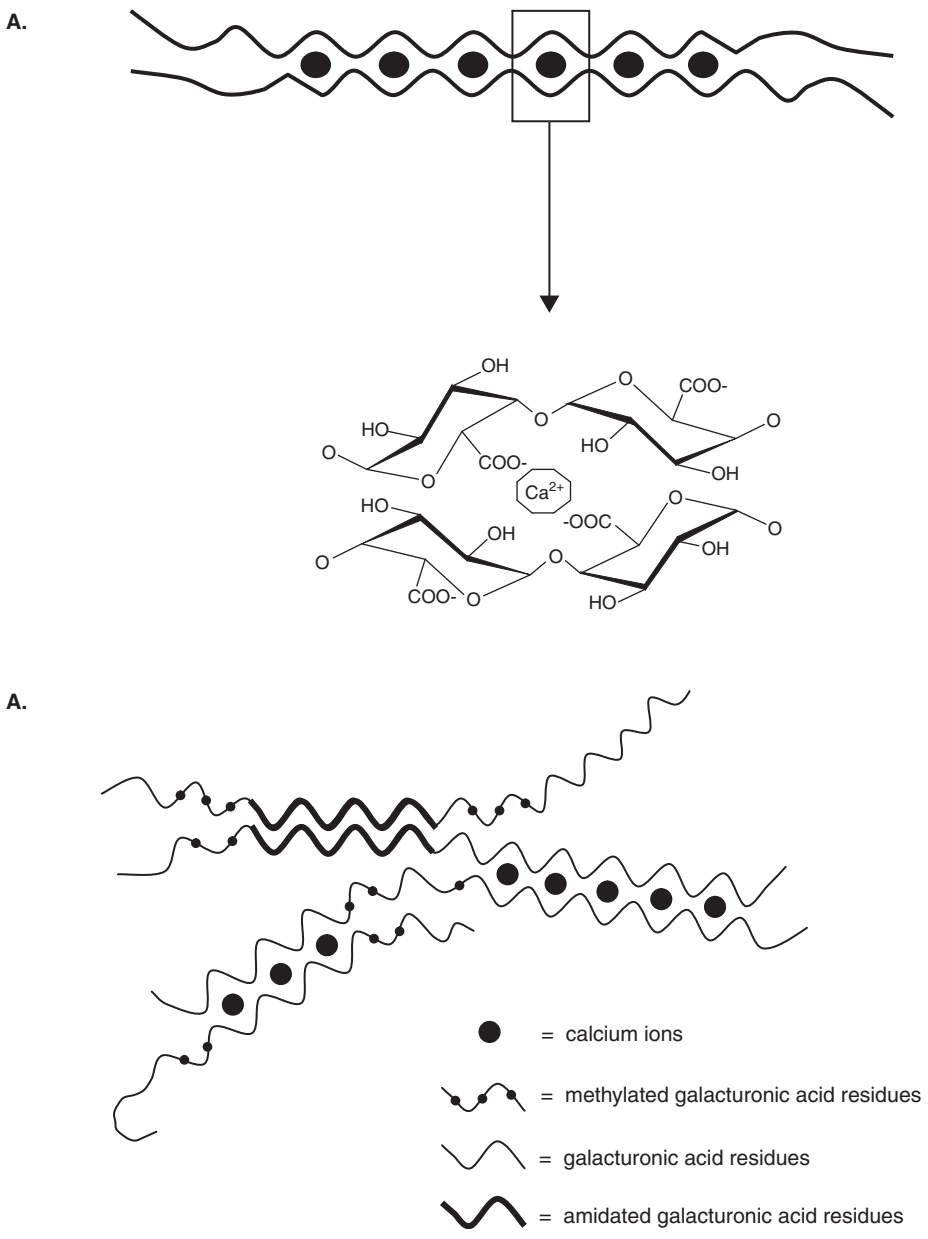

Figure 2. Schematic representation of (A) calcium binding to polygalactoronate sequences of LM-pectin: 'egg box' dimer and 'egg-box' cavity, and **(B)** a model for gelation of amidated LM-pectin [5].
LM-pectin: Low methoxy pectin.

when calcium was excluded, the pectin with different DEs showed similar release pattern. When the amount of calcium acetate was increased from 0 to 12 mg/tablet, the drug release was significantly slower. However, a large amount of added calcium (i.e., 24 mg/tablet) produced greater drug release because of the partial disintegration of tablets. Wei *et al.* [17] also reported the initial erosion of pectin matrix tablets containing a large fraction of calcium chloride which is induced by the quick escape of calcium chloride to the release medium. However, the erosion of the pectin in the matrix itself, which controlled drug release, decreased as the calcium level in the matrix increased.

