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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

Table 1
Various Phyto-based materials used for the cellulose production, synthesis condition, mechanical, biological and chemical pretreatment process and the obtained percentage of purified cellulose are tabulated.

Plant raw materials	Purification	Chemical/biological pre-treatment	Mechanical Pre-treatment	Cellulose composition (Wt. %)	Ref.
sugarcane bagasse - fiber, pulp, bleached pulp/pith, pulp, bleached pulp	Bleaching/ No bleaching	Hydrolysis-H_2SO_4	Retch mill	45, 83.7, 87.4 / 38.4, 67.1, 84.7	[35]
Sugar beet pulp	NaOH / $NaclO_2$	No	Blending	20	[36]
Ricinus communis	NaOH / Acetic acid	Acid detergent	–	65	[37]
acacia bark	Bleaching /NAOH, H_2O_2	No	Milled - Liquid nitrogen	–	[38]
Cornstalk	NaOH and chloroacetic acid	No	Ground – mesh sieve	30 – 40	[39,40,41]
Oil palm	Bleaching - $NaclO_2$/ Acetic acid	Hydrolysis - H_2SO_4	Power cutting mill (0.2 mm)	42.43	[42]
Flax *(Linum usitatissimum L.)*	NaOH / OHac	Hydrolysis-H_2SO_4	Oil bath (260 °C) freeze dry	81.56	[43,44]
Eucalyptus globulus pulp	Bleaching	pentafluorobenzoyl chloride	Vacuum dry (60 °C)	44.3	[45,46]
Phyllostachys pubescens i Fibres ii Parenchyma	acidified $NaclO_2$	benzyl/ethanol, HCL	homogenization – mesh sieve	i. 74.36 ii. 68.76	[47]
softwood pulp	Bleaching	–	PFI mill homogenize 22,000 rpm, 2 h	95	[48]
Hibiscus cannabinus v36	i bleaching/NAOH ii unbleaching	Anthraquinone	Cooked (rotatory digester) - grind (homogenize)	i 91.8 ± 0.9 ii 82.3 ± 0.6	[49]
Gossypium hirsutum	Acidic hydrolysis	H_2SO_4	ground - Wiley mill	81.51	[50]
Cotton gin waste	NaOH, sodiummono chloro acetic acid	H_2SO_4	Dried in oven	94	[51]
Phyllostachys heterocycla	NaOH, Urea	No	Cut	43.8	[52]
Coconut husk	NaOH, H_2O_2	H_2SO_4, acetic acid	Hydrothermal reactor (110 °)	70	[53]
Passion fruit peels	NaOH, H_2O_2	H_2SO_4,	Pulverized / sieved through 140-meshscreen	58.1	[54]
Setaria glauca (L)	NaOH, $NaclO_2$ and H_2O_2	HCl	Dry / room temperature	–	[55]

within the zein/EC/IND composite nanofibrous membrane, and it delivers controlled drug release which provides new insights for pharmaceutical benefits (Fig. 3) [70]. The intermolecular interaction between the drugs and EC determines the nano-fibrous drug carrier stability and also influences the IND release [71]. EC, zein and IND molecules had free hydroxyl groups, found in EC, Zein, and IND donate a proton, and the carbonyl groups served as the proton receptors [69]. The above discussed conventional drug delivery method release systems are limited with a significant drawback of premature or imperfect drug release, which was successfully tackled using a combination of pH- and time-dependent delivery system to the lower GI tract [72].

In another exciting report, hydroxyethyl cellulose (HEC) covered Fe_3O_4NPs loaded with DOX; a targeted drug delivery system was achieved with reduced oxidation behavior which induced cellular toxicity of Fe_3O_4NPs during hyperthermia treatment. This observation is highly encouraging for its implication as nano-drug carrier system in various therapeutic drug delivery applications [73]. ARGET-ATRP achieved cellulose membrane (CM) surface modification through polycarboxybetaine brush grafting (Activator Regenerated by Electron Transfer) ring opening reaction method delivered excellent blood compatibility [27]. Cellulose has been extensively applied as implantation vehicle in cellular therapy. Methylcellulose is gelling with laminin- collagen matrices promoted the survival of Schwann cells and promoted graft vascularization [74]. The Carboxymethylcellulose CMC-Calcium alginate (CA) beads loaded anticancer drug 5-fluorouracil (5-FU) formulation was primed by ionic gelation method, for prominent mucoadhesivity and pH-responsive drug release into the colonic environment. Thus, the succession of the potential deliverable formulation can be modified by altering the composition of beads [75]. Engineered cellulose has been successfully used as a thermal-sensitive system for drug delivery. The insolubility of CEL in the liquid phase was tailored to water-soluble by modifying the hydrophilic groups. Thus, the change enables an equilibrium of hydrophobic and hydrophilic moieties which could make CEL gel at prominent temperatures [76].

2.4. pH-responsive platforms for cellulose drug release

Undulations in the pH along the gastrointestinal tract is the major obstacle for oral drug delivery system. To overcome this setback, cellulose-based materials were engineered especially for the enhanced pH-responsive drug delivery micelles. These systems can be tailored to circumvent the release of specific drugs in the gastric environment

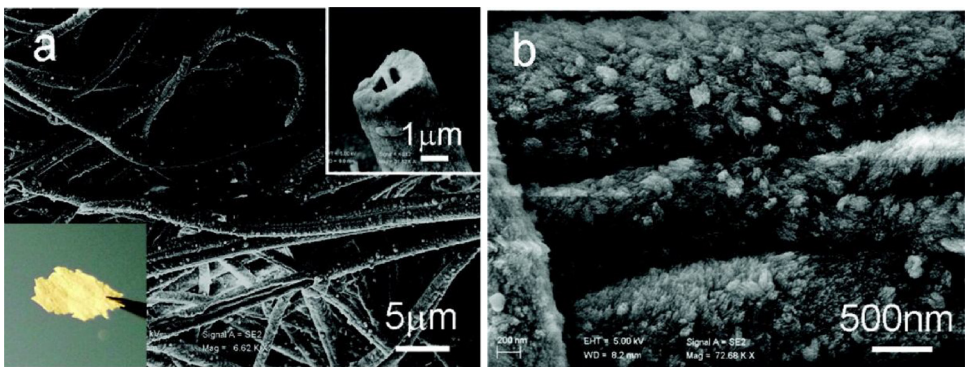

Fig. 1. (a) Electron microscopic image of calcite microtubes after the $CaCO_3$/CA composite was exposed with acetone for 30 min. Cross-sectional view of a single $CaCO_3$ microtube (top right) and a photograph of a $CaCO_3$ network after the removal of CA fibers (bottom left).(b) Enlarged image of the calcite microtubes shown inset panel a.
(Reproduced with permission from Ref. [66] Copyright © 2011, American Chemical Society).

