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# RECENT DEVELOPMENT OF POLYSACCHARIDE BASED GEL: POROSITY BASED CLASSIFICATION AND A FUTURE PERSPECTIVE

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**ABSTRACT**

*Polysaccharide is one of the most ancient and vast research field among natural sustainable biopolymers and they are readily available in nature as an essential component of our daily food. Hence, distribution of the entire field into some important factor-based classification like physical structure, stability, solubility become mandatory for clear understanding of whole polysaccharide chemistry. In some past decades, scientists mainly focused on general laboratory synthesis of this biopolymers with potential applications. Then, they broadened their vision to classify polysaccharide based composite materials and hydrogels based on majorly available polysaccharides in nature. Those gels are separated from entire polysaccharide based soluble biopolymers due to their three-dimensional physical or chemical crosslinked structure and hydrophilic, polymeric frameworks. But, a more compile classification was needed for better understanding of synthetic approach for those biodegradable hydrogels and their applications. Introducing gel porosity-based classification is a novel approach facilitating to understand the gel structure. The review mainly focused the recent advancement of polysaccharide-based gels with targeted porosity.*

**KEYWORDS:** *Hydrogels, biopolymers, polysaccharides, porosity*

## 1. INTRODUCTION

Polysaccharide is one of the most common biopolymers, naturally available in nature.[1] Recent development of polysaccharide-based materials has added in novel dimension in every industrial as well as bio applications such as environmental[2] and food packaging industry;[3] drug or gene delivery[4] and tissue engineering[5] and so on. Modern progression of science has categorized the polysaccharide-based materials into water soluble biopolymers; polymerics nano composite[6] and gels[7]. Among them, gels have attracted major attention due to their diverse ability to important properties inclusion and regulations as well as variable applicative side from the same polysaccharide-based gel.[8]

Hence, now a days, a major attention has been paid on synthesis of polysaccharide based three-dimensional network, called gels, because they are widely investigated self-organized materials with wide applications in toothpaste, shampoo, hair-gel and many more day-to-day usable products of human life.[9] Major polysaccharide-based gels are hydrogels due to their extensive water adsorption capability with incredible properties like biodegradability, biocompatibility, high cost-effectiveness, non-toxicity, reproducibility, and ready availability. Most of them exhibited low stiffness with high-water absorption capacity, which preferably introduced self-healing properties approximating natural tissues specifically in case of bulk gel. These properties facilitated several biomedical applications like drug delivery, tissue engineering, would healing. Porosity is one of the most important properties of hydrogel to dictate their structural stiffness feature and water adsorption and retention in this regard.[10] It not only dictates the leachability of incorporated drugs or genes, but actually decide the industrial and biomedical application capability of the same polysaccharide-based gel also in diverse perspectives as the same polysaccharide can form bulk, nano, micro and supramolecular gel based of different porous distribution and result in diverse properties. Numerous bioapplications of gel like drug delivery, tissue engineering, cell immobilization, wound healing abilities can be restricted due to irregular pour size. Hence, the gel porosity-based classification of synthetic approaches for polysaccharide-based gels are very urgent to explore future gel with higher efficiency.

Polysaccharide chemistry is a vast field; hence focusing on a particular aspect is very important to understand the whole science. In that respect, many reviews captured several perspectives like general synthetic approaches of individual polysaccharide materials; general or specific applications; the perspective of different porosity while classifying polysaccharide-

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based gels remain untouched. In recent days, numerous review articles discussed specific applications of different common polysaccharide composite,[11] bioapplications of their synthesized gels;[12] general synthetic approaches such as extraction and purification or characterization.[13] But, overall idea of porosity-based classification of polysaccharide-based gel and their specific synthetic approaches has not been explored yet in terms of an overview. This review mainly focused on porosity-based classification of common polysaccharide gels and their specific synthetic approach and an overall future perspective in terms of broad range of applications.

## 2. POROSITY BASED CLASSIFICATION

In several polysaccharide-based gels porosity can be incorporated by particle leaching technique through controlled sized particle called porogen dispersion into prepolymer solution. Goh *et al* reported a porous heparin-based hydrogel with fast gelling injectable property and an incredible pour interconnectivity utilizing gelatin microparticles as a porogen.[14] Another mixed polysaccharide based porous hydrogel matrix was synthesized by utilizing a gelatin-hydroxyphenyl propionic acid/carboxylmethyl cellulose tyramine (Gtn-HPA/CMC-Tyr) through horseradish peroxidase (HRP)-catalyzed oxidation. Based on the porosity, all the polysaccharide-based gels have been classified as follows (Figure 1).

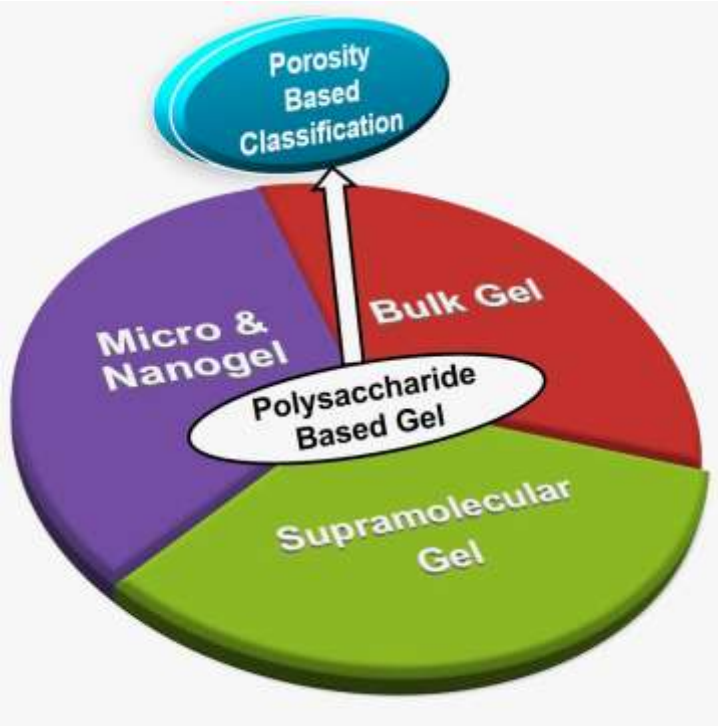


**Figure 1**. Porosity based classification of polysaccharide-based gel.

### 2.1. Bulk Gel

These categories majorly focused on three-dimensional heterogeneous network. Uniform texture is absent in most cases.

