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Pectin-based oral drug delivery to the colon

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This review presents an overview of studies concerning oral formulations intended for site-specific drug delivery to the colon with pectin as the main excipient. The biological aspects covered include gastrointestinal transit and the enzymatic degradation of pectin. Scintigraphic methods demonstrating the functionality of pectin formulations are discussed. The main focus is on the various formulations reported, including matrix tablets, multiparticulate formulations as pellets and hydrogel beads, and pectin-based coatings. Also included is an evaluation of common excipients employed to improve colon specificity by crosslinking or increasing the hydrophobicity. Finally, properties of the pectin molecules that are important for successful formulations are examined. The conclusion is that the studies found in the literature provide an excellent platform for the development of pectin-based colon delivery systems.

Keywords: biodegradable polymer, colon-specific drug delivery, oral formulation, pectin

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1. Introduction

The traditional pharmaceutical formulation is designed to obtain the fast release of the active drug, thereby ensuring maximum time for absorption in the gastrointestinal (GI) tract. However, on some occasions this is not a preferable scheme, either due to an intension of local treatment in the GI tract (e.g., inflammatory diseases) or a need for the avoidance of certain parts of the GI system (e.g., due to unacceptable pH or enzymes). On these occasions site-specific drug delivery is preferable.

The anatomical site focused on in this review is the colon. After spending ~ 3 – 6 h in the passage through the stomach and small intestine [1], particulate content stops for a number of hours at the ileocecal valve. However, delays of ≤ 20 h have been reported [2]. After entering the colon, a highly variable passage must be expected, with transit times ranging from 13 h to several days [3]. The colon consists of four parts (ascending, transverse, descending and sigmoid), with a decreasing amount of water present in the content and a correspondingly increased viscosity and decrease in the possibilities for molecular diffusion.

The most pronounced differences between the small and large intestine are the reduced area available for absorption and the presence of a large amount of bacteria in the colon. The release of enzymes from these bacteria leads to a high capacity for cleavage of especially azo- and polysaccharide bindings in the colonic content [4]. The presence of pectinolytic enzymes in the colonic content is the basis for the proposal of using pectin as an excipient for site-specific delivery to the colon. The primary aim of present colon-specific drug delivery systems is the local treatment of inflammatory diseases, but suggested future applications also include systemic therapy. In spite of the reduced absorption surface, the combination of a long residence time and a low level of peptidases have lead to the conclusion that the colon should be regarded as a promising site for systemic peptide delivery [5].

It should be noted that a number of other differences between the small and large intestine have been suggested as methods for colon-specific drug delivery. Examples include transit time, pH and osmotic pressure. Various aspects of these issues, including *in vitro*/*in vivo* correlation, have been highlighted in several recent

reviews that focus on polysaccharides or colon delivery in general [6-10].

A delayed-release formulation is pharmaceutically easy to obtain and control. Unfortunately, the large variation in mouth-to-colon transit time makes it difficult to guarantee colonic delivery of the content. Variations in pH between the small and large intestine must be regarded as highly uncertain as the pH show large variations in both physiological conditions and as a consequence of diseases. For example, are inflammatory conditions known to reduce the pH of the colonic contents?

Pectin is a name used for a group of polysaccharides found in the cell walls of higher plants. It mainly consists of galacturonic acids (> 65%) linked together by α-1-4 glycosidic bonds. However, rhamnose units in addition to arabinose and xylose are usually found. The polygalacturonic parts of the molecule are essentially linear, but the rhamnose units, especially, introduce kinks. Such smooth regions alternate with so-called 'hairy regions' containing highly branched neutral sugars [11]. Commercially available pectin is primarily extracted from apple or citrus peel and contains a few hundred to ~ 1000 saccharide units, corresponding to an average molecular weight of ~ 50,000 – 150,000 Da [201].