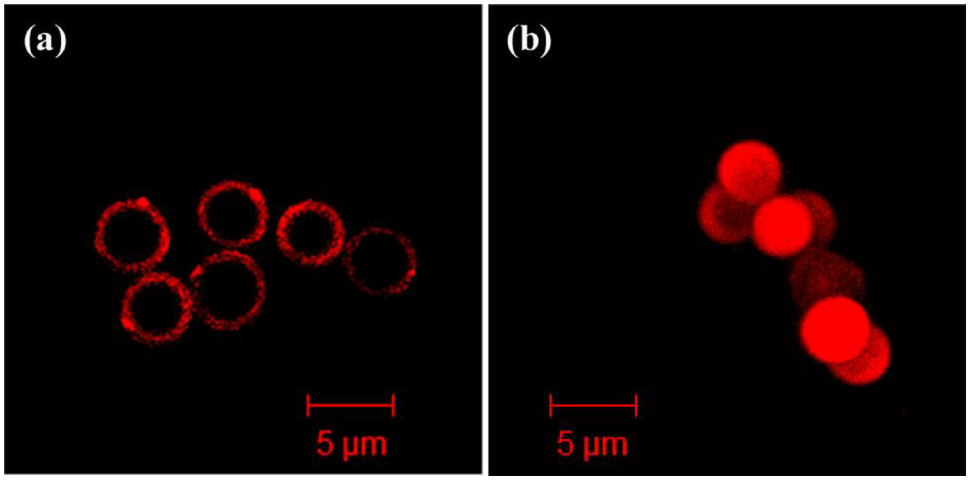

Fig. 2. CLSM image of DOX-loaded (a) MF particles coated with LbL assembled $(CH/NCC)_5$ and (b) hollow microcapsules. The red fluorescence is due to doxorubicin. (Reproduced with permission from Ref. [68] Copyright © 2014 American Chemical Society).

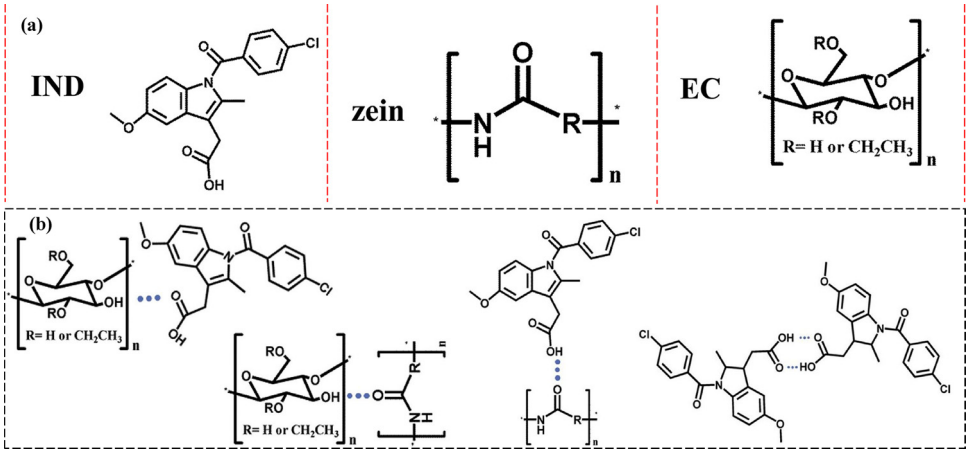

Fig. 3. (a) molecular structures of EC, zein, and IND (b) probable hydrogen bonding between EC-IND, zein-EC, zein-IND, and IND-IND. (Reproduced with permission from Ref. [70] Copyright © 2017 Elsevier).

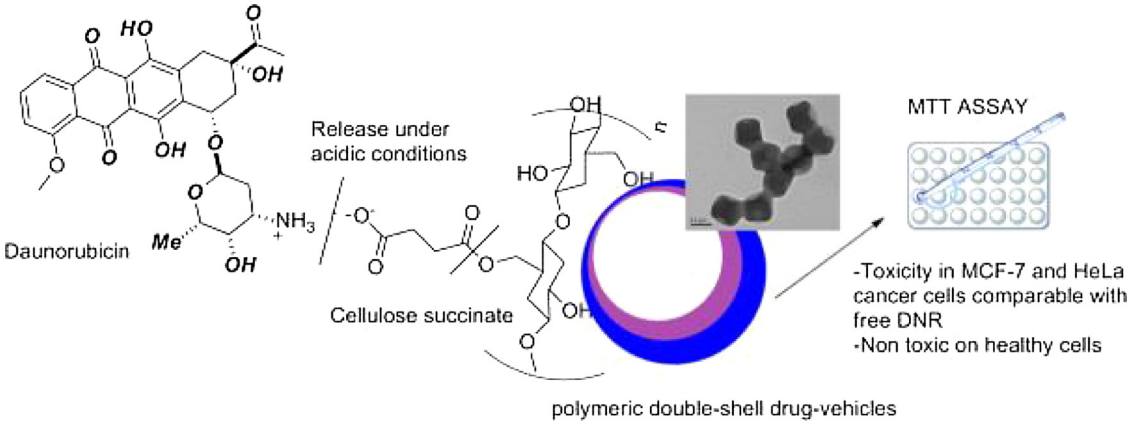

Fig. 4. Modified cellulose double layer microspheres loaded with daunorubicin, free daunorubicin and its cytotoxicity assessment using MCF-7 (breast cancer) and HeLa cells (cervical cancer) at various concentration and time intervals.
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while promoting site-specific delivery in the system [77,78]. Recently, the bacterial cellulose (BC) was embedded onto GO, and the BC/GO nano-composite was loaded with ibuprofen IBU to develop the pH-dependent release drug delivery system [79]. Cellulose chain modified through cross-linking poly-caprolactone (PCL) with lactic acid/glycolic acid/dimethylol-propionic acid loaded with felodipine was explored for pH-responsive vaginal and colon-specific drug delivery applications [80]. pH and thermosensitive double layered cellulose based microspheres were developed by poly(methyl acrylic acid-co-*N*-isopropylacrylamide- co-ethyleneglycol dimethacrylate) polymer coated with modified cellulose succinate (CS) (P(MAA-co-NIPAAM-co-EGDMA)@CS) via sol-gel method, copolymerization, distillation

