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Review article

Saccharides, oligosaccharides, and polysaccharides nanoparticles for biomedical applications

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ABSTRACT

Modern requirements for designing efficient nanocarriers against diseases such as cancer are very complex. A suitable nanocarrier should indeed remain colloidally stable in the body, be biodegradable, target specific tumor cells, and release efficiently drugs. These challenging tasks can be overcome by using the chemistry of saccharides and polysaccharides. We discuss here recent applications of carbohydrates-based materials for providing biodegradability, enhancing contrast in bioimaging, a stealth effect for controlling the composition of protein corona, and targeting ability.

1. Introduction

Saccharides, polysaccharides, and glycoproteins are fascinating molecules that play a key role in biological processes. Compared to proteins and polynucleotides, polysaccharides represent a family of polymers with very large variety of architecture (linear or branched) and type of linkages connecting the monomer units. Glycoproteins are key molecules in crucial biological processes such as immune defense, fertilization, and cell growth [1]. Polysaccharides such as cellulose, xylan, and chitosan are encountered in nature as structural material to build cell walls of plants and the shells of crustaceans and insects. Other polysaccharides such as glycogen, amylose, and amylopectin are very important for storing sugars in animals and plants. Synthetic carbohydrates have been prepared as vaccines [2] and conjugated with drugs [2, 3]. Oligosaccharides were found to possess anti-angiogenic and anti-tumor features in-vivo [4]. Moreover, cyclodextrins which are cyclic oligosaccharides, act as guest for the delivery of drugs [5]. Moreover, with the emergence of nanotechnology, glycans are now used to functionalize or prepare materials for drug-delivery, enzyme inhibition, or biosensors [6]. Carbohydrates can be also included as pendant groups or chains in polymers and dendrimers to form glycopolymers [7, 8] and glycodendrimers [9–11], respectively. These new classes of materials are suitable as drug-delivery systems and tissue engineering [12]. One of the main application of carbohydrates in biomedicine is the use of the recognition and internalization of carbohydrates or molecules or nanoobjects functionalized with carbohydrates by cell surface mammalian lectins [13]. Although multivalency, i.e. the binding of multiple motifs of a ligand on a target, multivalent ligand, was found to overcome the low affinity between carbohydrate and lectin receptors [14], they can interfere with lectin-mediated biological processes. Some authors have therefore proposed that the role of promiscuity was more important than multivalency for the development of efficient glycomimetics [15].

Interesting reviews related to the use of carbohydrates for the synthesis of nanoparticles were published. A review from 2008 is related to polysaccharide-based nanoparticles as drug delivery systems, but does not deal with nanoparticles from other types of carbohydrates such as mono-, di-, and oligosaccharides [16]. One review from 2012 discussed about dendrimers coupled with peptide- or saccharide groups for targeted drug delivery [17]. This review was limited to glycodendrimers. In 2013–2014, several reviews about glyconanoparticles have been published. They mainly focused on surface modification of inorganic nanoparticles (including gold, iron oxide, carbon nanotubes, graphene, silica, and quantmum dots) with carbohydrates for biomedical applications [6, 18–21]. A recent review from 2016 describes the use of carbohydrate-based amphiphilic nanocarriers for cancer therapy [22]. Finally, a review from 2015 mainly focused on nanocarriers decorated or synthesized from carbohydrates, with a focus on how the presence of carbohydrate in nanocarriers rendered the delivery of drugs more suitable to specific sites in the body [23]. We discuss here the applications of carbohydrates, essentially mono-, di-, and polysaccharides, for the fabrication of nanoparticles or the modification of the surface of organic/inorganic nanoparticles for biomedical applications. Carbohydrates are either used as core material to form biodegradable nanoparticles or as shell to provide nanoparticles with controlled release, stealth effect, or targeting via specific interactions