#### 2.1.1. Cellulose Based Gel

Cellulose is attractive and inexpensive natural hydrophilic polysaccharide, which is most abundant on Earth and possesses high biocompatibility with low density. [15,16] Simple methyl derivative of cellulose was originated by partial substitution of hydroxyl groups (-OH) with methoxy groups (-$CH_3O$) with enhanced viscosity with temperature induced sol-gel transition property as a result of hydrophobic interaction. The gelation behavior has been organized by degree of substitution, molecular weight and its concentration. [17] Great functional alteration leads to gel networking structure. A well-known cellulose derivative, carboxymethyl cellulose (CMC), has been extensively utilized to prepare hydrogels due to its water-solubility through numorous chemical modifications.[18] For example, hydrogels from thiol-modified CMC and polyethelene glycol (PEG)-tetra-norbornene through photopolymerization was reported by Lee *et al*.[19] However, applications of injectable hydrogels were restricted by ultra violet (UV)-triggered reaction mechanism. *In situ* Schiff base reaction could be more feasible in this regard. Shen *et al.* engineered a CMC-based injectable hydrogel *via* this reaction, where 3,3′-dithiobis(propionohydrazide) is crosslinked to oxidized CMC.[20]

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### 2.1.2. Chitin Based Gel

Chitin is a basic aminopolysaccharide obtained from crustaceans (shrimps and crabs). It is basically poly ($\beta$(1→4) *N*-acetyl-*D*-glucosamine) unit.[21] Being second most abundant after cellulose and common natural polymer with high viscosity, metal chelation capacity, polyelectrolyte tendency; chitin based hydrogels are very attractive materials in terms of applications.[22] Double crosslinked chitin hydrogels was reported recently by dissolving chitin in potassium hydroxide (KOH)/urea aqueous solution with freezing-thawing process through cross linking followed by coagulating in ethanol solution at low temperature.[23]

Chitosan was basically synthesized by *N*-deacetylation of chitin. They generally found in fungi and cell walls of algae, the exoskeletons of insects, mollusks and crustacean. [24,25] Easy physical and chemical modification of chitosan through reactive hydroxyl and amino groups resulted gelation. In contact with alkali, the amino functionality transformed to physically cross-linked hydrogel. Hydrogen-bonding played an important role to entangle macromolecular chains. Synthesis of chitosan hydrogels was trigerred by numorous chemical networking agents, including glutaraldehyde (GLA),[26] formaldehyde,[27] *N, N'*-methylenebisacrylamide (MBA),[28] genipin,[29] ethylene glycol diglycidyl ether (EGDGE) and epichlorohydrin (ECH).[30] Report showed that modification of chitosan with 1, 2-butene oxide and succinic anhydride (NSHBC) resulted gel as function of temperature ranging from 17 °C to 32 °C. Chemical modifications in acrylamide[31] or glycol chitosan obtaining *N*-hexanoyl glycol chitosan using hexanoic anhydride were able to form chitosan based gel.[32] Physical networking technique has been also taken to consideration in case of chitosan based gel formation. Ionic crosslinking was reported as a great approach in this regard. Anionic crosslinkers such as sodium tripolyphosphate,[33] sodium citrate, sulfosuccinic acid, and oxalic acid were used to prepare chitosan hydrogels.[34] Another method was freeze-thwing approach which led to combination of several polymers like starch, poly (vinyl alcohol) (PVA), poly (acrylic acid) (PAA) or alginate and capable of hydrogen bonding. [35] For example, synthesis of artificial bones composed of chitosan/PAA network using PVA and PAA by repeated freezing and thawing was reported. Another recent study exhibited that; a novel chitosan hydrogel was prepared through dissolution in alkaline-urea aqueous solvent. The entire gelation process was observed through aggregation induced emission fluorescence.[36] A composite hydrogel of chitosan, heparin and poly (gamma-glutamic acid) for wound healing was reported by Zhang and co-workers *via* crosslinking by addition of acetic acid.[37]

### 2.1.3. Starch Based Gel

Starch, one of the largest biomasses on earth, is a natural, abundant, cheap, available, renewable, and biodegradable polymer. But native starch extracted from plants cannot tolerate the extreme processing conditions like temperature or acid base treatment leads to limited applications.[38] Hence to enhance or inhibit particular properties according different industrial requirements as well as bioapplications, several modifications regarding physical, chemical or enzymatic modifications by debranching enzymes (isoamylase or pullulanase) have been performed.[39] Smaller blocks were generated from linear short chains through highly debranching of starch (H-DBS) with less water holding capacity, which leads to stronger smooth, non-sticky and glossy hydrogel.[40] These gels have potentially used in the food and pharmaceutical industries[41]

