World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

Utilization of pectin as a polysaccharide microcarrier for drug delivery

Paolina Lukova *

Department of Pharmacognosy and Pharmaceutical Chemistry, Faculty of Pharmacy, Medical University of Plovdiv, Bulgaria.

World Journal of Biology Pharmacy and Health Sciences, 2023, 15(02), 253–262

Publication history: Received on 11 July 2023; revised on 21 August 2023; accepted on 24 August 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.15.2.0364

Abstract

Pectin is a polysaccharide of natural origin, which has been widely exploited in the food and pharmaceutical industry due to its biodegradable and biocompatible nature. It is commonly used as an efficient texturizer and stabilizer in different food products due to its high stability and also as a pharmaceutical excipient in various drug formulations due to its valuable characteristics. The utilization of pectin as a drug carrier for achieving controlled drug release in pharmaceutical dosage forms has been extensively researched recently. Pectin has the potential for targeted drug delivery due to its degradation by colonic microorganisms, making it a popular subject of investigation for biomedical applications. The developed in recent years pectin microparticle systems have several advantages over classical pectin gel formulations. These advantages include higher drug loading efficiency, reduced burst drug release, and the ability to better control the drug release and limit the polymer swelling. This review outlines the recent developments of pectin as a microcarrier in the production of drug delivery systems, which include the properties of the polysaccharide material essential for microparticle production, specific formulation methods with their key technological parameters, influencing the final microparticle product and potential applications of the proposed pectin microsized formulations.

Keywords: Pectin; Polysaccharides; Drug-delivery systems; Microparticles

1. Introduction

In recent years, microspheres have become a successful approach for delivering medicinal substances. Research on micro-sized drug carriers for targeted therapy is increasing, with numerous examples of successful microencapsulation of therapeutic agents, proteins, peptides and nucleic acids. The use of microparticles as drug-delivery systems offers several advantages over conventional dosage forms. They enable targeted delivery of drugs to specific tissues or sites in the body, such as the gastrointestinal tract or nasal cavity. Polymer microcarriers allow for prolonged or controlled drug release, resulting in longer therapeutic plasma concentration, reduced side effects, and improved patient compliance (Figure 1). Microparticles also provide alternative routes of drug administration, which can improve absorption and bioavailability, and protect therapeutic agents from environmental factors [1,2].

The production of microparticles involves a variety of carrier materials and techniques, including spray drying, freeze drying, coacervation, and emulsion (Figure 2). The carrier material should achieve specific characteristics of the final product, including increased stability of the active substance, control over release, and targeted administration. A drug carrier can be chosen from a range of natural, semisynthetic, and synthetic polymers, with natural polysaccharides being widely used due to their biocompatibility, biodegradability, low toxicity, good mucoadhesive and encapsulating properties, and affordability [3,4].

* Corresponding author: Paolina Lukova

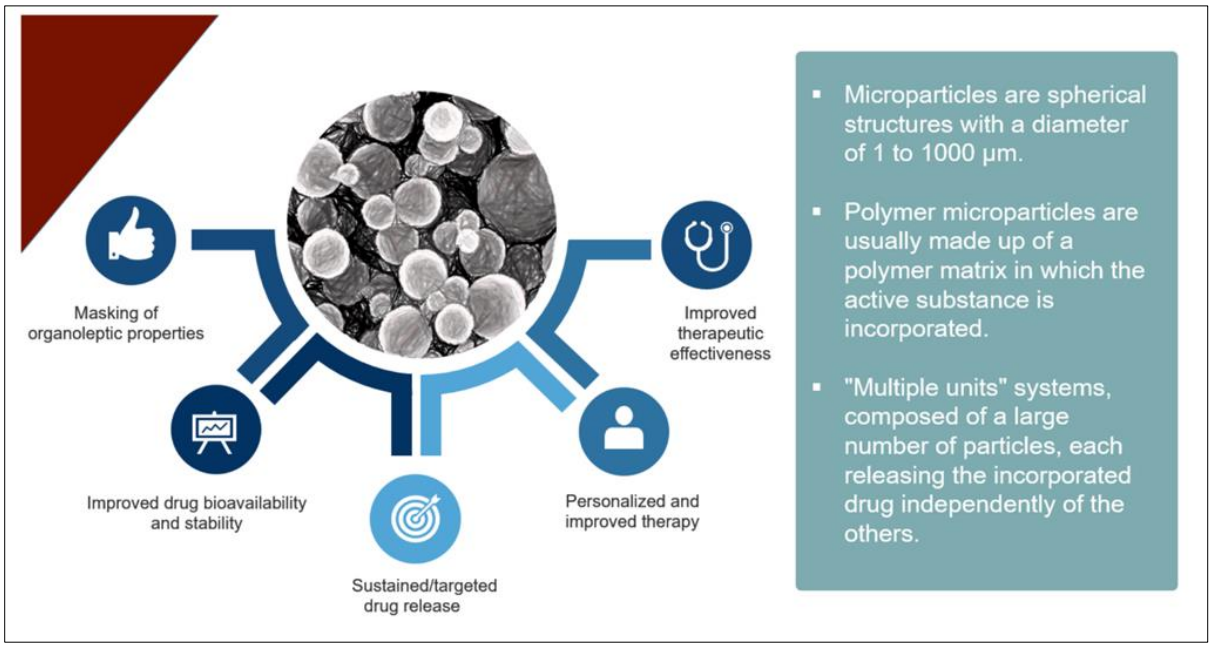

Figure 1 Polymer microparticle characteristics and advantages as drug delivery systems