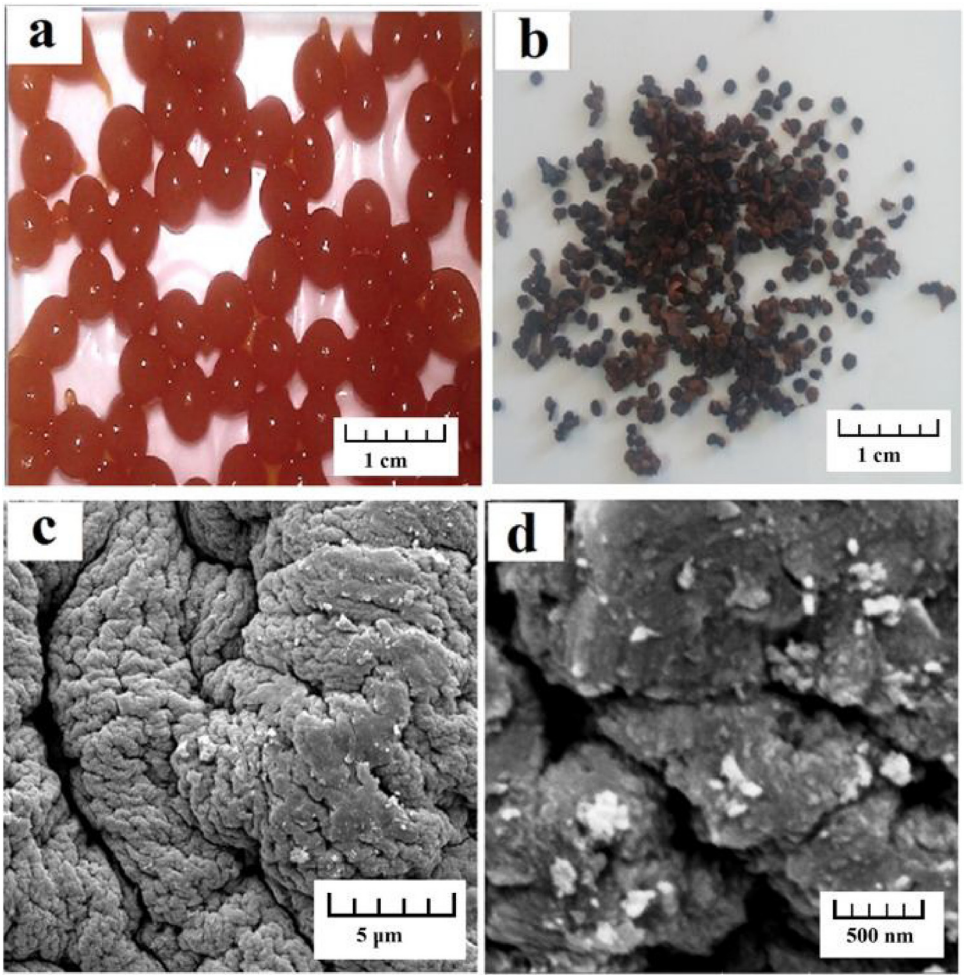

Fig. 5. (a) wet and (b) dry image of CMC/LDH-CPX nanocomposite beads. (c, d) SEM image of CMC/LDH-CPX nanocomposite at low and high magnification. (Reproduced with permission from Ref. [82]. Copyright © 2015 Elsevier).

precipitation, and chemical deposition method. The spheres loaded with daunorubicin (DNR) expressed sustained drug delivery exhibiting toxicity to cancer cells while sparing normal cells (Fig. 4) [81].

2.5. Cellulose for oral drug delivery applications

Delivering various therapeutic drugs and maintaining a pharmacological dose and activity across gastric pH is a significant setback after oral administration of certain vital drugs. To circumvent this issue, multiresponsive CEL derived materials were used for oral delivery due to pH-sensitive swelling nature and its cytocompatible behavior. The CMC hydrogel beads were encapsulated in the layered double hydroxides-Cephalexin (LDH-CPX) nano-hybrid for the gastric environment (Fig.5). The CMC/LDH-CPX expressed greater protection in the stomach pH and a controlled deliverance in the intestinal pH [82]. Together, the thermo-sensitive HPC and pH-responsive acrylic acid (AA) moiety smart microgel particles were engineered via emulsion polymerization between poly (l-glutamic acid-2-hydroxyethyl methacrylate) HPC-AA. The microgel system showed a controlled insulin delivery at intestinal pH 6.8 and very low delivery at the gastric pH 1.2 supporting its candidature for delivery drugs in the intestine and resisting gastric pH (Fig.6a,b) [83]. AA is commonly used in CEL hydrogel preparations to provide pH-responsive behavior, muco-adhesive property, enzyme inhibition, and paracellular transport [84]. A study also demonstrated the bacterial cellulose (BC) graft copolymerized with poly (AA-co-acrylamide (AM)) hydrogel carrier supplied a maximum theophylline (TP) release in simulated intestinal fluid (SIF) with pH 7 and also found the (TP) release was significantly low upon exposure to simulated gastric fluid (SGF) [85]. In an interesting study, a sophisticated zero-order sustained oral drug delivery system was developed with ketoprofen (KET) tri-layer (outer, middle and inner) medicated EC nano-fibre by a triaxial electro-spinning process. The KET ratio was upsurged towards the external of the inner fibre for gradient drug supply over 20 h [86]. In another study solubilized bacterial cellulose (BC) / acrylamide (Am) was irradiated with microwave, and the formed hydrogels were loaded with TP drug and assessed for drug delivery. Significantly higher percentage of drug release was noticed at pH 7.4, and only a minimal loss at pH 1.5 was recorded thereby indicating the effectiveness of the system in resisting gastric pH (Fig. 6c,d) [87].

