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Review Article

Application of Natural Biopolymers and its Derivatives as Nano - Drug Delivery Systems in Cancer Treatment

Amra Bratovcic

University of Tuzla, Faculty of Technology, Department of Physical Chemistry and Electrochemistry, Urfeta Vejzagica 8, 75000 Tuzla, Bosnia and Herzegovina

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ABSTRACT

This review mainly focuses on nanoparticle-based drug delivery systems fabricated from plants (starch, cellulose, pectin), animals (chitosan, gelatin) and microorganisms (dextran). Herein, the focus is on the physical-chemical properties of biopolymers and its derivatives and the mechanism of action in the treatments of cancer. Nanoparticle-based drug delivery systems improved efficacy by: increasing half-life of vulnerable drugs and proteins, improving the solubility of hydrophobic drugs, and allowing controlled and targeted release of drugs in diseased site. Of all the mentioned biopolymers, only dextran and pure pectin are problematic. Some clinical studies have shown unexpected side effects caused by dextran such as thrombocytopenia and hepatotoxicity and, pure pectin-based materials, undesirable swelling and corrosion properties. Doxorubicin has been used in combination with almost all of these biopolymers because it is widely used as an effective chemotherapeutic agent in the treatment of many types of solid tumors of the breast, lung, colon, ovary, prostate and bladder.

Keywords: chitosan, starch, biopolymers, drug delivery systems, cancer treatment

INTRODUCTION

Cancer is the second leading cause of death in the worldwide after cardiovascular disease [1]. To overcome the challenges associated with cancer treatment, considerable research effort has been invested in harnessing the beneficial attributes of nanotechnology. Nearly, 25% of the major pharmaceutical compounds and their derivatives available today are obtained from natural resources. Natural compounds are now being screened for treating several major diseases, including cancer, diabetes, cardiovascular, inflammatory, and microbial diseases. This is mainly because natural drugs possess unique advantages, such as lower toxicity and side effects, low-price, and good therapeutic potential [2].

Drug designing at the nanoscale has been studied extensively and is by far, the most advanced technology in the area of nanoparticle applications because of its potential advantages such as the possibility to modify properties like solubility, drug release profiles, diffusivity, bioavailability and

Address for Correspondence: Amra Bratovcic, University of Tuzla, Faculty of Technology, Department of Physical Chemistry and Electrochemistry, Urfeta Vejzagica 8, 75000 Tuzla, Bosnia and Herzegovina; E-mail: amra.bratovcic@untz.ba

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immunogenicity. The engineered drug delivery systems (DDS) are either targeted to a particular location or are intended for the controlled release of therapeutic agents at a particular site.

There are passive and self-delivery ways through which nanostructures deliver drugs. In the passive way, drugs are incorporated in the inner cavity of the structure mainly via the hydrophobic effect. When the nanostructure materials are targeted to a particular sites, the intended amount of the drug is released because of the low content of the drugs which is encapsulated in a hydrophobic environment. Conversely, in the self-delivery way, the drugs intended for release are directly conjugated to the carrier nanostructure material for easy delivery. In this approach, the timing of release is crucial as the drug will not reach the target site and it dissociates from the carrier very quickly, and conversely, its bioactivity and efficacy will be decreased if it is released from its nanocarrier system at the right time [3]. Targeting of drugs is another significant aspect that uses nanomaterials or nanoformulations as the drug delivery systems and, is classified into active and passive. In active targeting, moieties, such as antibodies and peptides are coupled with drug delivery system to anchor them to the receptor structures expressed at the target site. In passive targeting, the prepared drug carrier complex circulates through the bloodstream and is driven to the target site by affinity or binding influenced by properties like pH, temperature, molecular site and shape. The main targets in the body are the receptors on cell membranes, lipid components of the cell membrane and antigens or proteins on the cell surfaces [4].

The application of nano-drug delivery system can successfully overwhelm the limitations of chemotherapy, decrease the toxicity of drugs, and thus raise the efficiency of anti-tumor agents [5]. Nano-drug delivery systems primarily comprise nanoparticles, nanocapsules, liposomes, micelles, and microemulsions, among others [6-7]. By employing nano-drug delivery systems, drugs can be dissolved, adsorbed, and covalently bound to the surface of nanocarriers, or encapsulated and embedded inside nanocarriers. Nano-drug delivery systems have been successfully applied to medical diagnosis and treatment owing to the advantages of precise targeting, reduced drug toxicity, and significantly improved drug availability [8]. Nanoparticle-based drug delivery system is considered promising for cancer treatment.

Fang et al., 2020 provided a review of the progress of current research on anti-breast cancer drugs and the application of nano-drug delivery systems in breast cancer therapy. They summarized the novel concepts for the design of nanocarriers for the delivery of anti-breast cancer drugs [9].

Hani et al., 2021[10] described the most recent developments in early diagnosis and efficient treatments of pancreatic cancer by nano drug delivery systems.

Compared with traditional DDS, the nanoparticle-based DDS shows improved efficacy by: 1) increasing half-life of vulnerable drugs and proteins, 2) improving the solubility of hydrophobic drugs, and 3) allowing controlled and targeted release of drugs in diseased site [11].

A very small portion of the anticancer drugs reach that targeted site and a very high percentage of them never reach the tumor site. Because they lack the transportation and tools needed to carry these drugs to the place they are targeted for. It has been well documented that nanoparticles (NPs) seem to be potential vehicles for targeted DDSs [12-13]. Nano carriers improve a drug's performance and its targeting by changing the pharmacokinetic properties of the drug [14-15].

