Polysaccharide-Based Nanoparticles

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Polysaccharide biomaterials have gained significant importance in the manufacture of nanoparticles used in colon-targeted drug delivery systems. These systems are a form of non-invasive oral therapy used in the treatment of various diseases. To achieve successful colonic delivery, the chemical, enzymatic and mucoadhesive barriers within the gastrointestinal (GI) tract must be analyzed.

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1. Introduction

Polysaccharides are biopolymers constituted by simple sugar monomers. They are usually isolated from plant material, marine plants, and exogenous metabolites of some bacteria. The polysaccharides chain comprises monosaccharide units linked by glycosidic bonds with hydroxyl, carboxyl, and amino groups. Carbohydrates are stable, non-toxic, hydrophilic, and biodegradable biomolecules in the human body [1][2]. Polysaccharides can be used as matrices for encapsulation, immobilization, and controlled release for many active compounds. This matrix are also used in the food, pharmaceutical, biomedical, and chemical industries. Polysaccharides are the most abundant biomolecules, followed by proteins, lipids, and nucleic acids. Polysaccharides studied as a matrix for encapsulation include chitosan, pectin, alginate, starch, and dextran [3][4].

Encapsulation occurs when liquid and solid particles are trapped in a matrix or coated by a polymer material. The preparation of a proper encapsulating agent is an essential factor in enhancing encapsulation efficiency. Encapsulating agents must have the ability to preserve bioactive compounds under different processes and storage conditions [5]. A controlled release system will increase drug retention time and enhance paracellular and transcellular absorption. The release mechanisms occur by diffusion, biodegradation, and osmosis [6][7]. The application of nanotechnology to encapsulate nutrients and drugs has aroused significant interest and demand due to its great benefits. In addition, nanotechnology has been associated with safety, environmental, ethical, and regulatory problems related to human health and environmental impacts. Information related to the security of nanoparticles is limited. In general, nanoparticles have unique characteristics, such as their small size. This property allows them to cross different biological barriers (e.g., intestinal and mucosal epithelial cells) [8][9].

Natural biopolymers are considered biodegradable and safe for human consumption because they are not toxic and do not affect cell viability, making them ideal for drug delivery systems [10][11]. Other kinds of metallic, solid, and polymeric nanoparticles can be toxic for humans. Researchers have used strategies of coating toxic nanoparticles with biopolymers to reduce their toxicity [12][13]. At the moment, no legislation regulates the use of nanoparticles in

the food and pharmaceutical industries. Therefore, most countries have regulations for risk assessment when using nanotechnology. Relevant regulatory agencies include the U.S. Food and Drug Administration (FDA), the European Union, the Australian Government Department of Health, and Health Canada [14].

It is necessary to develop and appropriately evaluate nanomaterials to determine their risk to human health. When manufacturing these nanoparticles, the elements that must be considered are particle and distribution size, shape, state of aggregation/disaggregation, solubility, surface charge, and surface morphology [15][16]. The size and morphology of nanoparticles enhance their functionality, and are dependent on the manufacturing technique for each nanomaterial. These properties allow a high loading capacity, high encapsulation efficiency, stability, sustained release profile, bioavailability of bioactive compounds, and biocompatibility [17][18].

The nanoparticle technology based on polysaccharides plays a vital role in controlling drugs, bioactive agents, and genes for oral administrations. These release systems can occur by diffusion (barrier/matrix), degradation (chemical or physical matrix), or changes in the environment (e.g., pH, ionic strength, and pressure) [19]. Most drugs or bioactive agents administered orally are absorbed in the upper GI tract, but their delivery in the colon is necessary for additional results in specific therapies. Some areas of interest are colonic delivery of peptides and proteins, probiotic bacteria, and microbiota replacement therapies [20][21]. The main release mechanisms in the colon are degradation by colonic microbiota, time and pH-controlled release. Colon release formulations are generally designed to prevent degradation in the stomach and upper GI tract. The colon's main function is the absorption of water, ions, and the storage of feces. The large intestine is colonized by many bacteria—approximately 10^{12} per gram of intestinal content. The microorganisms in the colon are beneficial for human health because they are responsible for fermenting indigestible dietary fiber [22].