Recent reports highlighted the extended applicability of cellulose derivatives in the oral delivery of proteins where CNC could act as an interfacial barrier to prevent the digestion from pepsin [88]. pH, temperature, redox-responsive copolymeric (CP) hydrogels and semi-interpenetrating network (SIPN) were developed through N-isopropylacrylamide (NIPA) CP with methacrylate carboxymethylcellulose (MACMC) and SIPN was developed through polymerizing NIPA with the incidence of CMC. The materials were linked with redox cross linkers *N,N'*-methylenebisacrylamide (BIS) and *N,N'*-bis(acryloyl)cystamine (CBA). The BIS cross-linked hydrogels expressed higher swelling and maximum release of egg white protein lysozyme at pH 1.2 in the presence of glutathione [89]. The stimuli-responsive protein carrier hydrogel system further altered by using BC graft with poly AA BC-g-P (AA) via electron beam irradiation technique without using toxic cross-linkers. The system was loaded with the Bovine serum albumin (BSA)

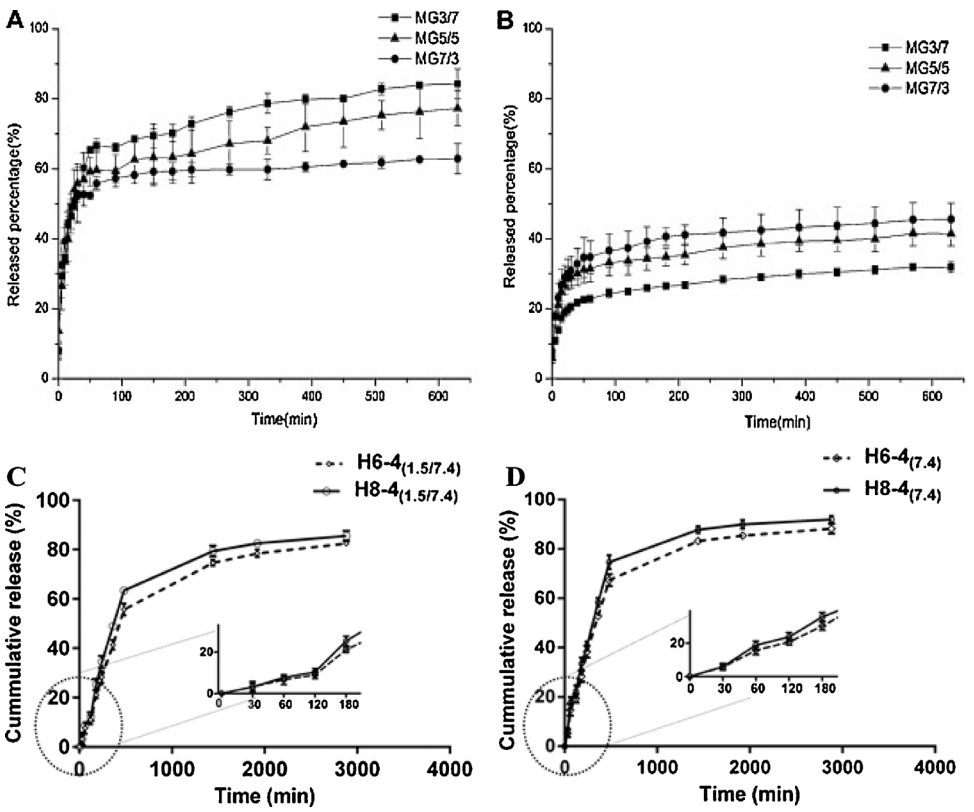

Fig. 6. (a) The collective release of insulin from the microgels at pH 6.8, (b) pH 1.2 as a function of time at 37 °C & In-vitro drug release of the superporous hydrogels (c) in buffer pH 1.5 followed by pH 7.4 (d) in phosphate buffer 7.4.
(Reproduced with permission from Refs. [83] & [87] Copyright © 2012 Elsevier & Copyright © 2014, American Chemical Society).

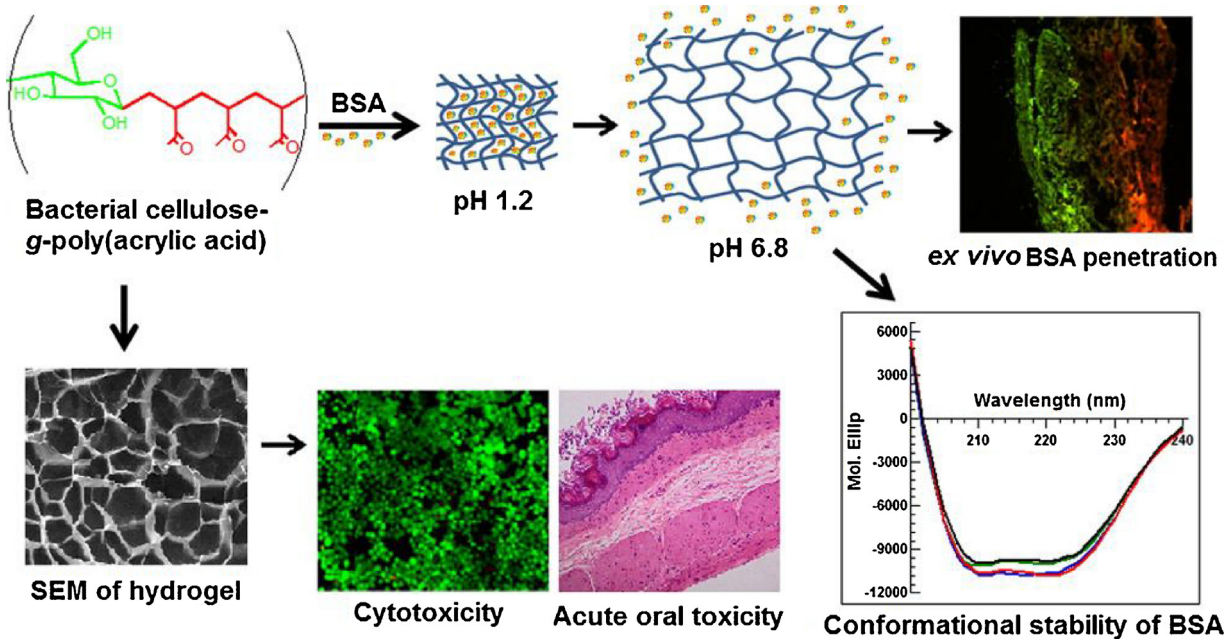

Fig. 7. Stimuli-responsive BC-g-P(AA) hydrogels system loaded BSA and its protein delivery on invitro / invivo toxicity assessment.
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and demonstrated a low level of BSA release in acidic SGF and a higher BSA penetration across the intestinal mucosa. The hydrogel system exhibited high bio-compatibility with no toxicity upon testing in *invivo* models (Fig.7) [90].