### 2.1.4. Hyaluronic Acid Based Gel

Hyaluronic acid (HA) is another well-known polysaccharide with large number of hydroxyl group, a non-sulfated glycosaminoglycan (GAG) and major constituent of skin extracellular matrix (ECM). In a work performed by Laurent, Gelotte, and Hellsing (1964), stability in aqueous solutions of HA was enhanced through crosslinking with 1, 2, 3, 4-diepoxybutane.[42] Similarly a stable and homogeneous hydrogel has been reported *via* mixing with butanediol-diglycidylether in sodium hydroxide solution followed by HA powder addition.[43] Hylase wound gel composed of emollients and sodium hyaluronate (2.5 %) was synthesized.[44] Fiorica *et al.* (2018) fabricated a hydrogel by crosslinking of a copolymer of HA (MW = $1.5 \times 10^6$ Da), (hyaluronic-(2-aminoethyl)-carbamate acid (HA-EDA)) with $\alpha$-elastin.[45] Wu *et al.* (2017) utilized 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to provide crosslinking of HA with gelatin to synthesize hydrogel.[46] Initially, gelatin (GEL) and HA at different ratio (8:2, 5:5 and 2:8) were prepared followed by crosslinking with 0.1 % EDC. The crosslinking agent did not damage the porous structure of the hydrogel, essential for several biomedical applications. A hydrogel with improved mechanical properties by mixing HA -tyramine (HA-Tyr) with collagen I-hydroxybenzoic acid derivative (COL-P) has been prepared, followed by crosslinking through blending with HRP and $H_2O_2$. Shi *et al.* (2018) reported HA (MW = $1.5 \times 10^5$ Da) modification through functionalization with pendant bisphosphonate (BP) groups.[47] HA based *in situ* injectable hydrogel could be formed through dynamic covalent bond between phenylboronic acid modified HA (HA-PBA) and PVA.[48] Another novel injectable DMEM (Dulbecco's Modified Eagle's Medium)-induced phenylboronic acid-modified HA self-crosslinking hydrogel was reported. Combination of the phenylboronic acid and a diol on HA resulted good self-healing properties and tissue adhesion properties to the hydrogels through dynamically reversible phenylboronic acid esters.[49]

### 2.1.5. Dextran Based Gel

Dextran primarily composed of repeating $\alpha$(1→6) linked *D*-glucopyranose residues with less percent of $\alpha$(1→2), $\alpha$(1→3), or $\alpha$(1→4) linked side chains and major components of many bacteria.[50] Main groups, which can be modified through physical and chemical cross-linking leading to gelation, are hydroxyl groups per glucose unit. Physically crosslikned dextran gel could be prepared through derivatization with lactic acid oligomers while functionalized with bifunctional glutaraldehyde, isocyanates or

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by partial oxidation of hydroxyl groups to aldehydes followed by crosslinking with gelation, results chemically crosslinked gels.[51] Another interesting example of injectable biomimetic hydrogel was dextran-tyramine conjugated HA with high moduli, enhanced bovine chondrocyte viability, proliferation and matrix secretion.

### 2.1.6. Agar Based Gel

Agar is a complex polysaccharide mixture of linear agarose and branched agaropectin, extracted from marine red seaweeds.[52] The linear polymer composes of 1→3-linked-*β*-D-galactose (G) and 1→4-linked 3, 6-anhydro-*α*-L-galactose; whereas branched agaropectin linked with several substituent groups for example sulfate esters, methyl esters, pyruvate acid ketals.[53] Hydrogen bonding played vital role for linear agarose hydrogels which could be used for three-dimensional chondrocytes encapsulation.

### 2.1.7. Alginate Based Gel

Alginate is an unbranched anionic heteropolysaccharide derived from brown seaweeds and some bacteria, also found in outer wall of some brown algae such as kelps, composed of 1–4 glycosidically linked *β*-D-mannuronic (M) and *α*-L-guluronic (G) acids in varying composition and sequences.[54] Effective quantification of alginate hydrogel formation along with its mechanical strength could be dictated by external gelation process using calcium chloride ($CaCl_2$).[55] Hence divalent cations, such as $Ca^{2+}$ and $Ba^{2+}$, played the mastered role as crosslinking agents to transform aqueous solutions of sodium alginate to gels. The predicted interaction strength order was reported as $Pb^{2+} > Cu^{2+} > Cd^{2+} > Ba^{2+} > Sr^{2+} > Ca^{2+}$.[56] Mechanistic elucidation revealed the gelation through ionic cross-linking of negatively charged carboxyl groups of the alginate chain and positively charged divalent metal ions.[57] It is important to note that, in order to obtain authentic information about molecular interactions, the knowledge of the initial values of the storage modulus in rheology was very important unlike the case of Alginate-$Ca^{2+}$ gelation studies. A new custom-made rheometric setup was able to record the fast response from the very beginning, thus both the concentration and volume of the crosslinker could be controlled.[58] Again, injectable self-crosslinking property was introduced through reaction between alginated dialdehyde and gelatin.[59]

### 2.1.8. Gums Based Gel

Gums are another class of naturally available polysaccharide derived from renewable sources. Capacity to hydration of these materials leads to form gel.[60] Common gums are generally classified as Gellan gum and Xanthan gum. Gellan gum is anionic exopolysaccharide, more precisely a linear tetramer composed of (1→4)-L-rhamnose-*α*(1→3)-D-glucose-1 *β*(1→4)-*D*-glucuronic acid-*β*(1→4)-D-glucose as repeating unit with one carboxylic side group; with high molecular weight, secreted by the bacteria *Sphingomonas paucimobilis.*[61] This polysaccharide resulted non-toxic, ionic and thermo responsive gels close to body temperature.[62] Gellan gum gel network was truly formed upon aggregation and ionic crosslinking through monovalent cations inspite of adopting ordered double helical architecture upon cooling. These monovalent cations broadcasted electrostatic repulsion amongst the carboxylate groups to induce gelation, but connection of two carboxylate groups was established by the divalent cations in addition to the screening effect. Thus, divalent cations formed stronger gels with higher viscosity than monovalent cations. Additionally, this gellan gum based photocrosslinkable hydrogels *via* methacrylation and blending was also reported.[63]

Xanthan gum composed of five monosaccharides comprising two D-glucose, two D-mannose and one D-glucuronic acid units.[64] It is basically an extracellular heteropolysaccharide produced by the bacterium *Xanthomonas campestris.* Trisaccharide units of glucuronic acid replaced the alternating glucose units flanked by mannose entities. The backbone was protected from the external environment through covering with the side chains in helical secondary structure *via* hydrogen bonding. This structural complication leads to highly viscous gel even at lower concentration. Stability at various stimuli like pH, temperature, ion concentrations are some basic natures of the gel resulting pseudo-plastic property. Various medical applicative sides such as wound healing, drug carriers could be shown by gum-based gel. Carboxymethyl derivatization at the glucose residues of xanthan resulted microcapsule entrapment.[65] Thus, the injectable property or encapsulation could trigger this method. Running of intra-articular xanthan injection has the ability to protect the articular cartilage in osteoarthritic rabbit models.