2. Polysaccharides

Various polymers with complex structures and specific functions have developed naturally. These include amino acids, nucleobases, and mono- and disaccharides. According to the nature of their heteroatom present in the main chain natural polymers can be classified into four types, as shown in **Table 1** [23][24]. Polysaccharides are biopolymers isolated from plant, animal, microbial, and algae sources. These are made up of more than ten monosaccharide units linked by O-glycosidic bonds. Due to their great abundance in hydroxyl groups polysaccharides can be modified by carboxylation, esterification, and amination, thereby improving their functional properties [25]. According to their nature, polysaccharides have excellent biocompatibility, biodegradability, non-toxicity, and cell specificity. Therefore, they are considered ideal for various biomedical applications, such as drug, gene delivery, and wound dressing [26][27].

Table 1. Natural polymers and their types.

Natural Polymers	Types	Examples
Hydrocarbon polymers	Natural rubber	

Natural Polymers	Types	Examples
Carbon-oxygen	Carbohydrates	Cellulose; starch; chitin; chitosan; pullulan
Carbon-oxygen-nitrogen/Sulphur	Proteins	Soya protein; gelatin; casein
Carbon-oxygen-nitrogen-phosphorus	Nucleic acids	DNA, RNA

2.1. Chitosan

Chitosan is a unique linear poly-cationic polysaccharide derived from chitin by deacetylation. It is found primarily in the exoskeleton of crustaceans, such as shrimp and crabs. Its chemical structure consists of a chain of β-(1-4)-linked glucosamine and *N*-acetyl d-glucosamine units. It has functional groups such as polyhydroxy and amino, and these groups can lead to hydrogen bonds. Chitosan is the second most abundant polysaccharide after cellulose. It is used for pharmaceutical applications due to its reactive functional groups, biocompatibility, biodegradability, gel-forming ability, non-toxicity, high charge density, and low pH solubility. This polysaccharide can interact electrostatically with mucus or negatively charged mucosal surfaces, giving it an excellent mucoadhesive property for developing systems for oral administration. The presence of its positively charged amino group ($–NH^{3+}$) can interact with negatively charged proteoglycans on the cell surface, enabling better intestinal absorption of the drug by opening the tight junctions between the epithelial cells [28].

2.2. Hyaluronic Acid

Hyaluronic acid is a non-sulfated, negatively charged glycosaminoglycan composed of D-glucuronic acid and *N*-acetyl-d-glucosamine linked by β-(1-3) and β-(1-4) bonds. It is a macromolecule produced and secreted by cells as a linear polymer that is not bound to a polypeptide. It is a biocompatible biopolymer of natural origin present in the skin, connective tissues, synovial fluid of the joints, neural tissues, vitreous humor, and has the ability to regulate lubrication. This polysaccharide can be chemically modified due to its groups, such as the carboxylic acid of glucuronic acid, primary and secondary hydroxyl groups, and *N*-acetyl groups, which can alter its properties such as hydrophobicity, biological activity, viscoelasticity, water retention, biocompatibility, cell proliferation, wound regeneration, and specific signal transduction and cell interactions through cell surface receptors [29].

2.3. Pectin

Pectin is a linear heteropolysaccharide that constitutes the cell wall of plants and consists of a linear unbranched chain of α-(1-4) linked d-galacturonic acid units (homogalacturonan) with uronic acids. This polysaccharide contains hydroxyl and carboxyl groups, residues esterified with methyl ether distributed in its linear chain, and a certain quantity of neutral sugars present in the side chains. It is principally composed of galacturonic acid, methyl ester, and sugar units such as arabinose, galactose, and rhamnose. Pectin can form hydrogels in the presence of its ionized carboxyl groups ($–COO^-$) that interact with its positively charged anions. For this reason, it is an anionic, biodegradable, biocompatible, and non-toxic polysaccharide used for its mucoadhesive properties in the oral

delivery of drugs to the colon. Pectin can remain intact in the upper gastrointestinal tract and be degraded in the colon by pectinases [30].