For instance, SR polyelectrolyte microcapsules were prepared by "charge controlled attraction" using CMC polyanion and poly (allylamine hydrochloride) (PAH) polycation via layer-by-layer deposition onto $CaCO_3$ micro-particles. Following the removal of $CaCO_3$ core, it resulted in capsule wall collapse and exhibited an ultrathin structure (Fig. 8). The CMC/PAH_2 hydrogel system demonstrated that the walls are permeable at acidic pH ≤ 6 and no permeability was observed at pH ≥ 7 due to the reversed pH change of capsule caused by the deprotonation shrinks the degree of electrostatic repulsion thus resulting in the closed state of capsules [91].

Hybrid hydrogel microsphere network prepared by CMC grafted with poly(dimethylaminoethyl methacrylate) CMC-g-PDMAEMA and mineralized with calcium phosphate via SBF. Thus the hybrid hydrogels displayed a lower % of swelling at pH 2.1, pH 7.4 and significantly

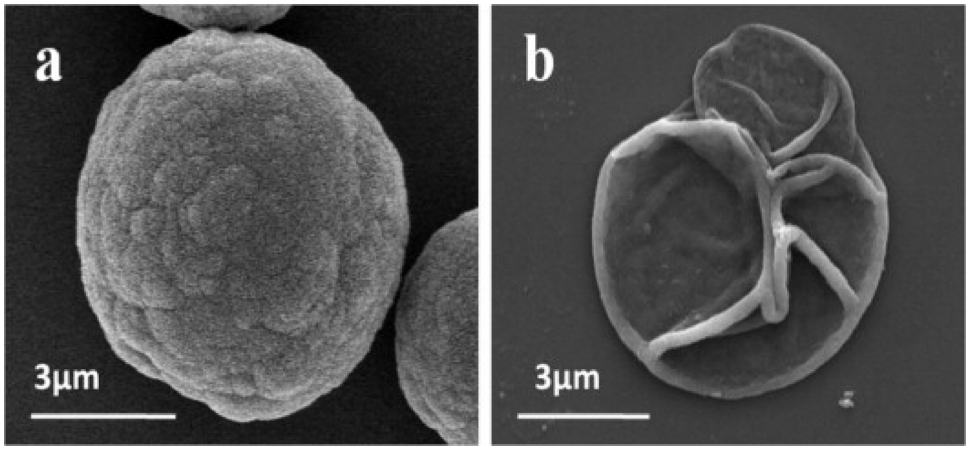

Fig. 8. (a) SEM image of $CaCO_3$ microparticle and (b) hollow microcapsule.
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delivered BSA at protracted equilibrium state [92]. BC graft with poly (AA-co-AC) by graft CP monomers (NaOH and urea) using a microwave irradiation technique. The BC-g-poly (AA-co-AM) expressed the lower level delivery of TP in SGF than SIF [93].

2.6. Injectable cellulose hydrogels

Hydrogels developed from natural polymers have been widely used for tissue engineering approaches. However, the translational potential is rendered due to batch-to-batch variation which encouraged the development of engineered polymers that can be tailored to desired structures and functions [94,95]. Researchers significantly focus on engineered cellulose-based injectable hydrogels over the decades as matrices for the controlled release of bioactive molecules and cells [96]. To provide a suitable environment for cell proliferation and nutrient exchange that mimic the native tissue, alginate-gelatin-NCC hybrid injectable hydrogel system was developed to promote the cell or biomolecules delivery for tissue engineering applications [97]. Most recently, CMC/sulphated CMC (sCMC)/gelatin cross-linked hydrogel was reported by Arora et al. [98] for the delivery of mesenchymal stem cells (MSCs) and articular chondrocytes to a cartilage defect area while enabling TGF-β1 mediated chondrogenesis. Besides the hydrogel system, sCMC mimicked heparan sulfate and thus assisted elastic binding with TGF-β1 leading to substantial delivery to the encapsulated cells. Altogether, the cellulose-based hydrogel system served as a low cost and adaptable delivery matrix for cartilage tissue engineering (Fig. 9).

Additionally, hydrogels incorporating Adipose-derived Mesenchymal Stromal Cells (Ad-MSCs) have been used to overcome the issues of low cell engraftment on the gastrointestinal complications associated radiotherapy. Silanized hydroxypropylmethylcellulose (Si-HPMC) hydrogel encapsulated Ad-MSCs exhibited a more significant therapeutic function by improving the structure of colonic mucosa impaired after irradiation [99]. Cell transplantation in vivo requires high precision in culture conditions, the usage of a proteolytic enzyme for confluence detachment and integrative adhesive agents [100], leads to disruption of extracellular matrices (ECM) and limited retention of the post-injected cell at the sites [101]. Thermo-responsive MC hydrogel system negated these potential drawbacks where MSCs developed a homogeneous spherical cell aggregate (Fig. 10) with the protection of endogenous ECM and retained their activity upon transplant via intramyocardial injection [102].

3. Structurally modified glycogen pharmaceutical potentials

Structural modification of Gly provides unique advantages to introduce a variety of bioactive species via multiple ways such as copper-catalyzed alkyne-azide cycloaddition (CUAAC), oxidative ring opening and free radical polymerization for therapeutic applications [103]. Glycogen dendrimer contains a spherical shaped small protein core (glycogenin) with a diameter of 50 nm, and molecular weight (Mw) in