Proteins NPs like albumin, lactoglobulin and gelatin are considered as outstanding alternatives to be formulated into the nanostructure platforms in conjugation with anticancer drugs because of their safety, biodegradability and biocompatibility. Also, their uncomplicated preparation and modification can be carried out under mild conditions with no concern toward the utilization of hazardous reagents. Therefore, the different methods for formulation of protein nanostructure including emulsification, simple desolvation/coacervation, complex coacervation (self-assembled), and electrospray are considered. Especially is reviewed the application of gelatin NPs (GNPs) as potential candidates in DDSs for cancer therapy [16].

Drug delivery system has been used clinically and pre-clinically to deliver therapeutic substances for disease treatment. Controlled drug delivery systems would be excellent carriers for chemotherapeutic agents, guiding the chemotherapeutic agents to the tumor site thus increasing the drug concentration in cancer cells and averting toxicity in normal cells [17-18]. Moreover, controlled DDSs protect the drugs from degradation, helpful for delivery of proteins and new therapeutic agents such as gene therapy and RNA interference.

Nanoparticles as DDS can improve the efficacy of the drug by increasing drug half-life, improve the solubility for some hydrophobic drug, and release the drug in a controlled or sustained fashion. Liposomes were the first discovered nanoparticles DDS and were used as carriers for drugs and

proteins in the 1960s [19]. Compared to synthetic polymers, natural biopolymers such as polysaccharides, proteins, and nucleic acids have many advantages for encapsulation and delivery of active pharmaceutical ingredients, including biodegradability, biocompatibility, nontoxicity, and nonimmunogenicity [20]. Numerous delivery systems with various structure designs such as nanoparticles, nanocomplexes, nanoemulsions, nanocrystals, and self-assembled micelles have been fabricated based on polysaccharides, including chitosan, dextran, pectin, alginate, starch, and heparin.

So far, various types of drug delivery systems encompassing nanomaterial scaffolds in combinations with organic, inorganic, and polymeric materials have been commercialized [21].

Generally, pH-responsive polymers contain ionizable basic or acidic residues whose ionization depends on solution pH. The lower pH value of tumor tissues than those of the normal tissues is the key point of applying pH-responsive polymers for targeted delivery of chemotherapeutics.

There are various kinds of natural polymers, including polysaccharides, proteins, peptides, polyesters and so on. Considering their biocompatibility and processability, polysaccharides and proteins have been widely explored in the DDS [22]. Natural biopolymers could be obtained from higher plants, animals, microorganisms and algae. Herein is discussed on polymers derived from plants, animals and microorganisms.

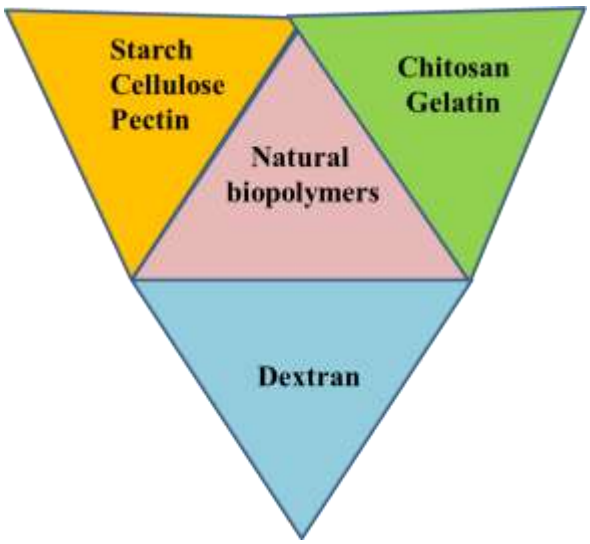

Figure 1. Different sources of natural biopolymers used in nanomedicine applications.

The aim of this review is to show recent advances in nano drug delivery systems based on natural biopolymers.

ANIMAL SOURCES OF NATURAL BIOPOLYMERS

Chitosan nanoparticles: Chitosan is the natural carbohydrate polymer that has got significant attention from drug carrier in medicinal applications. The unique property of a natural biopolymer is its cationic character that is not present in other polysaccharides [23]. Structurally, Chitosan is composed of (1–4)-2-acetamido-2-deoxy-β-D-glucan (*N*-acetyl- D-glucosamine) and (1–4)-2-amino-2-deoxy- β-D-glucan (D-glucosamine)units [24-25].

It is prepared through the alkaline deacetylation of N-acetyl glucosamine of chitin polymer, which is present in the shell of organisms like shrimp and crab. The fabrication of nanoparticles from chitosan is often conducted in mild conditions as chitosan is soluble in acidic aqueous solutions at room temperature, no toxic organic solvents or heat is required. Chitosan is solvable in a slightly acidic environment due to the amine groups' backbone, while it is insoluble in neutral and basic medium [26]. A broad category of drugs can be incorporated into chitosan DDS, including small molecules, proteins, and polynucleotides [27]. However, this specific solulility of chitosan creates a significant barrier for its application [28].

Chitosan, as a biopolymer with abundant sources, easy modification, and non-toxicity, can serve as an ideal carrier for the delivery of anticancer drugs. Chitosan has gradually become a research hotspot because it can be normally metabolized in the organism and excreted from the body. Chitosan can be prepared into hydrogels and microparticles in non-nanoscale drug carriers which can load several anticancer drugs including doxorubicin (DOX), curcumin (CUR), resveratrol, paclitaxel (PTX), doxazosin, ellagic acid, and 5-fluorouracil (5-FU) [29]. Chitosan nano drug delivery systems are mainly divided into the following types: nano gels, nano microspheres, nano fibers, and nano particles [30-31].

Moreira and his colleagues combined light with heat therapy to prepare a chitosan-based DOX delivery system. Results obtained from the experiment indicated that the modified material could control the release of DOX under the irradiation of near-infrared light (808 nm, 1.7 W/cm^2, 5 min), thereby displaying strong cytotoxicity to cervical cancer cells (the cell viability decreased to 3.8%)[32].

