Chapter 8
Cross-Linking, Modular Design and Self-assembly in Hydrogels

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Abstract Gels can be recognised as a stiff but flexible, soft everyday material. They survive the "inversion test", it is solid-like rheology that defies the character of the gel. Low-molecular-weight gels can be classified into organogels and hydrogels based on its constitution. All these gels have wide range of applications in the fields of biomedical engineering and pharmaceutical formulation. Hydrogels are highly tuneable viscoelastic hydrophilic polymers with 3D networks of cross-linking. Despite being mostly liquid, they have solid-like rheology due to its cross-linking. They are highly water-swellable polymer networks with water imbibing properties which gives them the flexibility to mimic natural tissues. The cross-linking is stabilised via interactions including Van der Waals, covalent bonding and hydrogen bonding. Hydrogels are formed by gelators of low molecular weight and exhibit colloidal properties. Stimuli-responsive nature of supramolecular gels can be utilised in targeted drug delivery systems. Natural polymeric hydrogels have a trending application in modern medicine due to its profound implication in sensing, targeted drug delivery, controlled release of a bio-active substance, etc. These gelators assemble by noncovalent interactions like π-π interactions and hydrogen bonding. The properties of hydrogels can be tuned by changing the external stimuli. These polymeric materials that can show both effector and sensor functions can be used to mimic the natural system, thereby fabricating intelligent systems. This chapter gives brief introduction on gels, following the different type of light molecular weight. Guanosine-based hydrogels and its applications are also discussed further.

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1 Gel Formation

Gels can be compared with a solid matrix that immobilises a liquid component by surface tension effects (Fig. 1).

Gels can be categorised based on its liquid phase as organogels and hydrogels. The common methodology for the synthesis of gels is by dissolving a low percentage (0.1–5 wt.%) of gelator molecule in an appropriate heated solvent. Upon cooling below the temperature of gelation (T_{gel}), the affinity between gelator and liquid phase decreases and the former self-assembles into a three-dimensional (3D) entangled network of solid, immobilising the liquid phase through strong intermolecular forces, allowing it to support its own weight without collapsing.

Gels can be further subcategorised into two different classes based on the nature and type of interaction as chemical gels and physical gels. In chemical gels the cross linking is via covalent bonds [2–4]. While noncovalent interactions like van der Waals forces, hydrogen bonds and Coulombic interactions maintain the fibrous network of a physical gel and due to these interactions, they are thermally reversible. Because their networks are covalently linked and essentially permanent, chemical gels swell or shrink when exposed to an external stimulus. Conversely, physical gels are held together by reversible, noncovalent forces and can often be degraded by appropriate stimuli [5–9] (Fig. 2).

In hydrogels, where polar groups which are generally highly solvated, the gelation process is generally dominated by hydrophobic effects. Directional hydrogen bonding and dipolar interactions tend to dominate in the case of organic gels [11].

1.1 Low-Molecular-Weight Gelators

Supramolecular gels are a type of physical gel in which noncovalent interactions like hydrogen bonding and van der Waals interactions help in the association of fibrous network in order to frame various building blocks. This association could principally include the noncovalent cross-linking of polymers. Supramolecular gels are mainly referred to gels made from "low-molecular-weight" gelators (LMWG), compounds with molecular weight less than 3000 Da, while, in polymer gels, most of the solid

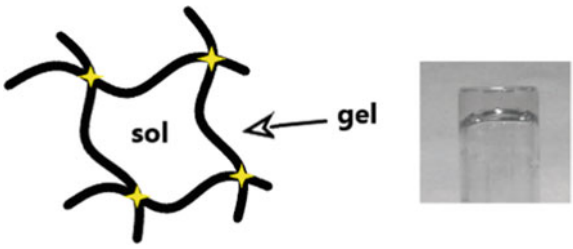

Fig. 1 Gels maintain solid-like rheology by establishing a fibrous network (gel) that immobilises the liquid phase (sol) [1]