In plant extracts, most of the acidic groups of the monosaccharide are methoxylated. Through purification and hydrolysis semisynthetic derivatives are obtained with degrees of methoxylation of ~ 25% – 75%. High methoxylated (HM) pectin has a degree of methoxylation > 50%, and low methoxylated (LM) < 50%. For special purposes pectic acid with degrees of methoxylation < 10% is available. It is worth noting that a consequence of the demethoxylation process is a reduction in the molecular weight of the polymer. Another modification commonly performed by the producers is the replacement of methoxy groups by amide (AM), typically up to a degree of amidation of 25%. Further information about commercially available qualities may be found on the internet [202].

In addition to being used as an excipient for colon delivery, pectin has been shown to increase the release rate compared with standard pellets employing microcrystalline cellulose in an extrusion spheronisation process [12], and to possess bioadhesive properties [13]. Pectin has even displayed therapeutic properties such as haemostasis or as a complexing agent for detoxification or weight reduction. [14]. Pectin's primary use is, however, as a stabiliser and thickening agent in the food industry.

2. Gastrointestinal studies

2.1 Gastrointestinal transit

The transit time through the GI tract has been shown to display large variations especially for single-unit formulations [1], mainly due to the large variations in gastric emptying. As can be seen in **Table 1**, the ranges of transit times for single-unit pectin-based formulations display the expected large variations. In contrast to the studies listed in **Table 1** a study by Munjeri *et al.* showed much smaller variations in transit times for the hydrogel beads tested [15]. It, therefore, seems reasonable to conclude that pectin does not significantly affect the rate of the transport through the GI tract. The important point is, however, that in spite of the large variations in the time elapsed before the formulations have passed the ileocecal valve, none of the studied formulations display significant signs of disintegration until the formulations have entered the colon. This fact supports the basic concept that pectin may be capable of protecting a drug throughout the small intestine and trigger release in the colon by enzymatic degradation.

2.2 Neutron activation

An objection towards scintigraphic studies has been that they are performed on carefully produced samples and are consequently not representative for formulations produced by ordinary production equipment. Neutron activation has been suggested as an approach for solving this problem. One of the studies listed employed this technique [16] (**Table 1**). The procedure involves adding minor amounts of a stable isotope of a suitable substance (e.g., samarium) to the formulation during production. The final product is subsequently subjected to neutron irradiation whereby γ-emitting isotopes are formed (e.g., $^{152}Sm \rightarrow {}^{153}Sm$), and the formulations may be followed *in vivo* by a γ-camera. However, this technique also has its limitations, as the irradiation may induce changes in the formulation. Waaler *et al.* [17] have demonstrated that Eudragit® (Röhm GmbH & Co. KG) coatings may be affected if sufficiently irradiated, and a study by Ahrabi *et al.* [18] showed that both pectin and hydroxypropylmethylcellulose (HPMC) are degraded by neutron irradiation. However, a study of entire tablets [19] revealed that the effect on the release rate was negligible and that a delayed-release coating consisting of Eudragit L100 may protect the formulation against the slight release-increasing effect of neutron irradiation.

Samarium oxide is the most common way of introducing ^{152}Sm into a formulation. These kinds of salts are, however, unusual in tablet formulations. Dobetti *et al.* [20], therefore, suggested samarium stearate as a possible replacement for magnesium stearate, combining the lubricating effect of stearate with the radiolabelling effect of samarium. However, Ahrabi *et al.* [19] concluded that in their formulation this replacement was not possible, as large amounts were necessary in order to obtain a sufficiently high activity after the irradiation. Such amounts were detrimental to the hardness of the directly compressed tablets.

2.3 Pectinolytic enzymes

The basis for pectin-based colon delivery formulations is the degradation of pectin by microbial enzymes present in the colonic content. Relevant enzyme-producing microorganisms and mechanisms are discussed in the review by Vandamme [7]. Papers [21-24] focus on the effect of enzymatic degradation on pectin-based formulations. Most of the publications referenced in this review have demonstrated the ability of pectinolytic

Table 1. GTT and SITT for single-unit pectin-based formulations.

