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MINI REVIEW

Cross-Linked Ionic Polysaccharides: Insights from the Structure to Stimuli-Sensitive Drug Delivery System Applications

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The review provides an insight regarding the state of the art of cross-linked ionic polysaccharides, which are a part of common drug delivery systems, which are involved in the regulation of release of drug in specific required sites. The changes in pH, ion concentration, wavelength, redox potential, temperature, electric and magnetic field intensity are the stimuli sensitive functions, which play a major roles. Due to their high reproducibility and better characterization from natural resources, the polysaccharides remains as a point of interest for compiling many stimuli-responsive drug delivery systems. The hydrogel networks are formed from ready cross-linking of ionic polysaccharides, subject to control of internal and external variables. These hydrogel networks become operative for drug release on-off through complex mechanisms. The polysaccharide-based drug delivery systems are now responsive to different hybrids, composites and grafted polymers with a broad range of stimuli functions.

Keywords: Ionic polysaccharides, Chitosan, Carboxymethyl cellulose, Heparin, Stimuli sensitive, Drug delivery system.

INTRODUCTION

It has been long time since natural polysaccharides, owing to their structural diversities and properties, have contributed immensely to the medical field. The developing nations have adopted the use of polysaccharides replacing the use of costly items widely in advanced diagnosis of a disease. Now-a-days, every effort is being made to convert the discarded wastes into useful materials from renewable sources with added properties. We are focusing here largely on the applications of polysaccharides family. Polysaccharides may be isolated and extracted from marine, plant, animal and synthetic sources [1]. The naturally growing seaweeds are a good source of sulfated polysaccharides, as reported in most of the cases [2]. In many cases, higher plants, edible fruit, bark, fungi and bacterial sources are reported to contain polysaccharides, which were extracted using standard procedures and cheap solvents, thereby discarding the other byproducts in the process. After the extraction process is over, chemical profiling, Smith degradation and linkage pattern determination is mostly done to establish the structure of the extracted polysaccharides from the natural or synthetic sources [3]. The proposed structure is thereafter confirmed from IR, NMR and GC-MS spectroscopic studies, compared to standard monosaccharides [4]. In fact, these polysaccharides may also be synthesized of diverse architecture with desired molecular weight and functional group. It is due to the coupling of the organic chemistry with the polymer science that has led to the formation of several new materials [5].

The polysaccharides and its composite materials were used in the aquatic feeds and agricultural byproducts in the last two decades. With passing time, gradually the synthetic materials have been replaced by these composite polysaccharide materials synthesized with the help of pharmaceutical technology. There has been an increase in search of the new materials using biomedical and pharmaceutical technology produced from daily household waste materials, which in turn would additionally reduce the large accumulation of unutilized waste. The polysaccharides are also found biocompatible due to their similarity in structure in many components in plants, animals and human systems. In food processing industries, there have been reports

where the polysaccharides were used as thickeners, gelling agents, binders, *etc.* in syrups, jellies and other edible foods. Similarly, using the same functionalities and pharmaceutical technologies polysaccharides composites finds potential applications in various solid-liquid formulations as fillers, binders and thickeners for specific drug delivery systems [6].

The term polysaccharides refer to carbohydrate molecules and consist of repeating units of either same or different monosaccharides. Due to the number of functional reactive moiety, variation in molecular weight and sugar composition, the polysaccharides may have different structures with a wide diversity and property. Now, they may also be categorized as polyelectrolytes and non-polyelectrolytes, which are further, divided into negatively charged polysaccharides (pectin, alginate, *etc.*) and positively charged polysaccharides (chitosan, *etc.*). Polysaccharides may be chemically and biochemically modified into its derivatives due to the different functional groups in their chains. These are naturally available, in plenty highly safe, stable, non-toxic, low-cost in processing, biodegradable and hydrophilic mainly due to the polar functional groups in their structures. It is mainly due to these properties that helps polysaccharides and their derivatives to function as stimuli sensitive and nanoparticle drug delivery system [7].

