Review

Nanoparticle-reinforced polyacrylamide hydrogel composites for clinical applications: a review

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ABSTRACT

Polyacrylamide hydrogels have made an immensely important place in various fields having bio-compatibility, high water-holding capacity, tunability and cheap synthesis, which has attracted researchers' attention. Polyacrylamide can be chemically infused with other elements or compounds to find applications in magnetic biosensors, drug delivery, cartilage repair and wound dressing. This paper throws light on the brief introduction of hydrogels and their classification. The polymerization method of polyacrylamide hydrogel followed by its clinical uses (cell biology and drug delivery) is adorned in the report. Keeping at the centre, the recent highlights on the research work done on polyacrylamide hydrogel composites using various reinforcing additives are crucially explored first time in the present report. The improvement practice in the strength, bonding and self-healing of the polyacrylamide hydrogel is demonstrated by the encapsulation of nanoparticles like silicon, carbon nanotubes, gelatine, cellulose, etc. The clinical aspects of the polyacrylamide are corroborated by the cell viability, proliferation and migration. Thus, polyacrylamide hydrogels are emerging candidates, precisely illuminated in the review, which can be an influential highlight designed for upcoming research.

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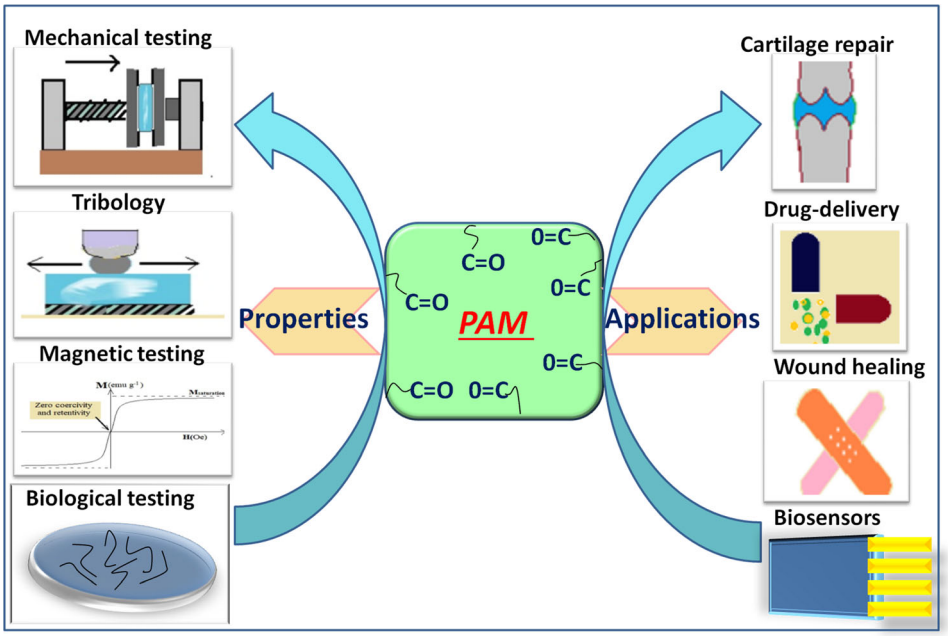
GRAPHICAL ABSTRACT



Introduction

Hydrogels are flexible polymers with excellent biocompatibility. Due to their three-dimensional network, hydrogels have high water-holding capacity. Further, hydrogels have the ability to form blends by using more than one monomers and cross-linkers. Chemical infusion of hydrogels has also been tested with several biocompatible materials. These hydrogel composites are tested for a 'new generational' changes in existing applications. This infusion using corresponding salts followed by reduction using a suitable reducing agent forms nanoparticles suspended in the hydrogel. Research in magnetic bio-sensing materials has tested hydrogels infused with magnetic nanoparticles also called ferrogels. For applications like cartilage replacement as well, hydrogel-based composites are carefully prepared for specific cartilage-like properties [1, 2]. Gels are formed when cross-linker forms bonds laterally linking two polymeric chains. This is much like the two sugar phosphate DNA backbones that are joined by chromosome pairs. Except that, the polymeric chains are flexible, unlike DNA backbones! Without cross-linking, the polymeric chains will dissolve into the aqueous phase and only interaction between the chains is through a physical bond. Cross-linking also decides the strength-related properties of the gel. Optimizing the cross-linking method and the cross-linking ratio is essential for strength-related properties.