2.4. Guar Gum

Guar gum is a non-ionic polysaccharide. It is extracted from the seeds of *Cyamopsis tetragonolobus* and consists of a linear chain of (1-4)-β-d-mannopyranosil units with α-d-galactopyranosyl units attached by (1–6) ramifications. This polysaccharide presents an extraordinarily viscous property due to its intermolecular chain entanglement of galactose side chains. It is a biocompatible and biodegradable polysaccharide with the ability to form gels in aqueous solutions, and is used to formulate hydrophilic matrices for drug delivery due to its enzymatic degradation in the colon [31].

2.5. Dextran

Dextran is a complex branched glucan consisting of α-d-(1-6) glycosidic links and branched at α-(1-3). It is obtained naturally from the lactic acid bacterium. It is a hydrophilic, biodegradable, and biocompatible polysaccharide with abundant hydroxyl groups. This polysaccharide is biocompatible, highly hydrophilic, and shows low protein adsorption. Like other polysaccharides, dextran has many hydroxyl groups, allowing it to be easily conjugated with drugs and proteins to prevent drug absorption in the small intestine [32].

2.6. Alginate

Alginate is an anionic polysaccharide consisting of β-(1-4)-d-mannuronic acid and α-(1-4) l-guluronic acid residues. The α-(1-4) l-guluronic bonds can be cross-linked with divalent ions by sodium ion exchange, forming a gel matrix and the retention of encapsulated charges. Due to their anionic nature, they can interact with cationic compounds. It is extracted mainly from brown marine algae (*Laminaria hyperborean*) and soil bacteria (*Azobacter vinelandii*). This polysaccharide has physicochemical properties such as biodegradability, biocompatibility, low immunogenicity, good mucoadhesion, and non-toxicity. Due to its composition, sequence of arrangement, and molecular weight, the alginate also has functional groups such as polyhydroxy and carboxyl distributed throughout its chain. It is highly reactive and with the possibility of chemical modification (oxidation, amidation, esterification, and sulphation) [33].

2.7. Arabinoxylans

Arabinoxylans (AX) are non-starch polysaccharides found mainly in the cell wall, outer layer, and endosperm of cereals. The AX are composed of a linear chain of β-(1-4) xylose units branched to arabinose units in positions C(O)-3 and C(O)-2. Arabinose can be esterified with monomeric or dimeric ferulic acid (AF). AX are desirable polysaccharides for application in the food, pharmaceutical, and biomedical industries. Similarly, they have become an attractive alternative due to their biodegradability, biocompatibility, non-toxicity, hydrophilic, and gelling properties. Due to their functional properties, AX can act as prebiotics, antioxidants, emulsifiers, and immunomodulators. The gels made from this polysaccharide have been studied for their potential as a drug delivery system directed to the colon because they are biocompatible and have the ability to retain water. These

covalent gels can cross the conditions of the upper gastrointestinal tract and be fermented in the colon by the colonic microbiota to release the drug [34][35].