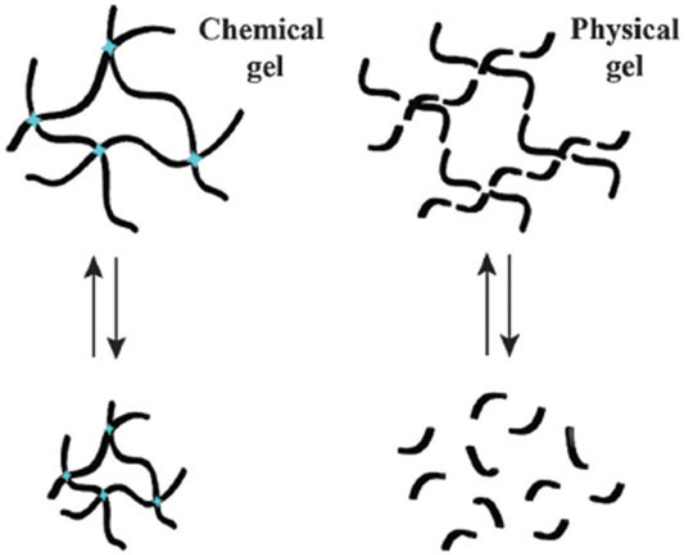

Fig. 2 Chemical gels can swell or shrink since the network or cross-linking is covalently linked and permanent when an external stimulus is applied. Physical gels get easily degraded with an appropriate stimulus since they are held together by reversible, noncovalent forces [10]

components establish themselves via covalent bonding. There is a microphase separation through molecular recognition pathways and self-assembly in LMW gelators. Molecular gelation mostly proceed via nucleation mechanism rather than the isodesmic process, that is, the process of gelation is hierarchical and stepwise. The molecular building blocks at first forms a one-dimensional nucleus, followed by nuclear growth to form fibres and larger aggregates, which can branch and bundle [10]. The entanglement of these fibres to a 3D mesh is referred to as a self-assembled fibrillar network (Safin) (Fig. 3).

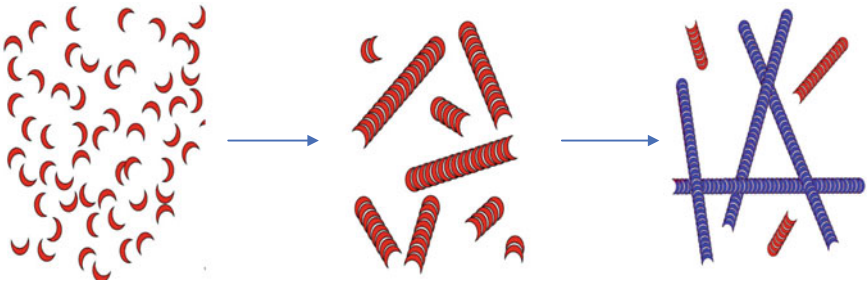

Fig. 3 Molecular gelation most often occurs via a nucleation process, in which the LMW gelator assembles to form a self-assembled fibrillar network (SAFiN) [10]

While gelation can sometimes occur by just mixing the LMW gelator with solvent at ambient temperature, more often than not, heating the sample is required to dissolve the gelator. Cooling the solution results in a supersaturated solution that then forms the gel. Because the gelation process involves reversible, multistep assembly, the resulting gel material is often responsive to various stimuli and, thus, is attractive for many applications [5–8, 10, 12–14]. The LMWGs are very versatile due to its diverse structure and functionality. There are numerous examples of multicomponent LMW gelating systems [15]. The molecular gels have been made from metal coordination complexes, polyaromatics [16, 17], dendrimers [18, 19], poly urea [1, 20] and quaternary ammonium salts [21].