The application of a binary polymer system, that is, HM-pectin and hydroxypropyl methylcellulose (HPMC), in drug release rate modulation for oral administration has been thoroughly studied by Kim and Fassihi [18,19]. Tablets are manufactured by direct compression and are used to deliver drug at variable rates according to zero-order kinetics. The achievement of total zero-order kinetics is due to the predictable swelling/erosion and final polymer chain

Table 1. Examples of controlled release formulation using pectin.

Dosage form	Type of pectin	Application	Ref.
Tablets	Pure and standardized pectin	Binding agents and delayed drug release	[11]
Tablets	HM-pectin	Sustained release properties of direct compression tablets	[12]
Tablets	HM-pectin (pure and standardized)	Hydrogel matrix system	[14]
Tablets	LM-pectin or HM-pectin (with calcium salts)	Hydrogel matrix system	[16,17]
Tablets	HM-pectin	Direct compression of the mixture of HM-pectin and HPMC	[18-21]
Gel beads	LM-pectin	Pectin beads prepared by ionotropic gelatin	[22]
Gel beads	LM-pectin (amidated)	Sustained release drug delivery using calcium pectinate gel beads	[23-25,96]
Gel beads	LM-pectin (amidated)	*In vitro* and *in vivo* studies of pectin hydrogel beads	[26,67]
Gel beads	LM-pectin	Calcium pectinate or calcium alginate-pectinate prepared by ionotropic gelation	[28]
Particulates	LM-pectin	Alginate-pectin-polylysine system	[97]
Coated pellets	LM-pectin (amidated and non-amidated)	Insoluble calcium pectinate gel coating for sustained release delivery prepared by interfacial complexation	[33-36,39]

HM-pectin: High methoxy pectin; HPMC: Hydroxypropyl methylcellulose; LM-pectin: Low methoxy pectin.

deaggregation and dissolution that are regulated by the gelling characteristics of polymers in the formulation. On the contrary, the combination of HPMC, HM-pectin and calcium chloride produces a biphasic drug release with a lag time of over 4 h with a high amount of calcium chloride (HPMC 100 mg/HM-pectin 100 mg/calcium chloride 100 mg) [20]. In the dissolution medium with high ionic strength (e.g., 2% sodium chloride), the pectin–calcium interaction was disrupted, resulting in very fast drug release [21].

2.2 Gel beads

LM-pectins form gels by the action of calcium, which crosslinks the poly-Gal chains [3]. Pectin beads prepared by the ionotropic gelation method [22] were used as a sustained release drug delivery system. However, the use of these beads has some disadvantages due to their rapid *in vitro* release. By changing the DE of LM-pectin, drug release pattern from calcium pectinate gel beads can be modified [23]. The effects of some variables on bead properties as well as drug release from the beads have also been studied. Slower drug release can be achieved from the formulations with higher calcium concentration, higher concentration of hardening agent and longer hardening time. The drying conditions, however, do not influence the drug release [24]. The drug loading methods as well as the drug loading factors (i.e., drug concentration, soaking time in drug solution, type of solvent) were found to influence the drug content and drug release from calcium pectinate gel beads [25]. The conventional mixing method provides a faster drug release than the absorption method (i.e., the blank wet-beads formed were soaked in drug solution before drying) and swelling method (i.e., the blank dried-beads were soaked in drug solution and dried again), respectively. Moreover, the increased drug concentration in soaking solution and soaking time result in higher drug content and thus faster drug release. The drug release is also affected by pH of release medium in which drug release in 0.1 N HCl was faster than in pH 6.8 buffer. Munjeri *et al.* [26] investigated the suitability of amidated pectin beads as a delivery matrix for chloroquine. Pectin beads with varying pectin:chloroquine ratios in the dried beads were prepared by the gelation of drug-loaded pectin solutions in the presence of calcium. *In vitro* release studies have shown that the release of entrapped drug from the beads was achieved between 4 and 7 h in simulated intestinal condition. Oral administration of the pectin beads to rats produces maximum plasma concentrations by 7 h, compared to the highest plasma concentration following chloroquine solution administration observed by 2 h.

Lee *et al.* [27] prepared catechin-loaded calcium pectinate gel beads by internal gelation method in which a pectin suspension containing drug and $CaCO_3$ particles is extruded drop-wise into an acidic water-in-oil emulsion and the beads are formed through the pectin gelation by the calcium ions dissociated from $CaCO_3$ at acidic pH in the dispersed aqueous phase. The catechin release is slower for the beads prepared with lower catechin:pectin ratio, longer gelling time, and higher concentrations of pectin and acetic acid in both simulated gastric and intestinal fluids. Calcium pectinate and calcium alginate-pectinate were prepared by ionotropic gelation and the structural and release behavior of crosslinked beads has been evaluated [28]. The rate of drug release ranges from rapid to slow (i.e., 100% drug release in 4 – 10 h in pH 6.6) but always proceeds in a controlled manner. The proper selection of rate-controlling polymers is, therefore, important and will determine release behavior, pH sensitivity, drug loading capacity and mechanism of drug release [28].