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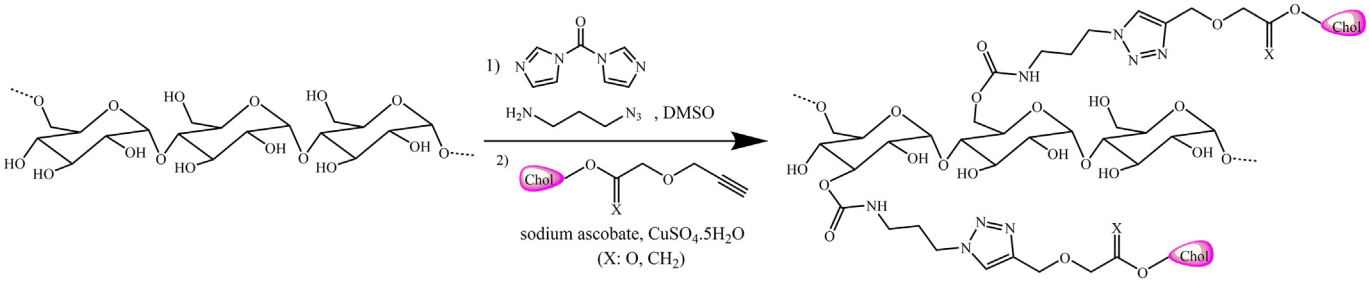

Fig. 1. Synthetic routes for the formation of acid-stable cholesteryl pullulan (acS-CHP) and acid-labile cholesteryl pullulan (acL-CHP) [50].

between proteins and carbohydrates. Moreover, saccharides at the surface of nanoparticles can act in some cases as gate to control the release of payload from nanoparticles, a phenomenon which is also discussed herein. Amphiphilic glycopolymers/glycodendrimers, polysaccharides, and inorganic nanoparticles modified with saccharide groups are also discussed in the present review.

2. Polysaccharide nanoparticles

Polysaccharides possess diverse types of functional groups including hydroxyl, amino, carboxylate, sulfate, and ester groups. Therefore, a cornucopia of reports has been dedicated to the chemical modification of polysaccharides for obtaining diverse derivatives [24–29]. Some polysaccharides and their derivatives such as alginate, starch, and especially chitosan have mucoadhesive properties, which were reported to be due to a balance between hydrogen bonding, electrostatic attraction, and hydrophobic effects [30]. Thanks to their biocompatibility, availability and non-toxicity, polysaccharides are outstanding materials for preparing nanoparticles (NPs) for biomedical applications [16, 31–33]. The compatibility of nanoparticles with the immune system [34] and their biodistribution [35] are significantly affected by their surface chemistry. Moreover, multifunctional nanoparticles containing imaging agents, targeting agents, drugs, and biocompatible polymers have been introduced as high performance nanomaterials for biomedical applications [36].

The methods for preparing nanoparticles based on polysaccharides can be categorized in the following types: (1) Synthesis of amphiphilic derivatives of polysaccharides and their association to form nanoparticles [16, 37, 38]; (2) Surface modification of inorganic/organic nanoparticles by polysaccharides [16, 32]. (3) Chemical or physical crosslinking of polysaccharides [16].