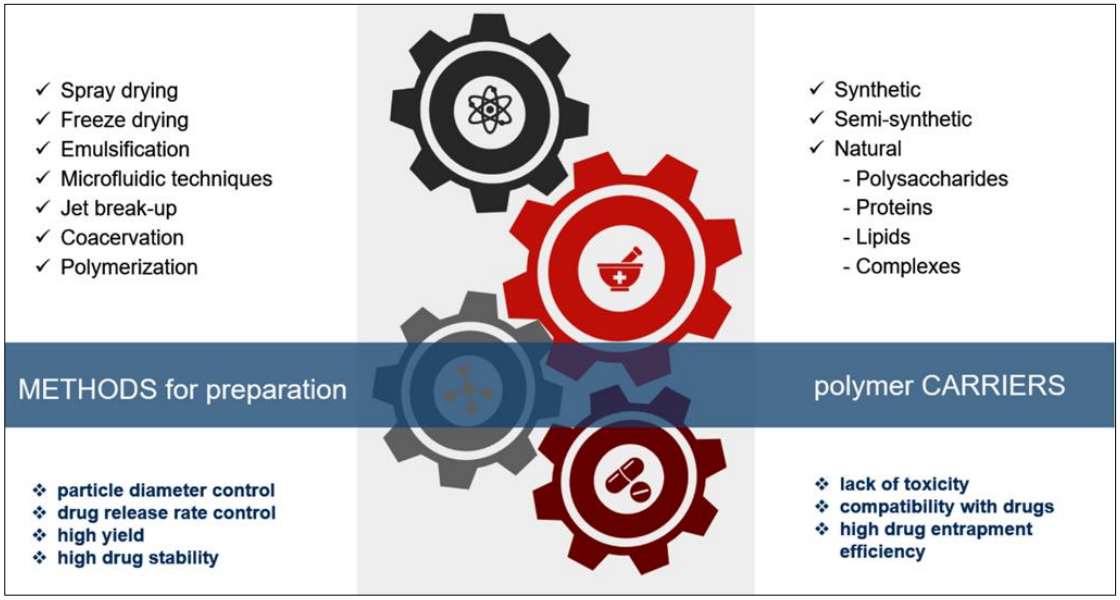

Figure 2 Methods and materials for the preparation of polymer microparticles as drug delivery systems

Pectins are biopolymers commonly employed in the food and pharmaceutical industries, possessing diverse applications. They function as thickening agents, gelling agents, and colloidal stabilizers. Furthermore, they serve as an excellent matrix for delivering drugs, proteins, and cells [5,6]. The following review is focused on pectin chemical structure and properties related to the development of drug-delivery systems, methods for the formulation of pectin microparticles, their characteristics and biomedical uses.

2. Chemical structure and properties of pectins

Pectin, a non-toxic natural polysaccharide, is mainly isolated from citrus fruits and apples. It is commonly used in the food industry as a viscosity-enhancing or gelling agent [7]. The chemical structure of pectin is composed of D-galacturonic acid residues linearly bound through α-1,4-bonds (Figure 3). These residues are partially esterified with

methanol or acetylated and may contain smaller amounts of rhamnose residues in the main chain as well as other neutral monosaccharides such as arabinose, galactose, xylose, etc. that are found in the side chains [8]. Pectic polymers vary in uronic acid and neutral sugar content, glycosidic bond type, degree of esterification, acetylation, amide content, and molecular mass. There are two main groups of pectin polysaccharides classified based on their chemical structure: acid pectin polysaccharides (homogalacturonan (HG), xylogalacturonan (XHG), apiogalacturonan (AHG), rhamnogalacturonan I (RG I), and rhamnogalacturonan II (RG II)) and neutral pectin polysaccharides (galactans, arabinans, and arabinogalactans (AG)) [9]. The ratio of esterified to free acid groups in pectin's structure determines its degree of esterification (DE), which affects properties like solubility and gel formation. Pectin can be classified as having a high (HM; DE>50%) or low (LM; DE<50%) methoxylation degree. Pectins with high methoxylation form gels at high concentrations, while low methoxylation pectins only form gels in the presence of divalent ions [10]. These polysaccharides remain stable in acidic environments, even at high temperatures. However, their molecules form aggregates in low pH media that dissociate in neutral conditions [11]. Pectin resists protease and amylase in the upper gastrointestinal tract (GIT) but is broken down by microorganisms in the colon [5].