This review aims to highlight the chemical profiling of the structures of cross-linked ionic polysaccharides and its application towards nanoparticle and stimuli responsive drug delivery systems. In the later part, this review also provides a detailed outline of the possibilities of ionic polysaccharides functioning as drug delivery systems to different environmental stimuli such as temperature, pH, electric field, ionic strength, *etc.* with a target to provide a functional group based selection criteria for selection of a particular class of polysaccharides for a suitable diagnosis. In this way, different polysaccharides may be assigned for use in specific drug delivery systems.

Ionic polysaccharides: This type of polysaccharides is in ionic state either in their original form or may be induced in a charged state through insertion with such moieties. If uncharged polysaccharide is subjected to a substitution reaction with some charged moieties or by grafting of ionic polysaccharides with suitable ions, ionic polysaccharides may be obtained (Table-1). A well known commonly available cationic polysaccharides is chitosan, synthesized by deacetylation of chitin in alkaline medium. The structure of chitosan is linear with random distribution of D-glucosamine and *N*-acetyl-D-glucosamine. The amine groups are responsible for pH responsiveness and attraction towards the drug with its counter ion and the cross-linked and or grafted modification reactivity.

The food industries have predominantly been employing anionic polysaccharides derived from algae (alginate, carrageens, agar) plant cell membrane (pectin) and secretes (gum arabic) as thickening or gelling agents. It is clear from the case of alginate acquired from brown algae is a straight chain polysaccharide made of β-D-mannuronopyranosyl (M) and α-L-guluronopyranosyl (G) blocks. The various position of the -COOH group in M and G blocks is the reason why their ratio and distribution influence the responsiveness of alginate towards pH and Ca^{2+} ions [8]. In the field of biomedicine, alginate has long range probabilities of application thus improving its efficiency [9]. The membrane of certain red seaweed species yield agar (or agar-agar), which finds application in food industry and microbes cultures, particularly as a stabilizing and thickening agent. A galactan based skeleton in the form of two unbranched polysaccharides, agaropectin and agarose, heterogeneously mix to produce agar. The neutral polysaccharide agarose has no charge and has long chains while agaropectin is ponderously altered with sulphate and pyruvate side-groups [10]. Recently, the use of agar as a component of DDSs is mostly limited to physical blendswith other polysaccharides [11-14]. Some other branched hetero-polysaccharides bearing carboxylic acid groups are pectin and gum arabic. Pectin is a polysaccharide composed of poly(D-galacturonic acid) with a linkage of α-(1,4) bonds along with neutral sugars such as rhamnose, arabinose, *etc.* existing in the plant cell membrane. A natural polysaccharide generated from the barks of Acacia trees is gum arabic. Gum arabic consists of β-D-galactopyranosyl units with a 1,3-linkage pattern and arabinose, rhamnose and glucuronic acid as other sugars.