The cancerous cell possesses a low pH of up to 5.0. Simultaneously, chitosan is protonated at pH under its pKa (~6.4), nanocarriers get triggered by pH change and enhance the drug release kinetics in tumor tissues. Protonation may raise the spacing between the chitosan chains that comprise the carrier through electrostatic repulsions and hydrogen bonds with water molecules, thus allowing drug diffusion into the exterior environment [33].

Chitosan can release the encapsulated drug in a controlled manner. The free amine groups on chitosan also provide ionic crosslinking ability [34]. Chitosan nanoparticles have been widely studied for their application in cancer therapies. Chitosan nanoparticles can target tumors on specific organs through passive targeting (also known as enhanced permeability and retention (EPR) effect [35]), active targeting, and physical targeting through stimuli-sensitive targeting. Literature suggesting Higuchi's diffusion-controlled model for the release of silver sulfadiazine from the chitosan matrix [36]. The release time of the drug was inversely proportional to the content of silver sulfadiazine and nature of the scaffold, while was increased the sustained release with an increase in glycerin level.

Sivasankarapillai et al., 2021 discussed on the advantages, limitations and applications of important biopolymers (natural rubber, chitosan, and cellulose) for the Transdermal (TD) drug release applications and related aspects [37]. The route of a specific drug carrier system is always a significant platform of development that combines the principles of biomedical technology, nanotechnology, and pharmaceutical drug design. The major drug delivery routes include oral, intramuscular (IM), intravenous (IV), subcutaneous (SC), and transdermal (TD). TD system encompasses the release of drugs through the stratum corneum of the skin into the sustained release by diffusion across the epidermal layer. The major concern is the improvement of bioavailability of the applied drug through the TD route that can reduce the degradation effects of the first-pass metabolism encountered in the oral route [38]. For instance, the drugs such as ranitidine or oestradiol can be successfully administered through the TD route that can resolve the toxic nature with an oral route like low bioavailability and liver damage, respectively.

Mechanism of anti-cancer activity of chitosan: A mechanism of anti-cancer functionality of chitosan is related to its capacity to increase the biodistribution level. The accumulation of the drug in tumor cells possesses high drug entrapment capacities. It introduces the acetate functional groups subject to cross-linking, forming the intended matrix for efficient encapsulation and sustained release of various drugs. Chitosan suspensions or microparticles have an immune-stimulating activity such as increasing accumulation and activation of macrophage and polymorphonuclear cells, suppressing tumor development, encouraging resistance to microorganism infections, induce cytokines, enhancing the response of antibodies, and improve the response of delayed-type hypersensitivity (DTH) and a cytotoxic T lymphocyte (CTL). Chitosan also has utility in the transmucosal delivery of drugs and peptides [39]. Due to chitosan improved permeability and retention effect and low cytotoxicity, chitosan nanoparticles can also improve the physicochemical properties of drugs and facilitate progressive apoptosis of distinctive carcinomas. The treatment of MDA-MB-231 human breast carcinoma cells with elevated chitosan concentration has been shown to prevent these cells' migration through a matrigel-coated membrane [40]. Smith et al. presented data showing that chitosan opening the tight junction between epithelial cells, thereby enhancing the permeability of carried drugs, causing tight junction disruption at the molecular level [41-42]. A positive surface charge implied an increased cell membrane interaction, which was necessary for increasing cell uptake and permeation of the membrane.

Protein nanoparticles in drug delivery

It has been well documented that the outstanding features of protein nanoparticles such as biocompatibility, biodegradability, bioavailability, safety, and stability make them promising agents in development of DDSs. The hydrophobic residues and hydrophilicity enable the protein nanostructures to protect the loaded cargoes for its controlled delivery systems. Therefore, an uncomplicated multifunctional drug-loaded nanostructure based on protein can be designed for combination therapy in combating cancer [43]. Indeed, proteins and peptides are one of the useful and major research areas in nanomedicine. Gelatin nanoparticles (GNPs) are known as protein nanostructures that have been widely used in development of DDSs. The hydrophilic nature of GNPs can improve the cargo penetration into the nanostructure and thereby increases the diffusion-based drug delivery and subsequent drug release. Also, the physicochemical properties of GNPs are tuned to serve as microenvironment-responsive agents for cancer therapy.

Breast cancer is the highest global spread of invasive cancer in women with a 75% survival rate in women [44]. Concerning chitosan-based chemotherapeutic therapies, the studies reported

cell migration resistance, improved drug absorption, membrane interaction and permeability, immune stimulating behavior, and extended *in-vitro* drug release. Nandgude and Pagar, 2020 [45] emphasized the efficient drug delivery to breast cancer cell lines using chitosan. Chitosan also exhibited excellent capabilities in gene packaging. For the interaction of bioactive molecules and the regulation of the drug release profile, chemical modification of chitosan is beneficial. Chitosan derivatives are promising materials for targeted and non-viral gene delivery in treatment of breast cancer.

Mechanism of Gelatin nanoparticles in drug delivery: Gelatin is known as a denatured protein that derived from acid or basic hydrolysis of collagen [46]. Gelatin is a polyampholyte compound containing cationic, anionic and hydrophobic groups with a 1:1:1 ratio. Indeed, gelatin molecules have positive charge, negative charge and hydrophobic amino acids (50%). The rest of the structure consists of glycine, proline and hydroxyproline. Proline and hydroxyproline play an important role in the properties of the gel, in particular, the rheological properties and strength of the gel [47].

Gelatin contains the arginine-lysine-glycine sequence in its primary structure which is existed in many extracellular matrix proteins and plays a key role in cellular binding and subsequent signaling by binding to the β-subunit of integrin receptors at the cell surface [48].

