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Review

A review of natural polysaccharides for drug delivery applications: Special focus on cellulose, starch and glycogen

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ABSTRACT

Natural polysaccharides are renewable with a high degree of biocompatibility, biodegradability, and ability to mimic the natural extracellular matrix (ECM) microenvironment. Comprehensive investigations of polysaccharides are essential for our fundamental understanding of exploiting its potential as bio-composite, nano-conjugate and in pharmaceutical sectors. Polysaccharides are considered to be superior to other polymers, for its ease in tailoring, bio-compatibility, bio-activity, homogeneity and bio-adhesive properties. The main focus of this review is to spotlight the new advancements and challenges concerned with surface modification, binding domains, biological interaction with the conjugate including stability, polydispersity, and biodegradability. In this review, we have limited our survey to three essential polysaccharides including cellulose, starch, and glycogen that are sourced from plants, microbes, and animals respectively are reviewed. We also present the polysaccharides which have been extensively modified with the various types of conjugates for combating last-ditch pharmaceutical challenges.

1. Introduction

With the emergence of last-ditch pharmaceutical challenges identifying a new class of therapeutic materials and utilziation of sustainable sources to produce polymeric material through cost-effective strategies are equally important. During the last half of the century, polysaccharide materials were widely used by mankind for its remarkable applications in the field of biomedical sciences [1]. Polysaccharides are an elaborate form of carbohydrate derivatives containing chains of mono-saccharide subunits with intermediate linkages. They are naturally found in plants [2], microbes and animal sources [3]. The broad availability, sustainability of plant biomass is considered as a potential bio-factory for the generation of various types of polysaccharides. The universal sustainable biomass energy source which is about 100 EJ/a and plants were contributed 41.6 EJ/a approximately [4]. Amongst the plant-derived polysaccharides, cellulose is the most abundant and naturally available polymer [5] which signifies 1.5×10^{12} tons (metric tonne) of total annual biomass from eco-friendly and bio-compatible products [5]. Cellulose is assembled in single chain-forming fibers, and roughly 36 individual cellulose molecules combined in the form of elementary fibrils (protofibrils), which combined into larger microfibrils, and formed to cellulose fibres [6]. Cellulose was originally derived from a variety of high fibre containing plants cotton, orange peels, oat husk, banana peel and sugarcane bagasse [7–12]. It is also found in certain species of bacteria [13], and the broad spectrum products have been applied in day-to-day life for more than 150 years [6]. Cellulose is a stable, water-insoluble and fibrous polysaccharide with the chemical structure of $(C_6H_{10}O_5)n$, organized by linear D-glucopyranose units with β-(1–4)-glycosidic bond [14,15] and has a role in the structural organization, plant growth and maintaining the tensile strength [16]. Bacterial cellulose production and extraction from raw ingredients are associated with a higher environmental burden compared to the nano-fibrillated cellulose (NFC) [17]. Various modifications to its chemical structure benefited by facilitating conjugation of required moieties in a cheaper route. The new dynamics in nano-technology offers the native cellulose fibers to be chemically modified into “nano-cellulose” materials in the form of cellulose nanocrystals or nanowhiskers, [18] cellulose nanofibers (CNF) [19] with rigid, rod-like structures such as [6], bacterial nanocellulose (BNC), [20] and cellulose acetate for advanced bio-materials. The

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economic burden, bulk raw materials consumption, and low production are the on-going concerns of industrialization. We have discussed the recent reports of high-yield production where it can be possibly applied to large-scale industries.

The neutral bio-polymers of starch are richly found in various plants, green algae, red algae, and glycogen is abundantly found in animal liver and muscles, certain species of bacteria and yeast [21–23]. Semi-crystalline state of the starch with its composition constituting non-branched amylose and amylopectin are widely arranged by 5–6% α-(1→6) linkages [24]. Glycogen is organized by a high percentage of random branching points and also comprises short linear chains. The chain length arrangements dictate the structural properties of glycogen. Interestingly, the thermoacidophilic red microalga *G. sulphuraria* accumulates a unique and highly branched glycogen with 18% of α-(1→6) linkages under heterotrophic conditions. Thus, the lack of longer chains and small molecular size protects the *G. sulphuraria* from stress and nutrient-limited conditions [21]. Glycogen has unique properties such as high bio-compatibility and bio-degradability, high availability, high water solubility, and ease of functionalization [25]. In the following sections, structurally engineered or fabricated, self-assembled, polysaccharides for pharmaceutical applications will be discussed.

2. Pharmaceutical benefits of modified polysaccharides

The major concern in the selection of suitable inexpensive polymers without losing specific bio-activity and minimizing serious side effects [26] are potentially negated by natural polysaccharides such as cellulose, starch, and glycogen [27]. These molecules were engineered onto biologically superior molecules by numerous methods such as chemical modification, co-polymer grafting, and atom transfer radical polymerization (ATRP) to promote its candidature in bio-pharmaceutics [28]. Here we have discussed the exciting applications of modified polysaccharides as drug delivery vehicles. Compared to starch; solubility is the main hurdle rendering the wide utilization of cellulose and its derivatives in drug delivery applications [29]. However, the recent efforts have made alternative platforms to overcome its limitations through hydrolysis of higher molecular weight cellulose to smaller fragments which can vividly enhance its water solubility. Commercially available cellulose derivatives, such as ethyl cellulose (EC) [30,31] and carboxymethylcellulose (CMC), [32] are excellent starting materials for easy tailoring properties and superior functions. Some ionic liquids (ILs) at room temperature were identified as suitable green solvents for relevant processes including catalysis. They have recently been utilized to synthesize highly substituted cellulose derivatives by directly using high molecular weight cellulose as starting materials. [33,34]. Reproducible plant materials are considered to be potential biofactories for the generation of cellulose and its derivatives. The plant materials utilized for the production of cellulose are tabulated in Table 1.