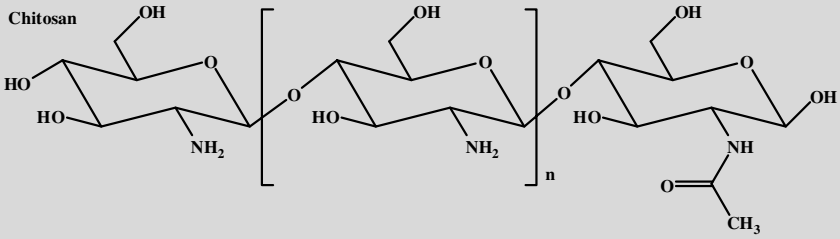
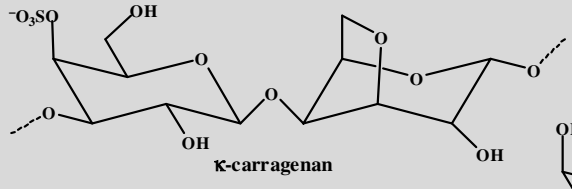
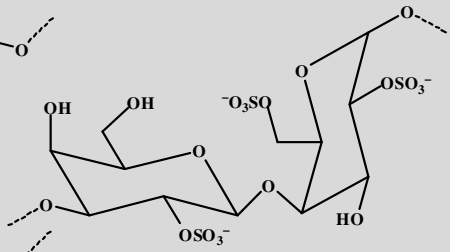
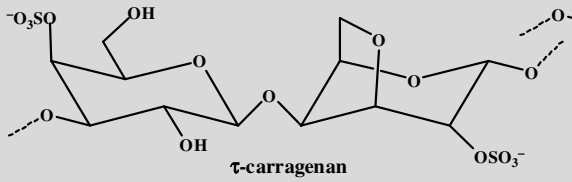
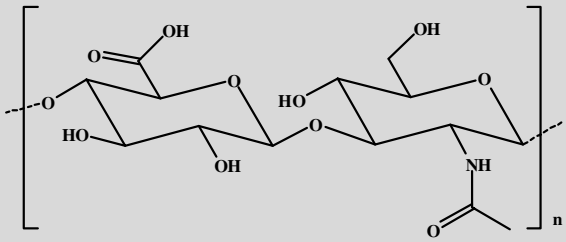
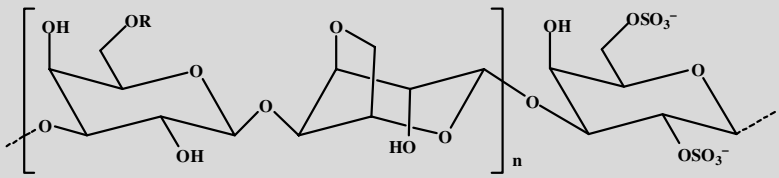
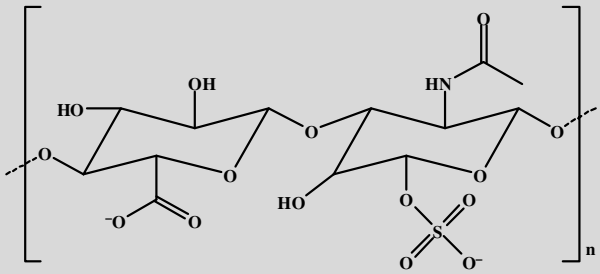
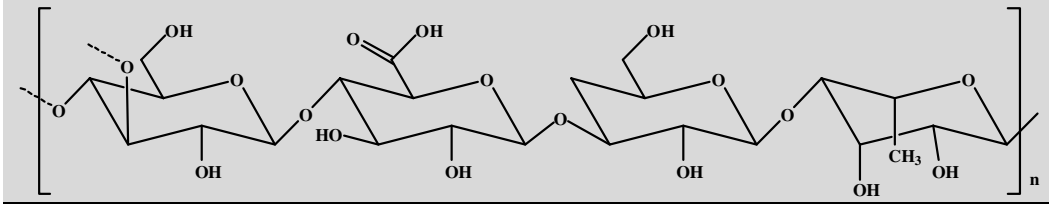
From animal sources, the ionic polysaccharides obtained are heparin, hyaluronic acid and chondroitin sulfate. The hyaluronic acid is a straight chain structure composed of basic glycosamino glycane. It is linked by α-(1→4) and β-(1→3) bonds alternately of the disaccharide D-glucuronic acid and *N*-acetylglucosamine respectively. Heparin is a highly sulfated glycosaminoglycan and possesses the highest negative charge density. It is widely used as an injectable anticoagulant in human body and recently as a component of growth factor delivery systems [15,16]. Another linear polysaccharide is chondroitin sulfate, which is composed of (1→3)-β-N-acetyl-D-galactosamine and (1→4)-β-glucuronic acid. Now, the polysaccharides obtained from xanthan gum, microorganisms, gellan gum and scleroglucan are very important, which is widely used in drug delivery systems. The exo-polysaccharide produced by *Xanthomonas campestris*, Xanthan gum, composed of β-(1,4)-D-glucose backbone and each alternating glucose unit has a branched chain of β-D-mannose-(1,4)-β-D-glucuronic acid-(1,2)-α-D-mannose units (Table-2).