The mechanical properties and drug release behaviors of calcium pectinate gel beads can be modified by adding oppositely charged polymers, for example, chitosan. Sriamornsak *et al.* [29] reported that the indomethacin release (in pH 7.4 buffer) from chitosan-reinforced calcium pectinate gel beads, which have slightly higher swelling, is faster than that from calcium pectinate gel beads. It is because of the dissolution of chitosan from the beads in acidic medium causing the less swelling in acidic medium and then faster drug release. Mennini *et al.* [30] reported the use of response surface methodology in the optimization of chitosan-calcium pectinate bead formulations, which allows identification of the best combination of three bead components, that is, chitosan, LM-pectin and calcium chloride, in order to maximize drug encapsulation efficiency.

The influence of microwave irradiation on the drug release properties of calcium pectinate and chitosan-calcium pectinate beads was investigated by Nurjaya and Wong [31]. The beads were prepared by ionotropic gelation method and subjected to microwave irradiation at 80 W. The results showed that treatment of calcium pectinate beads by microwave leads to an increase in the extent and rate of drug released while microwave treatment of chitosan-calcium pectinate beads is essential to reduce the rate and extent of drug released from the matrix, following an increase in drug–polymer and polymer–polymer interaction in beads. When chitosan was loaded internally into calcium pectinate beads, the extent of drug released is reduced as a result of drug–chitosan adsorption. Nevertheless, the microwave treatment of these beads produces an increase in the extent of drug released unlike those of chitosan-calcium pectinate beads [32].

2.3 Gel coating

Calcium pectinate has been investigated as an insoluble hydrophilic gel coating for sustained release delivery by interfacial complexation process [33,34]. The spherical pellets, which contain calcium acetate, are prepared using an extrusion-spheronization method and then coated in a pectin solution. An insoluble and uniform coating of calcium pectinate gel is formed around the pellets [35]. The pellet size, pectin type, pectin concentration and dissolution medium influence the swelling and drug release behavior but the swollen thickness of calcium pectinate gel coats is unaffected by pellet size or pectin concentration, except for amidated LM-pectin [36]. It is likely that the low swelling in acidic medium is related to proton–calcium ion exchange forming insoluble acid gels. In contrast, partial formation of soluble sodium pectinate induces water uptake, resulting in greater swelling.

Drug release profiles of coated pellets show a lag time when the gel coat hydrated and swelled, followed by a period of zero-order release. It is found that the zero-order release rate and the diffusion coefficient of theophylline are controlled by pellet size, pectin type and pectin concentration [36]. A dramatic difference between the diffusion coefficient of coated pellets and free films of calcium pectinate prepared by interfacial complexation [37] is observed, suggesting that the diffusion coefficient of the calcium pectinate gel coated pellets could not be simply predicted from the diffusion results of its free films [36,38].

The effect of drug solubility on the release behavior from calcium pectinate gel coated pellets is investigated by Sriamornsak and Kennedy [39]. The xanthine drugs with similar structure but having a significant difference in solubility, that is, caffeine, theophylline and theobromine, are used. The drug-loaded pellets show similar pellet shape, size distribution, moisture content and crushing strength. However, the encapsulation efficiency of these pellets is different due to the drug solubility. The coated pellets containing different drugs show different release kinetics. The release of theophylline from coated pellets is slightly slower than that of caffeine owing to the difference in the drug dissolution within the core before its partition and diffusion through the calcium pectinate gel coat. The release of theobromine from coated pellets is much slower than that of caffeine and theophylline because of its low solubility. However, the release of all drugs is about four to sixfold slower for coated than uncoated pellets, suggesting that the coating significantly retarded drug release from coated pellets. They concluded that there is an inverse relationship between the drug released from coated pellets and drug solubility.

3. Pectin for gastro-retentive drug delivery

Drug delivery to the stomach takes advantage of several attributes of its physiology, for example, low pH, motility and gastric emptying time. Many gastro-retentive drug delivery systems have been developed and not all of them are successful in improving gastric residence time. The different strategies for gastric retention can be suggested: changes on the density of the dosage forms after administration (e.g., high porosity, swelling or expansion, super porous hydrogels), bioadhesion and changes on geometry of dosage forms [40]. However, only floating drug delivery system has been developed, based on pectin, to prolong the gastric residence time.

Floating systems have a density lower than the density of gastric fluid. The concept of floating drug delivery has been used in the development of anti-reflux formulations. Washington *et al.* [41] investigated the gastric distribution and residence time of a pectin-containing formulation. They observed that the formulation is able to float and forms a distinct phase on top of the stomach contents. In fact, the product empties from the stomach more slowly than the food, and > 50% of the formulations remain in the fundal region for 3 h.