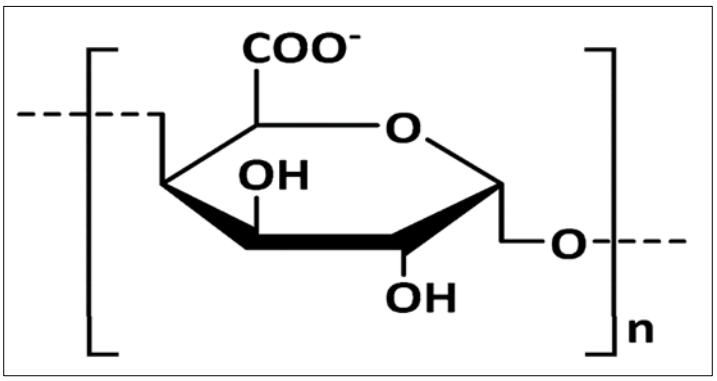

Figure 3 Pectin chemical structure

Pectin polysaccharides are incorporated in a complex way into plant cell walls. A pretreatment specific to the raw material facilitates separation from the cell and inactivates enzymes. Some common methods include mechanically degrading plant material with hot ethyl alcohol or acetone, washing with sodium deoxycholate, dimethyl sulfoxide, or a phenol/acetic acid/water mixture, and enzymatic hydrolysis. In industrial productions, pectin is typically extracted from agricultural by-products using a dilute mineral acid with a pH between 1.5 and 3.6, at a temperature of 60 to 100°C, for a duration of 1 to 6 hours. One drawback of the traditional method for pectin extraction is the environmental harm it can cause, such as acid effluent discharge. However, new and alternative methods, such as ultrasonic, microwave, and enzymatic extraction, have been developed in the "green industry". The application of enzymatic and ultrasonic extraction is an effective method for extracting pectin. These methods reduce the amount of solvents used and increase the polysaccharide yield while maintaining the selectivity of the hydrolysis process [12,13]. After being extracted, pectic polysaccharides undergo purification and fractionation using chromatographic techniques such as ion exchange, gel, or affinity chromatography. Ion exchange chromatography separates the polymer molecule based on the number of dissociated carboxylic groups. Pectic polysaccharides can be fractionated by ion exchange chromatography and depending on their esterification degree and the content of covalently bound neutral sugars. The pectin polysaccharides that are separated through ion exchange chromatography are subsequently purified using size-exclusion chromatography (SEC), which separates the polymer based on its molecular mass [12,13].

3. Preparation of pectin-based microparticles

Pectin has good mucoadhesive properties, attaching easily to mucin and mucosal surfaces in the body, making it a useful drug-carrier. Numerous studies have demonstrated the successful formation of drug-loaded microparticles using this polymer (Table 1, Figure 4) [5,6]. Hybrid microparticles are commonly used in polymeric drug delivery systems that involve pectin as a carrier. This is achieved by combining pectin with other polymers. Hydrophilic polymers like alginate or gellan gum are commonly used to create composite matrices that provide mucoadhesion, stability, and protection for active substances incorporated in them [14,15]. Only a small percentage of microspheres are made solely of pectin, and even fewer have a polysaccharide surface coating on the particles [16].

Table 1 Pectin microparticles as drug-delivery systems

Carrier	Drug	Reported results	Ref.
Pectin	Metformin	Diameter 34-71 μm; 15-33% DL; 26-67% EE; 98% released drug for 9 hours at pH 6.8.	[17]
Pectin	Ciprofloxacin	Diameter 4 μm; 20-48% DL; 98% EE; 100% released drug for 48 hours at pH 6.4.	[18]
Crosslinked pectin	β-lactamase	Diameter 1010 μm; 80% EE; 86% preserved biological activity 5 hours at medium with pH 6.0.	[19]
Crosslinked pectin	Ibuprofen	Diameter 280 μm; 4% DL; 77% EE; sustained drug release at pH 7.5 (62% for 45 days).	[20]
Crosslinked pectin	Methotrexate	Diameter 20-32 μm; 20% DL; 74% EE; 20% released drug for 24 hours at pH 7.0.	[21]
Crosslinked pectin	Resveratrol	Diameter 897-1108 μm; 93-98% EE; 90%; pH dependent drug release.	[22]
Pectin, Chitosan	Vancomycin	Diameter 3 μm; 16-32% drug loading; 70-80% released drug for 10 hours at pH 5.5.	[23]
Pectin, Chitosan	Metamizole	Diameter 3.05-3.69 μm; 0.14-0.15% drug loading; 85-88% entrapment efficiency.	[24]
Pectin, Alginate	Aceclofenac	Diameter 750 μm; 96% entrapment efficiency; sustained release at acidic pH; 90% released drug at pH 6.8.	[14]
Pectin, Alginate	Dexametha-sone	Diameter 2.76 μm; 3% DL; yield 45-70%; zeta potential -36 mV.	[25]
Pectin, Alginate	Metformin	Diameter 653-1108 μm; 59-95% EE; 90% released drug for 6-10 hours at pH 6.8.	[26]
Pectin, Alginate	Ciprofloxacin	47% EE; sustained drug release at pH 1.2; burst drug release at pH 7.4.	[27]
Pectin, Xyp-romellose	Melatonin	Diameter 17-22 μm; 25% DL; 96% EE; 80% released drug for 2 hours at pH 6.8.	[28]
Pectin, Gellan gum	Resveratrol	Diameter 914 μm; 76% EE; 90%; pH dependent drug release.	[15]
Pectin, Shellac	Vincristine	Diameter 30 μm; 73-82% EE; sustained release at alkaline pH, fast release at acidic pH.	[29]
Pectin, TiO_2, Fe_3O_4	Amoxicillin	Diameter 20-30 μm; 82% drug loading; 7% drug released after 5 hours at pH 2.0.	[30]
Pectin, Ag_3PO_4	Levofloxacin	Diameter 1.3-1.5 μm; yield 90%; pH dependent drug release.	[31]

DL – drug loading; EE – drug entrapment efficiency

The main purpose of pectin microparticles is to achieve controlled release of medicinal substances for diseases of the colon and digestive tract, targeting antitumor, anti-inflammatory, or antibacterial action. Such drug-delivery systems have been used for diabetes, bone diseases with regenerative function, and nasal drug delivery [6]. The emulsion technique is a reliable method for creating pectin microspheres. The polymer and the drug are dissolved in an organic solvent, emulsified in water, and microparticles are formed upon evaporation of the organic phase. Various emulsions can be made with pectin, such as ethanol in oil [32], water-in-oil (W/O) [33], or oil-in-water (O/W) [34,35]. The choice of a microsystem development technique depends on the drug substance properties and the intended application.