Study	GTT (min)	SITT (min)	Number of persons
Ofori-Kwakye *et al.* [43]	38 – 83	162 – 243	5
Macleod *et al.* [45]	15 – 113	142 – 202	4
Adkin *et al.* [16]	11 – 192	151 – 297	11
Ashford *et al.* [54]	36 – 174	108 – 510	6

GTT: Gastric transit times; SITT: Small intestinal transit times.

enzymes to significantly increase the release rate from their formulations. However, some of the studies indicate a variable effect of the addition of enzymes [25,26], or even a retardation [21]. There are no unambiguous explanations for this lack of accelerated release, but there are indications of breakdown of the pectin polymer, especially when release is retarded. This leads to the conclusion that it is the degradation products that interfere with the release mechanism rather than a failure of the enzymatic degradation. As these three studies employ film coatings containing a mixture of pectin and cellulose or methacrylate derivatives, release through a film seems to be more sensitive to these products than other formulations. This is, however, not a complete explanation as other studies have shown enzymatically induced increased release from pectin-based film coatings. Consequently, other factors affecting the release mechanism, such as the pectin type (degree of methoxylation) and the presence of other film formers are also of importance. An interesting observation was made by Ashford *et al.* [27] who found that increasing amounts of Ca^{2+} in the tablets let to an increase in the pectinolytic effect of the enzymes. In addition, a correlation between high gel strength and high effect of the enzymes on the release rate was observed. The pH is also of importance, as noted by Fernandez-Hervas *et al.* [28], in their study where the accelerating effect of enzymes was only observed after exposure of the formulation to conditions similar to those in the upper GI tract.

3. Formulations

Pectin-containing matrix tablets and coatings have been the most popular formulations, but several other approaches, such as spray-drying, microencapsulation or formation of hydrogel beads have also been suggested.

3.1 Matrix tablets

The compactibility of pectin in itself is poor [29,30]. This is mainly due to a high degree of fragmentation, some elastic and very little plastic deformation. The addition of plastic excipients, as in the study by Mura *et al.* [31] in which Emdex® was employed, is, therefore, necessary.

Ashford *et al.* [27] presented a study on pectin-based matrix tablets without additional excipients, and consequently the tablets had to be individually prepared. The study determined fundamental properties governing release from the tablets and

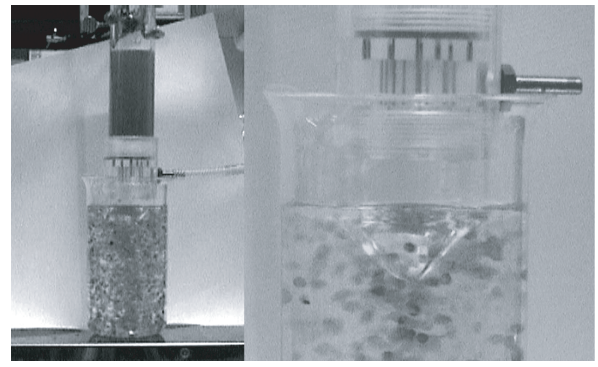

Figure 1. Example of apparatus for the production of hydrogel beads described in [68].

important parameters for reducing the release rate in an environment mimicking the gastric and small intestinal environment. Other approaches primarily involve the use of calcium pectinate [16,32] and the addition of cellulose derivatives such as HPMC and microcrystalline cellulose [19,29,30,33]. More elaborate techniques, such as the formation of zinc pectinate beads with subsequent compression [38] and epichlorohydrine crosslinked pectin [64] have also been suggested. All the three main types of pectin (HM, LM and AM) have been studied and recommended in one or more of these studies. The choice of optimal type of pectin is, therefore, clearly dependent on other formulation factors.

3.2 Multi-particulate dosage forms

Due to a more predictable gastric emptying, dosage forms made up of multiple particles are preferred. The disadvantage is an increased surface area accentuating the challenges imposed on the formulation by the hydrophilicity of pectin.