The hydrogels can be prepared by cross-linking methods, which can be either physical cross-linking, chemical cross-linking [3, 4] and physical–chemical dual cross-linking [5]. *Physical cross-linking:* The cross-linking is a result of physical interaction between two close-by points on different or same polymeric chain. The physical interaction cross-linking prevents the dissolution of the polymeric chain without any chemical bonds. Novel cross-linking methods in this category are [6]: cross-linking by ionic interaction; cross-linking by hydrophobic interaction; physically cross-linked hydrogels from an amphiphilic block and graft copolymers; cross-linking by crystallization; crystallization in homopolymer systems; cross-linking by stereo-complex formation. *Chemically cross-linked polymers*: In chemically cross-linked polymerization, a chemical bond is formed across the length

Table1 Types of hydrogels and their cross-linking method

Types of hydrogels	Examples	Cross-linking/gelation method	References
Natural hydrogels	Collagen/gelatin	Thermal/chemical cross-linking	[8]
	Chitosan	Thermal/chemical/ free-radical cross-linking	[9]
	Fibrin	Thermal cross-linking	[10]
	Alginate	Ionic/free-radical cross-linking	[11]
	Hyaluronic acid	Thermal/chemical/free-radical cross-linking	[12]
	Polyacrylamide	Free-radical cross-linking	[13]
Synthetic hydrogels	PEG-PEO	Chemical/free-radical cross-linking	[14]
	PVA	Chemical/free-radical cross-linking	[15]
	Polyanhydrides	Free-radical cross-linking	[16]
	PEO-PPO-PEO	Thermal cross-linking	[17]
	PLGA-PEG-PLGA		
	Poly(aldehyde guluronate)	Chemical cross-linking	[18]

of two polymeric chains. Chemical bonding results in a stronger structure in the polymer network. This cross-linking can be achieved through any of these novel methods: cross-linking by radical polymerization; cross-linking by high energy irradiation; cross-linking using enzymes; cross-linking by chemical reaction between complementary groups; cross-linking with aldehyde; cross-linking by condensation reaction; and cross-linking with addition reaction. *Physical–chemical dual cross-linking:* This method is the combination of physical and chemical cross-linking. For instance, in the preparation of polyethylene glycol polyurethane, trimethylolpropane can be used as chemical cross-linker followed by the immersion of single cross-linked polyurethane to the aqueous solution of tannic acid. The urethane groups polyurethane and phenol hydroxyl groups of tannic acid can form hydrogen bonds and represent second physical cross-linking [5]. Table 1 shows the types of hydrogels and their cross-linking methods [7].