This can be considered as one of the outstanding advantages of gelatin over natural or synthetic polymers that do not exhibit cellular recognition and binding site. Active groups of gelatin molecules are employed for a variety of chemical reactions to be done directly or by using different linkers, especially when producing targeted drugs. Actually, these groups and corresponding modifications allow the gelatin to serve as a drug carrier and binds significant amounts of drugs.

Toshio et al. [49] exhibited that selective targeting of mitomycin C to the liver, spleen and lung is performed through nanospherical or microspherical gelatin. Leo et al. [50] suggested that doxorubicin (DOX)-loaded GNPs stabilized by glutaraldehyde can be used as a potential DDS.

In the field of compatibility of GNPs, surface modification is done by using different surface coatings carried out so that biomedical properties and stability of these particles can be achieved. Indeed, surface modification can prevent the particulate effects and toxicity of GNPs due to their interactions with cells or biological proteins which increase the biocompatibility of GNPs [51]. Once NPs have been adapted to enter the body, they can be used to carry various compounds, including drugs.

Also, gelatin can be utilized as a linker and support platform to both adsorb anticancer drugs and mediate their adsorption on the surface of NPs. For example, gelatin-DOX conjugate -coated polyphenol functionalized AuNPs [52] and mercaptopurine (MER) loaded GFe_3O_4 NPs [53] have been manipulated for targeted drug delivery, imaging and reducing prostate cancer growth. It was shown that the conjugated NPs significantly reduced the growth of cancer cells. Redox-responsive GNPs can be used as promising DDSs against a wide range of cancer cells.

MICROORGANISM SOURCES OF NATURAL BIOPOLYMERS

Dextran: Dextran is a neutral complex branched glucan consisting of α-1, 6 glycosidic linkages between glucose monomers, with branches from α-1, 2, α-1, 3, and α-1, 4 linkages [54]. Dextran in nature is mainly produced extracellularly from sucrose by several lactic acid bacteria via dextransucrase which catalyzes the transfer of D-glucopyranosyl residues from sucrose to dextran. Being a natural polysaccharide, dextran has excellent properties to meet crucial requirements of nanomaterials for applications in pharmaceutics, such as biodegradability, biocompatibility, and nontoxicity. Because of a large number of reactive hydroxyl groups on the dextran backbone, different derivatives have been developed via chemical modification.

In recent years, numerous dextran-based delivery systems and its derivatives have been developed, including self-assembled micelles and nanoparticles, nanoemulsions, magnetic nanoparticles, microparticles, hydrogels and spray-dried particles. Dextran-based drug delivery systems are used in biomedicine for cancer treatment, magnetic resonance imaging, insulin oral delivery, spinal cord injury therapy, and bacterial skin infection treatment [55]. Dextran has many advantages as biopolymer to synthesize nanomaterials for drug delivery, such as excellent solubility, biocompatibility, biodegradability, and non-immunogenicity [56]. Dextran can be only depolymerized by dextranase in the lumen of the large intestine, liver, spleen, and kidney [57]. Thus, the dextran-based delivery systems can protect drug molecules throughout the stomach and small intestine against chemical and enzymatic degradation, increase the absorption by the intestinal epithelium, resulting in improved oral bioavailability. Dextran is an excellent starting

biopolymer for the design of structures. Its narrow molecular weight distribution and abundant active hydroxyl groups are advantageous for chemical modification. Numerous glycoconjugates have been derivatized by reactions, including esterification, etherification, and oxidation [58-59]. Many classes of dextran-based nanoparticulate systems for anticancer drug delivery have been reported in recent years [60-63].

Most of these nanocarriers are developed in response to natural stimuli to achieve the controlled release of cancer drugs in tumors and reduce harmful effects on normal cells. The pH-responsive system is one of the commonly used strategies. Nanoparticles containing pH-sensitive groups or formed by pH-cleavable linkages are protonated or deprotonated in the local microenvironment. The cleavage of such acid-labile chemical bonds in response to an acidic environment (pH 4–6) in the target tumor cells or endosome/lysosome leads to the disruption of the hydrophilic-hydrophobic balance, degrade nanoparticles, and trigger the drug release. As an example, a pH-sensitive deoxycholic acid-dextran micelle was developed for solid tumor therapy [64]. In another study, the author found that the pH-responsive release of doxorubicin (DOX) in an acidic environment was affected by the molecular weight of dextran moiety [65].

Mechanism of dextran in drug delivery: The physicochemical properties of dextran-based drug delivery systems, release mechanism, and therapeutic effects in animal experiments have been investigated in great detail to justify their wide applications in biomedicine, especially for cancer treatment. Although a tremendous amount of work has been done to develop dextran-based nanoparticles as delivery systems, some scientific challenges have also arisen. First of all, the clinical trials have shown some unexpected side effects caused by dextran such as thrombocytopenia and hepatotoxicity [66]. Also, most of the dextran derivatives are synthesized in the presence of organic solvents and sometimes toxic chemicals, which can trigger potential safety concerns. There is an urgent need for the exploration of eco-friendly fabrication methods. More clinical toxicity tests must be carried out before dextran-based nanoparticles can be practically applied for oral delivery of active pharmaceutical ingredients. Secondly, there is still a lack of knowledge about the biological fate or behavior of dextran-based nanoparticles inside living organisms. More *in vivo* studies need to be conducted soon to clarify the changes of nanoparticles in the morphological structure under physiological conditions and metabolism, which will eventually help guide the design of more effective dextran-based delivery systems. Last but not least, when testing the therapeutic efficacy of drug-loaded dextran-based nanoparticles, the major administration route was intravenous injection instead of oral delivery. Since the oral route is widely accepted to be the most convenient and comfortable drug administration, more efforts should be devoted to developing dextran-based nanoparticles as oral delivery systems with good gastrointestinal stability and mucus permeability, as well as transepithelial transportability.