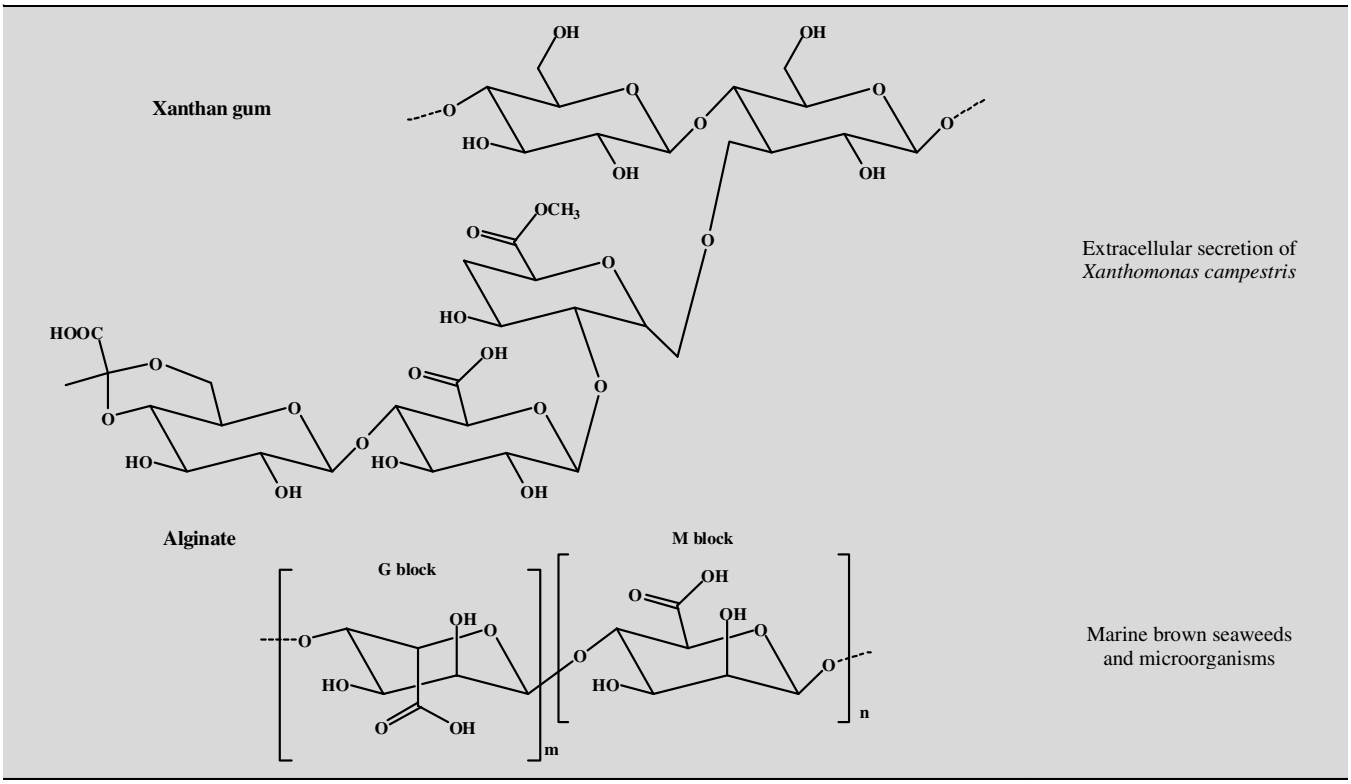
Ionically cross-linked polysaccharide nanoparticles: Among all other crosslinking techniques, we will focus here on ionic crosslinking due to the fact that it has more advantages owing to its simple synthetic techniques and methods. The low molecular weight of polyions acts as crosslinkers for charged polysaccharides. Till date, the most popularly used polyanion crosslinker is tripolyphosphate (TPP) and the TPP crosslinked chitosan nanoparticles were also reported [17,18]. TPP is non-toxic and assist in gel formation by the interaction between the NH_2 group from chitosan and counter ions from TPP [19].

