Hydrogels: Biomaterials for Sustained and Localized Drug Delivery

Ganesan Keerthiga, Pallavi Gupta, and Tuhin Subhra Santra

Abstract Hydrogels are three dimensional (3D) cross-linked polymer networks capable of holding a large volume of water. The hydrophilic polymeric system sometimes exists as a colloidal gel inside water, i.e., dispersion medium. Hydrogels aim to mimic the 3D microenvironment of cells with the advantage of surpassing adverse gastrointestinal effects on the drug, therefore increasing patient compliance. This polymer-based hydrogel formulation has tunable properties such as porosity, tensile strength, drug loading capacity, and release kinetics that contribute towards better biocompatible hydrogel design. The monomeric units in hydrogels bind through physical and chemical forces such as hydrophobic interaction, hydrogen bonding, UV crosslinking, and many others. Albeit hydrogel is known for its water holding capacity and high biocompatibility, the cytotoxicity of hydrogel depends on the polymer selection. Deformable and injectable hydrogels that can alter its physical state in room and body temperature are in the research pipeline to avoid surgery for implantation. Further, environmental stimuli-responsive hydrogels like pH, temperature-sensitive hydrogels are evolving as 'Smart drug delivery' systems. This distinctive property of tunable hydrogel design and formulation finds its application in sustained and localized drug delivery. This chapter discusses the different classifications of the hydrogel, along with its crosslinking chemistry involved. We also have summarised various forms of hydrogel from lab scale to industrial level. Finally, this chapter also covers the synthesis, functionalization, tailoring mechanism of the hydrogel matrix, followed by in vitro, ex vivo, and in vivo characterization and drug loading/delivery efficiency.

Keywords Hydrogel · 3D polymer · Nanocomposites · Stimuli-responsive hydrogel · Controlled drug delivery

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T. S. Santra and L. Mohan (eds.), *Nanomaterials and Their Biomedical Applications*,
Springer Series in Biomaterials Science and Engineering 16,
https://doi.org/10.1007/978-981-33-6252-9_9

1 Introduction

Hydrogels are three-dimensional cross-linked polymeric network capable of imbibing large volumes of water (90–99wt%) [145, 7]. These hydrophilic polymeric networks are formed by cross-linking monomers in addition to a physical or chemical cross-linking agent. Different polymeric sources (natural or synthetic) and varied crosslinking methodologies have led hydrogel into the limelight of research. Back in the early 1960s [215], a study on poly (2-hydroxyethyl methacrylate) comprehensively predicted a net repulsion between polymer network and a poor solvent causes phase transition, change in the degree of swelling and volume. Progress has been made to find a biocompatible and non-toxic formulation for in vivo delivery of drugs to overcome repeated dosing and drug loss during activation and transportation [19]. Significant research (publications over the years as shown in Fig. 1) and advances in polymer chemistry for understanding the underlying physiology has allowed researchers to consider hydrogel as a promising candidate for biomedical applications such as biosensors [157], micro-total analysis systems (μTAS) [204], molecular imprinting [20], contact lenses, targeted drug delivery vehicle for delivering biomolecule(s) of interest, mimicking extracellular matrix in tissue engineering applications.

Nanotechnology has extended its roots in various fields in the last two decades. Its fundamental property of a high surface to volume ratio of any material in the nanoscale dimension has found multiple applications in the fields of science and

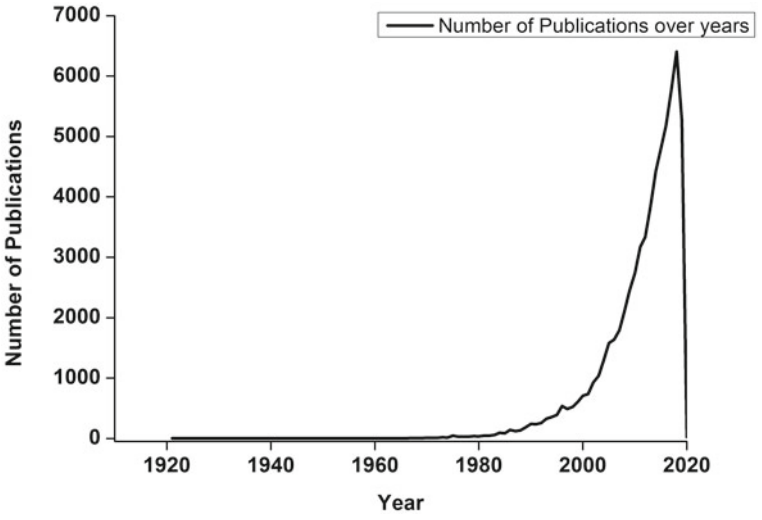

Fig. 1 Graph representing publications concerning hydrogel research over the years (Based on Scopus data)

engineering, including biomedical relevance [8–202]. Polymeric network encapsulated with nanoparticles that aim at targeted drug delivery has proven hydrogel a valuable biomaterial for pharmaceutics [42].

Nanocomposites take over the advantage of hydrophilicity of the polymers, versatility, biocompatibility as well as the increased surface to the volume aspect ratio of the nanoparticles. Diverse nanomaterials such as graphene, carbon nanotubes (CNTs) (see Sect. 4.2.1); polymeric/dendritic nanomaterial (see Sect. 4.2.2); inorganic/organic nanomaterials such as silicates, hydroxyapatite nanoparticle-based formulations (see Sect. 4.2.3); metallic nanoparticles such as gold, silver nanoparticles (see Sect. 4.2.4) are utilized in hydrogel nanocomposite formulation. This interdisciplinary field of research is known to have a significant effect on developing nanocomposites such as biodegradable polymeric nanoparticles, polymeric micelles, solid lipid nanoparticle (SLN), lipid drug conjugate (LDC), nanostructured lipid carriers (NLC), and quantum dots [12–160].

A combinatorial approach of nanotechnology and hydrogel for nanogel formulations produces three-dimensionally cross-linked submicron hydrophobic (or less soluble) particles for drug delivery. Nanogel increases the solubility of the drug, accumulation at the intended site of action, and stability of bioactive molecules in physiological conditions while reducing cytotoxicity. Temperature responsive, pH-temperature dual responsive nanogels are also constructed using copolymer blocks. Micro/nano-particles prepared by spray drying, microemulsion, phase separation procedures are used for mucoadhesive drug delivery systems (MDDS). Mucal adhesion occurs through the surface to surface contact in the form of micro/nanospheres or asymmetric patches. Stimuli responsive nanogels have gained considerable interest in research for its drug delivery capabilities and controlled drug release at the intended absorption site [19–69].

This chapter discusses the significant classifications of hydrogels based on their polymeric source and crosslinking techniques; different parameter constraints for hydrogel design; biomaterials for hydrogel nanocomposite formulation for biomedical applications; drug release mechanisms by diffusion to various stimuli in the physiological environment. Further, this chapter briefly emphasizes the current challenges and future research focus of hydrogel for clinical translations.

2 Classification of Hydrogel

Hydrogels are designed to encapsulate drug and release in a sustained mode in targeted location for prolonging the effect as well as minimizing repeated dosage. These are promising biomaterials for their unique physicochemical properties, which include molecular weight of the polymer, method of crosslinking and intermolecular bonding among monomer and between the monomer and crosslinking agent [37].

The physical nature of hydrogel plays a vital role in introducing the drug-loaded hydrogel into the target system. The ‘sol-gel’ characteristics of the prepared hydrogel decide the route of administration of the hydrogel into the host system [109].

Injectable hydrogel formulation is currently overpowering the matrix hydrogel for its capability to skip surgery for implantation [118]. Thus physical form significantly decides the route of hydrogel introduction, depending on the physical structure of the polymer, rigidity, covalent bonding and intermolecular interaction within the polymeric chains [37, 25–58].

On the other hand, chemical characteristics involve matrix density, the mechanical strength of the hydrogel formulation, biodegradability, and biocompatibility. These properties are constricted to the individual and collective properties of monomers and crosslinking agents used. Tailored hydrogel formulations are prepared by modifying the above parameters. Thus hydrogel formulation in itself contains various parametric choices such as polymeric source, natural or synthetic; polymeric composition (homo-polymeric, hetero-polymeric); their nature of gelation (physical, chemical crosslinking); their porosity as micro, macro or super porous; their degree of swelling and absorbance capacity [28–35]. The two main classifications depending upon the polymeric source and crosslinking (see Fig. 2) are discussed in this chapter as it encompasses various monomers involved in a hydrogel formulation.

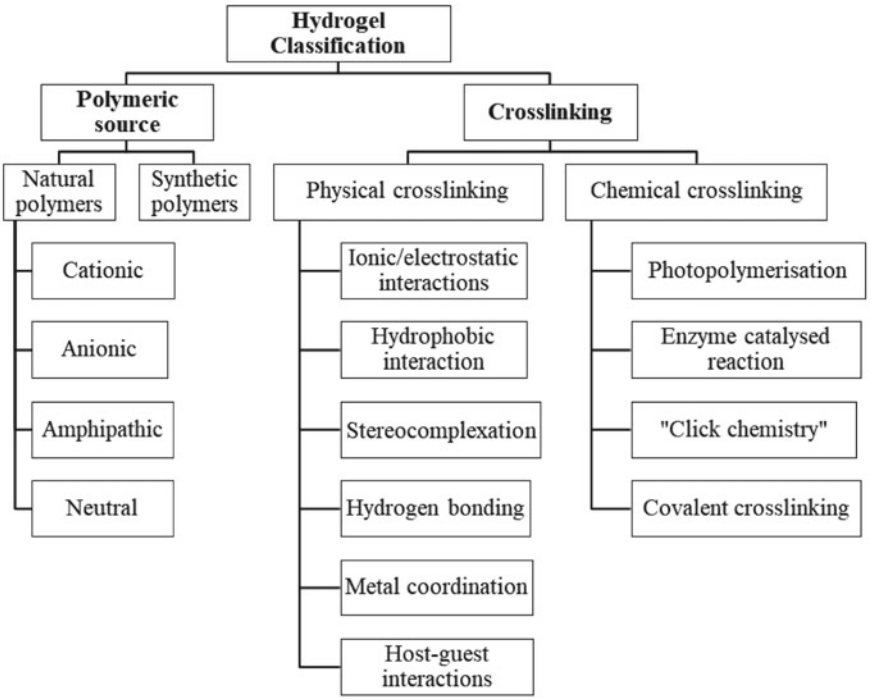

Fig. 2 Overall classification of hydrogel

2.1 Polymeric Source

The polymeric source can range from natural to synthetic monomers for hydrogel formulation depends upon the application intended.