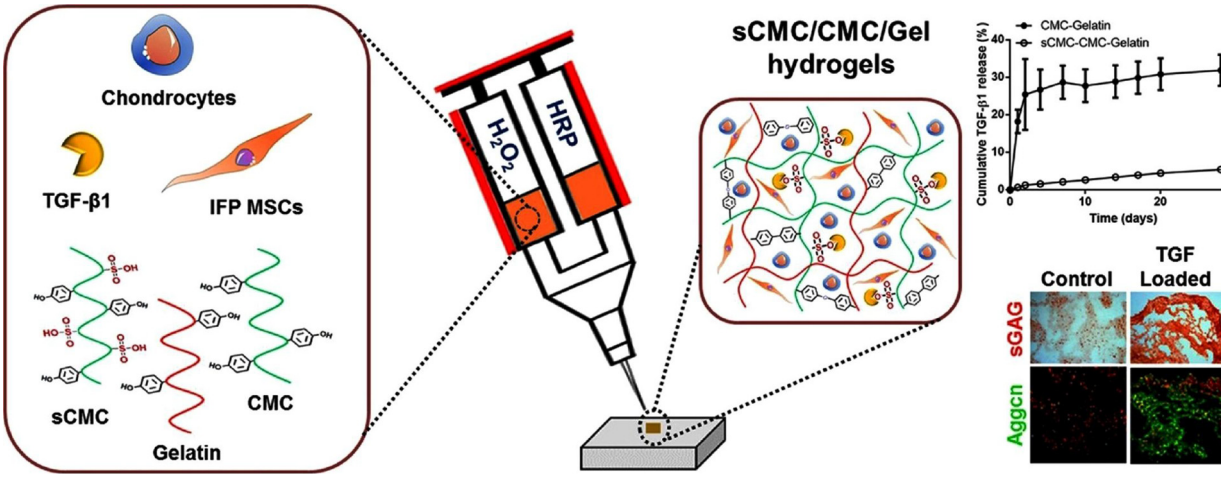

Fig. 9. Construction of novel enzymatically cross-linked injectable hydrogel composed of (CMC, sCMC, and gelatin for delivery of MSC and TGF-β1ito the damaged cartilage with high cytocompatibility.
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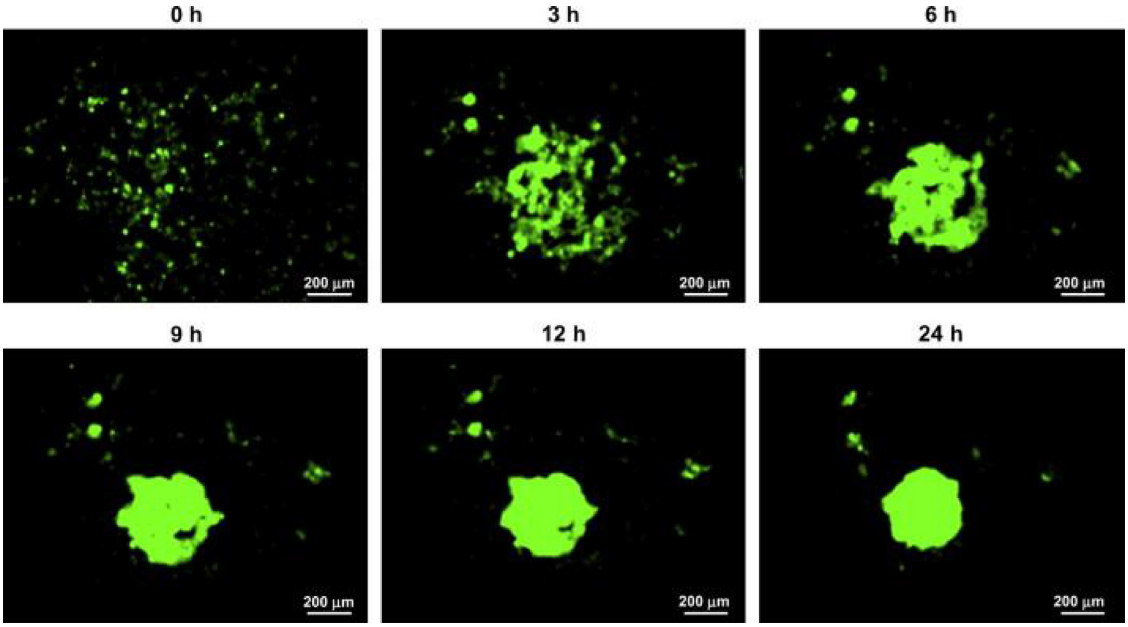

Fig. 10. Fluorescent images indicate the cell aggregate formation on methylcellulose hydrogel system. Followed by the cells were settled to the bottom, and began to self-assemble and constrict around the well and developed a single cell aggregate within 24 h.
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the range of 400KDa to few millions of daltons from the derived source likely on the complete polymerization and branching [104,105]. Under physiological conditions, the glycogen production and deprivation occurred intracellularly, and it is nearly passive to the bloodstream amylases. The administration of glycogen to the bloodstream restricts the elimination from the kidney without bio-degradation since the MW is higher than the renal threshold [22]. Due to these superior properties, the glycogen based conjugates or construction materials displayed a promising role in drug delivery and other pharmaceutical applications [106].

Engineered glycol-scaffold exhibited the multivalent binding site of lectins where the highly branched glucose polymer was activated with lactose and explored for targeting prostate cancer cells. The β- galactoside moieties strongly interact with peanut agglutinin (PNA), and binding of Gly-lectin was achieved [107]. Also, numerous hydroxyl groups present in the glycogen molecules facilitates more hydrophilic properties which ease the binding of more water molecules [108]. Cytocompatible hydrogel (cl-Gly/pNIPAm) was developed using glycogen, fabricated with N-isopropyl acrylamide (NIPAm) monomer by free radical polymerization with crosslinker ethylene glycol dimethacrylate (EGDMA) for ornidazole and 5-aminosalicylic acid (5-ASA) delivery. The targeted drug ornidazole/5ASA loaded hydrogel demonstrated extended release, whereas 97% of drugs persisted stable later 2 months. The cl-Gly/pNIPAm system was put forward as a substitute for colon targeted delivery [109]. Nano-structured glycogen were functionalized with intermediates at the particles surface and with higher degree oxidation [25]. Glycogen structure modification achieved by reductive amination of oxidative rings opening which eases the fabrication of cysteine/2-mercaptonicotinic acid (2MNA) with improved mucoadhesive properties [110]. Oyster derived glycogen structure was frequently sulfated by chlorosulfonic acid–pyridine method. Thus, the structurally engineered GG efficiently stimulated the lymphocyte proliferation at the c-6 position than the sulfated position at C2 and C3 [111]. Carbohydrate dendrite derived Cationic enzymatically synthesized glycogen (cESG) encapsulated with small therapeutic molecules tetraphenyl porphine sulfonate (TPPS) for enhanced cell death of ovarian cancer cells compared to free drug dosage. The system was further modified with short interfering ribonucleic acid (siRNA) for increased therapeutic potential [112].