PLANT SOURCES OF NATURAL BIOPOLYMERS

Starch as a drug delivery system

Starch is one of the potential candidates due to its high abundance as it is available from different sources as wheat, peas, corn, rice, potato and beans [67-69]. A drug delivery system can be made from starch due to its physical-chemical particularities of solubility, morphology, low toxicity and ease of digestion [70]. Starch is usually made in order to allow the control of the drug release in some specific place of interest and in small doses for long time-reducing the colateral effects of the drug when compared to conventional system [71]. Drug can be released by the swelling of the polymeric matrix degrading the base material and allowing the drug to migrate to the surface [72]. Queiroz et al. 2020 developed a chlorhexidine (CHX) long-term drug delivery system using starch as a biodegradable polymer base. Three batches of thermoplastic starch films, containing starch particles/nanoparticles and chlorhexidine, were manufactured by casting. CHX was partially bounded to starch and prevented starch crystallization. By incorporating CHX into the solution, the nanoparticles presented different morphology, suggesting absorption of the drug. In vitro drug release was observed for 21 days by UV–vis spectrophotometry and released CHX amounted up to 19 mg/100 ml. The developed film met the main requirements for a drug delivery system [73].

Cellulose-based TD delivery devices

Among polysaccharides, cellulose is the most abundant one, available worldwide and it combines hydrophilicity with good mechanical prop erties. Both of these competitive characteristics are due to the numerous hydroxyl groups that interact by hydrogen bonds preferentially with water (amorphous domains) or with hydroxyl groups of adjacent polymer chains (crystalline domains) [74]. Different variations of cellulose have found exciting applications in TD drug delivery. One of the primary reasons that make them promising for drug delivery application is its excellent biocompatibility, high water permeability, compatibility with other additives and

formulations, feasibility to form micro or nanoparticles, and lack of toxicity compared to synthetic polymers. There are various types of cellulose systems reported for transdermal drug delivery that includes cellulose esters, bacterial cellulose, cellulose nanocrystals, hydroxypropyl methyl cellulose (HPMC), and ethyl cellulose (EC). They are either used as such or in combination with each other and also in combining with other biopolymers like chitosan for developing TD drug delivery devices. The kinetics of pentazocine from matrix-dispersion type TD membrane containing ethyl cellulose followed Higuchi kinetics over a 24-h period [75]. Higuchi kinetics was followed for the release of flurbiprofen by matrix-dispersion-type transdermal drug delivery system of HMPC and also for the release of Verapamil [76].

Pectin in drug delivery applications

Natural macromolecules have attracted increasing attention due to their biocompatibility, low toxicity, and biodegradability. Pectin is one of the few polysaccharides with biomedical activity, consequently a candidate in biomedical and drug delivery applications.

The chemical structure of pectin is consists of (1 → 4)-α-D-galacturonic acid (Gal A) residues branched with different neutral sugars. Pectin can be classified by polymeric forms, such as Homogalacturonan (HG), Rhamnogalacturonan-I (RG-I), Xylogalacturonan (XGA), and Rhamnogalacturonan-II (RG-II). Rhamnogalacturonan-II, a smaller component in pectin, plays a major role in biomedical activities. The ubiquitous presence of hydroxyl and carboxyl groups in pectin contribute to their hydrophilicity and, hence, to the favorable biocompatibility, low toxicity, and biodegradability. However, pure pectin-based materials present undesirable swelling and corrosion properties. The hydrophilic groups, *via* coordination, electrophilic addition, esterification, transesterification reactions, can contribute to pectin's physical-chemical properties. Here the properties, extraction, and modification of pectin, which are fundamental to biomedical and drug delivery applications, are reviewed. Moreover, the synthesis, properties, and performance of pectin-based hybrid materials, composite materials, and emulsions can provide valuable information on pectin and its biomedical and drug delivery applications [77]. The biomedical and drug delivery applications of pectin is primarily due to its chemical composition and surface functional groups. Hydroxyl, amide, carboxyl, and methyl functional groups are the major functional groups in the pectin chain. Thus, pectin can shape into a composite with different feedstocks with opposite charges by adjusting the pH value of the medium. Chitosan, casein, gelatin, and zein which could provide positive charge are widely used, and electrostatic interaction played a key role in this process [78-79]. One of the most important properties of pectin is the gelling ability.

Pectins are considered the most promising components for colon targeted drug dosage forms as they are stable in the changing gastrointestinal media and easily degraded by pectinases produced by colonic microflora. A various range of the pectin-containing delivery systems were developed contributing higher concentration of the active drug molecules in particular site inside intestine and their lower blood level resulting in lowered risk of the severe side effects [80]. In colon, pectins are completely degraded due to the influence of bacterial enzymes with the following formation of short-chain fatty acids acting as the main energy source for colonocytes. Although it should be mentioned that any disturbances in normal microbial balance in the colon may significantly change the process of the pectin fermentation [81]. Besides, epidemiological data suggest that colon cancer occurrence is much higher in persons with pH of intestinal media 7.0 whereas generally pH of healthy people in the colon is 6.5 [82]. As these acids provoke acidic pH shift, pectin consumption was shown to be protective against cancer development.