2.1.1 Natural Polymers

Natural polymers are developing biomaterials that are the primary forms of renewable biomass. Extracted from a macromolecular matter of microbes, plants, and animals, they offer a range of properties such as biodegradability, biocompatibility, and non-toxicity. They are classified into cationic, anionic, neutral, and amphipathic, depending on their physicochemical property. Listed below in Table 1 are different types of naturally occurring polymeric sources (± crosslinkers) [73].

- **Chitin**, the next abundant polymer to cellulose is highly hydrophobic and insoluble in water and organic solvents. Deacetylation in alkaline conditions or by chitin deacetylase to yield chitosan is used in gel formulations at low pH. Chitosan-based hydrogels are mainly used to deliver drugs targeted to the mucosal layer [9, 33].
- **Hyaluronic acid (HA)**, an anionic copolymer of 2-acetamido-2-deoxy-D-glucose and D-glucuronic acid, allows us to form strong electrostatic interactions. Chemical reactions such as addition, condensation, or radical polymerization of the active moieties are carried out to obtain different physical formulations. Generally, HA is formulated as a firm hydrogel, viscoelastic liquid, mesh, and fiber that find its application majorly in nasal, pulmonary, ophthalmic, parenteral, and topical routes. HA-based hydrogels are also reported to show tissue healing, promotion of cell growth and proliferation, inflammatory response control, etc. [34–34].
- **Dextran** is a linear glucose polymer of 1,6-glycosidic bonds with some extent of branching through 1,3 linkages with many reactive moieties, makes it a great candidate for formulation. Dextran is known to have antithrombotic property. Its biodegradability and bio-compatibility have made it an efficient drug vehicle for carrying the drugs or bioactive agents of choice. Different forms of dextrans are hydroxyethyl methacrylate dextran, dextran urethane, glycidyl methacrylate dextran, and dextran hydroxyl-ethyl-methacrylate lactate [194], which are used for hydrogel formulations.

Table 1 Different types of naturally occurring polymers

Type	Polymer name
Cationic	Poly lysine, chitosan
Anionic	Pectin, Hyaluronic acid, dextran sulphate, alginic acid, carrageenan
Neutral	Dextran, agarose, pullulan
Amphipathic	Collagen (and gelatin), fibrin, carboxymethyl chitin

- **Collagen** is a triple helix protein found in the extracellular matrix (ECM) of fibroblasts and osteoblasts. Generally utilized form type I collagen is isolated from the body tissues, neutralized and broken down to single molecules called 'gelatin.' The final step determines the type of gelatin obtained. It is known to undergo a 'sol-gel' transition in response to the surrounding temperature, making it a suitable material for designing thermoresponsive hydrogel. Thus, collagen is an impending component for a 'smart drug delivery system' [52].

2.1.2 Synthetic Polymers

Natural polymeric sources are being entirely replaced by synthetic polymers, such as poly 2-hydroxylethyl methacrylate (pHEMA), polyvinyl alcohol (PVA), polyethylene glycol (PEG), etc. for increased of mechanical strength, acclimatized functionality, and degradability. The method of crosslinking effects hydrogel degradation that can be controlled in response to external stimuli such as pH, temperature, light, and electric field, resulting in making a 'smart drug delivery system' [51]. Some of the polymers, such as PEG, are amphiphilic, that aid in more natural absorption of hydrophobic drug molecules or intended cargos than conventional drug vehicles. Polyethylene glycol (PEG) is a synthetic polymeric unit that is a polymer or oligomer of ethylene oxide. Polyoxyethylene (POE), Polyethylene Oxide (PEO), polyvinyl alcohol (PVA), polypropylene oxide (PPO) are chemically synonymous and differentiated by their molecular weights. Polymers with molecular weight <100,000 are grouped under PEGs, and the higher molecular weight is arranged as PEOs. PEGs of low molecular weight (<1000) are generally colorless, viscous, and increased molecular weights are white color and waxy solids. All PEGs are soluble in both aqueous and organic solvents, such as chloroform, ethanol, toluene, methyl chloride [3]. It has unique properties such as biocompatibility, non-immunogenicity, and resistance to protein adsorption [135]. PEG is a Food and Drug Administration (FDA), USA approved polymer that has found application in various frontiers of biomedical applications, such as bone prostheses, wound healing and tissue engineering, and drug delivery [165]. PEG cannot be a standalone polymer for polymeric network formation. Additional functional groups such as acrylate, thiol, vinyl sulfone, amine, and carboxyl, determine together of its mechanical strength and degradability (both natural and stimuli-responsive) of the polymeric network. In situ gelling systems are designed on the principles of photosensitive systems that can be cross-linked upon ultraviolet (UV) or light irradiation and are self-assembled in vivo. The latter alters its physical state according to the physiological environment inside the host system [44–1].

Poloxamers are triblock polymers that contain a hydrophobic chain surrounded by hydrophilic units on either side to facilitate hydrophobic drug delivery [192]. Hydrophobic polymers cross-linked in aqueous environment exhibit sol-gel transition by reversible thermal gelation as shown in the scheme below (Fig. 3).

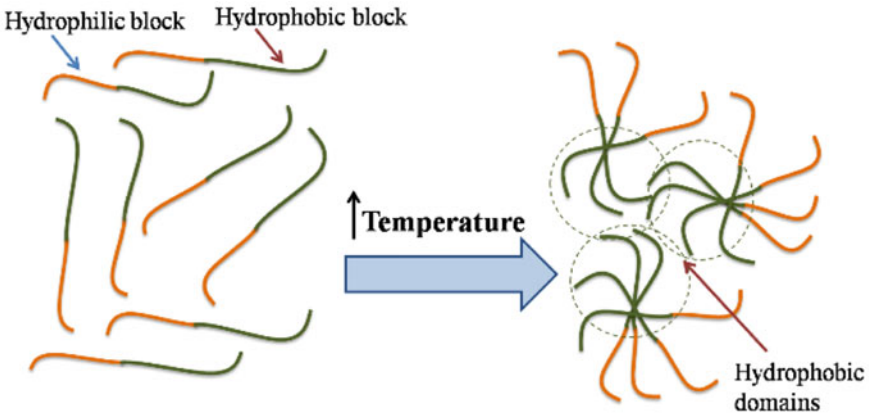

Fig. 3 Thermo-responsive physical gelation mechanism (Redrawn from [62])

Poloxamersare triblock polymers with two hydrophilic units and a hydrophobic entity flanked in between. They are noted as a potent drug delivery vehicle for delivering hydrophobic cargos (drugs or biomolecules) over conventional drug delivery vehicles. They do not entailthe natural absorption of hydrophobic molecules. Besides, thistri-block polymer offers various advantages such as biocompatibility, mechanical strength, and stability for targeted drug delivery [198, 182]. Pluronics were known to be an excellent drug vehicle until the polypropylene (PPO) unit in PEG-PPO-PEG triblock was non-degradable under physiological conditions. Modifications were made to replace the PPO by polypropylene glycol (PPG) using a template emulsion method to promote biodegradability. Other polymers with varying molecular weights can be used to control drug release purposes. Semi-hydrophilic triblock polymeric units such as PEO-PPO-PEO, hydrophobic polymer polycaprolactone (PCL) are also employed for site-specific drug delivery of poorly soluble drugs [201]. Pluronic/PCL blocks are known to change their size with respect to temperature precisely and for thermosensitive controlled drug release [93]. In addition to this, pluronic are also used in bioprinting for increasing tissue engineering augmentation. 3D printing limits the availability of the polymer substrate as a starting material. However, nanostructuring utilizing a mixture of polymers has resulted in better biocompatibility and cell stability. Acrylatedpluronic and pluronic F127 were cross-linked using UV, to preserve viability, enhance mechanical integrity, and cell adhesion [132].

Polyhydroxyethyl methacrylate (pHEMA) achieved considerable attention in the early 1960s. Popularly known for its high water absorbing capacity, biocompatibility, this polymer finds various applications in medical and biological fields. The mechanical and swelling properties of this polymer are tailored based on its use in mimicking bone substitute, tissue engineering, scaffold generation, synthetic biomaterial, and drug delivery purpose [123, 90]. The ability to release drugs or any bioactive agents of interest is directly proportional to its swelling property of the hydrogel pHEMA. This swelling property, in turn, depends upon the crosslinking agent employed for

hydrogel formulation [69]. For tissue engineering scaffold generation, positively charged polymer scaffolds show a better attachment than the negatively charged polymer [186]. Implantable hydrogels for drug delivery/tissue engineering frequently face rejection due to the immune response of the host system. A thick collagenous of matter around the implant is formed, that favorably thwarts the implant- body interactions preventing implant rejection. pHEMA does not favor non-specific protein absorption, thus supporting its non-fouling property, which is highly desirable for an implant. However, pHEMA can only partially prevent surface capsule formation, thereby necessitates for modification of pHEMA formulations. Zwitterionic hydrogels of poly carboxy betaine methacrylate (PCBMA) has known to develop smaller surface capsule formation, thus causing lesser inflammation, ultimately leading to a lowered chance of implant rejection [223].

Polyacrylamide (PAAm) based hydrogels are synthesized from monomers of acrylamide. Different conditions of polymer synthesis, co-polymerization with other different monomers, to achieve for tailored chemical properties of the hydrogel. Hydrogels constructed with PAAm backbone are often exploited for stimuli-responsive drug delivery. Gastrointestinal systemic delivery with varied pH, ranging from highly acidic to alkaline (pH 1.0–8.2), chronic wound treatment, and treatment for cancer employed by using PAAm based hydrogels are reported in the literature. These formulations contain weak acidic (carboxylic or sulfonic) or primary (ammonium) functional groups bonded to the main polymer configurations, that become ionized in micro-environmental pH conditions either by accepting or donating protons, thereby affecting the swelling pattern of the hydrogel [58–203].