3.2.1 Beads

Pectin-based hydrogel beads are formed by the drop-wise addition of dissolved pectin solution into a Ca^{2+}-containing solution [34-37] (e.g., as shown in **Figure 1**). Calcium crosslinks the pectin chains and insoluble calcium pectinate hydrogel beads are formed. After a suitable residence time, the beads may be filtered from the solution and dried. Calcium is the most usual crosslinking agent but El-Gibaly [38] have used zinc acetate and found this crosslinking agent to

be superior to calcium. The hydrogel beads are usually intended for capsule filling, but El-Gibaly successfully produced a matrix tablet from the beads together with pectin and dextran as excipients.

Loading the beads with drug is usually performed by dissolving the drug in the pectin solution. This results in acceptable entrapment efficiencies for drugs that diffuse slowly through the calcium pectinate hydrogel (large molecules, low aqueous solubility). For small hydrophilic molecules, optimisation of the residence time in the calcium solution will be crucial, as fast diffusion will lead to an equilibrium that reduces the entrapment efficiency to the ratio between entrapped and total volume.

The main challenge is, however, the prevention of complete dissolution of the hydrogel beads *in vivo* until the formulation reaches the colon. Calcium pectinate alone is not capable of enduring the 4 – 6 h journey through the upper GI tract, and consequently other measures must be taken. Sriamornsak [34,37] employed glutaraldehyde for chemical crosslinking of the pectin chains. Munjeri *et al.* utilised dextran [35] or chitosan [36] in order to obtain the same objective. Chitosan was also employed by Chang *et al.* [39] in a study focusing on reduced swelling as a function of calcium and chitosan concentration.

There are also some patents describing this kind of formulation. The patent [101] describes a method of manufacturing corresponding to that previously described, whereas patent [102] employs a coating to protect the hydrogel beads. A different approach is described in patent [103], in which microsponge particles are loaded with drug and the openings are sealed with pectin, for example, and a subsequent coating of the particles.

3.2.2 *Spray-drying*

Another method for preparation of small particles has been reported by Lee *et al.* [40], on which a solution of pectin and drug is spray-dried and subsequently crosslinked with calcium. The procedure successfully produced particles in the size range of 3 – 5 µm, but an initial burst release from the particles in buffer (nearly 40% in 1 h) indicates the need for further studies.

3.2.3 *Microparticles*

There have only been a few reports on microencapsulation employing pectin. Chavanpatil reports encapsulation of a drug in a mixture of alginate, pectin and calcium, thereby forming microcapsules with a polyelectrolyte complex (PEC) membrane [41], and Cheng *et al.* report formation of nanoparticles based on amidated pectin [42]. Another interesting technique is disclosed in a patent describing the delivery of short-chain fatty acids to the colon by covalent linkage to pectin, for example [104]. In spite of promising results, these interesting techniques have not gained widespread interest.

3.3 Coating

The hydrophilicity of pectin often calls for additional protection and some kind of coating is, therefore, convenient. Mura *et al.* [31] coated matrix pectin tablets with Eudragit S100, thus making it possible to overcome the low gastric and intestinal pH values, with a corresponding delay in the onset of release from the tablets. However, pectin itself has also been employed as a coating material in order to obtain colon-specific delivery. Fell has, together with various colleagues, published several studies on this topic [26,43-49]. As pectin alone does not allow sufficient protection, additional film-formers are included. Again Eudragit has been employed [25,50,51] but chitosan and HPMC or ethyl cellulose have also been studied as additives or principal film former [26,43,45,48,49].

In order to study the fundamental mechanisms of the coating, free films made by spraying [52] or casting [44,46,53] have been studied in addition to pure gels of amidated pectin with various amounts of calcium [47]. Chitosan improved the properties of both the sprayed and casted films [44,52] by stabilising the films and reducing the permeability to model drugs. The effect was particularly apparent at intermediate pH (~ 3) where both polymers are charged and a PEC may be formed. Several commercially available ethyl cellulose coating-formulations with excellent protective properties exist. By combining ethyl cellulose with pectin, a formulation may be obtained with appropriate colon-specific delivery, as demonstrated by [46,53]. In addition to these additives a combination of pectin and gelatine has been suggested and also granted a patent as a protective coating for selective colon delivery [105].