Floating drug delivery systems present promising approach for increasing the bioavailability of drugs with absorption windows in the upper small intestine. The systems should immediately float in the gastric fluid which can be achieved if the density of the systems is low at the very beginning. Talukder and Fassihi [42] developed a multiple-unit system

based on crosslinked beads of calcium pectinate or calcium pectinate/alginate. The freeze-dried beads remain buoyant over 12 h in pH 1.5 buffer while the air-dried (hot-air oven at 40°C for 6 h) beads sink. The floating is due to the hollow spaces inside the freeze-dried beads.

Recently, a new emulsion-gelation method to prepare oil-entrapped calcium pectinate gel beads capable of floating in the gastric condition has been developed [43]. The gel beads are simply prepared by mixing oil phase and water phase containing pectin, extruding into calcium chloride solution, and followed by washing and drying. It is found that the oil-entrapped beads float if a sufficient amount of oil (20 – 30%, depending on the type of oil) is used. Scanning electron micrographs demonstrate very small pores, ranging between 5 and 40 μm, dispersed all over the beads. However, the drug release from these beads is rapid, that is, about 80% of drug loading release within 20 – 80 min. The attempts to modify the drug release have been made [44]; for example, the additives (polyethylene glycol 10000, glyceryl monostearate and Eudragit® L) are combined into the starting solution prior to bead formation. Using 2% glutaraldehyde as a hardening agent slightly prolongs the drug release. Coating the beads with Eudragit® RL significantly prolongs the drug release while the beads remain buoyant. Mishra and Pathak [45] prepared the emulsion gel beads using a mixture of pectin and sodium alginate and found that the amount of oil can be reduced to about 15%. The release pattern of loratadine can be modified to zero-order release by coating the beads with ethyl cellulose.

Intragastric floating drug delivery system can also be prepared by incorporating low density materials, for example, oils and/or waxes [46]. The waxes in pectin–olive oil mixtures containing metronidazole are hot-melted, homogenized and extruded into calcium chloride solution. The beads formed are collected and dried. Incorporation of wax into the emulsion gel beads affects the drug release. Water-soluble wax (i.e., polyethylene glycol) increases the drug release while other water-insoluble waxes (i.e., glyceryl monostearate, stearyl alcohol, carnauba wax, spermaceti wax and white wax) significantly retard the drug release. Increasing the amount of hydrophobic wax in the formulation significantly prolongs the drug release but is insufficient for extending the release of highly water-soluble drug [46]. The hollow calcium pectinate beads have been developed for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy. Floating-pulsatile concept is applied to increase the gastric residence of the dosage form having lag phase (in gastric fluid) followed by a burst release in intestinal fluid. The hollow/porous floating beads of calcium pectinate with bulk density < 1 g/cm^3 are prepared and demonstrated gastric retention up to 5 h in rabbits [47].

The use of gas to decrease the density of the dosage form is an alternative to the previous strategy. Floating of dosage forms can be achieved by the inclusion of a gas-forming agent in an inert matrix. Calcium pectinate beads containing carbonate salt, as a gas-forming agent, are developed by dispersing carbonate salt in pectin solution and then extruding into either neutral or acidified solution of calcium chloride [48]. Incorporation of sodium bicarbonate into pectin solution results in porous structured beads. Acidity of gelation medium increases the pores in the structure of beads containing calcium carbonate, resulting from carbon dioxide generated from reaction of carbonate salts with acid. The highly porous structure of the freeze-dried beads provides a good floating ability with fast drug release. The drug release can be prolonged by using pectin with lower DE, 10% calcium carbonate, acidified gelation medium and high drug loading. Their floating ability, however, seems to be decreased.

4. Pectin for colon-specific drug delivery

The delivery of drugs to the colon for systemic action or a local effect is valuable in a variety of circumstances. These include the topical treatment of diseases such as ulcerative colitis, Crohn's disease, colon carcinoma and the potential for the oral delivery of peptides and other labile drugs. One approach for delivery drug to the colon is the use of materials which are degraded by bacterial enzymes that exist specifically in the colon. Pectin shows promise in this regard and is presently considered as a carrier material in colon-specific drug delivery systems, as indicated by the large number of studies published over the last 2 decades (**Table 2**). The potential of pectin or its salt as a carrier for colonic drug delivery is first demonstrated by two studies [49,50]. The rationale for this is that pectin and calcium pectinate can be degraded by colonic pectinolytic enzymes [51]. However, drug release from pectin matrices in the upper gastrointestinal tract can be retarded because pectin is not degraded by gastric or intestinal enzymes [52] and is poorly soluble. Liu *et al.* [53] and Sande [54] recently provided comprehensive reviews of pectin-based systems for colonic drug delivery.