In addition to pH sensitivity, temperature-responsive PAAm polymers are also used for their distinct properties. Frequently used thermoresponsive modified PAAm polymers are polyN-isopropylacrylamide (PNIPAAm), polyN, N-dimethyl acrylamide (PDEAAm) [100]. One another polymer is employed for similar thermoresponsive properties is PNIPPAm, and the additional functionality of the pendant groups is poly2-carboxy isopropyl acrylamide (PCIPAAm) [100]. Similar yet distinctive polymers that are used for varied applications are as tabulated in Table 2 [119].

Table 2 Thermoresponsive polymers and their applications

Polymer	Applications
Poly(N-(1)-1-hydroxymethyl-propylmethacrylame) (poly(1-HMPMAAm)	pH responsive and photosensitive
Poly(N-acryloyl-N-alkylpiperazine)	pH and thermoresponsive
Poly (N,N-diethylacrylamide) (PDEAAm)	Thermoresponsive yet distinct structures
Poly(2-carboxyisopropylacrylamide) (PCIPAAm)	

2.2 *Based on Crosslinking Methods*

Different crosslinking strategies are employed for hydrophilic monomeric units in hydrogel fabrication to form stable polymeric networks [118, 54, 71]. Different physical and chemical crosslinking methods are listed in Fig. 2. Physical crosslinking include charge ion interactions, hydrogen bonding, crystallization/stereo-complex formation mechanisms, while synthetic strategies involve radical polymerization [64–102], photo-polymerization [11, 127], high energy irradiation, enzyme induced crosslink reaction, addition reaction of the polymeric units [184], Diels-Alder "click reaction," and Schiff-base formation. Depending upon the structure and desirable mechanical properties, nature of polymers, the crosslinking strategy is preferred for fabrication.

2.2.1 Physical Crosslinking

The physically cross-linked hydrogel, also known as a reversible hydrogel, is usually created by inter-molecular bonding through ionic interactions, polymerized entanglements, hydrophobic/hydrophilic bonding, etc. This reversible property is exploited in designing stimuli-responsive hydrogel with self-healing and injectable features for efficient drug delivery purposes. They are also referred to as the 'smart drug delivery systems' (SDDS).

i. Ionic/electrostatic interactions

Molecules with opposite charges tend to attract each other influencing formation of a hydrogel. Alginate a natural source of polysaccharide with mannuronic and glucuronic acid units, are cross-linked to achieve gel formation by divalent cations such as magnesium (Mg^{2+}), calcium (Ca^{2+}) and barium (Ba^{2+}) [22, 107]. It is widely employed in wound healing, drug delivery, tissue engineering. A similar mechanism occurs in macromolecules with opposite charges through electrostatic interactions to give polyelectrolyte complexes (PECs) [141]. For example, chitosan forms PECs by the electrostatic interactions between its amino group (cationic) and from other natural polyelectrolytes such as pectin, alginate, chondroitin sulphate or artificial polymers like polylactic acid (PLA), polyacrylic acid, and polyphosphoric acid (anionic) [9, 63]. These hydrogels fabrication using PECscan be modulated using the charge density of the polymer, amount of the polymer, the mix ratio, and the surrounding microenvironment of the polymer [210, 114]. When the net charge of the polymer is zero, the hydrogel complex precipitates in its microenvironment. The significant advantage of the preparation of the hydrogel through the ionic/electrostatic interactions is their deformability under high stress and ability to reform once the pressure is removed, making it a candidate for SDDS. However, limitations of ionic/electrostatic interaction-based hydrogel include the decreased mechanical strength due to the bonding involved [9, 107, 63, 114].

ii. Hydrophobic interaction

Water miscible monomers with hydrophobic tail groups on the side chains or hydrophobic monomers are subjected to thermal induction or ultrasonic treatment promoting sol-gel transition in hydrogel formation by hydrophobic interaction. Specific conditions in favor the gel transition are maintained for gel formation, while removal of the same leads to reversible physical state [62].

Thermal induction based on lower critical solution temperature(LCST) [76–39]/upper critical solution temperature (UCST) [12, 221] is used for hydrogel fabrication when thermally treated at a critical temperature, the sol-gel transition occurs. Graft copolymers or amphiphilic blocks can self-assemble to form an organized structure in an aqueous environment with a hydrophobic core such as micelles. Polymers such as PNIPAM and its derivatives blend with hydrophilic PEO with hydrophobic PPO/Poly glycolide/Polylactide/PCL are generally fabricated for their thermoresponsive property through LCST. These polymers below LCST are in solution form, while at higher temperature form an insoluble gel structure through hydrophobic interactions. Methylcellulose containing Calcium Phosphate (CaP) nanoparticles using one-pot reaction by LCST gelation, has been reported as an experimental hydrogel drug reservoir at physiological pH [144].

On the contrary, in UCST induced hydrogel formation, the cooling temperature of the polymer solution plays an important role. Here, the hydrogel state is achieved at the temperature below UCST. However, at UCST, the hydrogel disintegrates, making the hydrophobic water-soluble micelle cores. Thermo reversible linear triblock comprising with inner hydrophilic poly-polyethylene glycol methyl ether methacrylate (PPEGMMA) part and outer polyacrylamide-co-acrylonitrile (PAAm-co-AN) units as a cooling induced sol-gel transition. This physical transition can be modulated by the polymer concentration [45].

Ultrasonic induction [79, 209] induced crosslinking involves phase variation. Natural or synthetic polymers such as collagen and silk fibroins that possess complex secondary structures can be physically crosslinked to form interpenetrating networks (IPNs) with improved physical properties and tunable gelation properties when treated with physical shear, organic solvents, and heat treatment.

iii. Crosslinking by Crystallization

Crystallites of polymer unit work as sites of physical cross-linking for hydrogel formation. An aqueous solution of PVA is subjected to repeat freeze-thawing to yield hydrogel. Parameters such as molecular weight, polymer concentration, time, and the number of freeze-thawing cycles and freezing temperatures influence the hydrogel formation [66]. Similarly, exploiting the property of crystallization, hydrogen bonding in polymers PVA, and hydrophobic polyacrylamide (HAPAM), physical double network (PDN) was developed by one-potpolymerization followed by repeated freeze-thaw cycles (Fig. 4).

More compact hydrogel structures are obtained by stereo-complex interaction between the two enantiomeric polymers. Based on the racemic crystallite Poly L-Lactic acid (PLLA) and poly d-Lactic acid (PDLA), a unique gel-sol-gel transition occurs upon heating and stereo-complexation. Novel enantiomeric mixtures of

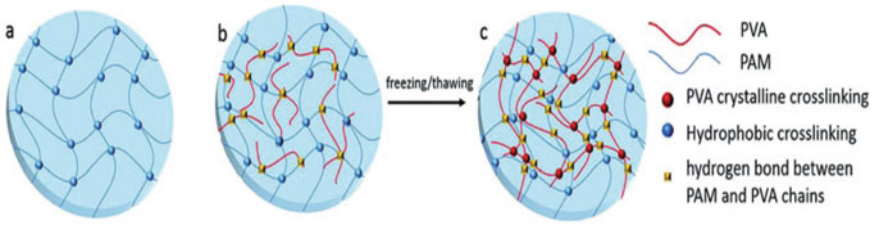

Fig. 4 Schematic illustration of Semi-IPN HAPAM/PVA hydrogel network structure fabricated via the freezing/thawing treatment: **a** HAPAM gel. **b** semi-IPN HAPAM/PVA gel. **c** PDN gel after subsequent freezing/thawing (Reproduced with permission from [80])

PDLA/PEG diblock polymeric systems and PLLA/PEG triblock copolymers are designed, where stereo-complex formation profoundly influence gel-sol-gel phase transitions [72].

iv. Crosslinking by Hydrogen Bonding

Hydrogen bonding is a crucial non-covalent interaction that widely influences by forming bonds within themselves, such as in hydroxyl, pyrrole, carboxylic acid, carbazole, or interact with electron donors such as imidazole and pyridine groups. Although a single hydrogen bond does not necessarily support healthy polymer network formation, multiple multivalent hydrogen bond interaction is found to influence the mechanical property of the hydrogel profoundly. Ureidopyrimidinone (Upy) dimer entrenched in hydrophobic domains of the PEG matrix assemble via 4-fold self-complementary hydrogen bonding, that reinforced networks (Fig. 5). This

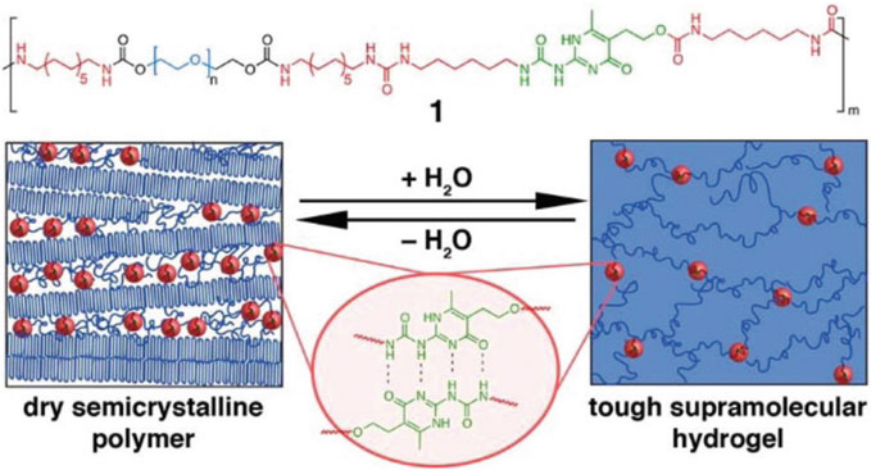

Fig. 5 PEG-UPy copolymers with multi-block architectures and self-complementary quadruple H-bonding interaction between 2 UPy segments. A graphical representation of drysemi-crystalline polymer and a reversible conversion to the hydrogel (Reproduced with permission from [59])

polymeric network is known to exhibit high resilience, increased strength, and shape memory behavior [59].