TABLE-1
GENERATION OF NEUTRAL/IONIC POLYSACCHARIDES FRAMEWORK

Polysaccharides	Cross-linker	Network
Neutral	Neutral	Neutral
Neutral	Ionic	Ionic mono-functional
Ionic	Neutral	Ionic mono-functional
Ionic	Ionic	Ionic bi-multifunctional

TABLE-2
STRUCTURE AND SOURCES OF POLYSACCHARIDES USED FOR DRUG DELIVERY

Structure	Sources
Chitosan 	Extracellular matrix of arthopods and in cell membrane of fungi or bacteria
Carragenan  **κ-carragenan**	Red seaweeds of genus Rhodophyceae
 **λ-carragenan**	
 **τ-carragenan**	
Hyaluronic acid 	Extracellular matrix of higher animals
Agar  **R = H, CH_3, SO_3^-**	Algae of genus Gelidium, *Euchema, Gracilaria* & others
Chondroitin sulfate 	Animals & humans
Gellan gum 	Extracellular secretion of *Pseudomonas elodea*



Its use in various drugs and macromolecules delivery is one of the vital use of the chitosan based nanoparticles. There have been recent reports of nanoparticles preparation from water-soluble chitosan derivatives. In addition, *N*-trimethyl chitosan nanoparticles were produced by ionic crosslinking with TPP and their efficacy as a nasal drug delivery carrier system was evaluated by Amidi *et al.* [20]. From the findings, the synthesized nanoparticles were observed to be of average size ~ 350 nm. They even depicted drug loading efficiency ~ 95% and capacity ~ 50% (w/w). The carboxymethyl chitosan nanoparticles were synthesized within narrow network through ionic crosslinking with Ca^{2+} ion and its potential as anticancer drug carriers, the efficacy of doxorubicin drug was evaluated. In a recent report, the utility of Ca-linked anionic polysaccharide nanoparticles as drug carriers have been noteworthy [17]. Even some polysaccharides with -COOH functional groups was reported to be crosslinked by Ca^{2+} to form newer nanoparticles of wide applications.

In another work, carboxymethyl cellulose was used to convert chitosan to a more stable positively charged nanoparticles and investigation of plasmid DNA coated cationic chitosan/carboxymethyl cellulose nanoparticles towards genetic immunization applications as reported by Cui *et al*. [21] (Fig. 1). Chen *et al*. [22] reported polysaccharide based nanoparticle delivery system employing aggregation procedure. The findings compared the effect of weight ratio of the two polymers on certain parameters *viz.* size, surface charge, *etc*. The insulin loaded nanoparticles was synthesized by the ionic gelation and complexation with the alginate as reported by Sarmento *et al*. [23]. The same group probed the structural integrity of insulin after being entrapped into chitosan/alginate nanoparticles [24]. From the reports, it is evident that no conformational changes in the α-helix and β-sheet content of insulin. In a similar way, neutral quaternized polysaccharide nanoparticles was designed for the oral drug delivery by Li *et al*. [25].

Applications towards stimuli-sensitive drug delivery systems

Temperature sensitive network system: Ionic polysaccharides in general show limited temperature sensitiveness. But with rise in temperature, the gum polysaccharides are found to be in a highly entropic coiled state from an ordered helical state [26]. This transition is an indication of substantial decrease in the viscosity of system [27]. To insert temperature responsiveness in ionic polysaccharide networks, neutral polysaccharides such as non-ionic cellulose ethers are merged [28-30] and synthetic functional groups are grafted [31]. It was found that with decrease in the temperature-responsiveness of the poly(*N*-isopropyl acrylamide), PNIPAAm network, the crosslinked chitosan population increases [32] (Fig. 2).