4.1 Tablets

Calcium pectinate is used as a carrier for colon-specific drug delivery by compression into tablets [50]. The potential of HM-pectin and combinations of calcium salts and LM-pectin has been investigated for preparation of matrix tablets for colonic delivery of several model drugs [49,55]. Ashford *et al.* [49] demonstrated that HM-pectin, when applied as a compression coat, proves capable of protecting a core tablet during conditions mimicking mouth-to-colon transit and is susceptible to enzymatic attack. *In vivo* γ scintigraphy confirmed the *in vitro* findings that the pectin-coated tablets disintegrate in the colon, indicating that site-specificity has been achieved [49].

In vitro and *in vivo* analyses of colon specificity of calcium pectinate formulations are studied by Rubinstein and Radai [56]. In *in vitro* studies mimicking the altering conditions in the gastrointestinal tract, they compared indomethacin release from calcium pectinate matrix tablets and calcium

Table 2. Examples of colon-specific drug delivery using pectin.

Dosage form	Type of pectin	Application	Ref.
Tablets	Calcium pectinate	Compression of calcium pectinate (matrix system)	[50]
Tablets	HM-pectin alone or mixed with HPMC	Compression coat	[49,57-58]
Tablets	HM- and LM-pectin	Matrix system	[55]
Tablets	Calcium pectinate	Matrix system and compression coat	[56]
Gel beads	LM-pectin (amidated)	Calcium or zinc pectinate gel beads for delivery of low molecular mass drug	[59,68,69,98]
Gel beads	LM-pectin (amidated)	Calcium pectinate gel beads coated or complexed with other polymers	[64,99]
Gel beads/nanoparticles	LM-pectin (amidated)	Calcium pectinate gel beads for protein delivery	[67,60,61,63,66]
Film coated tablets	HM-pectin	Coating with mixtures of HM-pectin and ethylcellulose aqueous dispersion	[71,72]
Film coated tablets	HM-pectin or LM-pectin	Coating with HM-pectin or LM-pectin combined with aqueous polymer dispersion	[73,75-76]
Film coated tablets	HM-pectin	Coating with mixtures of HM-pectin/chitosan/HPMC	[79,100]

HM-pectin: High methoxy pectin; HPMC: Hydroxypropyl methylcellulose; LM-pectin: Low methoxy pectin.

pectinate tablets that are compression-coated with a second layer of calcium pectinate. The *in vivo* performance of calcium pectinate matrix tablets and compression-coated tablets containing insulin is also compared following oral administration in dogs [56]. Compressed matrices are able to retain the drug load in simulated gastrointestinal fluids prior to their degradation by a mixture of pectinolytic enzymes. Therefore, these formulations can be used for colon-specific delivery of low water-soluble drug molecules. The delayed insulin absorption is related to a breakdown of the drug carrier in the dogs' large intestine. Non-coated calcium pectinate tablets are not able to prevent insulin diffusion and start to release right after administration. Thus, an additional protective coat may be required for highly water-soluble drugs. Ugurlu *et al.* [57] found that pectin alone is not sufficient to protect the incorporated drug in core tablets to be delivered to the colon due to the degradation of pectin. The addition of HPMC (5% w/w) with pectin in compression coat provides 2-h lag time for drug release. The *in vivo* evaluation in healthy volunteers demonstrated that, in all subjects, the drug releases from compression-coated tablets in the colon [58].

4.2 Beads and microparticles

The potential of calcium pectinate as a multiparticulate drug carrier for colon-specific delivery has been evaluated *in vitro* and *in vivo* by the use of drug markers, both water soluble and water insoluble, either small organic compounds or active protein drugs. Munjeri *et al.* [59] prepared calcium-induced gel beads of amidated pectin for colon-specific delivery. The results showed that drug release from the beads is a function of media pH and drug loading. In simulated gastric and small intestinal conditions, drug release is greater with the more soluble drug, but release of both drugs can be reduced by the formation of a chitosan polyelectrolyte complex around the beads. All the preparations release drug in simulated colonic conditions. Sriamornsak [60,61] prepared calcium pectinate gel beads by extruding protein-loaded pectin solution into agitated calcium chloride solution. Subsequent drying produces matrix beads in which protein is embedded. *In vitro* experiments are conducted on the release of a model protein (bovine serum albumin) from the beads under conditions pertaining to colonic delivery *in vivo*. Monitoring release gives a sensitive indication of the behavior of pectin under the different conditions. The presence of enzymes in the medium influences release characteristics. By changing the type of pectin, it is possible to protect proteins during the different conditions encountered from mouth to colon. The calcium pectinate gel beads can stabilize in intestinal condition by coating with polyethylenimine or by keeping in enteric hard capsules to prevent drug release before reaching the colon [62]. Bourgeois *et al.* [63] evaluated critical formulation parameters influencing the bioactivity of β-lactamases entrapped in pectin beads and found that increasing calcium chloride concentration and gelation time lead to a significant loss of enzyme activity. Liu *et al.* [64] developed complex hydrogel beads from pectin and zein. The pectin–zein complex hydrogels do not swell in physiological environments, but hydrolyze in the presence of pectinases. The physical and biological properties of the hydrogels are attributed to molecular entanglement of the two polymers.