Polyacrylamide hydrogels and their polymerization

Polyacrylamide is an organic polymer of acrylamide sub-units. Polyacrylamide hydrogel is a non-toxic, sterile and watery gel, which finds application in several fields. Polyacrylamide hydrogel experiences high volume transition during swelling, but they are deficient in hydrolytic stability. It can be increased by substituting polyacrylamide with a cross-linked polymer of acrylamide; due to this cross-linking, it is highly stable water absorbent and forms a soft gel, used in making of soft contact lenses. Polyacrylamide is prepared from acrylamide monomer, which can be cross-linked. Polyacrylamide hydrogels can be prepared through different routes. Depending on the application, specific methods of polymerizations are adopted. The following are the synthesis methods used for polyacrylamide hydrogels: *Radiation method: In* this method, the radiation energy is used to prepare hydrogels without the addition of a chemical cross-linker. In 1983, Rosiak and co-workers used the radiation technique to cross-link polyacrylamide chains dispersed in an aqueous solution into a gel-like material [19]. This technique offers the advantage of hydrogel formation from vinyl monomers without any chemical substance acting as cross-linker. Copolymers of acrylamide (AAm)/acrylic acid by irradiation with a 2.6–20.0 kGy γ-radiation dose have been prepared by Solpan et al. [20]. *Cross-linking method:* In this method, a chemically covalently bond is formed between the polymeric chains due to the addition of a cross-linking agent. The polyacrylamide-based hydrogels commonly use N,N′-tetramethylenebisacrylamide as a chemical cross-linker. High and uniform cross-linking is a result of chemically cross-linked hydrogels. Superabsorbent hydrogels have been synthesized by reacting chemically modified cashew gum (CGMA) and acrylamide (AAm) by Guilherme et al. [21]. Synthesis of polyacrylamide hydrogels by cross-linking resulting in simultaneous polymerization was tested by Camelia Mihailescuet al. [22]. *Free-radical polymerization:* Radical polymerization (also called free-radical polymerization) is one of the most industrially used

methods to attain polymerization. Plastics and polyethylenes are obtained by free-radical polymerization of unsaturated compounds, monomers as ethylene, vinyl chloride, acrylates and their derivatives. There are various sequential steps in free-radical polymerization as (i) radical formation (monomers are radicalized), (ii) initiation (monomers start to interact and form long chains), (iii) prorogation (chains move and attach to other chains) and (iv) termination (the chain reaction stops). A pH-sensitive terepolymeric hydrogel system is based on acrylamide, methacrylamide and acrylic acid by Bajpai and Dubey [23], using free-radical polymerization.

Polyacrylamide hydrogel in cell biology and drug delivery system

Polyacrylamide has been known to share physical properties with the extracellular matrix. The extracellular matrix is the binding matrix that connects cells together to form tissue. This matrix contains fibronectins, collagens, elastins, laminins, glycosaminoglycans and proteoglycans. The differentiation and other functions of the cells are influenced by the molecules in the extracellular matrix. Wichterle and Lim suggested that hydrogels (specially polyacrylamide based) are remarkably similar to extracellular matrix in their physical nature, but their chemical chain and morphology are very different [24]. Therefore, for the cells functions to remain normal in the presence of these polymers, the following three aspects are considered: The first aspect is that protein adsorption on the implanted polymer's surface should be efficient. The properties of the polymer surface such as interface free energy, surface energy and charge effect the protein adsorption process. It is generally known that highly hydrophilic surfaces are not good for protein adsorption [25]. A copolymer of ethyl methacrylate (EMA), which is hydrophobic, and hydroxyethyl methacrylate (HEMA) which is hydrophobic in ratio 1:1 provides better exchange of fibronectin than on the pure poly(EMA) or pure - poly(HEMA) surface. The biological activity also depends on the molecular conformation of absorbed fibronectin based on the concentration of other competing molecules in the body or experimental fluids [26]. Thus, over polymers with higher level of adsorption, polymers with lower adsorption but a more active conformation provide better cell colonization [27]. The second aspect is cell adhesion. It has been observed that hydrogels and copolymers of hydrogels that are highly hydrophobic are bad for eukaryotic cell adhesion [27, 28]. It is also seen that highly hydrophilic hydrogel surfaces are bad for adsorption of protozoan cell adhesion [29]. An efficient fibronectin adsorption and cell adhesion are provided by copolymers of hydrophobic EMA and hydrophilic HEMA their pure forms. The third aspect is interaction of macrophages with hydrogels. Macrophages are specialized cells that detect and kill any harmful organism such as bacteria. First, the surface of implanted polymers is colonized by inflammatory cells and subsequently by macrophages. The ability of the implanted to allow fusion of microphages is largely dependent on the occurrence of functional certain functional groups. The following is the order of macrophage fusion depending on the chemical groups:$(CH_3)_2$ N–>–OH= –CO–NH–>–S03H>–COOH (–COONa) [30, 31]. Thus, the spread and fusion of macrophages is low for higher carboxylate anions in the polymer [32].