3.3.1 *Compression coating*

As film-coating usually allows only a limited amount of coating material to be applied, compression coating has been suggested for improving the protective capacity of the coating. For the studies referred to in this review the coatings have weights ranging 5- to 10-times the weight of the core, and thicknesses off < 1 – > 3 mm. The substances studied include pure pectin coatings of high methoxylated pectin [51,54] and calcium pectinate [32] but also with the traditional additives HPMC [55], ethylcellulose [56] and chitosan [28]. The main findings in these studies are that pure pectin coatings may be acceptable if enough coating is applied, but additives are recommended.

3.4 Model substances

Some of the studies employ substances such as 5-aminosalisylic acid or ropivacain, which are presently in use for treatment of colic inflammatory diseases. However, most of the substances referred to in this review are pure model drugs chosen for their ease of analysis or other appropriate property (e.g., solubility). Colonic delivery of peptide drugs have gained widespread interest and the model substance usually chosen for this application is bovine serum albumin [34,37,39].

4. Crosslinkers and excipients

4.1 Calcium

Calcium in the form of $CaCl_2$ is the most common way of crosslinking pectin molecules. The mechanism of action is

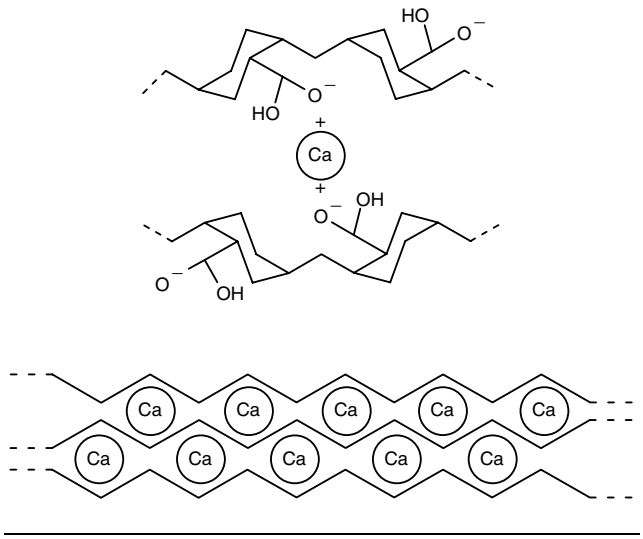

Figure 2. Egg-box model for calcium pectinate.

expected to follow the egg-box model [57,58], in which the divalent calcium ion enters a cavity between two dissociated acid groups, screening the otherwise repulsive force (**Figure 2**). Hereby a link is formed between two polymer chains, and gelation is induced. In order to obtain sufficiently large junction zones a low degree of methoxylation is necessary; a highly methoxylated pectin is incapable of being crosslinked by Ca^{2+}. Amidated pectins are generally considered to be especially sensitive to gelation by calcium; however, the egg-box model is not capable of a complete description of the interaction, and other types of chain association through hydrogen bonding have been suggested [59,60].

The amount of calcium is important for the formulation, and the effects on several properties have been investigated. Sriamornsak found that particle size and release rate from hydrogel beads decreased as concentration of the calcium solution was increased [37]. In another study in which the effect of increasing crosslinking time was studied, size reduction was observed without any impact on the swelling behaviour [34]. In this context a residence time of 10 min seemed sufficient for saturation of the gel beads with calcium. The effect of calcium in which pectin and calcium are mixed in the dry state. Wakerly *et al.* [47] and Ashford *et al.* [27] found optimum values for calcium with respect to gel strength at about the same level (12 – 14 mg Ca/g pectin). This is somewhat below the ~ 20 mg Ca/g pectin recommended by the manufacturers for optimum stability of gels for food applications [203,204]. In their study, Ashford *et al.* [27] thereby managed to demonstrate that an optimal amount of calcium led to high gel strength, low release rate and a high accelerating effect of pectinolytic enzymes.

According to the egg-box theory, any polyvalent cation capable of fitting into the pectin network should be able to stabilise crosslinks. El Gibali found that substitution of $CaCl_2$ with zinc-acetate resulted in lower swelling and release rates [38].