Perara *et al.* [65] developed pectin–4-aminothiophenole conjugate microparticles for colon-specific drug delivery. The conjugate microparticles can retard the drug release up to 6 h compared to control particles and shows low toxicity. The nanoparticles of calcium pectinate gel can be developed by adjusting the concentration of both pectin and divalent crosslinking medium. Cheng and Lim [66] prepared insulin-loaded calcium pectinate nanoparticles by ionotropic gelation. They found that formulation pH significantly influences the association efficiency and stability of the nanoparticles. The increase in association efficiency is correlated to the charge density on the pectin molecules as a function of pH.

The release of associated insulin from the nanoparticles is dependent on the extent of dilution of nanoparticle dispersion and the pH of dissolution medium. Moreover, Musabayane *et al.* [67] reported as more effective sustaining plasma insulin concentrations after oral administration of insulin-loaded calcium pectinate beads (30 μg of insulin) than that of subcutaneous insulin injection (30 μg) in diabetic rats. The pectin beads can reduce plasma glucose concentration in diabetic rats.

Other divalent cations, such as zinc, have been used for crosslinking with pectin. El-Gibaly [68] developed ketoprofen-loaded zinc pectinate gel microparticles and their compressed tablets. The zinc pectinate gels show a lower drug release than the conventional calcium pectinate beads. This could be due to the strength of the network formed during the process between the zinc cations and the LM-pectin following the 'egg-box' model. Chambin *et al.* [69] reported that zinc pectinate beads obtained with 10% of counter-ions solution at pH 1.6 exhibit strong gel network which is arranged in a compact three-fold conformation. This network is stronger and reduces the swelling and hydration on contact with dissolution medium, with subsequently a decrease of drug release. Khoder *et al.* [70] found that bead stability correlates with zinc content. The minimal amount of zinc (0.08 mg/mg pectin) can protect the egg-box structure against total disintegration.

4.3 Film coating

HM-pectins have been investigated for their potential as a practical film coating for colonic delivery [71]. Combinations of HM-pectin and ethyl cellulose, in the form of an aqueous dispersion, are used as coating formulations. The coatings are assessed by a flow-through dissolution system simulating the *in vivo* conditions of pH, residence time and pectinolytic enzymes that simulate the bacterial flora of the colon. Drug release is controlled by the ratio of ethyl cellulose:pectin in the film coat. Combinations of ethyl cellulose and pectin can provide protection to a drug in the upper gastrointestinal tract while allowing enzymatic breakdown and drug release in the colon as the addition of pectinolytic enzymes to media increases the drug release. The mechanical and permeability properties of cast mixed ethyl cellulose–pectin films have also been investigated [72]. Increasing concentrations of pectin impart increased brittleness and decreased toughness to the films. Despite the inclusion of increasing quantities of the hydrophilic pectin into the films, the permeability to moisture remains essentially the same. These results imply that there is a limit to the amount of pectin that can be included in the coating material in order to produce a satisfactory film, but the protective nature of the ethyl cellulose to moisture is not compromised.

Leaching of pectin from mixed pectin-insoluble polymer films, which are a combination of HM-pectin or calcium pectinate with commercially available aqueous polymer dispersions, is investigated [73]. The mixed films are prepared using Aquacoat® ECD30, Surelease® Clear, Eudragit® RS30D or Eudragit® NE30D containing 5, 10 or 15% w/w (related to insoluble polymer content) of HM-pectin or 10% w/w of calcium pectinate. The kinetics of pectin leaching from the isolated films in the absence of pectinolytic enzymes showed that HM-pectin or calcium pectinate is quickly released from the different films. Moreover, the leaching of pectin from Eudragit® RS films containing up to 10% w/w of HM-pectin or LM-pectin is significantly faster in the presence of enzymes than in their absence. Similar results on pectin/Kollicoat® SR30D films are also reported [74]. The use of these mixed films for coating pellets is reported [75,76]. The aqueous-based film coating is performed using a fluidized-bed apparatus. The effect of pectinolytic enzymes on the drug release from pellets coated with the mixed films is also investigated. It is surprising that the presence of enzymes in the dissolution medium results in the decrease of release rate from the pellets coated with Aquacoat® ECD30, Surelease® Clear, Eudragit® RS30D or Eudragit® NE30D, containing HM-pectin or calcium pectinate. This suggests that the enzymes degrade the pectin dispersed in the films, resulting in the leaching of its components from the coat [75]. The synthetic polymers in the mixed films suppress the hydrated pectin channels and decrease the swelling and hydration of the film coating. On the contrary, an increase in the release rate in the presence of enzymes in the medium is found when the pellets are coated with ternary mixtures, namely, HM-pectin–Eudragit® RL–Eudragit® NE [76], or coated with Eudragit® RS–poly-Gal combinations [77].