Usually, a water-in-oil emulsion is made by mixing a pectin solution with the drug and vegetable oil, such as corn or sunflower oil, and an emulsifier stabilizes the formed droplets. Stirring rate is essential for the size and shape of pectin microparticles [36]. The polymer concentration, emulsifier, stirring speed, duration and temperature affect polymer microparticle characteristics obtained through the emulsion technique. A higher polymer concentration increases the dispersed phase's viscosity, leading to larger droplets and microparticles [37]. Studies show that increasing stirring speed reduces microstructure size [38]. Pectin microparticle preparation by emulsion technique with solvent evaporation is a longer process. Duration depends on the solvent evaporation rate and the heating may affect drug substance stability.

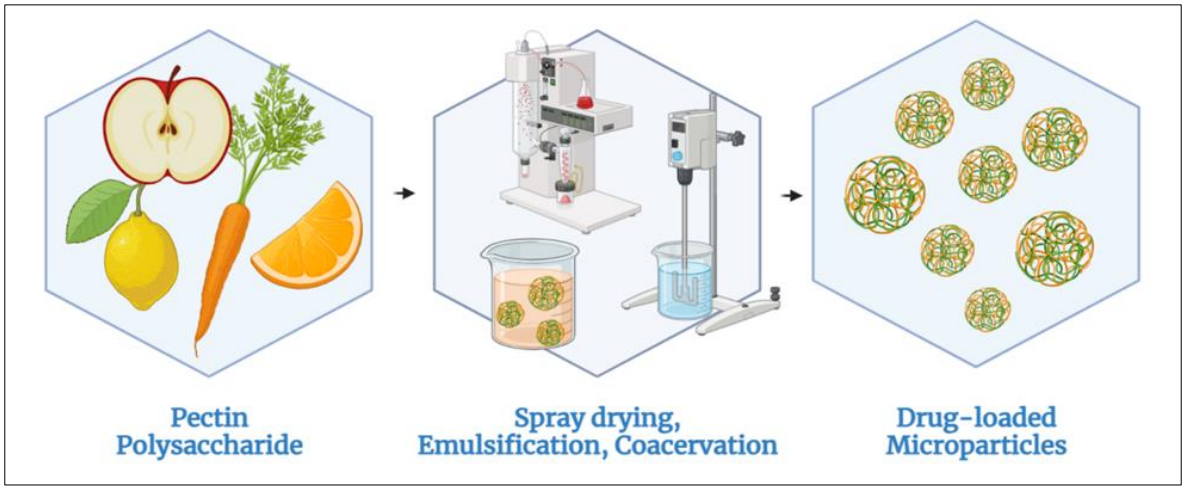

Figure 4 Pectin-based microparticles as drug delivery systems

Spray drying is an effective method for developing pectin microstructures with optimized particle characteristics like size, distribution, shape, and morphology. It is a single-stage process that directly transforms liquid material into dry particles. The small droplets produced increase the surface area/volume ratio of the liquid, leading to rapid solvent evaporation. The interaction time between the sprayed droplets and hot gas is brief, which does not affect the stability of the substances used [39,40]. The concentration of the starting material for spray drying, including the polymer and drug substance, significantly impacts the characteristics of the resulting microparticles. Therefore, it is crucial to pay close attention to this parameter, as well as the speed of the peristaltic pump, amount of compressed gas, temperature, and airflow rate [41,42]. Dosage forms with sustained drug release have been obtained using this technique, such as pectin microparticles for delivering albendazole, folic acid, and melatonin [28,43,44].

Complex coacervation is a technique where microspheres are formed by ionic interaction between oppositely charged polymer solutions, resulting in phase separation. A wide range of natural and semisynthetic polymers can be used in this technique. Studies indicate that higher polymer concentration leads to larger microparticles and higher drug entrapment efficiency, while low concentration results in microstructures with low density, wide size distribution, and rapid drug release. Achieving opposite charges between polymers is critical, and the ideal pH for effective phase separation varies based on the polymers used. Microparticle size and distribution depend on stirring speed and duration during coacervation, with excessive stirring leading to smaller microspheres and reduced drug incorporation efficiency [45-48]. By the complex coacervation method, controlled drug-release pectin microspheres can be designed e.g. microparticles with acetaminophen [49], various essential oils can be microencapsulated [50], and the resulting structures are usually resistant to mechanical stress and high temperature [51].

Although various other techniques have been described, the most common method for creating pectin microparticles involves ionotropic gelling of the polysaccharide [22,52,53]. Like alginate, pectin forms a gel structure in the presence of calcium, zinc, or copper ions due to strong ionic bonds between cations and galacturonic acid from the polymer structure [54,55]. The rapid swelling and dissolution of pectin in body fluids limit its use as a sustained-release vehicle for medicine. Esposito et al. suggest crosslinking the polymer to create a long-acting dosage form [56]. They evaluated the possibility of obtaining pectin microparticles loaded with the antibiotics metronidazole and tetracycline. Calcium chloride was used as an ionic crosslinking agent to limit the solubility of the polymer. Scientists have shown that by modifying pectin, microparticles of pectin with desirable morphological characteristics and sizes can be obtained to serve as promising modified-release drug carriers. Lasco et al. proposed using chlorhexidine as an alternative to divalent ions to gel pectin [57]. The chlorhexidine acts as a reagent to form microparticles and a crosslinking agent for

the polysaccharide, while also serving as an antiseptic. According to the report, the drug-polymer interaction was very strong, limiting the drug release. To improve the release, the authors added zinc ions to the optimal chlorohexidine microparticle model. The zinc ions compete with the drug substance for pectin binding, reducing the bonds between chlorhexidine and pectin. This produced a physically weaker gel structure that facilitates drug release.