v. Crosslink by Metal coordination

Metal-ligand interaction between the metal ions and functional groups in the polymeric chains has been considered as a unique Lewis acid-base interaction, which is regarded as more potent than other non-covalent bonds. This moderate energy facilitates metal-ligand interaction occurrence or breakdown, which helps in self-healing property [111]. Mechanical properties of metal coordination based hydrogels such as hydrogel strength, toughness, the strength of the coordination bond, required tunable temperature-sensitive/pH-responsive/shape memory ability can be acquired accordingly to the application intended as they form sol-gel characteristics based on their metal coordination bonds [90–222]. Listed below in Table 3 are the polymers and their unique property achieved by tuning their metal coordination bond.

i. Crosslinking by host-guest interactions

'Host' refers to the molecule with a large cavity, such as cyclodextrins (CDs), calixarenes (CAs), cucurbiturils (CBs). At the same time, 'guest' molecule is complementary shapes (polymer) that form reversible interactions through various non-covalent binding such as hydrophobic interactions, hydrogen bonding, Van der Waals, electrostatic interactions, etc. Host–guest interactions occur by hydrophobic guest

Table 3 Different polymers and corresponding metal ion facilitating hydrogel formation

Polymer	Crosslinking metal ion	Property achieved	Mechanism involved
Poly (2-oxazoline) [29]	Fe (II), Co (III)	Stable at room temperature but disintegrates at 30 C	Intermolecular crosslink to intramolecular crosslink conversion
	Ru (II)	Hydrogel stable at boiling water	Dry gel recovers gelation in water after liquid evaporation
PEG functionalized with 3,4-dihydroxyphenylalanine (dopa) [95–76]	Fe (III)	Controlled gelation and cross-linking density by pH variation	Catechol ligand iron (Fe (III)) ion coordination to form catechol- Fe^{3+} complexes (mono- (below pH 5), bis- (about pH 8), tris- (above pH 8))
Poly (acrylamide-co-acrylic acid) (P(AAm-co-AAc)) [228]	Aqueous ferric chloride ($FeCl_3$) solution	High toughness, stiffness, fatigue resistance, shape memory, and processing ability filled hydrogel	Supramolecular network formation by carboxyl-Fe3+ coordination bond

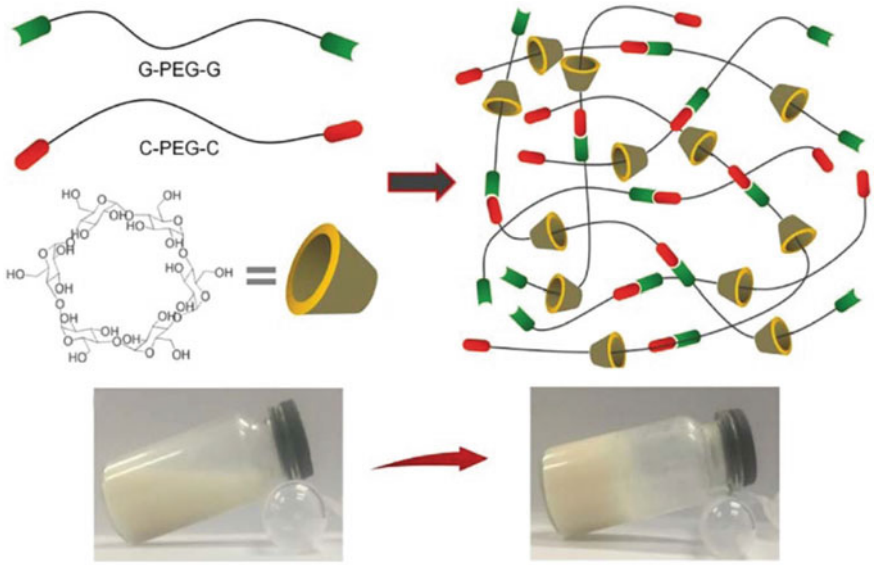

Fig. 6 Synthesis of supramolecular thermoresponsive hydrogels by host-guest inclusion between (G/C)-terminated PEG and α-CD. The G–C base pairing acts as additional network junctions and enhances the hydrogel mechanical properties (Reproduced from [80])

molecules encapsulation into the hydrophobic cavities in aqueous solution. Host–guest inclusion facilitates strong binding, fixed geometry, directionality, stimuli-responsive characteristics, making it useful for drug delivery [122]. One of the most universally used hydrophilic surfaces host molecule is cyclodextrin (CD). It is cross-linked with PEG to form injectable hydrogel for sustained drug release [109, 81]. The concentration of PEG and time required for gelation is dependent upon the molecular weight of PEG. Modified terminal ends of PEG with synthetic nucleobase guanine/cytosine (G/C) for base-pair formation can act as an additional network junction, as shown below in Fig. 6. This interaction enhances the storage module of PEG-CD inclusion complex increases mechanical integrity and cytocompatibility of the thermoresponsive controlled drug release [101–211].

2.2.2 Chemical Crosslinking

The chemically cross-linked hydrogel, also known as the permanent gel, is formed by covalent crosslinks in the polymeric chain with higher mechanical strength when compared to physically cross-linked hydrogels. Different chemical crosslinking strategies are employed such as free radical polymerization, enzyme-mediated crosslinking, Diels-Alder “click” reaction [136, 50], Michael addition reaction, Schiff base formation and oxime formation [131], etc. These hydrogels show

higher stability under physiological conditions, enhanced mechanical property, and modifiable degradation behavior.

i. Crosslinking by photopolymerization

Light-activated cross-linking has been broadly used for hydrogel formation and therapeutics encapsulation and delivery [107–85]. Hydrogel formation is rapid at ambient temperature under placid conditions and alterable mechanical properties by controlling crosslinking reaction [135]. The choice of photo-initiated polymerization site is crucial as hydrogel formation occurs only in the irradiated light areas [220]. The composition of photo crosslinked biomedical hydrogels usually involves the presence of unsaturated groups that are incredibly reactive to favor free radical chain intensification polymerization when exposed to light. Also, cytocompatible-photoinitiators such as riboflavin phosphonate [61], camphorquinone [44], eosin Y [181], Irgacure 1173 [80], Irgacure 819, Irgacure 2959 [216] are required depending upon the wavelength absorption needed and given at the intended site. Photoinitiators absorb at specific wavelengths such as UV (250–370 nm), visible blue and purple (405–550 nm) or red light (750–810 nm) and either deteriorate (Type I) or acquire hydrogen from donor molecule (Type II) for polymerization [226]. Type II photo-initiators always require a co-initiator and some of which are listed below in Table 4 for visible light activated photo-polymerization.

UV crosslinking of γ-PGA and glycidyl methacrylate (GMS) to form methacrylate γ-PGA, showed ionic sensitivity and low cytotoxicity. A chitosan hydrogel prepared by UV crosslinking method with a cell loading pattern showed low cytotoxicity as well [15]. As light can penetrate the tissues, a prepolymer solution of the desired polymer and photo-initiator (Type I)/a photoinitiator and co-initiator (If Type II) were prepared and given as a hypodermic injection [181]. As discussed earlier, it is necessary to select a light penetrating site for photo-crosslinking, and as UV exposure risks the DNA damage, favoring visible light as an alternative [74]. Some of the commonly used visible light initiators are CQ, eosin Y, riboflavin [78], ruthenium [10], and lithium phenyl-2,4,6-trimethyl eosin benzoylphosphinate (LAP). Chemical modification of the photo-initiators is also made to improve crosslink density, higher photoactivity, and better mechanical properties. Only a few millimeters depth is achievable in photo-crosslinking and limiting the maximum attainable cure. Also, the homogeneity of the polymer structure and uniform tensile strength is uncertain. To overcome these limitations, polymerization of co-monomers with complementary reactive groups, that can facilitate homogenous hydrogel formation rapidly, and at

Table 4 List of the combination of Type II photoinitiators and co-initiators [16]

Type II photoinitiator	Co- initiator
Camphorquinone (CQ)	4- N,N- dimethylaminobenzoate (4EDMAB)
Isopropyl thioxanthone	Triethanolamine (TEA)
Eosin Y	TEA and N- vinyl pyrrolidone (NVP)

greater depths with lack of light intensity, and absence of photo-initiator has gained much attention [139]. Thiol and acrylate reaction is one of the extensively employed Michael addition reactions that can be coupled with photopolymerization, which is referred to as mixed-mode polymerization. It can yield tunable polymeric network formation and degradation by adjusting the thiol and acrylate ratio. Thiol groups also facilitate the post-polymerization of the hydrogel. Poly butadiene and poly (allyl methacrylates) functionalized with thiol can undergo photocatalytic redox reaction in visible light to form linear polymers by step-growth addition reaction [127, 85, 121].

ii. Crosslinking by Enzyme catalyzed reaction

Enzyme catalyzed crosslinking offers rapid in situ gelation with a possibility of tuning gel formation by controlling enzyme concentration under physiological conditions. Many kinds of enzymatic crosslinking methods are identified, such as amide linkage between carboxamide and amine groups in the presence of transglutaminase (TG); horseradish peroxidase (HRP) catalyzed coupling of aniline, phenol and its derived tyramine catalyzed by hydrogen peroxide. Enzymatically conjugated collagen with tyramine (Collagen- Ph) in the presence of HRP and H_2O_2 has been employed for constructing novel vascularized tissue [86]. This hydrogel encapsulated with bone marrow-derived mesenchymal stem cells (MSCs) and with human blood-derived endothelial colony-forming cells (ECFCs). The encapsulation improved prolonged MSC differentiation in the mouse as model organism after one month of implantation [123–87].

iii. Crosslinking by "Click chemistry."

Chemical reactions that favor high yield under mild conditions, lesser by-products, and increased specificity and selectivity are termed as "click" reactions. This reaction highly depends upon the functional groups of the polymeric materials for hydrogel fabrication. Classical click chemistry reactions are discussed as follows.