Fernandez-Hervas and Fell [78] investigated pectin–chitosan mixtures as coatings for colon-specific drug delivery. Small tablets are coated with either HM-pectin (pectin United States Pharmacopeia (USP)) or HM-pectin in a 1:10 mixture with chitosan. Pectin alone is able to protect the cores from premature release. Pectin–chitosan mixtures achieve better protection at a lower coat weight. The use of pectinolytic enzymes to simulate breakdown in the colon shows that the pectin–chitosan mixture is susceptible to enzymic breakdown and allows drug release to occur. Macleod *et al.* [79] examined the potential of pectin/chitosan/HPMC films for colonic drug delivery by coating on the core tablets. Drug release in simulated gastrointestinal conditions shows a bimodal profile with the increased drug release rate being triggered by the action of pectinolytic enzymes. Radiolabeled tablets coated with a film mixture are administered to human volunteers and the gastrointestinal transit of the tablets is assessed [79]. The tablets are able to pass through the stomach and small intestine intact. Breakup of the tablets commences once they are in the colon due to degradation of the coat by colonic bacteria.

5. Pectin for mucoadhesive drug delivery

As pectin is a hydrophilic polymer containing a large number of H-bonding groups (e.g., carboxyl groups), it is possible to form H-bond with functional groups in mucus. This has been proposed as an adsorption mechanism in mucoadhesion

process [80]. Several reports have demonstrated the mucoadhesive properties of pectin. Smart *et al.* [81] reported that pectin gives fair adhesiveness with mucus gel using Wilhelmy plate method. On the contrary, Lehr *et al.* [82] found that pectin (with no identified source) shows no adhesion, compared to polycarbophil or chitosan. With this test, thin films containing 1 mg/cm^2 of polymers were hydrated in the saline medium for 5 min, then tested with the pig small intestinal mucosa under very slight pressure (~ 10 mN), and kept in this position for 1 min. The hydration time of 5 min may be too long and, then, the thin films could be dissolved before testing, resulting in loss of mucoadhesive properties. In fact, there are many factors affecting the mucoadhesive properties of polymers such as degree of hydration [83], ionic strength of medium and their molecular structure feature [84]. Additionally, the physical properties, for example, solution, gel-forming and swelling properties, of pectin are different, depending on the types or characteristics of pectin. This information should be mentioned in the literature and should not be disregarded.

Schmidgall and Hensel [85] reported that LM-pectin and linear oligogalacturonides derived from pectin show a significant mucoadhesion against colonic mucus membranes whereas HM-pectins and neutral polysaccharides are ineffective. Liu *et al.* [86] reported that pectin with higher net electrical charges shows a higher mucoadhesion with porcine colonic tissues than the less charged ones. The HM-pectin forms gel networks with endogenous mucin lining on the surface of mucosal tissues whereas LM-pectin is able to penetrate deeply toward the colonic intestinal wall, but does not adhere strongly on the tissue surface.

Thirawong *et al.* [87] investigated the mucoadhesive properties of various pectins using a texture analyzer and the mucoadhesive mechanisms with several techniques. The results demonstrated the mucoadhesive properties of pectin against GI mucosa with the strongest mucoadhesion in large intestine. For buccal tissue, dry pectin discs show stronger adhesion than wet ones [88]. Moreover, mucoadhesive performance of pectin largely depends on their characteristics, that is, DE and molecular mass. The wetting behavior of pectin surfaces increases with the decreased DE, indicating the hydrophilic nature of the molecules [89]. The rheological parameters increase after mixing of pectin and mucin indicating the interaction between pectin and mucin due to physical entanglement [90,91]. Infrared spectra show that water from mucin dispersion can diffuse through pectin films and forms H-bond with pectin molecules. The atomic force micrographs demonstrate physical morphology of the interaction [92]. The study of surface charge properties shows that pectin, mucin and the pectin–mucin mixture are negative charge, indicating that the interaction between pectin and mucin is not due to the electrostatic attraction [92].