2.1. Engineered Cellulose nanocarrier for drug delivery

Drug loading ability of natural cellulose is significantly low, and hence the modified cellulose with enhanced properties is utilized as carriers in drug delivery applications [56,57]. Cellulose nanocrystals (CNCs) is grafted with polyethyl ethylene phosphate (PEEP) (CNC-g-PEEP) through the ring-opening polymerization (ROP) and Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) by “click” chemistry methods. The azide-tailored negatively-charged CNC-g-PEEP nanocrystals were encapsulated with the anticancer drug doxorubicin (DOX) through electrostatic interactions and released the drug efficiently for targeting cancer cells [58]. CNC tailored with a cationic surfactant cetyltrimethyl ammonium bromide (CTMAB) followed pseudo-second-order kinetics with multimolecular layer adsorption (Freundlich adsorption) of two water insoluble anticancer drugs luteolin (LUT) and luteoloside (LUS) for enhanced anti-cancer activity [59].

Cellulose-based bio-hybrid nano-materials were developed with low polydispersity via grafting with hydrophobic poly (methyl methacrylate) (CE-g-PMMA) by precise long polymer chains controlled atom transfer radical polymerization technique. CE-g-PMMA represents high bio-compatibility with hydrophobic drug loading capacity. The anticancer drug betulinic acid (BA) loaded CE-g-PMMA green nano-particles delivered greater anticancer effect with reduced off-targeted side effects compared to the free BA [60]. Ethyl cellulose (EC) graft copolymerized with poly (2- (diethylamino) ethyl methacrylate) (PDEAEMA) loaded rifampicin micelles has also been explored for controlled drug release [31]. It has been reported that EC nano-crystals (ECNCR) and EC nanocarriers (ECNCS) showed differential release patterns of the encapsulated drug where ECNCS represents high therapeutic potency of dexamethasone (Dex) drug release in commercial cream and ECNCR delivers poor solubility or weaker biological effects [61]. Therefore, modified cellulose based polymeric systems were effectively used for sustained drug delivery and minimized unintended target reach.

2.2. CNC-Electrospun (ES) method for sustained release

Recently electrospinning method for the fabrication of drug-loaded polymers have gained more attention due to (a) unaltered structure, and bio-activity of loaded drugs during the spinning process, and (b) lessen in vitro drug burst release and (c) also can enclose a variety of biomolecules [62,63]. It has been demonstrated that (1-butyl-3- methylimidazolium chloride) electrospinning of cellulose micro/nanofibers (CMF) matrices loaded with ibuprofen (IBU) showed the faster release of drug within 5 h [64] whereas in the berberine hydrochloride embedded CE membrane, the release equilibrium was extended to 6 h [65]. Electrospun membrane of poly(3- hydroxybutyrate-co-3-hydroxy valerate) (PHBV) exhibited hydrophobicity, high crystallinity, and weak mechanical properties with fast drug release profile of tetracycline hydrochloride (TH) due to their hydrophobic surfaces. The mechanical, hydrophilic properties of PHBV were improved by CNCs addition which contributed to strong hydrogen bonding between PHBV and CNC. The modified nano-composite expressed greater cytocompatibility, high drug loading efficiency of 98.8%, and more than 86% drug was released to a period of 540 h for the nano-fibrous composite membranes with 6 wt. (%) CNC content [63]. The hydrophilicity, eco-friendly, bio-degradable, and more exceptional processability of almost all the form of cellulose products can be successively used in wide range of applications. For example, the presence of approximately two acetate groups on every three hydroxyl (− OH) groups in the CA is employed as calcium carbonate ($CaCO_{3)}$) crystal modifier and generation of calcite micro-tubes (Fig. 1). These micro-tubes could act as a suitable material for drug delivery applications [66]. The use of polymer blends in a drug delivery system expands the tuneability of the physical, mechanical and chemical possessions of the drug-loaded fibers. Such improvements benefit controlled drug release, and the release could be altered by altering the amount of polymers in the mixture [67].

2.3. Microcapsules for sustained drug release

NCC was fabricated on the microcapsules template melamine formaldehyde (MF) using the layer-by-layer (LBL) assembly drug carrier system. The nano-fibrous nature of NCC with the inner porous surface was used to load DOX. The drug in the CH/NCC was confirmed under confocal microscopy with fluorescent red color in the periphery of the particles due to multilayers assembly and fluoresces red throughout the hollow microcapsules, confirms the drug load in the aqueous interior (Fig. 2) [68]. Lu Et al. developed a cost-effective nano-fibre drug composite using water-stable corn protein zein electrospun with hydrophobic EC and incorporated with Indomethacin (IND). The free OH-groups in EC, zein, and IND could act as proton donors, and also carbonyl groups serve as potential proton receptors [69]. The hydrogen links between zein-EC, EC-IND, zein-IND, and IND themselves may exist