Nanoparticles usually have very small sizes with an average diameter in the range 350–500 nm that let them get into the cell through membranes via pinocytosis mechanism. This capacity provides very valuable benefits for antitumor therapy. Pure drug molecules usually get inside cells via a mechanism of simple diffusion. Therefore, these substances go into the tumor cells as easily as into the normal cells in the body. It results in substantially reduced efficiency of the therapy and dramatically increased risk of toxicity [83]. Polymer nanoparticles having larger size can get inside cells only through the mechanism of pinocytosis providing their selective activity against malignant cells only, because this mechanism of absorption is mostly typical of tumor cells whereas simple diffusion basically typical of normal cells occurs much rarer. Doxorubicin is a well-known DNA intercalating agent. It has been widely used as effective chemotherapeutic agent in the treatment of many types of solid tumors in breast, lung, colon, ovarian, prostate, and bladder. However, the doxorubicin therapy is always associated with the very severe toxic effects substantially limiting its use in patients. In order to reduce or avoid toxic effects of chemotherapy, the use of specific targeted drug delivery systems was suggested.

Zhu et al., 2018 [84] designed a simple, colon target drug delivery system by using porous starch (PS), pectin and chitosan. The porous maize starch granules was prepared by hydrolysis with a combination of α-amylase and amyloglucosidase and has specific surface area (0.8768-0.9448 m^2/g) with an average pore diameter of 40.52-62.42 nm. The cationic anticancer drug doxorubicin was successfully loaded into PS granules, which were then coated with a pectin/chitosan complex solution. The pectin/chitosan beads containing doxorubicin-loaded PS successfully passed through the simulated stomach and small intestine, indicating that most of the loaded doxorubicin could reach the colon. In addition, an *in vitro* simulated digestion method demonstrated the effectiveness of this delivery design, as only a 13.80% release rate of doxorubicin was observed in the upper gastrointestinal tract, whereas release rates of 17.56% and 67.04% were observed for pectin/PS/doxorubicin and pectin/doxorubicin beads, respectively. The use of PS and a pectin/chitosan coating is an effective method for colon targeted drug delivery compared with the simple polysaccharide system.

CONCLUSION

The increasing incidence of cancer has resulted in a large number of natural-based materials being prepared into anticancer drug carriers which display remarkable drug delivery effects in *in vitro* experiments. The development of material science has gradually minimized the scale of natural-based drug delivery materials to the nanometer level which ensures that the delivery of drugs is more convenient and faster. Natural based polymers are non-toxic to normal cells. However, the metabolic changes of the drug carrier in the organism must be taken into account when applied in clinical practice. In the future of cancer research, cutting-edge technologies should be actively and flexibly introduced to prepare a drug carrier that can accurately load the drug with a therapeutic dose. In addition, more pharmaceutical excipients can be combined with natural polymer - based materials so as to extend the use of them in drug delivery.

REFERENCES

1. Soleimani K et al. Stimuli-responsive natural gums-based drug delivery systems for cancer treatment. Carbohydr. Polym. 2021; 254: 117422.
2. Patra JK et al. Nano based drug delivery systems: recent developments and future prospects. J. Nanobiotechnol. 2018; 16:71.
3. Lu H et al. Recent progress on nanostructures for drug delivery applications. J Nanomater. 2016; 2016:20.
4. Kumari et al. Nanotechnology: a tool to enhance therapeutic values of natural plant products. Trends Med Res. 2012;7:34–42.
5. Xu R et al. An injectable nanoparticle generator enhances delivery of cancer therapeutics. Nat. Biotechnol. 34 (2016) 414.
6. Mei L et al. Pharmaceutical nanotechnology for oral delivery of anticancer drugs. Adv. Drug Deliv. Rev. 2013; 65: 880–890.
7. Jain AK, Jain S. Advances in oral delivery of anti-cancer prodrugs. Expet Opin. Drug Deliv. 2016; 13:1759–1775.
8. Nadimi AE. et al. Nano-scale drug delivery systems for antiarrhythmic agents. Eur. J. Med. Chem. 2018; 157: 1153–1163.
9. Fang X et al. Advances in anti-breast cancer drugs and the application of nano-drug delivery systems in breast cancer therapy. Journal of Drug Delivery Science and Technology, 2020; 57: 101662.
10. Hani U et al. A systematic study of novel drug delivery mechanisms and treatment strategies for pancreatic cancer. Journal of Drug Delivery Science and Technology, 2021; 63: 102539.
11. Dang Y, Guan J. Nanoparticle-based drug delivery systems for cancer therapy. Smart Materials in Medicine, 2020; 1:10-19.
12. Rizvi SA, Saleh A.M. Saudi Pharmaceutical Journal; 2018, 26:64.
13. Patra JK et al. Nano based drug delivery systems: recent developments and future prospects. J. Nanobiotechnol., 16, 2018: 71.
14. Attia MF et al. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. J. Pharm. Pharmacol. 2019; 71(8): 1185-1198.
15. Thorat ND et al. Silica nano supra-assembly for the targeted delivery of therapeutic cargo to overcome chemoresistance in cancer. Colloids Surf. B: Biointerfaces. 2020; 185: 110571.
16. Hussain A. et al. Application of gelatin nanoconjugates as potential internal stimuli-responsive platforms for cancer drug delivery. J. Mol. Liq. 2020; 318: 114053.
17. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv. Enzym. Regul. 2001; 41: 189–207.

18. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv. Drug Deliv. Rev. 2013; 65 (1): 36–48.
19. Gregoriadis G, Ryman BE. Liposomes as carriers of enzymes or drugs: a new approach to the treatment of storage diseases. Biochem. J. 1971; 124 (5): 58.
20. Qin Y. et al. Preparation of bioactive polysaccharide nanoparticles with enhanced radical scavenging activity and antimicrobial activity. Journal of Agricultural and Food Chemistry, 2018; 66(17): 4373–4383.
21. Khorsandi Z. et al. Carbon nanomaterials with chitosan: A winning combination for drug delivery systems, Journal of Drug Delivery Science and Technology 2021; 66:102847.
22. Tong X et al. Recent advances in natural polymer-based drug delivery systems, Reactive and Functional Polymers, 2020; 148:104501.
23. Nair SS. Chitosan-based transdermal drug delivery systems to overcome skin barrier functions. J. Drug Deliv. Therapeut. 2019; 9 (1): 266-270.
24. Bratovcic A. Physical – Chemical, Mechanical and Antimicrobial Properties of BioNanocomposite Films and Edible Coatings. IJRASB. 2021; 8(5): 151-161.
25. Fonseca AC et al. Bioabsorbable polymers in cancer therapy: latest developments, EPMA J. 2015; 6: 22.
26. Raza ZA et al. Recent developments in chitosan encapsulation of various active ingredients for multifunctional applications. Carbohydr. Res. 2020; 492:108004.
27. Tiyaboonchai W. Chitosan Nanoparticles: a promising system for drug delivery, Naresuan Univ. J. 2003; 11 (3): 51–66.
28. Xing Y et al. Chitosan-based coating with antimicrobial agents: preparation, property, mechanism, and application effectiveness on fruits and vegetables. Int. J. Polym. Sci. 2016; 2016: 1–24.
29. Bratovcic A. Antioxidant Enzymes and their Role in Preventing Cell Damage. Acta Scientific Nutritional Health 2020; 4(3): 01-07.
30. Bratovcic A. Nanocomposite Hydrogels Reinforced by Carbon Nanotubes. IJERA 2020; 10(5) (Series-IV):30-41.
31. Tian B et al. Chitosan-based nanoscale and non-nanoscale delivery systems for anticancer drugs: A review. Eur. Polym. J. 2021; 154:110533.
32. Moreira AF. Poly (vinyl alcohol)/chitosan layer-by-layer microneedles for cancer chemo-photothermal therapy. Int. J. Pharmaceut. 2020; 576: 118907.
33. de Oliveira Pedro R. et al. Self-assembled amphiphilic chitosan nanoparticles for quercetin delivery to breast cancer cells. Eur. J. Pharm. Biopharm. 2018; 131: 203–210.
34. Nagpal K et al. Chitosan nanoparticles: a promising system in novel drug delivery. Chem. Pharm. Bull. (Tokyo) 2010; 58 (11):1423–1430.
35. Park JH et al. Targeted delivery of low molecular drugs using chitosan and its derivatives. Adv. Drug Deliv. Rev. 2010; 62 (1):28–41.
36. Zepon KM et al. Manufacture of Starch-Cellulose Acetate Matrices Extruded Containing the Antibiotic Silver Sulfadiazine: Characterization and Evaluation of Antibacterial Effectiveness, 2017.
37. Sivasankarapillai VS et al. Progress in natural polymer engineered biomaterials for transdermal drug delivery systems. Materials Today Chemistry, 2021; 19:100382.
38. Prausnitz MR et al. Current status and future potential of transdermal drug delivery. Nat. Rev. Drug Discov. 2004; 3(2):115-124.
39. Seferian PG, Martinez ML. Immune stimulating activity of two new chitosan containing adjuvant formulations. Vaccine 2000;19 (6): 661–668.
40. Nam K-S, Shon Y-H, Suppression of metastasis of human breast cancer cells by chitosan oligosaccharides. J. Microbiol. Biotechnol. 2009; 19 (6): 629–633.
41. Smith J et al. Effect of chitosan on epithelial cell tight junctions. Pharm. Res. (N. Y.) 2004; 21 (1): 43–49.
42. Liu K et al. Carbohydrate-based amphiphilic nano delivery systems for cancer therapy. Nanoscale 2016; 8 (36):16091–16156.
43. Wang K et al. Self-assembled IR780-loaded transferrin nanoparticles as an imaging, targeting and PDT/PTT agent for cancer therapy. Sci Rep. 2016; 6:27421. PMID: 27263444; PMCID: PMC4899881.
44. Yazdi Rouholamini SE et al. Effect of silibinin-loaded nano-niosomal coated with trimethyl chitosan on miRNAs expression in 2D and 3D models of T47D breast cancer cell line. Artif. Cells Nanomedicine Biotechnol 2018; 46 (3): 524–535.
45. Nandgude T, Pagar R. Plausible role of chitosan in drug and gene delivery against resistant breast cancer cells. Carbohydrate Research, 2021; 506:108357.
46. Sahoo N et al. Recent advancement of gelatin nanoparticles in drug and vaccine delivery. Int J Biol Macromol. 2015; 81:317-31. PMID: 26277745.