Diels Alder (DA) reaction is a one-step, highly selective, cycloaddition (4 + 2) between a dienophile (maleimide) and a diene (furan), that can occur in the absence of any initiators, catalysts and coupling agents. Polymers are customized accordingly with furan or furan derivatives to react with poly (ethylene glycol) dimaleimide for hydrogel formation [43]. Modifications are further being made to increase the DA reaction rate at physiological conditions, such as replacement of furan as methylfuran [189].

Schiff base formation is a condensation reaction between formyl or carbonyl-containing derivative and primary amines in the presence of catalysts like alkaline earth metal ions to form imine linkages. It has been extended to form injectable in situ gelling hydrogel as aldehyde end can adhere to tissues or organs [130]. Schiff linkages can be considered to be pseudo- covalent bonds that facilitate uncoupling and re-coupling of these linkages in polymeric networks result in self-healing capability. The amino group of the acrylamide modified chitin (AMC) and dialdehyde yield oxidized alginate for self-healable polymeric hydrogel. The molar ratio of the monomers and the microenvironment pH largely influence hydrogel formation [38].

Oxime crosslinking reaction requires an amino-oxy/hydroxylamine group and a functional aldehyde or ketone. These reactions are highly specific and occur even in the presence of other functional groups. It offers an advantage of crosslinking at the acidic condition and the only by-product being water. Self-healing, oxime cross-linked hydrogel can undergo reversible gel-sol conditions at acidic conditions [31].

Michael addition is a simple reaction between nucleophiles (donor) and activated electrophilic alkene or alkynes (acceptor). Often referring to thiol-containing polymers are added to the α and β unsaturated carbonyl polymers under necessary conditions that are well suited for the formulation of a cellular scaffold, gene transfection, and tissue replacements [124, 158].

iv. Covalent chemistry crosslinking

Reversibility of crosslinking helps to develop self-healing hydrogel that maintains strong integrity and internal annuity. This property of physical crosslinking is extended to covalent bonding. For example, boronate esters prepared from boronic acids and 1,2- and 1,3-diols that are pH-responsive, and it is designed based on its pKa (Hydrogel formation is favored when pH > pKa; remains as an aqueous solution when pH < pKa). Polymers such as PEG, polyphenols such as ellagic acid, epigallocatechin gallate (EGCG), and tannic acid (TA) were modified with linkers to provide boronate ester bonds for gelation at pH 7.4 that promote self-healing property at the physiological environment [77]. Native enzymes such as cytochrome-c can also be incorporated into hydrogel by structural integration to provide controlled stimuli-responsive hydrogel [178].

3 Hydrogel Design

Biomedical applications of the hydrogel are highly depended upon the bulk structure and parameters such as polymer volume in the swollen state ($v_{2,s}$), the molecular weight of the polymer chain between two crosslinks ($\overline{M}c$) and its corresponding mesh size (ξ). The measured quantity of water imbibed and retained by the hydrogel is given as polymer volume fraction. As random polymerization occurs, molecular weight between two crosslinks (physical/chemical) is calculated as average value (M_c) in the hydrogel. The correlation distance between adjacent crosslinks is also an average quantification that gives a measure of space existing between the polymer chains in the hydrogel. These parameters are related to each other, and dependent on the nature and charge of the polymer, type of crosslink, which measured both theoretically and experimentally [105, 104]. Two prominent theories widely used to explain configuration of the hydrogel are [149]:

1. Equilibrium—swelling theory.
2. Rubber—elasticity theory.

Hydrogels with no ionic moieties can be analyzed by Flory-Rehner theory, which is a combinatorial conjecture of thermodynamics and elasticity. This theory states that, when a cross-linked polymer gel plunged in a fluid, it is allowed to reach in equilibrium exerts, which is equal to the thermodynamic force of mixing and the retraction force of the polymer chains. Defining in terms of Gibbs free energy as Eq. 1,

$$\Delta \boldsymbol{G}_{\text{total}} = \Delta \boldsymbol{G}_{\text{mixing}} + \Delta \boldsymbol{G}_{\text{elastic}} \tag{1}$$

Where, $\Delta G_{\text{elastic}}$ is the total refractive elastic force developed inside the gel; ΔG_{mixing} is the spontaneous mixing force of the polymer with the surrounding fluid. The above equation is differentiated with respect to the number of solvent molecules, the temperature and pressure as constants result in Eq. 2,

$$\mu_1 - \mu_{1,\,\text{o}} = \Delta\mu_{\text{elastic}} + \Delta\mu_{\text{mixing}} \tag{2}$$

Where μ_1 is the chemical potential of the solvent (fluid) in the polymer gel and $\mu_{1,\,\text{o}}$ is the chemical potential of the pure solvent.

At equilibrium, the difference between the chemical potential of the fluid inside and outside of the gel will be 0. Thus, making the chemical potential due to mixing and elastic forces are equal (Eq. 3).

$$\Delta\mu_{elastic} = \Delta\mu_{mixing} \tag{3}$$

Change in the chemical potential due to elastic forces of the polymer chain can be evaluated using rubber elasticity theory. The interaction between the polymer and the surrounding fluid is given as χ_1. Below, Eq. (4) is used to calculate molecular weight between adjacent crosslinks $\overline{M}_c$ of a neutral hydrogel in the absence of solvent.

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\left(\frac{\overline{v}}{V_1}\right)\left[\ln\left(1 - v_{2,s}\right) + v_{2,s} + \chi_1 v_{2,s}^2\right]}{\left(v_{2,s}^{1/3} - \frac{v_{2,s}}{2}\right)} \tag{4}$$

Where M_{n} is the molecular weight of the polymer prepared identically in the absence of cross-linking agent; v is the polymer specific volume, and V_1 is the molar volume of water.

Ideal conditions are modified according to the real-time application and speculated to accord the need. The presence of water influences the elastic force, and polymer is subjected to influencing the chemical potential. Considering the volume fraction density of the neutral hydrogel, the molecular weight is calculated by Eq. (5),

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\left(\frac{\overline{v}}{V_1}\right)\left[\ln\left(1 - v_{2,\,s}\right) + v_{2,\,s} + \chi_1 v_{2,\,s}^2\right]}{v_{2,\,r}\left[\left(\frac{v_{2,\,s}}{v_{2,\,r}}\right)^{1/3} - \left(\frac{v_{2,\,s}}{2v_{2,\,r}}\right)\right]} \tag{5}$$

Where, $v_{2,s}$ is the polymer volume fraction in a relaxed state (hydrogel immediately after crosslinking, but before swelling). The above equations are extended to calculate the molecular weight of cationic and anionic hydrogels in Eqs. (6) and (7), respectively.

$$\frac{V_1}{4IM_r}\left(\frac{v_{2,s}}{\overline{v}}\right)^2\left(\frac{K_b}{10^{-pH}-K_a}\right)^2 = \left[\ln(1-v_{2,s})+v_{2,s}+\chi_1 v_{2,s}^2\right] + \left(\frac{V_1}{\overline{v}\overline{M}_c}\right)\left(1-\frac{2\overline{M}_c}{\overline{M}_n}\right)v_{2,r}\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3}-\left(\frac{v_{2,s}}{2v_{2,r}}\right)\right] \tag{6}$$

$$\frac{V_1}{4IM_r}\left(\frac{v_{2,s}}{\overline{v}}\right)^2\left(\frac{K_b}{10^{pH-14}-K_a}\right)^2 = \left[\ln(1-v_{2,s})+v_{2,s}+\chi_1 v_{2,s}^2\right]+ \left(\frac{V_1}{v\overline{M}_c}\right)\left(1-\frac{2\overline{M}_c}{\overline{M}_n}\right)v_{2,r}\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3}-\left(\frac{v_{2,s}}{2v_{2,r}}\right)\right] \tag{7}$$

Where I is the ionic strength; K_a & K_b are the dissociation constants of acid and base, respectively; M_r is the molecular weight of the repeating entity. Hydrogel under stress can go through structural deformation. Rubber—elasticity theory is a means to scrutinize the structure of hydrogel in the presence of a solvent. Remarkably, it is used to analyze polymers formed by physical, chemical, and impermanent crosslinking processes. Equation (8) is used to calculate the stress that hydrogel can sustain theoretically.

$$\tau = \frac{\rho RT}{\overline{M}_C}\left(1-\frac{2\overline{M}_c}{\overline{M}_c}\right)\left(\alpha-\frac{1}{\alpha^2}\right)\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3} \tag{8}$$

Here, τ is the stress applied to the hydrogel; ρ is the density of the polymer; R is the universal gas constant; T indicates an absolute temperature and $\overline{M}_c$ is the desired molecular weight between the crosslinks. To evaluate this theory, the hydrogel is subjected to a tensile testing system [147].

3.1 Hydrogel-Porosity

One vital structural parameter for hydrogel analysis is the pore or mesh size, which refers to the space present between the polymer chains. Different hydrogel classification with their pore size is given below in Table 5.

This size of the pore is calculated using correlation length (ξ) (Eq. 9),

$$\xi = \alpha\left(r_0^2\right)^{1/2} \tag{9}$$

Table 5 Hydrogel classification based on pore size

Hydrogel	Pore size
Macroporous	mm to cm
Microporous	5 μm- ~1 mm (<5 μm for oral/pulmonary DD)
Nanoporous	10–100 nm

Here, α is the elongation ratio of the polymer chain in any direction; $(r_0^2)^{1/2}$ is the root mean square of the collective, end to end distance of the polymer chains between two neighboring crosslinks. These parameters help much in tailoring the molecular structure of the hydrogel, therefore influencing its mechanical, responsive, and diffusive properties [149]. Thus, the hydrogel is an actively studied material for its application in biomedical science. This chapter focuses on the potential biomedical applications of hydrogel and is described in the next section.