4.2 Chitosan

Combining pectin with a polycation and thereby forming a PEC is a very attractive method of stabilising the formulation. Chitosan is such a polycation and has been shown to form a PEC with pectin [61]. The prerequisite is that the pH of the medium is such that both polymers are sufficiently charged. Depending on the $-\log_{10}$ dissociation constant for an acid (pK_a) for the pectin and chitosan this will be the case, at least to some degree, for pH values of 3 – 6. The pK_a of the polymers will primarily be dependant on the degree of methoxylation and acetylation for pectin and chitosan, respectively. The exact configuration of the network is not known, but as pectin is usually employed in a higher amount than chitosan [61,62] the standard picture is a pectin network crosslinked with chitosan. On the other hand, it is worth noting that chitosan usually has a higher molecular weight than pectin [52]; therefore, it may also be vice versa (i.e., a chitosan network with pectin primarily in the junction zones [63]). Irrespective of the actual structure, the complex has been shown to clearly reduce the release rate compared with pectin alone [28]. This study, in addition to others, also demonstrates that it is not necessary for the PEC to be formed in advance as it may as well be formed during the dissolution process [28,52,61]. On entering the colon, the polysaccharides in the PEC will be available for degradation by hydrolytic enzymes with a subsequent breakdown of the network and increased release rate [36].

4.3 Covalent crosslinking

Ionic bonds such as those formed by Ca^{2+} and chitosan are dependant on the pH of the medium, and weaker than the covalent bonds formed by epichlorohydrin, for example [64,65]. In these studies, Semdé *et al.* observed an almost fourfold increase in the $t_{½}$ for the release from matrix tablets containing epichlorohydrin crosslinked with pectin. A further increase in crosslinking density decreased the $t_{½}$. This was explained by the increased erosion of the tablet. In spite of the chemical modification, clear signs of enzymatic degradation of the pectin were observed. The authors conclude that in spite of the reduced release rate, other measures would have to be taken in order to obtain a proper colon-specific delivery of substances with high water solubility. A very thorough removal of traces of the reactant is needed with this approach. Substances capable of covalent crosslinking are by their nature reactive, and any official authorities would require extensive documentation on the safety of the product.

4.4 Methacrylate

In order to slow down the hydration process of pectin, several studies have employed Eudragit coatings, either as a pure enteric coating or as a pH-independent protection. Semdé *et al.* [53] have studied the release of pectin from combination films. They found a fast leakage of pectin from both ethyl cellulose and acrylic polymers, but Eudragit RS was found to be the best choice. Eudragit RS was the polymer employed by Sriamornsak *et al.* [50] in a study in which perfect protection was obtained until pectinolytic enzymes were introduced to

the dissolution vessel. The subsequent release showed clear effects of enzymatic pectin degradation, but in all cases release was slow.

Methacrylates must, therefore, be considered as a substance well suited for delaying the onset of release, but finding a balance between enough methacrylates to provide protection without adding too much to adversely effect the colonic release is difficult.

4.5 Cellulose

Cellulose derivatives, usually in the form of HPMC or EC, have a widespread use in combination with pectin, both in coatings and within matrix tablets. The primary rationale for their application is the low water solubility of the cellulose derivatives with the associated retardation in pectin hydration. Semdé *et al.* [53] support the findings of Wakerly *et al.* [26] that state the dissolution mechanism was compatible with channel formation through the EC films by pectin dissolution. Depending on the ratio of cellulose to pectin it seems that a correct description of combination films would be as cellulose films with pectin as a modifier. The dominating effect of EC was also noted by Macleod *et al.* [46] when they concluded that in spite of increasing amounts of the hydrophilic pectin in the films, the permeability to moisture remained essentially the same.

For tabletting purposes, an additional function of including a cellulose derivative is to improve the compactibility of pectin [29,30].

4.6 Other polysaccharides

In addition to pectin, several other polysaccharides are broken down in the colon (e.g., dextran). Some studies have combined pectin and dextran without any pronounced benefits compared with the pure pectin formulations [35,38]. Another polysaccharide included in some studies is galactomannan. In the study by Adkin *et al.* [16] its primary function was as a binder slowing down the disintegration process, but it is also included in a patented film coating intended for colon delivery [106].