References

1. Liu, J.; Willför, S.; Xu, C. A review of bioactive plant polysaccharides: Biological activities, functionalization, and biomedical applications. Bioact. Carbohydr. Diet. Fibre 2015, 5, 31–61.
2. Pawar, V.; Bavya, M.C.; Rohan, K.V.; Srivastava, R. Advances in Polysaccharide-Based Antimicrobial Delivery Vehicles. In Racing for the Surface; Springer Science and Business Media LLC: Berlin/Heidelberg, Germany, 2020; pp. 267–295.
3. Krishnamurthy, R. Giving Rise to Life: Transition from Prebiotic Chemistry to Protobiology. Acc. Chem. Res. 2017, 50, 455–459.
4. Datta, L.P.; Manchineella, S.; Govindaraju, T. Biomolecules-derived biomaterials. Biomaterials 2020, 230, 119633.
5. Shishir, M.R.I.; Xie, L.; Sun, C.; Zheng, X.; Chen, W. Advances in micro and nano-encapsulation of bioactive compounds using biopolymer and lipid-based transporters. Trends Food Sci. Technol. 2018, 78, 34–60.
6. Reinholz, J.; Landfester, K.; Mailänder, V. The challenges of oral drug delivery via nanocarriers. Drug Deliv. 2018, 25, 1694–1705.
7. Estevinho, B.N.; Rocha, F. Application of Biopolymers in Microencapsulation Processes. In Biopolymers for Food Design; Elsevier BV: Amsterdam, The Netherlands, 2018; pp. 191–222.
8. Gupta, R.; Xie, H. Nanoparticles in Daily Life: Applications, Toxicity and Regulations. J. Environ. Pathol. Toxicol. Oncol. 2018, 37, 209–230.
9. Patra, J.K.; Das, G.; Fraceto, L.F.; Campos, E.V.R.; del Pilar Rodriguez-Torres, M.; Acosta-Torres, L.S.; Diaz-Torres, L.A.; Grillo, R.; Swamy, M.K.; Sharma, S.; et al. Nano based drug delivery systems: Recent developments and future prospects. J. Nanobiotechnology 2018, 16, 71.
10. Hao, J.; Guo, B.; Yu, S.; Zhang, W.; Zhang, D.; Wang, J.; Wang, Y. Encapsulation of the flavonoid quercetin with chitosan-coated nano-liposomes. LWT 2017, 85, 37–44.
11. Prabhu, S.; Chenreddy, S.; Thio, A.; Khamas, W.; Wang, J.; Thakkar, A. Preclinical systemic toxicity evaluation of chitosan-solid–lipid nanoparticle-encapsulated aspirin and curcumin in combination with free sulforaphane in BALB/c mice. Int. J. Nanomed. 2016, 11, 3265–3276.
12. Saha, S.K.; Roy, P.; Mondal, M.K.; Roy, D.; Gayen, P.; Chowdhury, P.; Babu, S.P. Development of chitosan based gold nanomaterial as an efficient antifilarial agent: A mechanistic approach. Carbohydr. Polym. 2017, 157, 1666–1676.

13. Andreani, T.; Fangueiro, J.; Severino, P.; De Souza, A.L.R.; Martins-Gomes, C.; Fernandes, P.M.V.; Calpena, A.C.; Gremião, M.P.; Souto, E.B.; Silva, A.M. The Influence of Polysaccharide Coating on the Physicochemical Parameters and Cytotoxicity of Silica Nanoparticles for Hydrophilic Biomolecules Delivery. Nanomaterials 2019, 9, 1081.
14. Boverhof, D.R.; Bramante, C.M.; Butala, J.H.; Clancy, S.F.; Lafranconi, M.; West, J.; Gordon, S.C. Comparative assessment of nanomaterial definitions and safety evaluation considerations. Regul. Toxicol. Pharmacol. 2015, 73, 137–150.
15. Cao, S.-J.; Xu, S.; Wang, H.-M.; Ling, Y.; Dong, J.; Xia, R.-D.; Sun, X.-H. Nanoparticles: Oral Delivery for Protein and Peptide Drugs. AAPS PharmSciTech 2019, 20, 1–11.
16. Yu, W.; Liu, R.; Zhou, Y.; Gao, H. Size-Tunable Strategies for a Tumor Targeted Drug Delivery System. ACS Cent. Sci. 2020, 6, 100–116.
17. Tapia-Hernández, J.A.; Torres-Chávez, P.I.; Ramírez-Wong, B.; Rascon-Chu, A.; Plascencia-Jatomea, M.; Barreras-Urbina, C.G.; Vazquez, N.A.R.; Rodríguez-Félix, F. Micro- and Nanoparticles by Electrospray: Advances and Applications in Foods. J. Agric. Food Chem. 2015, 63, 4699–4707.
18. Carvalho, P.; Felício, M.R.; Santos, N.; Gonçalves, S.; Domingues, M. Application of Light Scattering Techniques to Nanoparticle Characterization and Development. Front. Chem. 2018, 6, 237.
19. Tiwari, A.; Verma, A.; Panda, P.K.; Saraf, S.; Jain, A.; Jain, S.K. Stimuli-responsive polysaccharides for colon-targeted drug delivery. In Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications; Elsevier BV: Amsterdam, The Netherlands, 2019; Volume 1, pp. 547–566.
20. Naeem, M.; Awan, U.A.; Subhan, F.; Cao, J.; Hlaing, S.P.; Lee, J.; Im, E.; Jung, Y.; Yoo, J.-W. Advances in colon-targeted nano-drug delivery systems: Challenges and solutions. Arch. Pharmacal Res. 2020, 43, 153–169.
21. dos Santos, A.M.; Meneguin, A.B.; Akhter, D.T.; Fletcher, N.; Houston, Z.H.; Bell, C.; Thurecht, K.J.; Gremião, M.P.D. Understanding the role of colon-specific microparticles based on retrograded starch/pectin in the delivery of chitosan nanoparticles along the gastrointestinal tract. Eur. J. Pharm. Biopharm. 2021, 158, 371–378.
22. Wahlgren, M.; Axenstrand, M.; Håkansson, Å.; Marefati, A.; Pedersen, B.L. In Vitro Methods to Study Colon Release: State of the Art and An Outlook on New Strategies for Better In-Vitro Biorelevant Release Media. Pharmaceutics 2019, 11, 95.
23. Di Mascio, P.; Martinez, G.R.; Miyamoto, S.; Ronsein, G.E.; Medeiros, M.H.G.; Cadet, J. Singlet Molecular Oxygen Reactions with Nucleic Acids, Lipids, and Proteins. Chem. Rev. 2019, 119, 2043–2086.