4 Hydrogel Nanocomposite: Biomedical Perspective

Hydrogel formulated using various physical and chemical cross-linking methods has been significantly explored as a biomaterial for drug delivery [152]. Controlled drug delivery system (DDS) is a significant research area for more than a decade, for increasing patient compliance, avoidance of repeated dosage, overcoming peak valley effect of the drug and prolonged drug release at the desired site of action [40, 128]. Targeted, extended drug release by a biocompatible material significantly influences the conventional routes of drug delivery. Hydrogel offers a complete paradigm of satisfying as a biomaterial for drug delivery. This is a 3D polymeric network, can carry water and deliver drug molecules (cargo) into cells. There are high similarities with extracellular matrix aid in being a support material for tissue regeneration and DDS in drug payload [142–30]. Deformable, elastic hydrogel with augmented drug residence time and tissue permeability facilitates bioadhesive drug delivery. Hydrogels with shape conforming features eliminate the need for implantation surgery, making it more efficient. This DDS also poses challenges, such as not being able to carry and release hydrophobic drugs, by the addition of solubilizing moiety, cell-selective therapy by introducing targeted functional group, controlled drug release of low steric interference molecules by employing spacers or modification of polymer backbone. Thus favoring the alternative of polymeric nanoparticles (NPs) for drug encapsulation and release [145–60]. The schematic compilation of nanocomposite hydrogels in the biomedical application is shown below (Fig. 7).

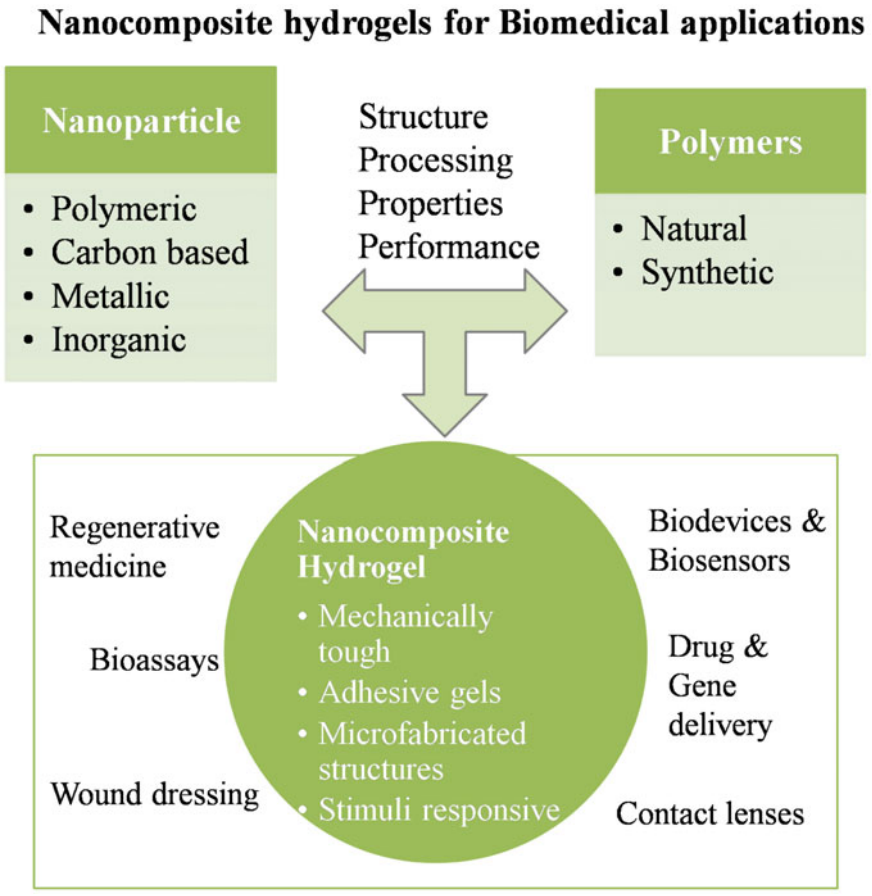

Fig. 7 Nanocomposite hydrogels for biomedical applications

4.1 Microfabrication Techniques for Hydrogel Formulation

In the last two decades, microfabrication approaches using polymeric materials to make hybrid materials are in research focus, to overcome the complexities in tissue engineering applications. Many such advanced techniques have been reported to locate different types of cells within the hydrogel and aid for active tissue formation. Fibrillar structures are necessary for intrinsic influence on cell morphology, differentiation, and polarity. Hydrogel offers fibrils of a wide range of diameters that can be prepared by various methods. Self-organization of the peptides with other hydrophilic and hydrophobic groups [173, 125], electrospinning method can provide fibers of nano to micrometer diameter with direct orientation and spacing [150–155], microfluidic co-flow of polymer and gelation solution in patterned devices are some of the techniques reported. Microfluidic devices are fabricated by well-established

Table 6 Comparative analysis of various microfabrication methods

Technique	Resolution	Description	Demerits
Bioprinting	~ 10 μm	Accurate deposition by the printer.	Expensive; Limited to specific hydrogel
Stereolithography	~ 1 μm	Photopolymerisable hydrogel block formation layer by layer with laser irradiation	Expensive; Limited to photopolymerizable polymers
Laser printing	~ 1 μm	Hydrogel block formation by laser ablation	Expensive; Time consuming; Non-homogeneous hydrogel network formation
Bioprinting	~ 100 nm	Hydrogel mold with master structure from microfabrication techniques	Highly sophisticated; trained personnel; multiple steps

micropatterning methodologies, such as photolithography, soft lithography [153–36], microcontact printing [151], bioprinting [83] and laser printing [57]. Comparative methods of microfabrication are listed below in Table 6 [205].

4.2 Crosslinking Techniques for Hydrogel Nanocomposite (HNC) Formulation

Hydrogel nanocomposite (HNC)/nanogels are fabricated by using physical/chemical crosslinking of polymers with different nanoscale features (see Fig. 8). It depends significantly on hydrogel mesh size, size of the nanoparticles (NPs), and nature of the NPs. The size of the NPs is crucial, as particles of diameter less than 10 nm are cleared by extravasation and renal filtration. With a diameter greater than 200 nm, HNCs can be seized by the spleen and eliminated eventually by the phagocytes. The optimal NPs diameter ranges from 70 to 200 nm for prolonged circulation, whereas 10–70 nm NPs can penetrate through tiny capillaries and immune system barriers [159–24]. Polymer crosslink formation can be inhomogeneous, thus necessitating novel NPs dispersion into the matrices. Different categories of nanomaterials and nanoparticles are involved in hydrogel nanocomposite formation are classified in Fig. 8.

4.2.1. Carbon-based nanomaterials have been well employed for various biomedical applications, such as CNTs, graphene/and its oxides, nanodiamonds, diamond-like carbon (DLC) [185] and diamond-like nanocomposite (DLN) [165–167], fullerene (C60) [163, 156], etc. Various studies are being carried out on CNTs due to its high electrical conductivity, mechanical strength, and optical properties [91].

Besides, these high aspect ratio cylindrical hollow tubes of carbon with sp^2 hybridization, Van der Waals force aid in the formation of ions of different molecular weight and charges. Therefore, carbon-based nanomaterials are a superior choice of

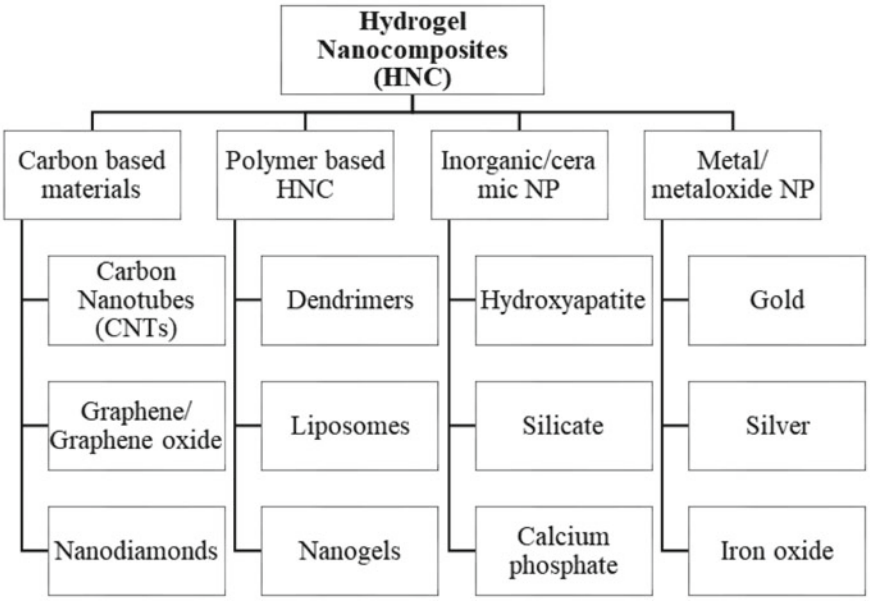

Fig. 8 Schematic classification of hydrogel nanocomposites

material for electrically conductive nervous, cardiac, and muscular tissues [99]. CNTs have limited interaction with the hydrophilic polymer, thus require surface modifications to enhance dispersion with polar groups, such as amines (NH_2), carboxyls (COOH), hydroxyls (OH) or polymeric inclusion. The diverse structures are being proposed with increased functionality for enhancing dispersion in the physiological conditions [173–225]. On the contrary, graphene is treated with strong oxidizers for surface attachment of oxygen, to get Graphene oxide (GO), one of the most explored 2D hydrogel actuators [208, 219]. The GO is less electro-conductive, but more hydrophilic, and making it inexplicable for site-specific genetic material delivery [146, 47]. Although carbon-based hydrogel offers various advantages, replacements to the body tissue require detailed cytotoxicity studies under in vitro and in vivo conditions [48].

4.2.2. Polymeric HNC comprised of monomers of similar or different nanostructured, that has gained enormous attention for its versatility like drug entrapment (hydrophobic/hydrophilic drugs, protein, genetic material, and other bioactive molecules) and stimuli responsiveness upon a change in temperature, light, concentration or pH [89, 174]. Dendrimers are hyperbranched polymers with a highly porous structure, and have multiple peripheral functional groups, that offering high reactivity and drug loading efficiency. The concentration of the dendrimer influence the stiffness of the hydrogel, degradation properties, hydration kinetics [184–224]. Nanocomposites containing dendrimers, demonstrate high stress absorbing capacity, and making it a viable candidate for cartilage tissue engineering. Disruption of cell membrane

yields a hydrophilic core and hydrophobic shell yield phospholipid molecules, which offers a great advantage of loading all kinds of bioactive molecules. Drug entrapped liposomes can be conjugated with the degradable polymers by crosslinking to obtain HNCs for targeted drug delivery (see Fig. 9) [188].