### 2.1.9. Pectin Based Gel

Extraction from plant cell walls results pectin, a water-soluble polysaccharide, composed of *α*-D-galacturonate residues linked by (1→4) glycosidic bond, and Rhamnogalacturonan I (RGeI) and Rhamnogalacturonan II (RGeII). Monosaccharides such as D-xylose, D-glucose, L-rhamnose, L-arabinose or D-galactose are the major constituents[66] with partly methoxylated or amidated galacturonic acid (GalA) as a main building block. Classic egg-box model explained the gelation process which was regulated by several intrinsic and extrinsic factors such as pH, temperature, ion strength, molecular weight, Ca-binding blocks distribution, the degree of methoxylation. Egg-box dimers could be constructed from two antiparallel polyuronate chains with $Ca^{2+}$ and further aggregated laterally to form multimers.[67]

### 2.1.10. Heparin Based Gel

Heparin is a highly sulfated linear glycosaminoglycan with alternating units of *β*-(1→4) linked uronic acids (mainly D-glucuronic, L-iduronic or L-2-sulfated iduronic) and glucosamine residues (mainly D-*N*-acetyl glucosamine and *O*- and *N*-sulfated glucosamine).[68] Presence of carboxyl and sulfate reactive groups result high negative charge leads to the electrostatic interaction

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with proteins and chemical modifications. Numorous capacity of cellular signaling and growth could be regulated *via* enzymes like proteases and chemokines. An enzymatically crosslinked injectable heparin and dextran-based hydrogel exhibited higher storage modulus (~48 kPa), chondro compatibilty and cartilage matrix secretion. [69]

**2.1.11. Chondroitin Sulfate Based Gel**

Polyelectrolyte chondroitin sulfate, renowned anionic polysaccharides composed of disaccharide units consisting *β*-(1→4) D-glucuronic acid and *β*-(1→3) *N*-acetyl galactosamine with sulfate group glycosaminoglycan. Being major matrix components of cartilage, the presence of chondroitin sulfate empowered constricted strength of the scaffold through proteoglycan secretion. Combination of chondroitin sulfate with other synthetic or natural polymers like PEG through its reactive hydroxyl and carboxyl functional groups lead to gel formtion.[70] For example, injectable biomimetic hydrogels was generated from collagen type II (Col II) and activated chondroitin sulfate under physiological conditions without addition of any catalysts or crosslinker.[71]

**2.1.12. Carrageenan Based Gel**

Carrageenan is a linear hydrophilic polysaccharide composed of sulfated disaccharides with (1→3)-linked *β*-D-galactose and (1→4)-linked *α*-D-galactose units, which could be altered into the 3, 6-anhydro derivative depending on the extraction situation and starting materials. Due to structural resemblance to glycosaminoglycans, a large scientific attention has been paid to carrageenans based gel. *κ*-Carrageenan (kappa) extracted from *Kappaphycus cottonii* results strong rigid gels. On the contrary, elastic, dry, soft gels were prepared by the iota (*ι*-type) in the presence of calcium ions. Rigidity of this hydrogels can be monitored by changing potassium concentration. Another interesting property possessed by this polysaccharide-based gel is temperature triggered sol-gel transformation along with ionic gelation, since carrageenan can show upper critical solution temperature.[72]

**2.1.13. Pullulan Based Gel**

Pullulan, a component of the cell wall in the yeast-like fungus *Aureobasidium pullulans*, composed of linear maltotriose oligosaccharide connected through *α*(1→4) and *α*(1→6) glycosidic bonds. Chemical functionalization or mixing with other organic or inorganic materials could transform highly water-soluble pullulan to gel with enhanced stability. Carboxymethylated pullulan conjugated with heparin and hydroxyapatite/pullulan/dextran composite has been developed with tissue regenerative ability.[73]

**2.1.14. Xylan Based Gel**

Xylan is a natural, biodegradable polysaccharide composed of arabinose, 4-*O*-methyl-glucuronic acid and xylose in a ratio of 1:2:11 respectively.[74] Low molecular weight and high degree of side chain substitution could not lower water solubility of xylan. Hence, hydrogel network was formed through crosslinking from hydrophilic xylan polymer.[75] Modification of carboxylic groups present in glucuronic acid residues could be used for transfoming gel. *In situ* injectable xylan-tyramine gel through enzymatic crosslinking using HRP and $H_2O_2$ has been synthesized.[76]

**2.1.15. Curdlan Based Gel**

Curdlan, composed of (1 → 3)-linked *β*-D-glucose, is a crystalline polysaccharide with high molecular weight over 1,000,000. Its unique gelation ability caused by heating or neutralization of its alkaline solution is well known. A novel curdlan hydrogel was recently reported through chemical cross-linking. This gel exhibited high compression ability and exceptional shape recovery capacity. Variable cross-linker such as ethylene glycol diglycidyl ether (EGDGE, C2), 1, 4-butane diol diglycidyl ether (BDDGE, C4), and 1, 6-hexane diol diglycidyl ether (HDDGE, C6) were recently utilized for this type of gel synthesis.[77]

**2.2. Supramolecular Gel**

Supramolecular hydrogels are generally formed through noncovalent interactions. Though it is similar as polymer hydrogel, different physical and chemical properties have to be taken in consideration in terms of three-dimensional entanglement, thermal stability and reversibility. Unlike to the typical molecular gels, thermal stability at lower temperature is an essential characteristic for supramolecular gel.[78] They are mostly homogeneous such as uniform pour size, sometimes heterogeneous network like the bulk gel.[79] Again, completely reversible sol-gel transition of these gels facile desired biomedical applications harmonizing to existing polymer driven soft materials.[80] Generally polysaccharide based supramolecular gel can be prepared through host-guest interaction by accommodating organic/inorganic guest molecules, where cyclodextrins (CDs), cyclic oligosaccharides extracted through enzymatic hydrolysis of starch and was reported to act as a potential host. The polar hydrophilic external surface and hydrophobic internal cavity are the major characteristics of CDs. Again, it contains numorous hydroxyl groups with variable reactivity. CDs can be classified into three categories namely *α*-cyclodextrin (*α*-CD), *β*-cyclodextrin (*β*-CD), and *γ*-cyclodextrin (*γ*-CD). They can be differentiated by the number of glucose subunits. Some reports regarding supramolecular polysaccharide gels are demonstrated here. A supramolecular polymer coassembly, composed of Fmoc-tetrapeptide and light-responsive arylazopyrazole (AAP), was mixed with *β*-CD vesicles (CDVs) to result supramolucar gel by using host–guest chemistry.[81] Several iclusion complex based supramolecular polysaccharide gels were reported. For example, development of inclusion