1.2 LMGO

Gels are colloidal in nature, and LMNOs appear to have entirely versatile architecture including tapes, sheets, rods derived by the hierarchical assembly of gelator molecule which is facilitated by the physical molecular interactions such as hydrogen bonding, van der Waals forces, p–p stacking, London dispersion forces and electrostatic interactions [22, 23]. The mechanism of fibre formation was depicted successfully by Estroff and Hamilton in 2001. They individually characterised the primary, secondary and tertiary structure of the fibrous assemblies. Fibres form a network which is responsible for gelation via series of assembly. Initially, the assembly into the primary nanostructure is driven by one-dimensional interaction on the molecular level (Fig. 4).

Molecular interactions are essential for the formation of 1D fibres rather than other structures. But the gelation is determined by the delicate balance between the molecules ability to dissolve and aggregate into solution. The interactions are

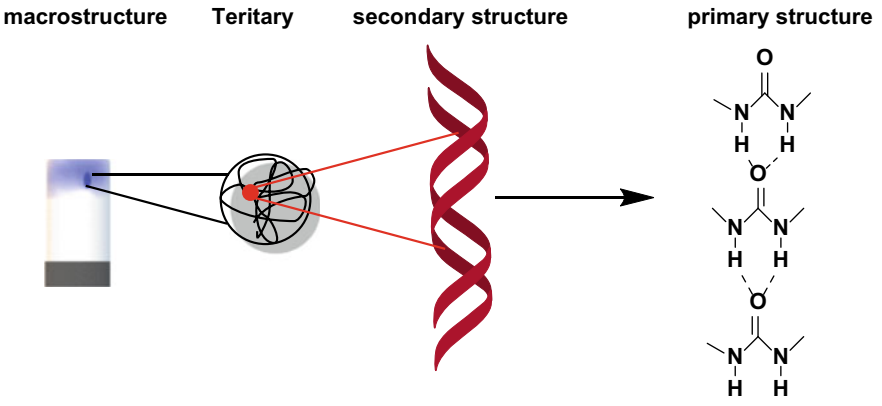

Fig. 4 Primary, secondary, tertiary and macrostructure of a self-assembled physical network [13]

mostly noncovalent such as hydrogen bonding helps in the self-assembly while the weak interactions in the aqueous environment play an important role in anisotropic and aggregation in water. Gelation requires a continuous network of fibres which is achieved by cross-linking which results in the fibre branching, fibre enlargement and trapping in the mobile phase [24–28]. It was proposed by Terech and Weiss that gelation in organic media happens via attractive forces that are largely dipolar, and in case of metal coordinate bonds, it may involve specific intermolecular hydrogen bonding.

The formation of fibres is via three steps: initially, fibre nucleation, repeated crystalline fibre branching and fibre growth. Within the fibres, the packing is primarily determined by a balance between weak. The arrangement or packing between the fibres is primarily by the balance between the weak physical interactions as with the hydrogels including forces such as intermolecular hydrogen bonding, London dispersion forces, electrostatic forces and p–p stacking. In contrast to the traditional crystallisation, in self-assembled fibrillar networks (SAFINs), there is only growth among one axis of the three-dimensional structure similar to the pattern with radial arms initiating from the core in a Cayley tree structure. Several models have been developed to explain the transition of amphiphilic gelator molecules from their molecular to primary and secondary aggregate structures. But the small number of studies reported do not offer a single mechanism for self-assembly. Unidirectional formation of the thin branched fibres into 3D networks occurs due to anisotropic interactions via aggregation and the minimisation of the large surface energy that results from individual fibre formation [29–34].

1.3 Hydrogels

Peppas defined hydrogels as macromolecular networks which are swollen in biological fluids or water. Having various possible definitions hydrogels can be classified based on the nature and type of network into three, namely entangled networks, networks formed by secondary interactions and covalently cross-linked networks. These intelligent materials are sensitive and can respond to various chemical and physical changes including the pH [34–37], electrical field strength [38–40], ionic strength [41, 42], magnetic stimuli [43, 44], heat [33, 45–47] and ultrasound irradiation [48–51]. The basic principles, the structural features of gelators, the influence of solvents and role of noncovalent interactions, and properties of gels are discussed below.

The permanent network is formed by covalent cross-linking which allows the free diffusion of water, enhancing the mechanical properties of the gel [52–55].