47. Liu D et al. Collagen and gelatin, Annu. Rev. Food Sci. Tech 2015; 6: 527.
48. Davidenko N et al. Evaluation of cell binding to collagen and gelatin: a study of the effect of 2D and 3D architecture and surface chemistry. J Mater Sci Mater Med. 2016; 27(10):148. Erratum in: J Mater Sci Mater Med. 2018 Mar 21; 29(4):39. PMID: 27582068; PMCID: PMC5007264.
49. Toshio Y et al. Specific delivery of mitomycin c to the liver, spleen and lung: Nano- and m1crospherical carriers of gelatin. Int. J. Pharm. 1981; 8 (2): 131-141.
50. Leo E et al. Doxorubicin-loaded gelatin nanoparticles stabilized by glutaraldehyde: Involvement of the drug in the cross-linking process. Int. J. Pharm. 1997; 155: 75-82.
51. Foox M, Zilberman M. Drug delivery from gelatin-based systems. Expert Opin Drug Deliv. 2015;12(9):1547-63. PMID: 25943722.
52. Tsai LC et al. EGCG/gelatin-doxorubicin gold nanoparticles enhance therapeutic efficacy of doxorubicin for prostate cancer treatment. Nanomedicine (Lond). 2016 Jan;11(1):9-30. PMID: 26654241.
53. Sirivat A, Paradee N. Facile synthesis of gelatin-coated Fe_3O_4 nanoparticle: Effect of pH in single-step co-precipitation for cancer drug loading. Materials and Design. 2019; 181:107942.
54. Heinze T et al. Functional polymers based on dextran. Polysaccharides II, Advances in Polymer Science, 2006; 205: 199–291. Springer.
55. Hu Q et al. Recent advances in dextran-based drug delivery systems: From fabrication strategies to applications. Carbohydrate Polymers, 2021; 264: 117999.
56. Anirudhan TS. Dextran based nanosized carrier for the controlled and targeted delivery of curcumin to liver cancer cells. International Journal of Biological Macromolecules, 2016;88: 222–235.
57. Shingel KI. Current knowledge on biosynthesis, biological activity, and chemical modification of the exopolysaccharide, pullulan. Carbohydrate Research, 2004; *339*(3): 447–460.
58. Dhaneshwar SS et al. Dextran: A promising macromolecular drug carrier. Indian Journal of Pharmaceutical Sciences, 2006; 68(6): 705.
59. Varshosaz J. Dextran conjugates in drug delivery. Expert Opinion on Drug Delivery, 2012; 9(5): 509–523.
60. Fang Y et al. Doxorubicin-loaded dextran-based nano-carriers for highly efficient inhibition of lymphoma cell growth and synchronous reduction of cardiac toxicity. International Journal of Nanomedicine,2018; 13: 5673.
61. Liu L et al. Acid-responsive dextran-based therapeutic nanoplatforms for photodynamic-chemotherapy against multidrug resistance. International Journal of Biological Macromolecules, 2020;155: 233-240.
62. Su H et al. Schiff base-containing dextran nanogel as pH-sensitive drug delivery system of doxorubicin: Synthesis and characterization. Journal of Biomaterials Applications, 2018; 33(2): 170–181.
63. Wannasarit S et al. A virus-mimicking pH-Responsive acetalated dextran-based membrane-active polymeric nanoparticle for intracellular delivery of antitumor therapeutics. Advanced Functional Materials, 2019; 29(51): 1905352.
64. Jin R et al. Amphipathic dextran-doxorubicin prodrug micelles for solid tumor therapy. Colloids and Surfaces B: Biointerfaces, 2017; 158: 47–56.
65. Li D et al. Acid-sensitive dextran prodrug: A higher molecular weight makes a better efficacy. Carbohydrate Polymers, 2017; 161: 33–41.
66. Danhauser-Riedl S et al. Phase I clinical and pharmacokinetic trial of dextran conjugated doxorubicin (AD-70, DOX-OXD). Investigational New Drugs, 1993; 11 (2–3): 187–195.
67. Zia F et al. Starch based polyurethanes: a critical review updating recent literature, Carbohydr. Polym. 2015; 134:784-798.
68. Mendes JF et al. Biodegradable polymer blends based on corn starch and thermoplastic chitosan processed by extrusion, Carbohydr. Polym. 2016;137: 452-458.
69. Ortega-Toro R et al. Improvement of properties of glycerol plasticized starch films by blending with a low ratio of polycaprolactone and/or polyethylene glycol, Food Hydrocoll. 2016; 56: 9-19.
70. Jacob J et al. Biopolymer based nanomaterials in drug delivery systems: a review, Mater. Today Chem. 2018; 9:43-55.
71. Onnainty R. et al. Targeted chitosan-based bionanocomposites for controlled oral mucosal delivery of chlorhexidine, Int. J. Pharm. 2016; 509(1-2):408-418.
72. Fu Y, Kao WJ. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. Expert Opin. Drug Deliv. 2010; 7(4):429-444.
73. Queiroz VM. et al. Corn starch films as a long-term drug delivery system for chlorhexidine gluconate. Materials Science and Engineering: C, 2020; 112: 110852.
74. Klemm D. et al. Comprehensive Cellulose Chemistry; Wiley-VCH: Weinheim, Germany, 1998; Volume 1.

75. Verma PP., Chandak A. Development of matrix controlled transdermal delivery systems of pentazocine: in vitro/in vivo performance, Acta Pharm. 2009; 59 (2): 171-186.
76. Charoo NA. et al. Improvement in bioavailability of transdermally applied flurbiprofen using tulsi (Ocimum sanctum) and turpentine oil, Colloids Surf. B Biointerfaces 2008; 65 (2): 300-307.
77. Li D.-q. et al. Pectin in biomedical and drug delivery applications: A review, International Journal of Biological Macromolecules, 2021; 185: 49-65.
78. Tian L. et al. Synthesis and characterization of pectin-chitosan conjugate for biomedical application. Int J Biol Macromol. 2020;153:533-538. PMID: 32114170.
79. Soubhagya AS. et al. Preparation and characterization of chitosan/pectin/ZnO porous films for wound healing. Int J Biol Macromol. 2020; 157:135-145. PMID: 32339591.
80. Khotimchenko M. Pectin polymers for colon-targeted antitumor drug delivery, International Journal of Biological Macromolecules, 2020; 158: 1110-1124.
81. Jin M. et al. Faecal microbiota from patients with cirrhosis has a low capacity to ferment non-digestible carbohydrates into short-chain fatty acids. Liver Int. 39 (2019) 1437–1447. PMID: 30919578.
82. Juloski JT. et al. Colorectal cancer and trace elements alteration. J. Trace Elem. Med. Biol. 2020; 59: 26451.
83. Tian G et al. In vitro Anticancer Activity of Doxorubicin-Loading Pectin Nanoparticles. J. Pharm. Biomed. Sci. 2016; 6: 338–342.
84. Zhu J et al. Preparation and characterization of pectin/chitosan beads containing porous starch embedded with doxorubicin hydrochloride: A novel and simple colon targeted drug delivery system. Food Hydrocolloids 2019; 95:562-570.