The temperature, pH and ionic strength sensitive hydrogels have been prepared by mixing PNIPAAm with carboxymethyl-cellulose [33], gellan gum [34,35], xanthan gum [36], dextran [37] or alginate [38-41].

The reaction between Ca^{2+} and HPO_4^{2-} ions to form nanoparticle bead composites have depicted the importance of inorganic compound to lower the size of the beads markedly [42]. A recent study reveals the polyelectrolytic beads from alginate, poly(acrylic acid) and chitosan with PNIPAAm grafting [32]. In another work, temperature responsive system involving chitosan was prepared from glycol chitosan and benzaldehyde capped poly(ethylene oxide)-poly(propylene oxide)-poly-

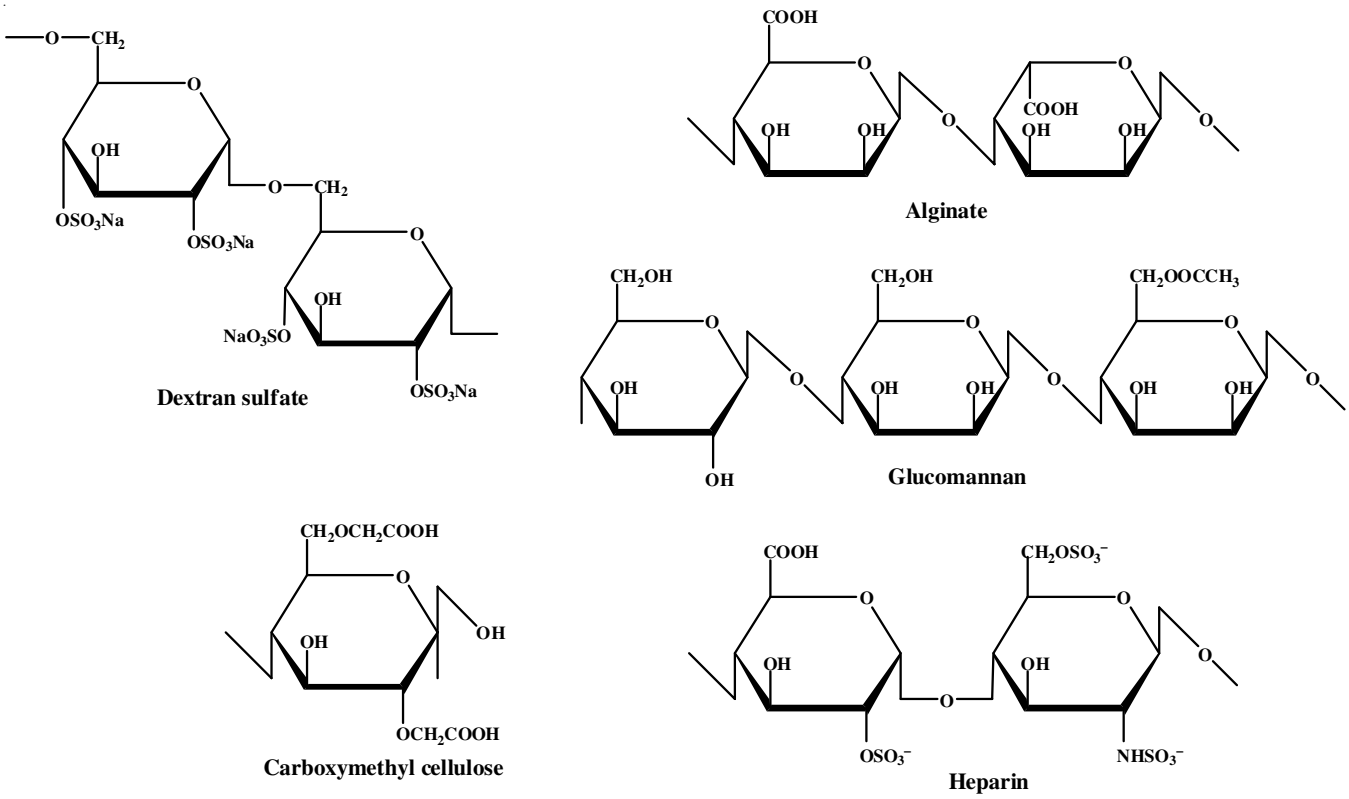


Fig. 1. Scheme of chemical structures showing chitosan complexed anionic polymers

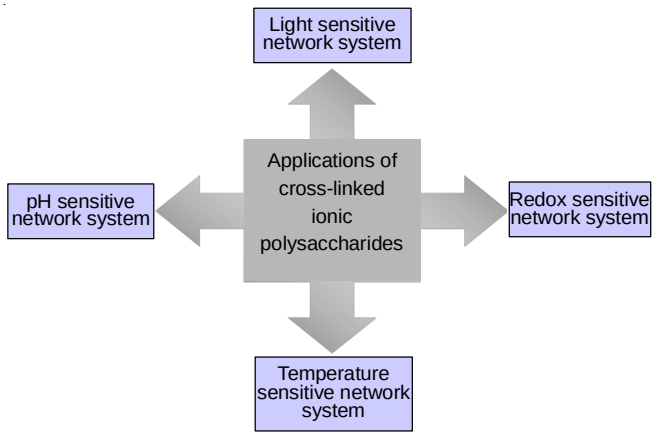


Fig. 2. Applications of cross-linked ionic polysaccharides towards stimuli-sensitive drug delivery systems

(ethylene oxide). The materials instantly formed gels due to the imine linkages and the PhCHO groups [43,44]. Further, the benzoic-imine linkage cleaved as the pH of the hydrogel decreased, loaded with hydrophilic doxorubicin hydrochloride drug and hydrophobic prednisone, resulting in a drug release at proper site [43].

Light sensitive network system: It has been established that polysaccharides may be supplied with light-sensitive property by grafting method due to particular functional groups. The poly-(ethylene glycol), PEG-anthracene basic unit was grafted with alginate skeleton to generate hydrogels, which was found to show different property subject to the UV light sensitivity, after crosslinking with adipic dihydrazide [45,46]. On exposure of these hydrogels to the light of wavelength > 300 nm, dimerization of the anthracene occured leading resulting in enhanced crosslinking porperty. As a result, a comparative study of this photo-responsiveness on the small (coomassie blue) and large (myoglobin) molecules release was done. The decreased rate of small molecules release and complete cease of protein release was due to the irradiation > 300 nm [45].