4. Starch for anticancer drug delivery

The recent advancements in starch-based materials were specially tailored for controlled release of anticancer drugs by such polymeric micelles, polymeric capsules, graft, and hydrogel. Starch grafted with polyethylene glycol (Starch-g-PEG) co-polymers micelles were designed via starch grafting with carboxyl-terminal PEG. The copolymer disulphide bond cross-linked through lipoic acid (LA) with the anticancer drug doxorubicin (DOX) for efficient glutathione (GSH) responsive intracellular DOX delivery was successfully investigated [113]. A pH-responsive hydroxyethyl starch (HES) oxidized conjugate (HES-CHO) with DOX/LHRH via acid-sensitive Schiff base bond was fabricated. The target developed self-assembled micelle HES-DOX/LHRH displayed superior anticancer and anti-metastasis progression with lesser toxicity towards prostate cancer, than the free DOX·HCl and also HES-DOX (Fig. 11) [114]. Recently, potato starch-based modified micro-particulate system developed by oxidation, and polyamine coupling ligand enabled the use of radionuclides system as readymade kits and sterilized without any change for in vivo diagnostic and therapeutic applications [115]. Furthermore, a variety of renewable plant materials was successively utilized for the starch isolation and explored for pharmaceutical applications are tabulated in Table 2.

4.1. Acetylated starch modification

Native rice starch nano-crystals (SN) acetylated using acetic anhydrous with different degree of the substituent (DS) such as 0.4, 0.8 and 0.14 to different sized acetylated starch nano-crystals (ASN) platform was explored for drug delivery applications. The ASN loaded with DOX, delivered a stronger drug loading efficiency and served as potential anti-tumor drug delivery systems. DS 0.14 ASN were loaded with 6.07% of drug including a high loading efficacy of 91.1% with constant release compared to the SN and AS [125]. Native moth bean starch was modified with acetic hydride in pyridine medium and loaded with antiviral drug lamivudine (LAM) was explored for controlled drug delivery [117]. For instance, Epichlorohydrin and ethylene diamine aminated starch molecules were fabricated with iron oxide nanoparticles (IONPs) and loaded with anticancer drug curcumin was developed by co-precipitation method. The cross-linking molecules

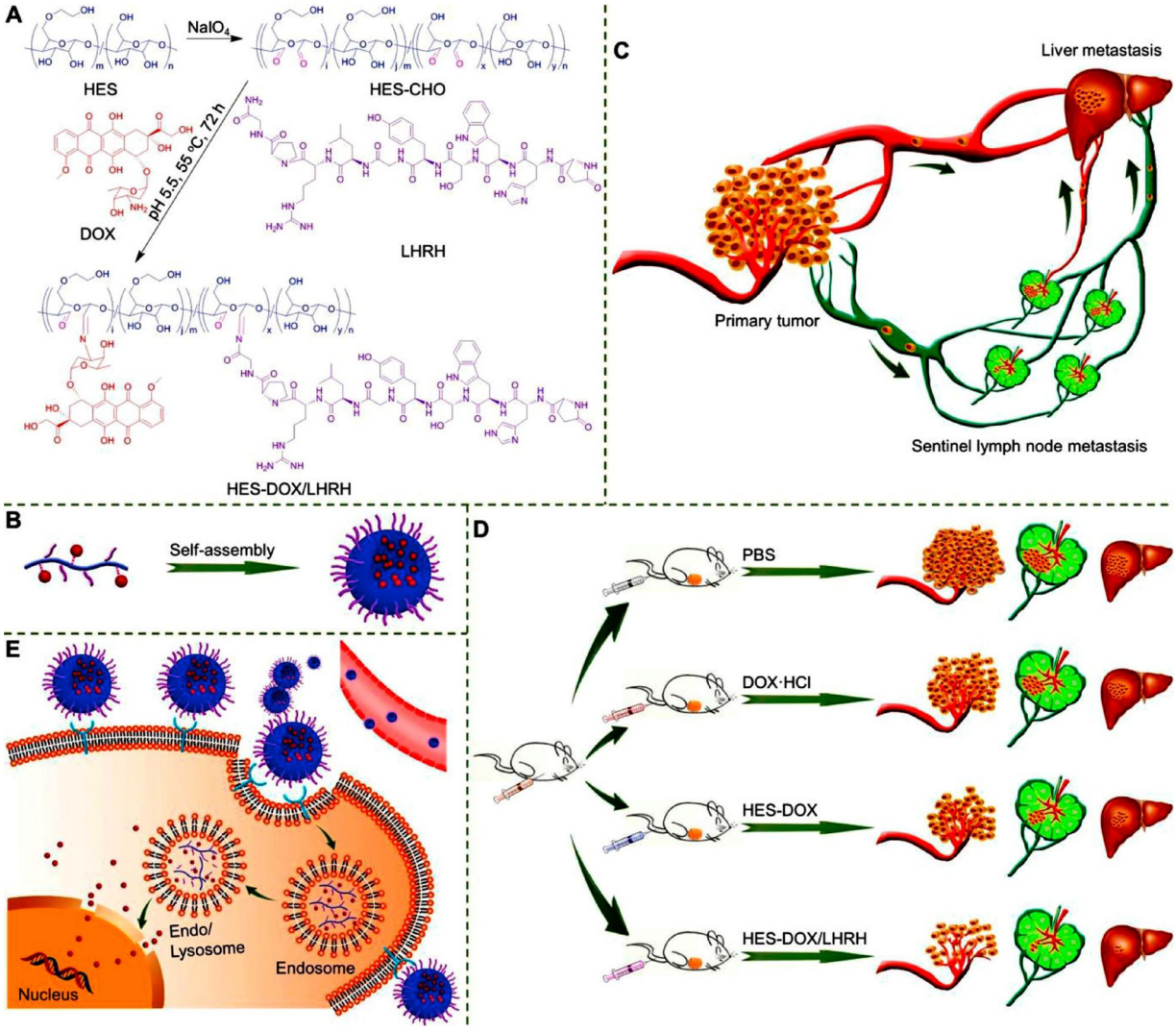

Fig. 11. (A) Synthesis of prodrug micelle, and (B) self-assembly of HES − DOX conjugate. (C) Cancer metastasis to the sentinel lymph nodes and liver, (D) preparation of tumor model and corresponding curative effects of different administrations, (E) receptor-mediated endocytosis and final pH-triggered intracellular sustained release of DOX after intravenous injection.
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glutaraldehyde, genipin and citric acid enhanced the drug loading efficiency and controlled the drug release to the system with improved mucoadhesive properties [126]. The IONPs was further altered with folic acid labeled genipin crosslinked aminated starch/ZnO to develop a controlled drug release system [127].