Hydrogels may undergo minute change in environmental conditions with a larger change in physicochemical properties, sol–gel phase transition, degradation and shape transformation. Ordinary hydrogels when compared to the smart ones undergo only the swelling–deswelling process depending upon the availability of water in the system. Hydrogels turn out to be smart when it has additional properties over the

basic properties like a swelling–deswelling. The environmental factor or the external stimuli can be chemical (pH, ion type, ionic strength and solvent), physical (temperature, electricity, magnetic field, ultrasound and pressure) or biological (enzyme, antibody and glucose). Despite having similar properties and appearance, polymeric hydrogels differ from supramolecular hydrogels in various subtle ways.

Unlike the polymeric hydrogels that originate from a randomly cross-linked network made of strong covalent bonds, hydrogels are the consequence of molecular self-assembly driven by weak, noncovalent interactions among hydro-gelators in water. This subtle yet fundamental difference not only renders more ordered molecular arrangement in the supramolecular hydrogels but also manifests itself in the process of hydrogenation. While simple swelling usually confers a polymeric hydrogel, a stimulus or a triggering force is necessary to bias thermodynamic equilibrium for initiating the self-assembly process or phase transition to obtain a supramolecular hydrogel. Therefore, there are many forms of stimuli or triggers for manipulating weak interactions. For the transition from a non-gel state to a hydrogel to occur, the free energy must be negative. Thus, the overall impact of the stimuli or triggers usually is negative ΔH or positive ΔS or both, which can be achieved by either physical methods (e.g. changing the temperature, applying ultrasound or modulating the ionic strength) or chemical methods (e.g. pH change, chemical or photochemical reactions, redox and catalysis) [56].

Due to the diverse applications in various fields of science, water gelating compounds (hydro-gelators) have been studied extensively. Moreover, low-molecular-weight hydro-gelators (LMWH) are preferred over their polymeric counterparts due to its thermo-reversible nature and rapid response to external stimuli and intermolecular associations within the three-dimensional network of the self-assembly. The type of interactions in the association is noncovalent in nature including the van der Waals interactions, dipole–dipole interactions, hydrogen bonding and interactions, p–p interactions.

2 Nucleobases

Self-assembly and molecular recognition properties of nucleobases, nucleosides and nucleic acids play a quintessential role in the formation of molecular gels. These N-bases have the ability to form hydrogen bonds and to π-stack, these are some the fundamental interactions that have the potential to control the structure and function of DNA and RNA assemblies.

These interaction possibilities make them capable for supramolecular assemblies; based on this nature, numerous molecular gels are synthesised from nucleobases, nucleosides and nucleic acids (Fig. 5).

Nucleobases are nitrogen-containing heterocycles which are the basic components of the nucleosides, nucleotides and nucleic acids. These five nitrogen bases are classified into two categories purines (including adenine A and guanine G) and pyrimidines (uracil U, thymine T and cytosine C). They differ in the basic structure

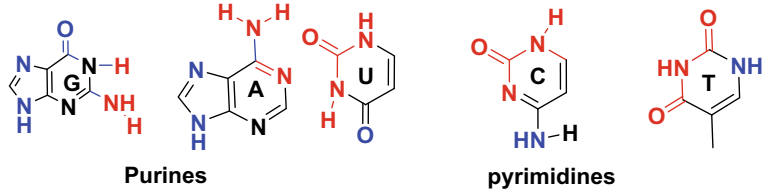

Fig. 5 Purines and pyrimidines

and the number of hydrogen bonding ability. Purines have multiple hydrogen bonding possibilities, while the pyrimidine bases have a single edge of the three hydrogen bond donors and acceptors. The aromatic nature of these nucleobases gives the ability to p-stack (Fig. 6).

The ribose sugar present in the nucleosides and nucleotides can also be a factor for the supramolecular structure and function. The nitrogen bases are attached to the ribose sugar via N-glycosidic linkage which results in the formation of a nucleoside (Fig. 7).