An important feature of pectin is its ability to create electrostatic complexes with oppositely charged macromolecules, including polysaccharides, nucleic acids and proteins. Complexation by electrostatic bonds leads to the formation of stable colloidal structures that combine the advantages of the polymers used [58]. A number of studies have used polyelectrolyte complexes of pectin with chitosan, alginate, and other natural polysaccharides as carriers for drug-loaded microparticles. For instance, hybrid microspheres of pectin and chitosan have been developed for oral insulin delivery. The resulting systems showed good stability at the acidic pH of the stomach and a sustained release of the incorporated drug substance at pH 6.8 [58].

Polyelectrolyte complexes of pectin and chitosan of size 5-10 μm have been developed by the spray drying method at different ratios of the two polymers (1:9, 1:1, 9:1). They were designed carriers for nasal administration of tacrine - drug substance, used in the treatment of Alzheimer's disease. The results showed that the different amount of the two polysaccharides in the proposed models affected their wetting after administration, their mucoadhesive properties and drug absorption [59]. Hybrid microparticles of pectin and chitosan have been studied as carriers of resveratrol [22], vancomycin [23], nicin [60], metamizole [24], etc. Polyelectrolyte binding between pectin and alginate has also been well studied, in the formation of microsystems for the delivery of proanthocyanidins [61], polyphenols [62] and other biologically active substances. Other possible complexes include pectin-gelatin [63], pectin-casein [64], pectin-albumin [65], pectin-starch [66].

Pectin is widely used in the development of drug-delivery systems for targeted delivery in the colon. As already mentioned, pectin is less susceptible to degradation in the gastrointestinal tract compared to other natural polysaccharides. Its lysis occurs in the large intestine under the influence of enzymes secreted by the microorganisms there. This makes the polysaccharide a promising drug carrier for targeted delivery and modified drug release. Dashora et al., for example, have developed pectin microparticles loaded with prednisolone for topical treatment of ulcerative colitis [67]. An emulsion technique with solvent evaporation was applied, varying different technological parameters such as stirring time and rate, polymer and emulsifier concentration, in order to obtain microspheres with uniform size. In vitro solubility tests performed in gastric and intestinal juice mimicking media showed limited release of prednisolone (30-45%) over 4 hours. In the presence of rat ileocecal content, which is rich in enzymes from the large intestine, the polymer released up to 80% of the drug substance included in it. Unlike conventional oral formulations, in which prednisolone is quickly absorbed and does not reach the desired site in GIT, the proposed microsystems of pectin can effectively deliver the drug to the colon, providing local action and limiting its systemic side effects.

Das et al. have developed different variants of pectin microparticles as carriers of resveratrol. They found that the optimal model obtained by adding 1% chitosan, crosslinking the polymer with zinc acetate, and at pectin:drug ratio of 3:1, demonstrated a targeted release of the drug into the colon. The pharmacokinetic parameters of the proposed drug system have been determined in vivo on rats [22]. Other studies reported pectin microparticles for targeted drug delivery in the colon of 5-fluorouracil [68,69], metronidazole [70-72], vancomycin [23], indomethacin [73,74], ciprofloxacin [75], curcumin [76,77], methotrexate [21], sulfasalazine [78], etc.

4. Conclusion

Pectin is an extremely promising excipient for the pharmaceutical industry, owing to its exceptional ability to deliver a wide range of drugs for controlled release applications. The widely adopted techniques for manufacturing pectin-based microparticle systems can be used to fabricate dosage forms with various morphology and characteristics. Moreover, pectin can serve as a reliable carrier for directing drugs to specific sites in the organism, thereby providing a localized treatment or a systemic action. The recent rapid development of micro- and nanotechnologies has opened up new possibilities for pectin as a drug carrier and has outlined this polysaccharide as a preferred polymer for different biomedical applications.

References

[1] Midha K, Nagpal M, Arora S. Microspheres: a recent update. Int. J. Recent. Sci. Res. 2015. 50(8):5859-67.

[2] Yawalkar AN, Pawar MA, Vavia PR. Microspheres for targeted drug delivery-A review on recent applications. Journal of Drug Delivery Science and Technology. 2022.103659.

[3] Barclay TG, Day CM, Petrovsky N, Garg S. Review of polysaccharide particle-based functional drug delivery. Carbohydrate polymers. 2019. 221:94-112.

[4] Abedini F, Ebrahimi M, Roozbehani AH, Domb AJ, Hosseinkhani H. Overview on natural hydrophilic polysaccharide polymers in drug delivery. Polymers for Advanced Technologies. 2018. 29(10):2564-73.

[5] Mishra RK, Banthia AK, Majeed AB. Pectin based formulations for biomedical applications: a review. Asian J Pharm Clin Res. 2012. 5(4):1-7.

[6] Gutierrez-Alvarado K, Chacón-Cerdas R, Starbird-Perez R. Pectin microspheres: synthesis methods, properties, and their multidisciplinary applications. Chemistry. 2022. 4(1):121-36.

[7] Gawkowska D, Cybulska J, Zdunek A. Structure-related gelling of pectins and linking with other natural compounds: A review. Polymers. 2018. 10(7):762.

[8] Bonnin E, Garnier C, Ralet MC. Pectin-modifying enzymes and pectin-derived materials: applications and impacts. Applied microbiology and biotechnology. 2014. 98:519-32.

[9] Voragen AG, Coenen GJ, Verhoef RP, Schols HA. Pectin, a versatile polysaccharide present in plant cell walls. Structural Chemistry. 2009. 20:263-75.

[10] Chen J, Liu W, Liu CM, Li T, Liang RH, Luo SJ. Pectin modifications: a review. Critical reviews in food science and nutrition. 2015. 55(12):1684-98.