Nanogel (nanosized gels) is yet another polymeric nanocomposites, that can trap the intended bioactive molecule into its nanoscale core. This preparation can be carried out by chemical (covalent bonds) or physical (hydrogen bonds) crosslinking methods. Amphiphilic block copolymer, self assembles in water as mono dispersive polymer micelles, with hydrophilic or hydrophobic chains in core or shell [170].

The size-controlled nanogels can be prepared through nano or microemulsion polymerization. This reaction occurs in the presence of surfactants, within the core of water-in-oil (w/o) or oil-in-water (o/w), using micro or nano-emulsions (Fig. 10). The different sizes of monodispersed nanogel fabrication have been reported using atom transfer radical polymerization (ATRP) water-in-oil nano-emulsion. Nanogels are hydrophilic (e.g., doxorubicin) and bioactive macromolecules (e.g., proteins) and potentially applicable for drug delivery purposes [190–171].

4.2.3. Inorganic/organic nanomaterials: Essential body minerals such as nano-hydroxyapatite (nHA), synthetic silicate nanoparticles (nanoclay), bioactive calcium phosphate, silica, glass, glass-ceramic, wollastonite are required for normal body functioning. These inorganic materials are widely used for hydrogel formulation and related bone applications, as they favor osseointegration through its chemical bonds as elaborated in Table 7,

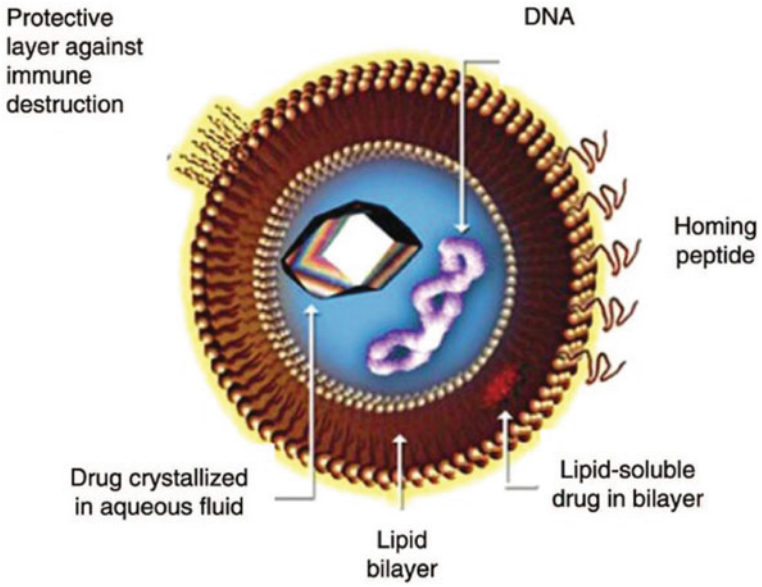

Fig. 9 Structure of Liposome and its drug delivery mechanism (Reprinted with permission from [154])

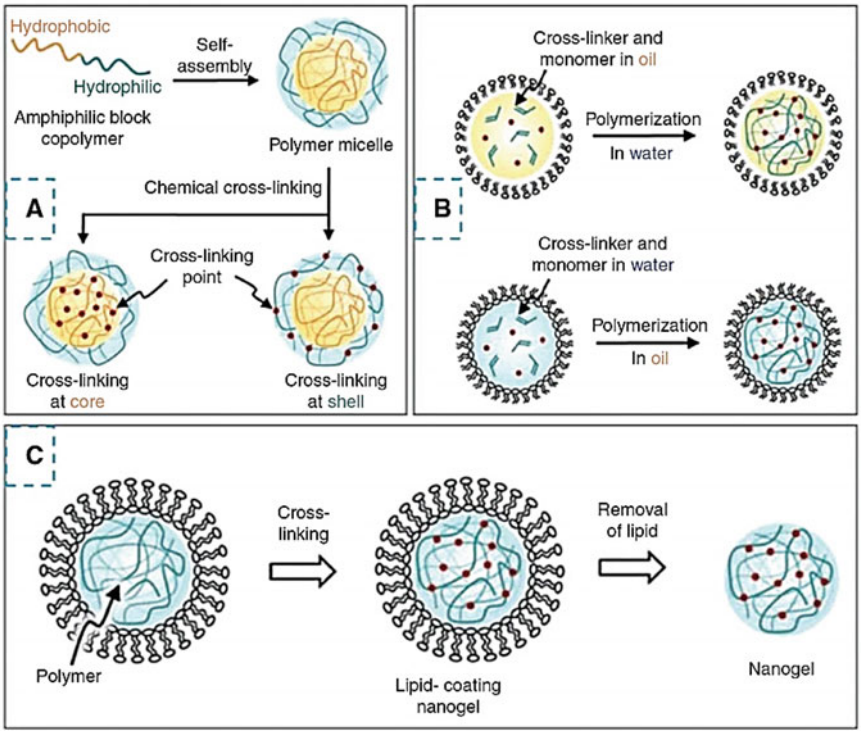

Fig. 10 Chemically prepared nanogel by **A** Crosslinking of amphiphilic block copolymer at core or shell of the polymer micelles in water. **B** Emulsion polymerization with/without emulsion. **C** Using liposome as a template (Reprinted with permission from [154])

Table 7 Interaction of various chemical bonds with body tissues

Chemical bond	Interaction with body tissues
Divalent covalent- ionic bond	PO_4^{3-} attached to the cation or oxygen ion on the ceramic surface and organic matter of the bone
Electrostatic bond	Involving positively charged amine (bone) and negatively charged oxygen (ceramic)
Hydrogen bond	Hydroxylated ceramic surface and the carboxyl group of amino acid
Van der Waals bonding	Negatively charged ceramics interacting with rigid hydrosphere of organic constituents

- Hydroxyapatite, filler for a bone substitution or implant coating, can be modified using silicon or methacrylate hyaluronic acid to lessen crack resistance and fatigue durability of the hydrogel in in vivo conditions. It also improves biodegradation properties, protein adsorption, and adhesion of the coating to the metal substrate [193–70].

- Nanoclays also show improved mechanical, high aspect ratio, and anisotropic morphology with tissue adhesive properties. When mixed with linear and branched polymers, it can form reversible structures, due to non-covalent interactions helping in absorption and desorption [195].

4.2.4. Metallic nanoparticles are classified as 0D hydrogel additives are used to prepare hydrogel nanocomposites [198–143]. In addition to the above, metallic NPs are widely used in creating conductive scaffolds, actuators, sensors, tracking agents in DDS. They can be functionalized to enhance polymer-NPs interactions.

5 Drug Release Mechanisms

Fabrication of drug-loaded polymeric network for the targeted and sustained release can follow any of the above mention methods. The drug release mechanisms largely depend upon the nature of the hydrogel. While in most cases, hydrogel follows diffusion controlled drug release (see Sects. 5.1 and 5.2). Stimuli-responsive smart polymer for drug release has been an incredible challenge. These polymeric systems respond to environmental stimuli (both physical and chemical) are called as environment-sensitive polymers (ESP)/stimuli-responsive polymer/intelligent polymers (refer Sect. 5.3).

5.1 Diffusion Controlled Drug Release

The hydrogel is one of the most explored biomaterials for designing both pulsatile and prolonged drug delivery systems (DDS). Diffusion controlled drug release kinetics is generally calculated as the amount of drug released concerning the given time interval. It is calculated by the 'Ritger- Peppas equation' where the mass fraction of the drug released follows by the power-law relationship Eq. (10)

$$\frac{M_t}{M_\infty} = kt^n \tag{10}$$

Where M_t is the amount of drug released at time 't'; M_∞ is the total amount of drug released; k is the rate constant, and 'n' is the diffusion constant that is between 0.5 and 1.

The following parameters can elucidate comparative drug release studies between two drug-laden hydrogel systems:

1. 'k' the rate constant measured over the given time. It can also indicate a burst release.
2. Half-life drug release, $t_{1/2}$ defined as the 50% mass fraction ($M_t \big/ M_\infty$) that signifies the sustained release in the given system

Different methods are used to control drug delivery in various hydrogel systems. Diffusion controlled hydrogel systems (given by the above equation) typically gives a half-life of 1 day and relatively higher burst release (k > 50%). To increase $t_{1/2}$ ~ 2–3 days, drug release is slow down by several mechanisms, such as the introduction of chemical bonds or polymer network degradation systems.

5.2 *Effect of Hydrogel Mesh Size in Diffusion Mediated Drug Release*

Diffusion is interrelated to the mesh size of the hydrogel, as it largely influences the drug-polymer interactions. When,$r_{mesh}/r_{drug} > 1$, drug release is governed by diffusion. Smaller drug molecules can freely move through the polymeric network, and diffusion is independent of the mesh size. In this case, Stokes-Einstein equation (Eq. 10) is used to measure the diffusivity (D), that is interdependent on the radius of the drug molecule (r_{drug}), usually ranges with its molecular weight and viscosity of the solution (η),

$$D = \frac{RT}{6\pi \eta r_{drug}} \tag{10}$$

Where R is the gas constant and T is the absolute temperature. In addition to this diffusion controlled drug release mechanisms, polymeric swelling, mechanical deformation, and network degradation are also considered, depending upon the nature of the polymer, crosslinking mechanism and intended application.

5.3 *Stimuli-Responsive Drug Release Mechanism*

HNCs, which are designed to respond to stimuli such as pH/temperature/concentration/light and release the drug act as controlled drug release centers. It is, therefore, necessary to understand the underlying principles of the same in drug delivery. Tabulated below in Table 8 are some of the physical/chemical/biological stimuli for ESP response [202–21].