G. sulphuraria sourced Gly, and highly branched starch (HBS) was modified with amyloglucosidase (AMG) enzyme to enhance the branching linkages together with lower molecular weight. AMG hydrolyze the α-(1 → 6) bonds as well as α-(1 → 4) linkages to convert starch into glucose [128,129] and significantly increased branched linkages of both the Gly and HBS. Gly-AMG showed 32% nearly twice the quantity of α -(1 → 6) bonds than 17.7% Gly also HBS-AMG contain 3 times higher (27.7%) α -(1 → 6) bonds than HBS (8.2%) with smaller Mw compared to the native molecules. Since the natural Gly of *G. sulphuraria* expressed improved digestive and rheological properties than potato/starch treated AMG. Thus, it represents the natural Gly of *G. sulphuraria* as the substitute for starch-derived polymers [128].

Table 2
Isolation, extraction and purification process of starch from different renewable plant materials.

Plant raw materials	Chemical / biological pre-treatment	Mechanical Pre-treatment	Starch composition (Wt %)	Ref.
Unripe poovan banana (Musa AAB)	sodium sulphite (1.22 g/L)	Hand blender mesh sieve	26.62%	[116]
moth bean starch	Acetic anhydride	Blending / pregelatinize with 70 °C H_2O		[117]
Broken rice	–	–	80%	[118]
Green banana	Acetic acid	Kitchen knife		[119]
Pineapple stems	Water wash / centrifuge	Small piece / grinding	30%	[120]
Bambara groundnut	–	Wet milling	45%	[121]
Oat kernel	NaOH	Centrifugation / filtration	–	[122]
Aesculus hippocastanum	60 °C for 30 min / centrifuge 4000 rpm	Wet milling	Over 35%	[123]
Cucurbita maxima D.	washed with 10% toluene in 0.1 M NaCl	Ground with 0.01 M $HgCl_2$	–	[124]

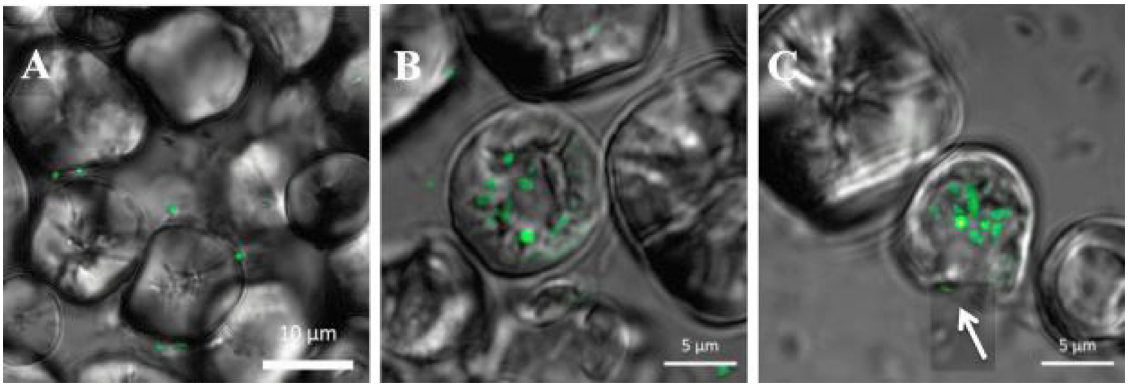

Fig. 12. (A) CLSM images showed the maize starch microcapsule fluorescent green color specifies the probiotic cells attached to the surface. (B) hydrolyzed (30 min) Str microcapsule and (C) 120 min hydrolyzed microcapsule showed the cells loaded into the cavities (the arrow indicates the pore opening). (Reproduced with permission from Ref. [133] Elsevier Copyright © 2018).

4.2. Starch for delivery of probiotics

The probiotic bacterium L. acidophilus has been encapsulated with porous starch with increasing concentration of 4%, 6%, 8%, 10%, 12% and 14% (w/v) and a higher degree of the cell survival rate was observed at the increasing concentration of glycogen wall material. The starch encapsulation protects the cells from SGF and intestinal environment [130]. Also, the cornstarch/pectin encapsulated *Lactobacillus plantarum* ATCC:13643 expresses higher resistance in the SGF and SIF where pectin also additionally served as a protectant and efficiently cleaved by pectinases produced from the colonic environment [131].

The rice extracted resistance starch has been successfully encapsulated with *Lactobacillus brevis* (MTCC 01), *Lactobacillus casei* (MTCC 297) and *Lactobacillus plantarum* (MTCC 021). The microencapsulated probiotics survived well in SGF, adverse heat conditions and also the higher degree of cell viability (> 7 log CFU g^{-1}) was observed at 4 °C for 2 months [132]. Interestingly the probiotic starch capsules were developed using native maize Str or partially hydrolyzed maize Str were enzymatically loaded with *L. plantarum* 299 V. The probiotic capsule expressed high loading efficiency, higher cell survivability against the stressful conditions such as acid, bile salt and heat resistant at 60 °C for 15 min (Fig. 12) [133]. It has been reported that the starches/pullulan obtained from different sources were showing different probiotic loading efficiency and viability [134]. Hence, apart from drug delivering properties, starch based systems were profoundly investigated for probiotic delivery.

5. Conclusion

The present review discussed the recent advancements in synthesis, processing, and application of different renewable natural bio-polymers such as cellulose, glycogen, and starch. The applications of each polymer were reviewed concerning drug delivery properties. Both cellulose and starch are promising materials for the biomedical applications with natural availability, easy tailoring properties, low cost and high biocompatible nature. As it has been reviewed, the most recent and attractive properties of the engineered bio-materials such as flexibility of high drug loading efficiency, controlled drug delivery, ability to support tissue engineering, protein delivery, and antimicrobial properties are playing a significant role in the medical and biopharmaceutical industries. Moreover, highly precise physio-chemical surface modification procedures to achieve the suitable nano-carrier could be considered with a greener approach to negate associated toxicological profiles. The bio-compatibility nature of that bio-polymeric material in different bio-medical strategies has been expanded and critically discussed. Indeed, with a strong knowledge of biomaterials science and medicine for manipulating polymer composites (drugs/biomolecules) and synthesis methods to project the futuristic materials, the novel properties can be achieved for precise applications.

We hope that this detailed review will increase the interest of further greener biomaterials on the preparation of suitable cellulose, glycogen and starch-based nano-particles, conjugates for their functional characteristics, and bio-compatibility, mainly in pharmaceutical and bio-medical industries.

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