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complex between PEG grafted dextran and $\alpha$-CDs could originate a supramolecular hydrogel.[82] Another report showed star-shaped poly-*N*-isopropylacrylamide (PNIPAM) polymer with a $\beta$-CD molecule forming supramolecular self-assembled architectures through mixing with adamantly terminated eight-arm PEG polymer. Inclusion complexation between the $\beta$-CD molecules and the adamantyl groups played the major role here.[83] Hence inclusion triggered supramolecular architecture resulted from $\alpha$-CD conjugated curdlan with photoirradiated gel–sol transition at 365 nm. Mixing of $\alpha$-CD and PEG-terminated poly(amino amine) dendrimer bearing NIR-active platinum (Pt) nanoparticles in the core resulted self healing supramolecular network.[84] Poly(acrylic acid) functionalized cyclodextrins (pAA-CDs) (host) and pAA modified with ferrocene (pAA-Fc) (known for its redox-responsive properties) (guest) fabricated an interesting system upon addition of oxidant sodium hypochlorite (NaClO).[85] Again mono-carboxylated PEG modified chitosan was combined with $\alpha$-CD resulting thermo-responsive supramolecular hydrogel leading to supramolecular gel.[86]. Hence it is already established that supramolecular gels could respond to various chemical (pH change, ionic, etc.) and physical (light, sonication, mechanical force, etc.) stimuli along with reversible phase transitions resulting advantageous bioapplications. For example, hydroxypropyl methyl cellulose (HPMC)-based pH-triggered *in situ* gel containing HP-$\beta$-CD-drug inclusion complex exhinited a novel nasal delivery of Paliperidone (PLPD).[87] Simply mixing of $\beta$-cyclodextrin-modified chitosan (CS−CD) with $AgNO_3$ under basic condition leads to a stable supramolecular hydrogel resulting high antibacterial and wound healing capacity (Figure 2).[88]

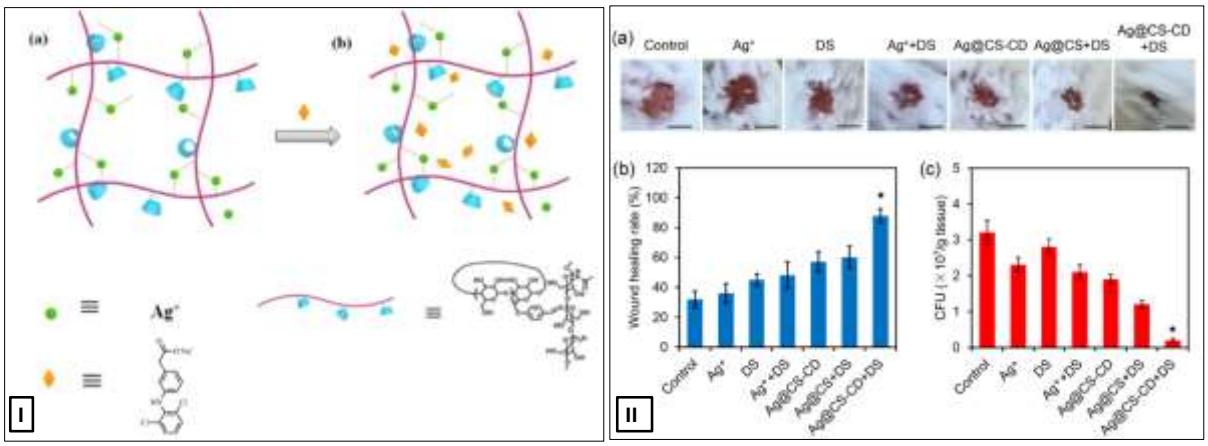


**Figure 2**. (I) (a) Illustration of the Prepared Hydrogels through Supramolecular Complexation (b) Illustration of the Supramolecular Hydrogels Loading Anionic Drugs. (II) In vivo antibacterial and wound healing capacity of the hydrogels in the mouse wound-infection model. (a) Images of wounds on mouse back in different treatments after 6 days of treatment. Scale bar = 0.5 cm. The calculated areas of each wound were 0.56, 0.5, 0.33, 0.25, 0.17, and 0.08 $cm^2$ from light to right. (b) Wound healing rate of different groups. (c) Bacterial numbers of different groups in wound tissues evaluated by colony forming unit (cfu) assays. Reproduced with permission from ref 88. Copyright 2021 American Chemical Society.

High attention has been paid in low molecular weight gelators (LMWGs) over recent dates in this regard, due to multi-stimuli responsive properties, which can lead to higher flexibility for the creation of smart materials.[89] The unique properties of LMWGs like reversible gel formation in different solvents arise from its lower molecular weight less than 2000 D. The resulting gels processed through non-covalent driving force including hydrogen bonding, hydrophobic interactions, π- π stacking, and van der Waals interactions, hence termed as physical gels or supramolecular gels. Several common monosaccharides and oligosaccharide units like D-glucose, D-glucosamine, *N*-acetyl-D-glucosamine, D-lactose, D-maltose based LMWGs are exceptionally good in this regard due to high biocompatatability, biodegradability (Figure 3). For example, severals sugar building blocks starting from D-glucose has been synthesized through functionalization with triazole, alditol. Similarly, derivatization of glyconamide at annomeric position or C-2/3 position from methyl glycosides leads to glycocluster formation and results LMWGs which leads to supramolecular assembly. Enzyme-responsive supramolecular hydrogel has also been reported using LMWGs.[90] Glucoside-introduced supramolecular hydrogel in response to a protein is wellknown. Lactose containing amphipathic ureas forms LMWHGs, aimed at site-specific drug release in the small intestine.[91,92]