The phosphorylation of the nucleoside results in the formation of nucleotide which are the building blocks of nucleic acids. These nucleic acid polymers are RNA and DNA. The phosphate anion part of the nucleotide enhances electrostatic interactions. The most prominent noncovalent interaction is the base pairing between these nucleotides [1]. The complementary nucleobase pairs, adenine–uracil (thymine T in DNA) and guanine-cytosine form two and three hydrogen bonds, respectively. If we

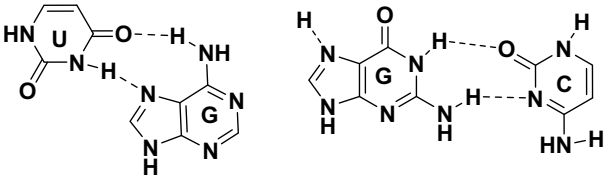

Fig. 6 Hoogsteen interaction

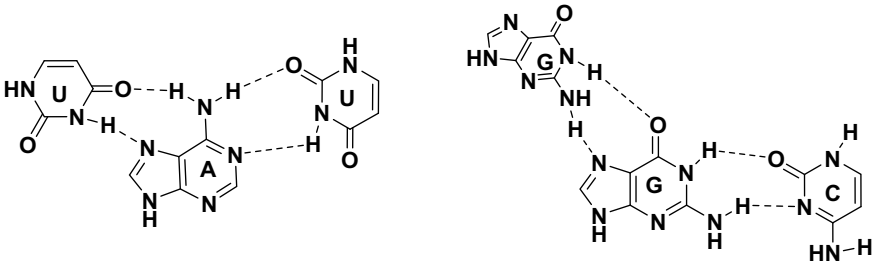

Fig. 7 Base triplets

consider base pairs in which at least two hydrogen bonds are formed, there are 28 base pairing motifs possible among the four nucleobases [53–57].

3 Guanosine-Based Hydrogels

Guanosine is a natural nucleoside that has the capability to homodimerise and unique self-assembly properties (Fig. 8).

Guanosine contains natural nucleobase purine that can provide multiple edges for hydrogen bonding interactions, improving its self-assembly properties. Guanosine and its derivatives self-assemble into dimmers, sheets and ribbons. Non-canonical base pairing can lead to the formation of macrocycles. Mostly, G-based hydrogels are based on the supramolecular assembly of macrocyclic G-quadrant units. The stacking of the quadret units can lead to the formation of G-quadruplex which can extend its network to form hydrogels. G-quadret can bind with mono or divalent ions form G8-M sandwiched structure. The gelation process of G-wires is driven by branching, physical cross-linking ad lateral aggregation. The gel network can be easily broken down by disrupting the supramolecular assemblies using appropriate external stimuli. This reversible nature guanosine-based hydrogels make them stimuli-responsive "smart" biomaterials. G4K+ borate hydrogels can be used to deliver the cargo molecule [58] (Fig. 9).

The multistep hierarchical nucleation process helps in the sol–gel transitions which can hydrogenate the guanosine. In gelation, guanosine or its derivatives are heated to dissolve the gelator, and cooling of this homogenous solution can give rise to the formation of a metastable state that do not free flow leading to the synthesis of self-supported hydrogel. All the process of heating and cooling guanosine is associated through Hoogsteen-type hydrogen bonding and forms a planar aromatic G-quadret

