

New Pectin-based Approaches for Colon Cancer Treatment

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Pectin is a natural polymer composed by a mixture of polysaccharides (Figure 1). The origin and method of extraction can influence its structure, for example variation in the degree of esterification (DE) of the galacturonic acid residues (DE high or low). This polymer can be found in almost all plant tissues, but in major quantities in apple pomace and citrus peel. Pectin is well known for its application in food industry as gelling and thickening agent. Moreover, its use for pharmaceutical applications has already been reported, especially for oral administration, as its non-toxicity has been proven. Pectin, as a dietary fiber (DF), can be used for, but not limited to, reducing blood cholesterol levels, treating overeating disorders and for anti-tumor activity. It has been reported that a pectin rich diet reduced, in rats, the number and size of colon tumors by apoptosis activation. Besides that, this polymer can be used for targeted drug delivery in the colon since DF pectin is not digested in the small intestine but it can be degraded by colonic microbiota. Due to these characteristics, researchers have been proposed pectin for colon targeted drug delivery. In this briefly communication, the use of pectin in association with antitumor drugs for colon cancer treatment will be summarized. Scifinder database was used and the terms “pectin coating” and “colon cancer” were searched. Focus was given to research papers using antitumor drugs.

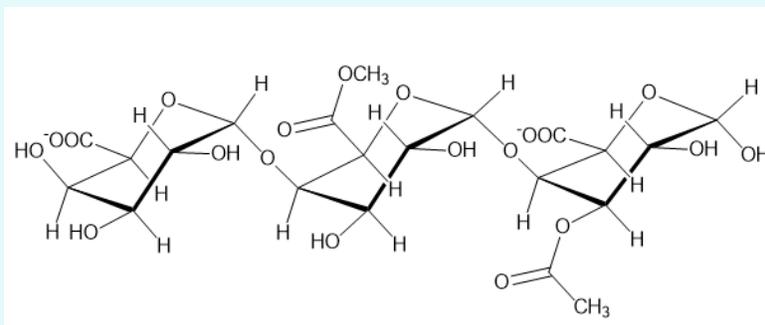


Figure 1: Chemical structure of pectin.

5-fluorouracil was the most recurrent drug in the majority of papers. It is a commonly used drug for colon cancer chemotherapy. Formulations capable of directing 5-fluorouracil action to the colon could reduce systemic toxicity and decrease the dose used. He and co-workers [1] evaluated pectin/ethylcellulose film-coated pallets with 5-fluorouracil. Coated and uncoated pallets were tested in Wistar rats and the drug content in the stomach, small intestine, cecum and colon was evaluated. They observed that coated pallets released

the drug mainly in the cecum and colon, while uncoated pellets release the drug mainly in the upper gastrointestinal tract. Moreover, lower quantities of drug were measured in the plasma of rats after oral administration of coated pellets (9.06 μg), in comparison with the rats treated with pellets without coating (49.08 μg). This is an important finding when it comes to reducing adverse effects caused by this antitumor drug. The same drug (5-fluorouracil) was used to produce pectin/ethylcellulose coated pellets by *in situ* intra-capsular coating methodology [2,3]. While Elyabogy and co-workers [2] focused on testing different coating techniques and determining the polymer proportion that most controlled drug release, Bose and co-workers [3] tested this optimized formulation and observed that 5-fluorouracil release was increased in simulated colon medium and delayed in simulated gastric and intestinal medium. They also observed that the number and size of tumors decreased in rats treated with the coated pellets, in comparison with unprocessed drug and uncoated pellets.

Another dosage form has also been proposed using pectin named calcium pectinate capsules [4]. Calcium pectinate was considered a rigid and water-insoluble gel that can be degraded by colon microflora. *In vitro* drug release experiment was carried out with 5-fluorouracil and it was observed that drug release was influenced by percentage of calcium in the capsules, thickness of the capsules and coat amount. Gamma scintigraphy study in healthy volunteers corroborated with *in vitro* experiment, as it demonstrated small quantity of tracer in the stomach and intestine and a large quantity of tracer distributed in the entire colon.

Tablet was a dosage form widely studied for 5-fluorouracil delivery [5-8]. Dev and co-workers [6] developed pectin-based 5-fluorouracil tablets -by wet granulation method-coated with Eudragit® S100 (6%). The authors evaluated different concentrations of pectin and starch paste to produce the tablets. The best formulation presented maximum hardness, minimum percent of 5-fluorouracil released in 5 hours of *in vitro* drug release study and minimum time to release 90% of the drug in pH 6.5 containing rat caecal contents. They evaluated this formulation in rabbits since their pH throughout the gastrointestinal tract is similar to humans. Roentgenographic study showed that the tablet remained intact in the stomach and small intestine and decreased in size in the colon (after 5 hours) indicating drug release. Moreover, they observed that pectin-based tablets took more time to reach maximum plasma concentration (169.56 ng/ml at 6 hours) in comparison to immediate release tablets (208.67 ng/ml at 0.5 hours) proving increased target action in the colon. Furthermore, tablets produced with guar gum, pectin or a mixture of the polymers were proposed [7]. The authors observed that all developed formulations could delay drug release in the upper gastrointestinal tract and increase drug release in the colon, however pectin tablet was chosen as best formulation since the percentage of drug release was higher when compared with the other tablets.

Pectin was extracted from mango peel and its purity and degree of esterification were determined [8]. This polymer was used to produce 5-fluorouracil tablets, which were coated with Eudragit L100. A 3² randomized full factorial design was performed and concentration of pectin (30, 60 or 90%) and concentration of Eudragit (3.5, 8 and 12.5%) were used as independent variables. They observed that both parameters affected drug release rate. The highest amount of Eudragit (12.5%) was needed to delay drug release in the stomach pH. This amount of Eudragit combined with 60% or 90% of pectin resulted in the formulations that presented higher percentages of released drug in the colon (70.31% and 72.01%, respectively).

Other antitumor drugs were also used to produce pectin-based formulations aiming targeted colon delivery, i.e., cisplatin [9], doxorubicin [11] and methotrexate [12]. Tsai and co-workers [9] developed hyaluronan-cisplatin nanoparticles, considering the overexpression of hyaluronan receptors in some malignant tumors. Cytotoxicity study in colorectal carcinoma cells showed that these nanoparticles could decrease more cell viability than cisplatin alone. Afterwards, the nanocapsules were used to produce pectin/alginate microbeads containing Eudragit® S100 coating by previously described methodology [10]. They evaluated this end formulation in Wistar rats and observed decrease in renal damage (side effect caused by cisplatin) in comparison to the antitumor drug alone, indicating colontargeted action. Cheewatanakornkool and co-workers [11] also developed microbeads coated with Eudragit® S100 but containing thiolated pectin-doxorubicin conjugates. They observed that their formulation decreased tumor volume and number and size of secondary metastases. Besides that, they examined other sections of the gastrointestinal tract and did not detect damage. Sogali and co-workers [12]

developed methotrexate tables coated by compression with a mixture of guar gum and pectin in different proportions. The formulation that presented better drug release was the one composed of 50% of gums in ratio 1:1.

Considering the information provided here, it is possible to conclude that pectin can be successfully applied in different pharmaceutical dosage forms aiming targeted colon delivery. Moreover, characteristics such as concentration of pectin and combination with other excipients should be carefully planned according to the desired release profile and the methodology used.

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