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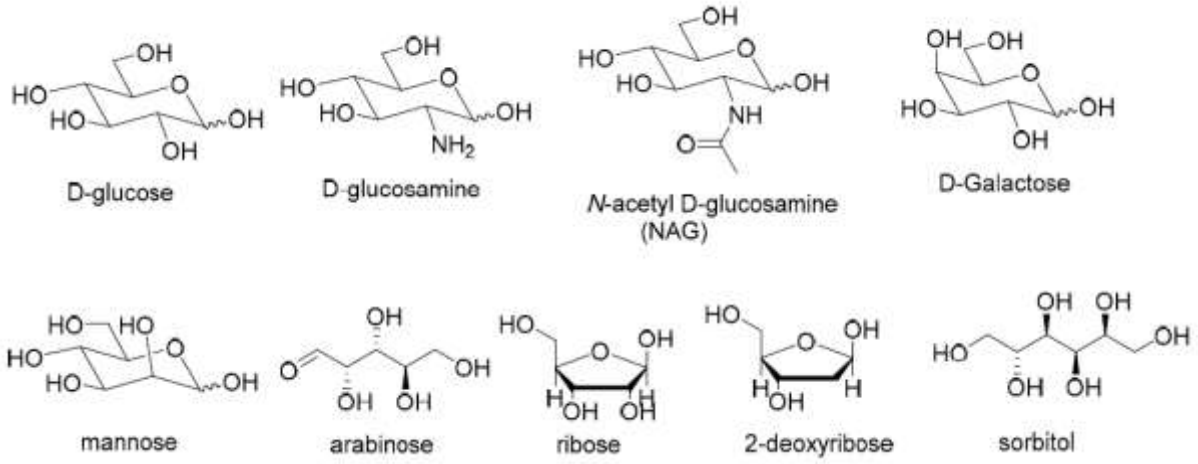


**Figure 3**. Structures of the sugar starting materials used often for designing low molecular weight gelators (LMWGs). Reproduced with permission from ref 80. Copyright 2021 MDPI.

**2.3. Microgel and Nanogel**

Depending on the gel particle dimension, the classification of micro and nanogel was made and today's biomedical field is basically ruled by those materials. Microgels are the hydrogels on a microscopic scale and nanogels are on a submicron scale. Now the basic question arises what are the properties which make them so evolitionary to modernize medical procedures. Basically, those materials are more interesting compared to their bulk analogue due to smaller particle size,[93] superior encapsulation efficacy of many therapeutics, such as proteins, genes, drugs and contrast agents, enhanced colloidal stability,[94] inertness which facilitates drug delivery and gene therapy. Again, they respond faster to their surroundings and effectively circulate in the blood to arrive at target sites after injection. Their high interfacial area per unit mass leads to higher exchange rate.[95] These exceptional characteristics add a new dimension to polysaccharide-based gel research field. A detail consideration about polysaccharide micro and nanogels are discussed in this regard.

Polysaccharide based microgels are physically cross-linked polymer of colloidal size between 1 and 1000 nm and leads to soft and porous architecture. This physical entrapment by cross-linking into a polysaccharide-based hydrogel network might happen *via* hydrazide aldehyde interaction; afterward, this hydrazide-functionalized microgel transformed to covalently crosslinked bulk hydrogel.[96] Generally they are distinct particles with colloidal dispersions ability and good swelling capacity depending on cross-linking density, synthetic process, initial monomer concentration, composition and solvents. General synthetic methods used generally are anionic copolymerization, emulsion polymerization in presence or absence of sufactant, precipitation method, inverse microemulsion polymerization, cross-linking of neighboring polymer chains (Figure 4).

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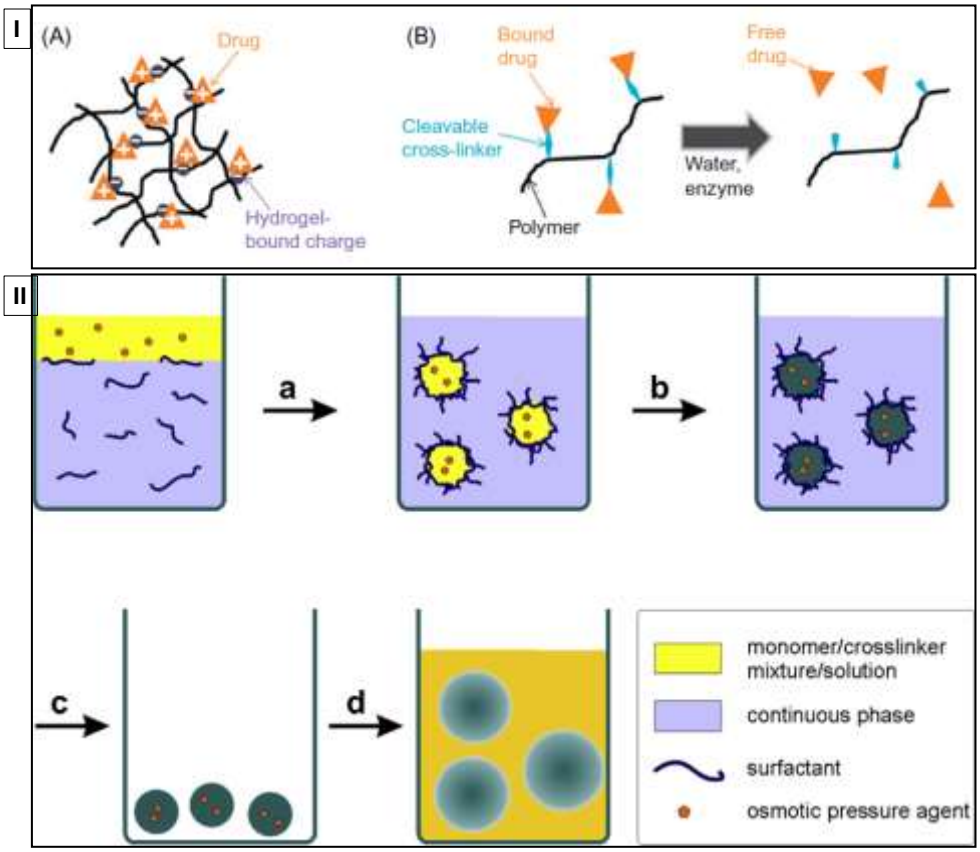