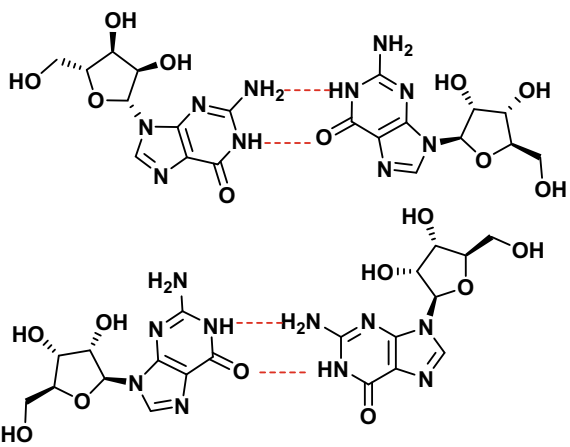

Fig. 8 Guanosine quadruplex

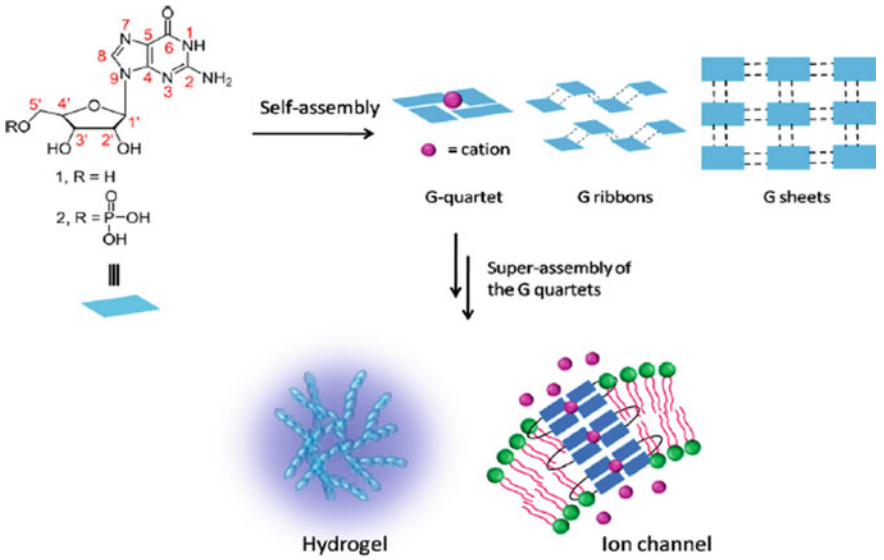

Fig. 9 Schematic illustration of hierarchical assemblies formed by guanosine derivatives [58]

that stacks upon each other and grows into G-wires. The process like physical cross-linking, aggregation and branching of G-wires is the driving force to the gelation process. The building block of these G-wires is the guanosine tetrad which is formed via Hoogsteen hydrogen bonding between each of the guanosines and its neighbours. The gelation and gel formation in solutions of individual guanosine compounds are widely studied since a long time using visual detection, bulk physical measurements, circular dichroism spectroscopies and absorption, light scattering, X-ray diffraction, neutron scattering, and NMR [51, 59, 60].

Supramolecular models studied on the basis of results have columnar structures formed by the self-assembly of G-quadrets through stacking and stabilised by the metal ion that is centrally located and coordinated to eight oxygen atoms in guanines [12, 15, 61–63].

An alternative model was proposed in which the GMP monomers associated by the Hoogsteen hydrogen bonding form a helical network which is further stabilised base stacking of two cations. In either of the cases, the concentration of guanosine increases and organises itself into higher ordered, anisotropic liquid crystalline phases with hexagonal organisation. The biological significance of G-quartet structures formed by G-rich sequences of DNA and RNA and the implications of guanosine self-assembly for the origin of life triggers the interest in guanosine. A second area of interest has been the enantiomeric selectivity exhibited by lipophilic derivatives of guanosine. The potential applications of guanosine gels in the broader arenas of nanotechnology and biotechnology are worth exploring due to the reversibility, tunability, aqueous solubility, physical stability, biocompatibility and chemical and chiral selectivity of the gels, as well as their potential for reversible encapsulation