24. Borchmann, D.E.; Carberry, T.P.; Weck, M. “Bio”-Macromolecules: Polymer-Protein Conjugates as Emerging Scaffolds for Therapeutics. Macromol. Rapid Commun. 2013, 35, 27–43.
25. Ding, W.; Wu, Y. Sustainable dialdehyde polysaccharides as versatile building blocks for fabricating functional materials: An overview. Carbohydr. Polym. 2020, 248, 116801.
26. Hu, H.; Xu, F.-J. Rational design and latest advances of polysaccharide-based hydrogels for wound healing. Biomater. Sci. 2020, 8, 2084–2101.
27. Barclay, T.G.; Day, C.M.; Petrovsky, N.; Garg, S. Review of polysaccharide particle-based functional drug delivery. Carbohydr. Polym. 2019, 221, 94–112.
28. Ahmed, T.; Aljaeid, B. Preparation, characterization, and potential application of chitosan, chitosan derivatives, and chitosan metal nanoparticles in pharmaceutical drug delivery. Drug Des. Dev. Ther. 2016, 10, 483–507.
29. Huang, G.; Huang, H. Application of hyaluronic acid as carriers in drug delivery. Drug Deliv. 2018, 25, 766–772.
30. Khotimchenko, M. Pectin polymers for colon-targeted antitumor drug delivery. Int. J. Biol. Macromol. 2020, 158, 1110–1124.
31. BeMiller, J.N. Guar, Locust Bean, Tara, and Cassia Gums. In Carbohydrate Chemistry for Food Scientists; Elsevier BV: Amsterdam, The Netherlands, 2019; pp. 241–252.
32. Chen, F.; Huang, G.; Huang, H. Preparation and application of dextran and its derivatives as carriers. Int. J. Biol. Macromol. 2020, 145, 827–834.
33. Severino, P.; Da Silva, C.F.; Andrade, L.N.; Oliveira, D.D.L.; Campos, J.; Souto, E.B. Alginate Nanoparticles for Drug Delivery and Targeting. Curr. Pharm. Des. 2019, 25, 1312–1334.
34. Mendez-Encinas, M.A.; Carvajal-Millan, E.; Rascon-Chu, A.; Astiazaran-Garcia, H.F.; Rivera, D.E.V. Ferulated Arabinoxylans and Their Gels: Functional Properties and Potential Application as Antioxidant and Anticancer Agent. Oxidative Med. Cell. Longev. 2018, 2018, 1–22.
35. Martínez-López, A.L.; Carvajal-Millan, E.; Sotelo-Cruz, N.; Micard, V.; Rascón-Chu, A.; López-Franco, Y.; Lizardi-Mendoza, J.; Canett-Romero, R. Enzymatically cross-linked arabinoxylan microspheres as oral insulin delivery system. Int. J. Biol. Macromol. 2019, 126, 952–959.