pH sensitive network system: It has been observed that the chitosan network shows a marked swelling in acidic medium and are found to shrink in the alkaline and neutral condition, typically depicting a pH sensitive system. Therefore the stable drug molecules are released very quickly in the pH of acidic medium [47]. The pH responsive networks also come in bulk forms, or as micro- or nano-gels [48]. Most interestingly, the pyrophosphate and the TPP forms the chitosan films by suitable crosslinking [49].

In general, the combination of chitosan with neutral hydrophilic polymers enhances the responsiveness to pH [50]. Films based on blends of chitosan and polyethylene glycol (PEG) can be obtained by a casting/solvent evaporation method that promotes intermolecular hydrogen bonding [51]. The hydrogen bonds are broken in media of acidic pH or with a high content in ions, resulting in a faster release of the drug loaded. Another interesting approach to the synthesis of chitosan hydrogels consists in using polysaccharides as macromolecular cross-linking agents. Carboxymethyl chitosan (CM-chitosan) is an amphoteric variety of chitosan with good biocompatibility. Glutaraldehyde cross-linked networks of CM-chitosan showed typical amphoteric character, shrinking at the isoelectric point

(pH 2-4) and swelling as the pH shifts from the isoelectric point. As a consequence, protein loaded hydrogels showed faster release in higher pH buffer than in lower pH solution [52]. The anionic groups of sodium carboxymethyl cellulose (CMC) make it suitable as component of hydrogels and inter-penetrating networks (IPNs) that shrink at acid pH and swell at neutral-alkaline conditions, particularly when the ionic strength of the medium is low [53].