The incorporation of hydrophobic molecules in the hydrophilic structures of polysaccharides is a straightforward method. Diverse types of hydrophobic agents including cholesterol, drugs, fatty acids, and polymers have been conjugated to the polysaccharides. Nanogels based on cholesterol-modified pullulan (CHP) have been evaluated as carriers for the delivery of proteins [39–45]. Proteins were loaded into CHP due to strong hydrophobic interactions. Hydrogel nanoparticles of cholesterol-modified pullulan (CHP) were prepared [46] and their complexation with bovine serum albumin (BSA) was studied [45]. Firstly, pullulan was hydrophobized by reaction of hydroxyl groups of pullulan with an isocyanate derivative of cholesterol. Self-assembly in water of CHP with various degree of substitution produced nanoparticles with a radius of gyration (R_G) around 15 nm. Cholesterol groups provided non-covalent crosslinking between pullulan chains. Therefore, higher degree of substitutions yielded denser nanoparticles with smaller sizes. Complexation of BSA with CHP nanoparticles showed that each BSA molecule (M_w = 67,000 g mol^{-1}) produced complex with one CHP nanoparticle. In other reports, the authors proved that depending on the molecular weight of the protein, one CHP nanoparticle can make complex with various amounts of proteins. Each CHP nanoparticle was able to form stable complexes with a dimer of α-chymotrypsin (M_w = 50,000 g mol^{-1}) [47], four cytochrome *c* molecules (M_w = 12,500 g mol^{-1}), or ten insulin molecules (M_w = 5735 g mol^{-1}) [48]. BSA was tightly complexed to CHP nanoparticles and no release of BSA was detected even after one week. Due to the complexation, the BSA was more stable against heating and denaturant. Whereas free BSA can be unfolded in the presence of 9 M urea or upon heating around 60 °C, complexed BSA tolerated these conditions. Neutral and cationic nanogels (~ 30–40 nm) from CHP were loaded with *C. Botulinum* type-A neurotoxin subunit antigen Hc (BoHc/A) and evaluated as a new vehicle for adjuvant-free intranasal vaccine to immunize mice intranasally [49]. The performance, for creating BoNT/A-specific antibody response, of the neutral CHP-BoHc/A material was the same as the naked BoHc/A. On the other hand, the cationic CHP could interact strongly with HeLa membrane cells through electrostatic interactions with the anionic epithelial cell layer followed by endocytosis. Effective in vitro delivery of proteins in cells with cationic CHP was proved in another report [42]. Furthermore, in vivo studies revealed a successful delivery of BoHc/A to the nasal mucosa that remained in the nasal tissues for > 2 days whereas naked BoHc/A cleared from the nasal cavity 6 h after administration [49]. Two derivatives of cholesterol with ester or vinyl ether bonds were conjugated to pullulan via click reaction and used as protein carriers. Acid-stable cholesteryl-pullulan (acS-CHP) and acid-labile cholesteryl- pullulan (acL-CHP) bearing 1.7 cholesterol groups per 100 pullulan glucose units were synthesized (Fig. 1) [50]. Nanogels of acS-CHP (18 nm) and acL-CHP (27 nm) were obtained by self-assembly of the polymer conjugates at neutral pH value. The pH value did not show any effect on the swelling of acS-CHP nanogels. On the contrary, ~ 135% increase in the swelling of acL-CHP was recorded after 8 h at pH 4.0. Around 80% of the linkages to cholesterol units were degraded. These studies showed that acL-CHP nanogels were good candidates for protein delivery because of the formation of stable complexes with proteins at neutral pH value. The proteins were released upon acidification.

Heparin is a well-known glycosaminoglycan used as biological drug for thrombosis and haemostasis [51–53]. Hydrophobic drugs were conjugated to heparin through its carboxylate groups to form polymer-drug conjugates. Doxorubicin was conjugated to dendronized heparin through a hydrazone bond (Fig. 2) to produce pH-responsive drug conjugates for breast tumor therapy [54]. The obtained prodrug with 9.0 wt% Dox was self-assembled in nanoparticles with an average size of ~ 90 nm. After 56 h, around 20 and 80% of conjugated Dox was released from the nanoparticles at pH 7.4 and 5.0, respectively. In vitro cytotoxicity studies using mouse breast cancer cell line (4 T1) indicated that after 48 h unmodified heparin was not toxic whereas heparin-Dox exhibited an IC_{50} of 300 ng/mL. In fact, toxicity of heparin-Dox was approximately 11 times higher than free Dox.

Various amounts of dexamethasone (Dex) were conjugated to a heparin-hydrazide derivative to produce amphiphilic polymer conjugates with ~ 6–13 wt% dexamethasone (Fig. 3) [55]. Nanoparticles with an average size ~ 140–170 nm were formed by self-assembly and were used to entrap Dox. Relatively slow release profiles were detected for both conjugated dexamethasone and entrapped Dox. Indeed, at pH ~ 5.0 only around 18% dexamethasone and 23% doxorubicin were released after 3 days. At pH ~ 7.4, ~ 3% Dex and 7% Dox were