Table 8 Different stimuli for ESP response

Physical stimuli	Chemical stimuli	Biological stimuli
• Light • Temperature • Ultrasound • Mechanical forces	• pH • Ionic strength • Solvent	• Enzyme • Glucose Concentration

One crucial feature of HNCs is its ability to surpass the immune system due to its nanoscale structures and, in some cases, of the blood-brain barrier itself. It is conceptualized by the Enhanced Permeability and Retention (EPR) mechanism using nanocarriers [2].

5.3.1 pH-Responsive Hydrogel for Drug Delivery

pH variation is observed in body tissues and cellular compartments. For instance, blood has pH in the range of 7.35–7.45; stomach 1.0–3.0; and duodenum 4.8–8.2 [6]. This difference in pH is exploited in formulating localized and sustained drug release in the intended areas in response to the specific substrates. The pH-sensitive hydrogel comprises of ionizable weak acids or a base is an attribute of the pendant groups of the polymeric unit. Hydrogel with numerous acidic groups is referred to as polyanions or polyacids, while the polymers with basic units are polybases or polycations [97]. Polycations, at basic pH, deprotonate and in the acidic environment, becomes positively charged. Combinational usages of nanocarriers that target and accumulate at the intended site and act as a localized drug storehouse embedded with drug are employed to design pH-sensitive hydrogel. It is the charge density of the acidic or basic polymer backbone of the polymer that induces pH-dependent swelling and deswelling of the hydrogel. Nanoparticles of poly β-amino ester (PbAE) were prepared to increase of biocompatibility and pH sensitivity, for paclitaxel drug delivery [180]. Another pH and temperature-sensitive HNC designed for treating breast cancer using poly ε-caprolactone (PCL) for tamoxifen drug delivery. It is channeled towards the estrogen receptor (ER) for targeted drug delivery [27]. The degree of a pH-responsive polymer depends upon the level of ionization, protonation, and deprotonation caused in response to its surroundings, as shown in Fig. 11 [129].

After completion of drug delivery, the degradation of the hydrogel is a mandatory requirement for clearance from the host system. It is achieved by cleaving the polymer backbone using hydrolysis or enzyme action [92]. Many drug delivery applications that involve drug entrapped pH-sensitive nanogels as a carrier have been reported, namely as anti-cancer doxorubicin, antibacterial tetracycline [218]. PLGA- Chitosan-based nanogel coated with eucalyptus oil is encapsulated with 5-fluorouracil (5-FU) by the 'solvent evaporation emulsification' process for prolonged drug release for skin cancer therapy [161].

5.3.2 Temperature Responsive Hydrogel for Drug Delivery

Polymers that exhibit sol-gel transition in response to the temperature alteration are one of the most widely studied physical stimuli responsive ESPs. Homogenous solutions of polymers that show temperature sensitivity at critical solution temperature (CST) are separated into polymer-rich and polymer-lean phase. When the polymer solution reaches CST, an alteration occurs between hydrophilic and hydrophobic chains of the polymer in an aqueous solvent. Phase diagram of the polymer/solvent

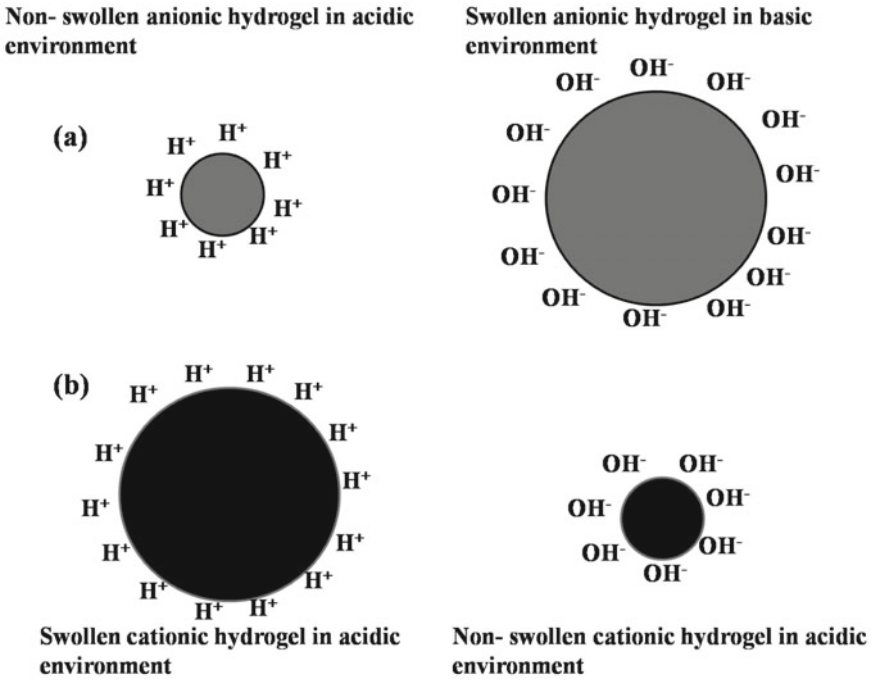

Fig. 11 pH-responsive swelling of **a** anionic. **b** cationic hydrogel (Redrawn from [6])

mixture against temperature, LCST, and UCST can be located. LCST is the lowest temperature value, at which the polymer remains soluble in the solvent and becomes biphasic on increasing the temperature. On the other hand, polymers that form gel below the CST and monophasic solution above CST are categorized as UCST polymer systems [213–108]. (Refer Sect. 2.2.1.)

Thermogelling polymer solutions find inexplicable applications for designing injectable biopolymers [112, 133]. In situ gelling of the physically cross-linked injectable polymer solution can deliver biomolecules such as transforming growth factor (TGF) - β1) [229], nanoparticles (super paramagnetic iron oxide nanoparticles (SPIONs)) [32], drugs (5-FU [4], daptomycin [23]) to the physiological systems are reported in the literature.

5.3.3 Enzyme Mediated Hydrogel Drug Release

Enzymes act as biocatalyst, that helps in controlled and sustained release of the drug payload from hydrogel [213]. One significant advantage of enzymes as stimuli is that it is highly selective and tightly regulated. Phase transition of enzyme sensitive hydrogel occurs by,

i. Ease of access and recognizable enzyme and substrate [26].

ii. Functional unit to regulate molecular interactions (Vander Waals forces, hydrogen bonding, hydrophobic interactions, electrostatic interaction, π-π interactions) that contribute to transitions in hydrogels.

Potential applications include PEG-based hydrogel microparticles for pulmonary drug delivery, and peptide delivery of PEG incorporated Gly-Leu-Lys (GLK) by overexpression of metalloproteinases [177].

One another major biological stimuli-responsive hydrogel is 'glucose responsive hydrogel' [101]. Insulin-dependent diabetes mellitus (IDDM), requires drug release in response to the changes in physiological blood glucose concentration [148]. Hydrogel designed to facilitate glucose-responsive mostly combines the use of saccharide-lectin complex as a crosslinker, incorporation of glucose binding site into a thermoresponsive polymer, utilizing enzymatic activity by the conjugating enzyme to pH-responsive polymer [175].

6 Current Trends and Future Prospects

Hydrogel though widely studied, has less translational efficiency. The reasons attributing to its limitation include reduced control over polymerization rate, weak mechanical property, stability, and inertness in the in vivo physiological conditions. Sterilization of mass production of the hydrogel, to withstand severe temperature cycles without losing its intended property is a significant challenge. Any biomaterial research is carried out to reach for clinical translation ultimately. Multiple problems arise for hydrogel formulation, storage, regulatory complexity, and cost are yet to be needed to overrun by researchers, to obtain robust data before clinical trials. As hydration is a typical mechanism involved, thus terminal sterilization is complicated to make it step-by-step validation from raw material to complete fabrication. Degradation or deterioration of the drug-polymer complex can occur during premature hydrolysis, calling out for optimum storage conditions. Regulatory approvals of the hydrogel drug systems also present a significant concern.

Stimuli-responsive polymers will have to stride through upfront challenges, such as availability of limited functional monomers, low binding capacity, template leakage, and small target intended delivery due to reduced recognition of particular site and cell surface receptors [153].

Current HNC development involves optimization of stimuli responsiveness for the improvement of mechanical strength and biodegradation. It mainly depends upon the embedded NPs in the polymeric networks for pH/enzyme/ion/temperature/magnetic/electric field responsiveness. HNCs also have embarked on its frontier in mimicking native tissues by multiphase combination. Concerning nanoparticle synthesis, biogenic sources such as plants, bacteria, yeast, fungi, and physical/chemical methods would be favorable. The organic, eco-friendly manner of NPs synthesis is yet to be achieved [154].

The functionalization of NPs-Polymer by covalent and non-covalent interactions is a crucial step to achieve HNC. The former involves unstable chemical bonds that can cause the loss of NP properties, while the latter is limited due to its weak interactions. Thus calling for alternative surface modifications that involve non-destructive approaches with more bond stability [113].

7 Conclusions

Despite several decades of research and development towards ideal hydrogel formation, aided by advances in material science, fabrication techniques, polymer chemistry, understanding of molecular and cell biology, and tissue engineering, till now, unmet challenges and need for sufficient clinical trials remain. The term 'ideal hydrogel' is expected to have an on-demand drug release with a predictable rate throughout its clearance from the system. The current research involves proof-of-concept studies for tissue repair and regeneration, which include multiple signaling molecules release and response. Advancement in hydrogel formulation is expected to withstand chemical and enzymatic reactions.

Theoretical modeling of the drug release profile remains challenging as drug release mechanisms can be combinatorial or vary in different hydrogel systems. Drug release systems with an integrated understanding of drug release and transport through a local tissue will be facilitating better hydrogel formulation.

Advancement of bioelectronics and biosensors research has widened prospects towards next-generation controlled drug delivery systems. Tailorable physical and chemical properties of hydrogel have extended its applications towards remote-controlled drug delivery purposes. Finally, the progress in the formulation, addressing the challenges, and clinical translation setbacks can make hydrogel an inevitable component for drug delivery systems.

Acknowledgements The authors greatly appreciate the financial support from the DBT/Wellcome Trust India Alliance Fellowship under grant number IA/E/16/1/503062. We also acknowledge all authors and publishers, who provided copyright permissions.

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