[11] Esposito E, Cortesi R, Luca G, Nastruzzi C. Pectin-Based Microspheres: A Preformulatory Study. Annals of the New York Academy of Sciences. 2001. 944(1):160-79.

[12] Yang Y, Wang Z, Hu D, Xiao K, Wu JY. Efficient extraction of pectin from sisal waste by combined enzymatic and ultrasonic process. Food Hydrocolloids. 2018. 79:189-96.

[13] Robledo VR, Vázquez LI. Pectin-Extraction, purification, characterization and applications. InPectins-extraction, purification, characterization and applications 2019 Dec 3 (pp. 1-19). London, UK.

[14] Chakraborty S, Khandai M, Sharma A, Khanam N, Patra C, Dinda S, Sen K. Preparation, in vitro and in vivo evaluation of algino-pectinate bioadhesive microspheres: An investigation of the effects of polymers using multiple comparison analysis. Acta pharmaceutica. 2010. 60(3):255.

[15] Prezotti FG, Boni FI, Ferreira NN, Silva DD, Campana-Filho SP, Almeida A, Vasconcelos T, Gremião MP, Cury BS, Sarmento B. Gellan gum/pectin beads are safe and efficient for the targeted colonic delivery of resveratrol. Polymers. 2018.10(1):50.

[16] Puga AM, Lima AC, Mano JF, Concheiro A, Alvarez-Lorenzo C. Pectin-coated chitosan microgels crosslinked on superhydrophobic surfaces for 5-fluorouracil encapsulation. Carbohydrate Polymers. 2013. 98(1):331-40.

[17] Banerjee P, Deb J, Roy A, Ghosh A, Chakraborty P. Fabrication and development of pectin microsphere of metformin hydrochloride. International Scholarly Research Notices. 2012.2012.

[18] Orhan Z, Cevher E, Mülazimoglu L, Gürcan D, Alper M, Araman A, Özsoy Y. The preparation of ciprofloxacin hydrochloride-loaded chitosan and pectin microspheres: their evaluation in an animal osteomyelitis model. The Journal of Bone & Joint Surgery British Volume. 2006. 88(2):270-5.

[19] Bourgeois S, Laham A, Besnard M, Andremont A, Fattal E. In vitro and in vivo evaluation of pectin beads for the colon delivery of β-lactamases. Journal of drug targeting. 2005. 13(5):277-84.

[20] Fullana SG, Ternet H, Freche M, Lacout JL, Rodriguez F. Controlled release properties and final macroporosity of a pectin microspheres–calcium phosphate composite bone cement. Acta biomaterialia. 2010. 6(6):2294-300.

[21] Chaurasia M, Chourasia MK, Jain NK, Jain A, Soni V, Gupta Y, Jain SK. Methotrexate bearing calcium pectinate microspheres: a platform to achieve colon-specific drug release. Current drug delivery. 2008. 5(3):215-9.

[22] Das S, Chaudhury A, Ng KY. Preparation and evaluation of zinc–pectin–chitosan composite particles for drug delivery to the colon: Role of chitosan in modifying in vitro and in vivo drug release. International Journal of Pharmaceutics. 2011. 406(1-2):11-20.

[23] Bigucci F, Luppi B, Monaco L, Cerchiara T, Zecchi V. Pectin-based microspheres for colon-specific delivery of vancomycin. Journal of Pharmacy and Pharmacology. 2009. 61(1):41-6.

[24] Lemos TS, de Souza JF, Fajardo AR. Magnetic microspheres based on pectin coated by chitosan towards smart drug release. Carbohydrate Polymers. 2021. 265:118013.

[25] Dukovski BJ, Mrak L, Winnicka K, Szekalska M, Juretić M, Filipović-Grčić J, Pepić I, Lovrić J, Hafner A. Spray-dried nanoparticle-loaded pectin microspheres for dexamethasone nasal delivery. Drying technology. 2019. 37(15): 1915–1925.

[26] Okunlola A, Akindele O. Application of response surface methodology and central composite design for the optimization of metformin microsphere formulation using tangerine (Citrus tangerina) pectin as copolymer. British Journal of Pharmaceutical Research. 2016. 11(3):1-4.

[27] Islan GA, de Verti IP, Marchetti SG, Castro GR. Studies of ciprofloxacin encapsulation on alginate/pectin matrixes and its relationship with biodisponibility. Applied biochemistry and biotechnology. 2012. 167:1408-20.

[28] Nižić L, Potaś J, Winnicka K, Szekalska M, Erak I, Gretić M, Jug M, Hafner A. Development, characterisation and nasal deposition of melatonin-loaded pectin/hypromellose microspheres. European Journal of Pharmaceutical Sciences. 2020. 141:105115.

[29] Ahirwar D, Ahirwar B, Chandy A. Microspheres for targeting an alkaloidal anticancer drug in colon cancer. Research Journal of Pharmacy and Technology. 2013. 6(6):618-21.

[30] da Silva EP, Sitta DL, Fragal VH, Cellet TS, Mauricio MR, Garcia FP, Nakamura CV, Guilherme MR, Rubira AF, Kunita MH. Covalent TiO2/pectin microspheres with Fe3O4 nanoparticles for magnetic field-modulated drug delivery. International journal of biological macromolecules. 2014. 67:43-52.

[31] Bayón B, Bucalá V, Castro GR. Development of antimicrobial hybrid mesoporous silver phosphate–pectin microspheres for control release of levofloxacin. Microporous and Mesoporous Materials. 2016. 226:71-8.

[32] García-González CA, Jin M, Gerth J, Alvarez-Lorenzo C, Smirnova I. Polysaccharide-based aerogel microspheres for oral drug delivery. Carbohydrate polymers. 2015. 117:797-806.