The pectin-based mucoadhesive dosage forms have been designed and evaluated. Wattanakorn *et al.* [88] prepared the pectin-based discs for buccal adhesion in order to administer carbenoxolone sodium for the treatment of aphthous ulcers in oral cavity. They found that the bioadhesion of dried pectin discs decreases when either the discs are hydrated or the buccal tissue is wet with a small volume of medium. Addition of sweetener in the formulations also affects bioadhesion of the discs. The pectin discs containing a sweetening agent show a higher drug release than those without sweetener. Pectin–liposome nanocomplexes are prepared by mixing cationic liposomes with pectin solution [93,94]. Nanocomplexes containing fluorescein isothiocyanate–dextran with molecular mass of 4300 Da (FD4) are then intragastrically administered to male Wistar rats. The rat GI tissues are excised and observed under confocal laser scanning microscopy. High intensities of FD4 are found in rat's small intestine even after 6 h of an oral administration of FD4-loaded nanocomplexes, compared to FD4 solution and FD4-loaded cationic liposomes. The pharmacological effect of nanocomplexes containing calcitonin is also investigated and demonstrates that blood calcium concentration is decreased after administration of nanocomplexes containing calcitonin into rat, compared to calcitonin solution [94].

Modification of pectin structure may increase the bioadhesion to the mucus membrane. For this purpose, pectin has been conjugated with thiol moieties of cysteine for improving mucoadhesive properties [95]. The new polymer, thiolated pectin, shows no severe toxicity in caco-2 cells; higher permeation enhancement for sodium fluorescein, approximately five-fold, increased *in vitro* adhesion duration and improved cohesive properties, compared to unmodified pectin. The release of insulin from zinc pectin-cysteine beads follows the same profile as unmodified zinc pectinate beads [95].

6. Expert opinion

Pectins form gels in acidic media or by crosslinking with calcium ion, depending on their molecular composition. The acid-induced gelation and calcium crosslinking have been studied for the development of pectin-based drug delivery systems. Essentially, pectin from different sources provides the different gelling abilities due to variations in the molecular size and DE. Pectin is generally regarded as one of the safest and most acceptable of food additives; this is recognized by Generally Regarded as Safe status in the US legislation. In general, there are some restrictions on the use of pectin in pharmaceuticals. To date, only HM-pectin is officially available for pharmaceutical applications according to USP. The LM-pectin is not yet available as pharmaceutical grade. Until the pharmaceutical grade of all pectins is available, thorough characterization of the material is important.

A major problem with pectins, like other natural polymers, is inconsistency in their reproducibility, degradability and mechanical properties between samples. Such variability in properties may result in poor reproducibility in delivery characteristics, such as drug loading and release kinetics. Moreover, pectin extracted and purified from natural sources

often varies significantly in their purity. For example, pectin is available in > 100 grades and is extracted from various sources that differ in Gal content and molecular mass. Some properties, for example, viscosity, may be commercially standardized by addition of sugar to assure the reproducible gelling.

For the preparation of controlled release systems, HM-pectin alone or LM-pectin with suitable amount of calcium salts seems appropriate for using as oral matrix tablets while amidated LM-pectin is the best for producing pectin beads that are crosslinked by calcium or zinc. For gel coating, amidated LM-pectin gelled with calcium would be the best in all kinds of pectin when considering mechanical strength and permeation. The *in vitro* release studies of these systems have shown the contribution of pectin for optimal controlled release. A major concern with *in vitro* release studies, however, is the lack of direct correlation between *in vitro* release and *in vivo* absorption studies. The physiological conditions in gastrointestinal tract are more complicated than buffer solutions commonly used *in vitro* and may give different results when tested *in vivo*.

Pectin gels can be degraded by colonic enzymes and, therefore, it is useful in colonic drug delivery. Pectin shows promise in this regard, as indicated by the large number of studies published since 1990s. Although the activation of the system by the bacterial enzymes in colon is quite slow, the long residence time in the colon may be sufficient to overcome this disadvantage of colonic delivery. This has been confirmed by the *in vivo* studies in both animal models and human volunteers. However, the efficacy of these systems is affected by lack of consistency which may be due to the variation of pectin sources and methodology implemented for different experiments. Systematic study should be used to compare different pectin grades by using reliable *in vitro* and *in vivo* models.

Pectin-based floating drug delivery systems and mucoadhesive systems using pectin present promising approaches for increasing the bioavailability of drugs but are in their infancy. To extend the application of pectin, functional groups can be introduced into pectin by a number of chemical or physical modifications in order to provide pectins with improved or specific properties. Modified pectins could markedly alter physicochemical properties, compared to their native pectins, depending on the degree of substitution and the type of functional groups introduced. It is clear that this is a challenging area that offers many opportunities to the formulation scientist. However, because this area offers unique opportunities to the formulation scientist, the emergence of new products that use this form of oral drug delivery technology might be expected in the future.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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