**Figure 4**. (I) Physical (A) and chemical (B) strategies for enhancing the interaction between a loaded drug and a polymeric gel to slow drug release. Reproduced with permission from ref 121. Copyright 2019 Elsevier. (II) Schematic representation of microgel preparation by radical crosslinking polymerization in (inverse) miniemulsion: (a) emulsification and homogenization, (b) polymerization, (c) removal of excess surfactant by washing/dialysis and subsequent freeze-drying and (d) redispersion of microgels in a good solvent for the network-forming polymer by swelling. Reproduced with permission from ref 97. Copyright 2012 Elsevier.

Thus, several well-known polysaccharides like dextran, gelatin or chitosan formed microgel materials by using those methods.[97] Chitosan can form microgel through self-assembly or derivatization. Dual stimuli (temperature and pH) responsive microgel was reported through copolymerization of ionizable chitosan with poly(*N*-isopropylacrylamide).[98] UV-crosslinkable and injectable chitosan based microgel has been synthesized by Wang *et al*.[99] Reversible binding of lectin metalloprotein, conA to glucose and mannose with high affinity resulted microgel.[100]

On the other hand, polysaccharide based nanogels are basically physically or chemically crosslinked nanosized polymer particles and can be prepared through nanoemulsions and nanosuspensions. Synthetic approach of several polysaccharide nanogels are as follows. Monodisperse dextran nanogels were synthesized through the self-assembly of amphiphilic poly (D-/L-lactide)-grafted dextran.[101] Combination of azobenzene and dextran was reported by Patnaik *et al*. and lead to azodextran-based nanogels by a self-assembly physical technique.[102] Aguirre *et al*. demonstrated emulsion polymerization process followed by electrostatic interaction to produce cationic and biodegradable polyvinyl chloride (PVCL) & polydiethylaminoethyl methacrylate (PDEAEMA) based core-shell nanogels utilising dextran-based macro-cross-linkers. Positively charged core-shell nanogels could interact with the negatively charged siRNA after loading and exhibited a charge reversal in zeta potential values. Another dextran based cationic nanogels combination with (2-(methacryloyloxy)-ethyl) trimethyalammonium chloride are also reported. Thus, stimuli responsiveness can be introduced including thermo-responsive PVCL and pH-responsive PDEAEMA, and dually thermo- and pH-responsive PDEAEMA/PVCL-based core-shell nanogels. These syntheses are basically driven by utilizing different biocompatible and biodegradable dextran-methacrylates as macro-cross-linkers. Modern studies show that bio-orthogonal and reversible reaction play important role to synthesize multistimuli-responsive dextran based nanogels. These reactions mainly fascilitated the nanogel preparation through formation of a polyhydrazone network by the cross-linking of nanodroplets obtained from functionalized dextran with *N*-reactive carbonyls. These systems would be oxido reductive stress and pH sensitive, as disulfide groups are exhibits reducing environment responsiveness.[103] Nanogels possessing dextran and oligolactide (OLA) chains connected through disulfide bonds (Dex-g-SS-OLA) were reported as an efficient drug delivery system. Galactose (Gal) based nanogel was reported leading to receptor-mediated endocytosis. Another report shows, colloidal chitin nanogels has been prepared

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in calcium chloride solution with saturated methanol.[104] Nanofibrous microsphere with high cellular affinity resulted from chitin in NaOH/urea.[105] Chondroitin sulfate-nisin nanogel with variable morphology and different loading capacity was reported with electrostatic complexation.[106] Chondroitin sulfate based nanogels with enhanced solubility was prepared through direct crosslinking.[107] The major component for synthesizing these nanogels was *N*-diethylamino-4- hydroxymethylcoumarin (CM) and functional modification HA could enhance the selectivity towards cancer cells.[108] According to sevelar reports, HA is an extensively used polysaccharide for nanogel preparation with biomedical applications. HA based nanogels with good immunocompatibility and hemocompatibility could be prepared *via* radical copolymerization, emulsion and precipitation polymerization through functionalization with thiolated hydrophobic molecules.[109] Fluorescent HA-iodixanol nanogels (HAI-NGs) were synthesized by Zhu *et al*. and used for targeted X-ray computed tomography (CT) imaging and chemotherapy.[110] Synthesis of injectable nanocomposite temperature responsive gel from andhydroxypropyl methylcellulose (HPMC) as a matrix with nano-sized inorganic filler and biphasic calcium phosphate (BCP) has been reported.[111] Wu *et al*. demonstrated injectable nanogels with poly(NIPAM), poly(3-acrylamidophenylboronic acid) using maleic acid–dextran as a crosslinker with monodisperse property.[112] Another NIPAM and polysaccharide based hybrid nanogel was reported through chemically cross-linking with alginate used for as efficient anticancer drug delivery. Doxorubicin loaded DNA aptamer linked myristilated chitosan nanogel, Chitosan/albumin hybrid nanomaterials have also been explored by renowned research groups with anticancer drug delivery applications.[113] Some reports include formation of nanocomposite gel from analogous bulk structure. For example a novel chitosan-based thermosensitive hydrogel using a sol-gel method has been synthesized and by adding silica/calcium phosphate (SiCaP) nanoparticles it was transformed to nanocomposite hydrogels including chitosan and $\beta$-glycerophosphate (Ch-$\beta$) as a matrix.[114] Modification of an injectable thermoresponsive hydroxypropyl guar-graft-poly(*N*-vinylcaprolactam) (HPG-g-PNVCL) copolymer with nano-hydroxyapatite covalently crosslinked *via* divinyl sulfone (DVS) lead to HPG-g-PNVCL/n-HA/DVS as an efficient nanocomposite thermogel acting as a biocompatible scaffold for osteoblastic cell growth.[115] Glucose responsive nanogel based on electrostatic interaction between chitosan and alginate was reported with potential bioutilizations.[116] Modern research indicates the development of a new concept for brachytherapy based on intrinsically radiolabeled gold-palladium (AuPd) alloy nanoparticles, followed by functionalization with carbohydrate-ester based liquid. Thus, the system was transformed to biodegradable injectable nanogel allowing lower administration through small-gauge needles. Dispersion of nanoparticles in ethanol along with water insoluble carbohydrate esters resulted "nanogels" (Figure 5).[117]