5. Important properties of pectin

5.1 Substituents

As previously stated, the acid groups of pectin extracted from natural sources are highly methoxylated. These hydrophobic substituents primarily affect the rate of polymer hydration and the gelling mechanism of the polymer, as hydrophobic interactions will dominate. The consequence is that the degree of swelling, and thereby the release rate, will be lower for high methoxylated pectin compared with low methoxylated pectin [31]. On the other hand, as crosslinking of the polymers with polyvalent cations (Ca^{2+}) is not possible with high methoxylated pectin, there is little room for improvement in the gel strength and thereby the release rate. Ashford *et al.* [27] found that high and low methoxylated pectin, with a carefully controlled amount of calcium, were equally effective in reducing the release from matrix tablets.

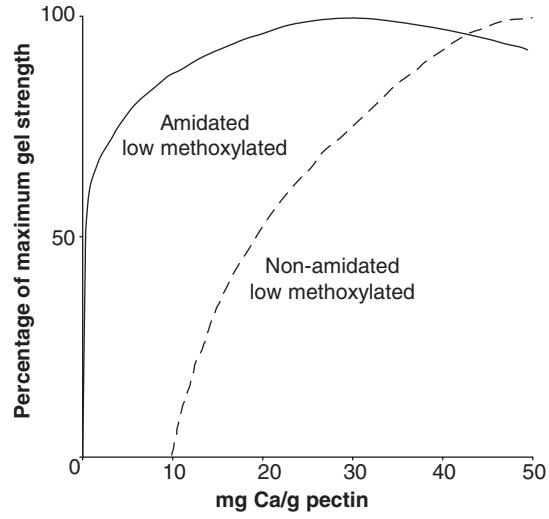

Figure 3. Effect of calcium on gel strength. Redrawn from [203] with permission from CP Kelco.

The tabletting properties of high and low methoxylated pectin seem fairly similar, although Kim *et al.* [30] found high methoxylation to result in more coherent, but still weak, compacts.

At the far end of demethoxylation is a group of substances denoted pectic acid (degree of methoxylation < 10%) or polygalacturonic acid. These highly acidic substances have been employed for coating in combination with Eudragit [50] but also for bioadhesive systems [13]. The linear polygalacturonides allow strong possibilities for entanglement within the mucosa as well as hydrogen bonding. A disadvantage is ionic repulsion between the negatively charged mucin and the dissociated acid groups of the polygalacturonides at neutral pH. It is also worth noting that these substances, due to the extensive hydrolysis necessary for their formation, will usually have lower molecular weights than the starting material.

The effect of amidation on the release from the formulations is difficult to assess as either the total degree of substitution will be increased or the degree of methoxylation will be decreased. Both Mura *et al.* [31] and Hiorth *et al.* [52] showed increased release or permeability, respectively, from formulations based on amidated pectin. It should, however, be noted that in both studies the amidated pectin had a higher total degree of substitution and a lower degree of methoxylation. Ahrabi *et al.* [29] found about the same release rate for amidated pectin and calcium pectinate, but a higher susceptibility for enzymatic degradation by the amidated pectin. It is also worth noting that for the commercially available qualities the increased sensitivity towards gelation by calcium for amidated pectin does not necessarily mean a stronger gel, but rather a steep increase in gel strength reaching a plateau at low calcium concentrations and, thereafter, insignificant influence of increased calcium concentration (**Figure 3**) [203,205].

Table 2. Differences between apple and citrus pectin.

Feature	Apple pectins	Citrus pectins
Chemical structure	Higher molecular weight	Lower molecular weight
	(90,000 – 130,000 Da)	(60,000 – 90,000 Da)
	Long side chains	Short side chains
	Terpene free	Contains terpene
	Contain flavonoids	Contains less flavonoids
	Contain hemicellulose, starch and xylans	Contains less hemicellulose
	Regular esterification	Block by block esterification
Appearance	Yellowish-brown colour	Brighter, whitish-beige colour
Reactivity	Less calcium-reactive	More calcium-reactive
Texture	Softer and more viscous gels	Firmer and more elastic gels
	Lower tendency towards syneresis	Higher tendency towards syneresis
Flavour	Supports the inherent taste of fruits	Neutral to bitter

Adapted from [206] with permission from Obipectin AG.