The hydrogels are formed from alginate with Ca^{2+}, which places itself in the gaps between G blocks, forming an ordered conventional arrangement called "egg-box" structure [54]. The single valence cation (Na, K) do not form gels, but certain di- and tri-valence cation (Ba, Sr, Al) are useful cross linkers [55, 56]. This peculiar behaviour of the cations has been emphasized for preparing formulations in ophthalmic drug delivery. The presence of calcium ions in the eye drop is very important for the gelling formulation [57,58]. The applications of pre-crosslinked Ca-alginate beads as oral drug delivery is well established. The drug release ability from such hydrogels, cross-linked with Ca^{2+} depends on the solubility of the drug and the pH of the medium.

Redox responsive network system: The responsiveness of the ionic polysaccharides in oxidation and reduction reaction has played a major role in the drug delivery process at specific sites and feedback regulated release. The chemical cross-linking of the hyaluronic acid networks have the main reason behind degradation of -OH radicals produced by the reaction of H_2O_2 and $FeSO_4$ [59]. Networks of modified chitosan and poly(γ-glutamic acid) have been found with conformational changes and better drug releasing capacity due to gluconic acid [60]. The insertion of disulphide bonds in polysaccharides has been an interesting approach for the intracellular controlled release of drugs, which proceeds with cleavage to -SOH groups by glutathione in the cells [61]. Moreover, the tumour cells are found to have enhanced concentration of glutathione compared to the healthy ones. For better application of the physiological changes, there has been a report of 6-mercaptopurine-modified carboxymethyl chitosan synthesis with enhanced properties. The modified system showed a release of 6-mercaptopurine totally dependent on the pH change and glutathione concentration [62].

Conclusion

As reviewed above, it may easily be inferred that ionic polysaccharides are apparently furnished with pH- and redox sensitivity and these are suitable to replace the polymers from synthetic origin for designing novel stimuli-sensitive drug delivery systems. Cationic and anionic polysaccharides both are found to change physiologically depending upon the pH medium. With the help of osmosis, ions control the swelling degree thereby enhancing the population of cross-linked state and the drug release is tuned, which is very important. Besides, the affinity-controlled mechanisms may occur between the macromolecules and its counter charged drug molecules by means of ionic interactions. In the latter case, the drug release at specific sites is not controlled by the pH induced swelling. Although from the features shown, it may be inferred that the drug delivery by mouth is possible for these polysaccharides. The release of ionic drugs from externally applied polysaccharide gels along with inorganic composite materials essential for on-off cycles may be controlled by the electric field. The ionic polymers on grafting strengthen the stimuli responsive factors. There is a continuous search for particular moieties added to different polymeric network by grafting techniques to expand the scope of applications of the stimuli sensitive factors *viz.* temperature, pH, *etc.* There have been reports of characteristic sensitivity of chitosan and hyaluronic acid to –OH radical and different products of oxidation using sulfide bonded grafting/crosslinking methods applied for intracellular and colonic drug delivery purpose. Overall, there is plenty of information on old-known compatible multifunctional ionic polysaccharides and their applications and recent advances in the field of composite polymer materials have been a point of interest to world-wide researchers. More researches can be explored regarding the biocompatibility and *in vivo* consequences when injected repeatedly *via* parenteral route will identify a polysaccharide with its specific application in the near future. Crosslinked polysaccharides found from these naturally occurring polymers are leading to generate more newer and precise use as drug delivery system.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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