[33] Nernplod T, Sriamornsak P. Effect of solvent on properties of pectin microspheres prepared by emulsion-dehydration technique. Asian Journal of Pharmaceutical Sciences. 2016. 1(11):217-8.

[34] Almeida EA, Bellettini IC, Garcia FP, Farinácio MT, Nakamura CV, Rubira AF, Martins AF, Muniz EC. Curcumin-loaded dual pH-and thermo-responsive magnetic microcarriers based on pectin maleate for drug delivery. Carbohydrate polymers. 2017. 171:259-66.

[35] Johnson DL, Ziemba RM, Shebesta JH, Lipscomb JC, Wang Y, Wu Y, D O'Connell K, Kaltchev MG, van Groningen A, Chen J, Hua X. Design of pectin-based bioink containing bioactive agent-loaded microspheres for bioprinting. Biomedical Physics & Engineering Express. 2019. 5(6):067004.

[36] Paques JP, van der Linden E, van Rijn CJ, Sagis LM. Preparation methods of alginate nanoparticles. Advances in colloid and interface science. 2014. 209:163-71.

[37] Chan ES, Lim TK, Voo WP, Pogaku R, Tey BT, Zhang Z. Effect of formulation of alginate beads on their mechanical behavior and stiffness. Particuology. 2011. 9(3):228-34.

[38] Zhai P, Chen XB, Schreyer DJ. Preparation and characterization of alginate microspheres for sustained protein delivery within tissue scaffolds. Biofabrication. 2013. 5(1):015009.

[39] Wang Y, Selomulya C. Spray drying strategy for encapsulation of bioactive peptide powders for food applications. Advanced Powder Technology. 2020. 31(1):409-15.

[40] Sarabandi K, Gharehbeglou P, Jafari SM. Spray-drying encapsulation of protein hydrolysates and bioactive peptides: Opportunities and challenges. Drying Technology. 2020. 38(5-6):577-95.

[41] Ziaee A, Albadarin AB, Padrela L, Femmer T, O'Reilly E, Walker G. Spray drying of pharmaceuticals and biopharmaceuticals: Critical parameters and experimental process optimization approaches. European Journal of Pharmaceutical Sciences. 2019. 127:300-18.

[42] Poozesh S, Bilgili E. Scale-up of pharmaceutical spray drying using scale-up rules: A review. International Journal of Pharmaceutics. 2019. 562:271-92.

[43] García A, Leonardi D, Piccirilli GN, Mamprin ME, Olivieri AC, Lamas MC. Spray drying formulation of albendazole microspheres by experimental design. In vitro–in vivo studies. Drug Development and Industrial Pharmacy. 2015. 41(2):244-52.

[44] Assadpour E, Jafari SM. Spray drying of folic acid within nano-emulsions: Optimization by Taguchi approach. Drying Technology. 2017. 35(9):1152-60.

[45] Frent OD, Vicas LG, Duteanu N, Morgovan CM, Jurca T, Pallag A, Muresan ME, Filip SM, Lucaciu RL, Marian E. Sodium alginate—Natural microencapsulation material of polymeric microparticles. International Journal of Molecular Sciences. 2022. 23(20):12108.

[46] Uyen NT, Hamid ZA, Tram NX, Ahmad N. Fabrication of alginate microspheres for drug delivery: A review. International journal of biological macromolecules. 2020.153:1035-46.

[47] Yang YY, Chung TS, Bai XL, Chan WK. Effect of preparation conditions on morphology and release profiles of biodegradable polymeric microspheres containing protein fabricated by double-emulsion method. Chemical Engineering Science. 2000. 55(12):2223-36.

[48] Timilsena YP, Akanbi TO, Khalid N, Adhikari B, Barrow CJ. Complex coacervation: Principles, mechanisms and applications in microencapsulation. International journal of biological macromolecules. 2019. 121:1276-86.

[49] Villicaña-Molina E, Pacheco-Contreras E, Aguilar-Reyes EA, León-Patiño CA. Pectin and chitosan microsphere preparation via a water/oil emulsion and solvent evaporation method for drug delivery. International Journal of Polymeric Materials and Polymeric Biomaterials. 2020. 69(7):467-75.

[50] Noello C, Carvalho AG, Silva VM, Hubinger MD. Spray dried microparticles of chia oil using emulsion stabilized by whey protein concentrate and pectin by electrostatic deposition. Food Research International. 2016. 89:549-57.

[51] Aloys H, Korma SA, Alice TM, Chantal N, Ali AH, Abed SM, Ildephonse H. Microencapsulation by complex coacervation: Methods, techniques, benefits, and applications-A review. American Journal of Food Science and Nutrition Research. 2016. 3(6):188-92.

[52] Pliszczak D, Bourgeois S, Bordes C, Valour JP, Mazoyer MA, Orecchioni AM, Nakache E, Lantéri P. Improvement of an encapsulation process for the preparation of pro-and prebiotics-loaded bioadhesive microparticles by using experimental design. European journal of pharmaceutical sciences. 2011. 44(1-2):83-92.

[53] Jung J, Arnold RD, Wicker L. Pectin and charge modified pectin hydrogel beads as a colon-targeted drug delivery carrier. Colloids and Surfaces B: Biointerfaces. 2013.104:116-21.

[54] Grant GT, Morris ER, Rees DA, Smith PJ, Thom D. Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS letters. 1973. 32(1):195-8.

[55] Cao L, Lu W, Mata A, Nishinari K, Fang Y. Egg-box model-based gelation of alginate and pectin: A review. Carbohydrate polymers. 2020. 242:116389.