5.2 Molecular weight

Exact determination of the average molecular weight for a pectin sample is difficult as assumptions will have to be made with respect to interactions between the molecules. The most accurate values are obtained by gel filtration and light scattering [66].This combination will, in addition to an estimated value of the molecular weight based on the light scattering, also give the molecular weight distribution. The approach taken by authors of the papers studying colon delivery formulations referenced here is either a pure comparison of viscosity measurements [41] or the calculation of molecular weight from the Mark–Houwinks relationship ($[\eta] = K \cdot M_w^{\alpha}$) [42,52]. This model requires the determination of the intrinsic viscosity (η) and acquiring the constants K and α, usually from other papers. As these constants will depend on several conditions (e.g., degree of methoxylation) only approximate estimates of molecular weights are possible. Differences were observed, but no clear trend with respect to an effect of molecular weight was found in any of the studies. This calls for further studies as the influence on gelation from the molecular weight of polymers is firmly established.

5.3 Source

The effect of different pectin sources is usually not studied, and sometimes even not specified. Hiorth *et al.* [52] found nonamidated citrus pectin to be less permeable than apple pectin in buffer, whereas no significant differences were observed in acidic medium or for amidated pectin. The differences between various sources of pectin are mainly due to the variation in monosaccharide content or structure (distribution of substituents) [67,206]. In **Table 2** the characteristics of two commercially available pectin products from apple and citrus pectin are given. The effects of these differences are probably less than the effect of substitution and molecular weight, but, especially in optimisation studies, due consideration is warranted.

6. Expert opinion and conclusion

From the papers cited in this review it should be clear that several pectin-based drug delivery systems have great potentials for site-specific delivery to the colon due to the specific degradation of pectin in the colon. The basic mechanisms for retaining the drug in the delivery system are established, and the main challenge is evidently the combination of the hydrophilic nature of pectin and an extended transit time through the stomach and small intestine. It is, therefore, not surprising that the best results have been obtained for water-insoluble drugs. Techniques for reduced swelling and water uptake are necessary in order to obtain a successful pectin-based drug delivery system. The suggested solutions to this problem primarily involve increasing the amount of polymer employed and the addition of insoluble substances or crosslinking. However, synthesis of pectin derivatives with hydrophobic substituents in order to optimise chemical and physical properties has shown promising results, and further studies are definitely warranted. This approach is especially promising as the pectinolytic enzymes are apparently capable of handling relatively large variations in the pectin molecules, and even enzymatic degradation of chemically crosslinked pectin has been reported [65].

A major problem with the interpretation of the experimental results reported, as well as for possible future industrial production of pectin-based formulations, is the large diversity of pectin types and wide ranges in the quality specification for each type. As the food industry is the major market for the producers, the focus on quality is assuring reproducible gelling. This is also reflected in the equipment used for standardisation of pectin types [205]. Gelation is a complex process dependant on several factors and, although important, may camouflage differences in factors such as molecular weight or distribution of substituents that may be important for the formulation in question. Until

highly specified products are available, thorough purification and characterisation of the material is important.

The focus of this review has been the delivery of drugs to the colon. Except for substances intended for local therapy, this is, however, not the end of the line. The primary function of the colon is not absorption of substances; the area available for absorption is much smaller than in the small intestine (no villi); modern drugs tend to be quite large and modification of drug absorption by the formulation is only possible to a limited extent. The longer residence time and reduced level of peptidases may not be sufficient to overcome these disadvantages of colon delivery, and inclusion of absorption-enhancers may, therefore, be necessary. Studies on the combination of colon-delivery systems and enhancers are, therefore, likely to be an important topic for future research and, hopefully, therapy.

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