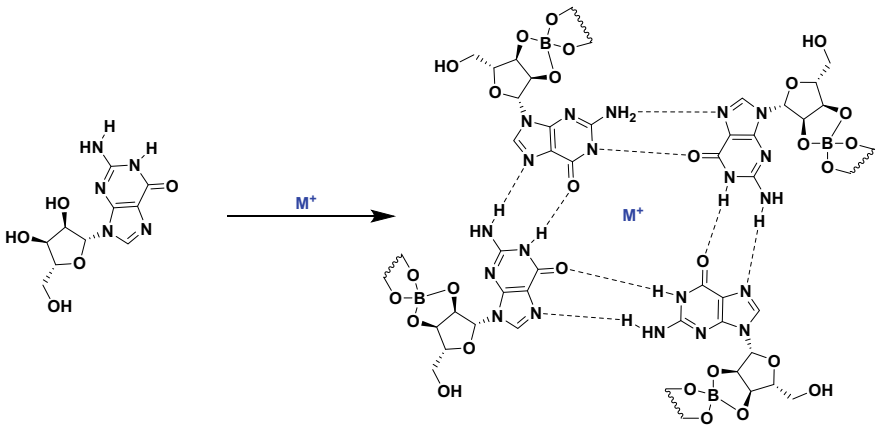

Fig. 10 K+ stabilised self-assembly of guanosine

and reversible introduction of functionality. It was recently discovered that guanosine gels formed by binary mixtures of the soluble 5-guanosine monophosphate (GMP) and relatively insoluble guanosine (Guo) in aqueous solution exhibit unique thermo-responsiveness that can be controlled by adjusting the Guo/GMP ratio, cation content and pH. At neutral pH and room temperature, GMP alone is too soluble in water to form firm gels, while Guo is too insoluble to form a stable gel even in the presence of high K+ concentrations. The present studies of GMP-Guo mixtures reveal, not surprisingly, that GMP helps to solubilise Guo while the insolubility of Guo promotes gelation at lower concentrations of GMP (Fig. 10).

Many guanine nucleosides and nucleotides were subsequently found to form hydrogels through the formation of similar helical arrangements. In the two decades that followed, the implications of pH on GMP assemblies and the role of stabilisation played by alkali cations were both established. In recent years, the interest in G-quadruplex structures has heightened due to the potential biological implications of these suprastructures (i.e. as a pertinent motif for fragile X syndrome, gene expression and telomerase inhibition). Additionally, the structural composition of G4-quartets and higher order assemblies has been extensively characterised through advanced solution and solid-state NMR techniques.

4 Biological Applications

The major goal of synthesising supramolecular hydrogels is to develop systems that can be effective for biological applications. Appropriate external stimuli can be used to disrupt the supramolecular assemblies to break down gel network. Owing to this reversible nature, guanosine-based hydrogels have been considered as stimuli-responsive "smart" biomaterials. Small molecular cancer drugs are not target specific

and can cause systemic toxicity. Guanosine-based systems have the same goals to accomplish, while the high concentration of the K+ which is helpful in gelation.

These are ideal for biomedical applications, there have been some significant advances towards utilising these materials for tissue scaffolding and drug delivery. Recently, Rowan and co-workers showed that hydrogels formed with 8-methoxy-20,30,50-tri-O-methylguanosine derivative could not only form gels at physiological concentrations of monovalent cation. Reports suggest that guanosine-based gels could indeed be promising for tissue scaffolding applications [13, 55].

5 Conclusion

Hydrogels are soft and versatile materials that can form a three-dimensional network which encapsulate large amount of water. This versatility is attained from its three-dimensional gel matrix which consists of cross-linked polymer. The gels are standardised by noncovalent interactions including van der Waals, covalent bonding, electrostatic interactions, dipole–dipole interactions and hydrogen bonding. Supramolecular smart hydrogels are stimuli responsive and can be used in targeted drug delivery systems. Guanosine-based hydrogels have a tandem amount of importance in the field of water purification and drug delivery systems. Exploration of potential applications of guanosine gels has only recently begun to attract interest, with the major focus on columnar "G-wires" and layered thin films of guanosine "nanoribbons" as molecular wires for nanoelectronics and tissue scaffolding applications. Recent studies have focused primarily on developing novel guanosine-based gelators, improving the lifetime stability of guanosine hydrogels and utilising these materials for biomedical and drug delivery applications.

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