[56] Esposito E, Cortesi R, Luca G, Nastruzzi C. Pectin-Based Microspheres: A Preformulatory Study. Annals of the New York Academy of Sciences. 2001. 944(1):160-79.

[57] Lascol M, Bourgeois S, Barratier C, Marote P, Lantéri P, Bordes C. Development of pectin microparticles by using ionotropic gelation with chlorhexidine as cross-linking agent. International Journal of Pharmaceutics. 2018. 542(1-2):205-12.

[58] Maciel VB, Yoshida CM, Pereira SM, Goycoolea FM, Franco TT. Electrostatic self-assembled chitosan-pectin nano- and microparticles for insulin delivery. Molecules. 2017. 22(10):1707.

[59] Saladini B, Bigucci F, Cerchiara T, Gallucci MC, Luppi B. Microparticles based on chitosan/pectin polyelectrolyte complexes for nasal delivery of tacrine hydrochloride. Drug delivery and translational research. 2013. 3:33-41.

[60] Qian J, Chen Y, Wang Q, Zhao X, Yang H, Gong F, Guo H. Preparation and antimicrobial activity of pectin-chitosan embedding nisin microcapsules. European Polymer Journal. 2021. 157:110676.

[61] Chen K, Zhang H. Alginate/pectin aerogel microspheres for controlled release of proanthocyanidins. International Journal of Biological Macromolecules. 2019. 136:936-43.

[62] Belščak-Cvitanović A, Bušić A, Barišić L, Vrsaljko D, Karlović S, Špoljarić I, Vojvodić A, Mršić G, Komes D. Emulsion templated microencapsulation of dandelion (Taraxacum officinale L.) polyphenols and β-carotene by ionotropic gelation of alginate and pectin. Food Hydrocolloids. 2016. 57:139-52.

[63] Silva DF, Favaro-Trindade CS, Rocha GA, Thomazini M. Microencapsulation of lycopene by gelatin–pectin complex coacervation. Journal of Food Processing and Preservation. 2012. 36(2):185-90.

[64] Baracat MM, Nakagawa AM, Casagrande R, Georgetti SR, Verri WA, de Freitas O. Preparation and characterization of microcapsules based on biodegradable polymers: Pectin/casein complex for controlled drug release systems. AAPS pharmscitech. 2012. 13:364-72.

[65] Li X, Fang Y, Al-Assaf S, Phillips GO, Yao X, Zhang Y, Zhao M, Zhang K, Jiang F. Complexation of bovine serum albumin and sugar beet pectin: Structural transitions and phase diagram. Langmuir. 2012. 28(27):10164-76.

[66] Carbinatto FM, de Castro AD, Evangelista RC, Cury BS. Insights into the swelling process and drug release mechanisms from cross-linked pectin/high amylose starch matrices. asian journal of pharmaceutical sciences. 2014. 9(1):27-34.

[67] Dashora A, Jain CP. Development and characterization of pectin-prednisolone microspheres for colon targeted delivery. International Journal of ChemTech Research. 2009. 1(3):751-7.

[68] Paharia A, Yadav AK, Rai G, Jain SK, Pancholi SS, Agrawal GP. Eudragit-coated pectin microspheres of 5-fluorouracil for colon targeting. Aaps Pharmscitech. 2007. 8:E87-93.

[69] Ramana G. Preparation and In-vitro characterization of ethylcellulose coated pectin alginate microspheres of 5-fluorouracil for colon targeting. Journal of Applied Pharmaceutical Science. 2011. 170-6.

[70] Jain A, Khare P, Agrawal RK, Jain SK. Metronidazole loaded pectin microspheres for colon targeting. Journal of pharmaceutical sciences. 2009. 98(11):4229-36.

[71] Vaidya A, Jain S, Agrawal RK, Jain SK. Pectin–metronidazole prodrug bearing microspheres for colon targeting. Journal of Saudi Chemical Society. 2015. 19(3):257-64.

[72] Amidon S, Brown JE, Dave VS. Colon-targeted oral drug delivery systems: design trends and approaches. Aaps Pharmscitech. 2015.16:731-41.

[73] Lee CM, Kim DW, Lee HC, Lee KY. Pectin microspheres for oral colon delivery: preparation using spray drying method and in vitro release of indomethacin. Biotechnology and Bioprocess engineering. 2004. 9:191-5.

[74] Chandy A, Rai S, Manigauha A, Sahu S. Entric-Coated Pectin Microspheres of Indomethacin for Targeting Inflammation in Lower Gastro intestinal tract. Research Journal of Pharmaceutical Dosage Forms and Technology. 2009. 1(1):29-32.

[75] Reynaud F, Tsapis N, Guterres SS, Pohlmann AR, Fattal E. Pectin beads loaded with chitosan–iron microspheres for specific colonic adsorption of ciprofloxacin. Journal of Drug Delivery Science and Technology. 2015. 30:494-500.

[76] Zhang L, Cao F, Ding B, Li Q, Xi Y, Zhai G. Eudragit® S100 coated calcium pectinate microspheres of curcumin for colon targeting. Journal of microencapsulation. 2011. 28(7):659-67.

[77] Cai R, Pan S, Li R, Xu X, Pan S, Liu F. Curcumin loading and colon release of pectin gel beads: Effect of different de-esterification method. Food Chemistry. 2022. 389:133130.

[78] Costas L, Pera LM, López AG, Mechetti M, Castro GR. Controlled release of sulfasalazine release from “smart” pectin gel microspheres under physiological simulated fluids. Applied biochemistry and biotechnology. 2012. 167:1396-407.