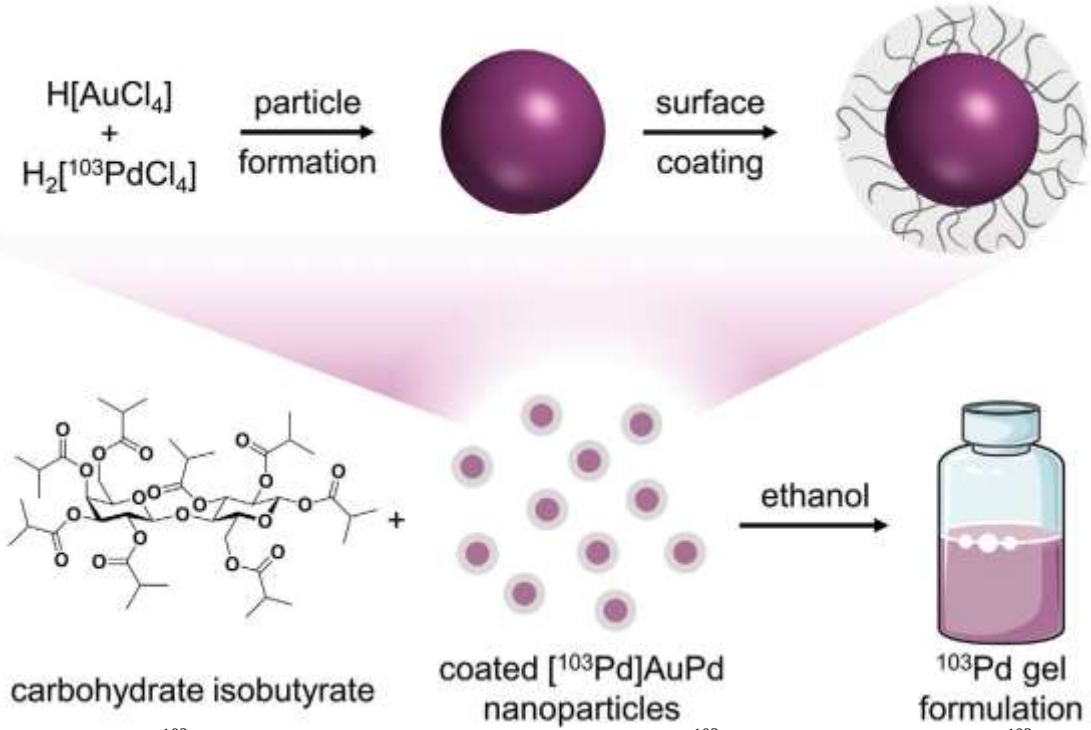


**Figure 5.** Preparation of the $^{103}$Pd-nanogel formulation for immobilization of $^{103}$Pd-containing AuPdNPs. [$^{103}$Pd] AuPdNPs were prepared from their chloride salts using trisodium citrate. Surface coating of the particles was carried out with thiol-terminated PNIPAAm. The liquid $^{103}$Pd-nanogel formulation was prepared by adding the [$^{103}$Pd] AuPdNPs directly to a premixed solution of LOIB or SAIB in ethanol. Reproduced with permission from ref 117. Copyright 2021 Wiley.

As per the last section, these materials have been used in several biomedical applications. Hence sterilization is very important in this regard. A novel approach to get purified nanogel is autoclave method at high temperature and pressure. Montanari *et al*. reported the synthesis of gellan- and HA-cholesterol derivatives followed by dispersion in aqueous solutions, and

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then, sterilization through autoclave leads to pure polymeric nanogels.[118] An interaction between hydrophobic cholesterol moieties and hydrophilic polysaccharide chains under autoclave condition (temperature (121 $^{o}$C) and pressure (1.1 bar for 20 min) was explored.

## 3. CONCLUSIONS AND FUTURE PERSPECTIVE

The above discussion has given an overview on porosity-based classification of recently developed polysaccharide-based gel. I have discussed every case as an applicative viewpoint. Numerous common polysaccharide based highly porous hydrogel network composed of cellulose, alginate, chitin, chitosan and hyaluronic acid can provide a biomimetic and moist cellular outgrowing environment, where the porous structure not only accommodates the living cells, but diffuse gases, nutrients and waste products.[119]

Though scientists are making progress in this field, more development is required in this aspect. The clarity of understanding about the porosity will not only define the structural pattern of the gel, classify them as bulk, nano or microgel, but several properties like in situ injectability and self-healing properties can be incorporated. These are essential requirements for wide biomedical applications and industrial uses. Hence, better understanding should be built on porosity specific synthetic approaches through functional group modification via a cost-effective process. Moreover, industrial method with higher economical feasibility to introduce porosity for a broad range of therapeutic applications should also be explored further. Hence, this review climaxes that more analytical research, which should get a good appreciation in polysaccharide-based gel synthetic field in future.

**Conflict of Interest**

The authors declare no conflict of interest

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**Recent development of Polysaccharide Based gel: Porosity Based Classification and A Future Perspective**

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A modern and compile classification was needed for better understanding of synthetic approach for biodegradable common polysaccharide-based hydrogels and their applications. Introducing gel porosity-based classification is a novel approach facilitating to understand the gel structure. The review mainly focused the recent advancement of polysaccharide-based gels with targeted porosity.

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