The first and foremost of all conditions for suitability of a materials for drug delivery in human body is its biocompatibility. The materials must also dissolve and allow the release of drug only after the packet reaches the target organ. Thus, controlling the water content controls the drug release time. Polyacrylamide-based hydrogels are not only bio-compatible but also non-reactive to almost all deliverable drugs. Further polyacrylamide gels can be made denser by changing the gelation ratio allowing the drug delivery time. The gelation ratio controls the permeation of the drug through the gel layer before spreading in the target organ. Thus, the diffusion rate depends on the cell size of the gel, which depends on the gelation ratio [33]. Using the first-order diffusion term in the Fick's law,

$$J = -D\frac{\partial c}{\partial x} \tag{1}$$

where J is the flux of a diffusing substance per unit membrane area along the direction of concentration gradient.

For a fractional release or concentration ratio M_t/M_∞ of less than 0.5, Crank obtained an approximation from the solution to the diffusion equation. For a release of amount M_t of solute into the solution at a time 't' through a membrane of thickness 'l_o,' M_∞ is the initial mass of solute in the hydrogel:

$$M_t/M_\infty = \left(4/l_o\pi^{1/2}\right)D^{1/2}t^{1/2} \quad (2)$$

where M_∞ is the total amount of solute in the hydrogel, l_o is the thickness of hydrogel membrane, M_t is the amount of solute released after time 't' and D is the diffusion constant [34]. Besides a brief introduction to hydrogels followed by the polyacrylamide preface, a broad range of classification of gels is discussed in the subsequent section.

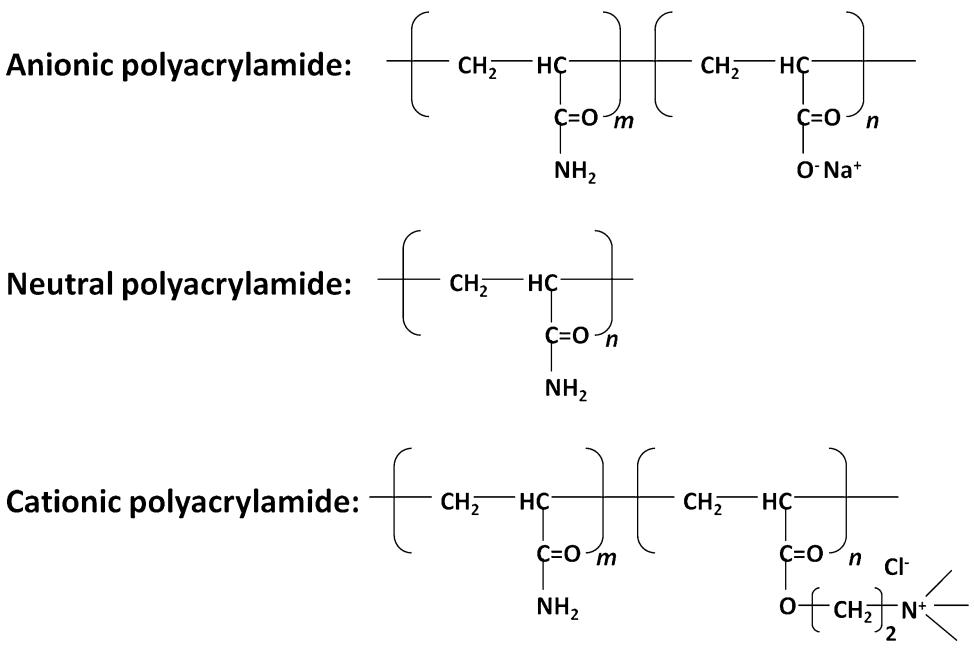
Classification of hydrogels: a broad overview

The classification of polyacrylamide (PAM) hydrogel is based on the ionization of the gel. The PAM hydrogel can be classified as given in Scheme 1.

In addition to PAM classification, the different groups of other hydrogels are narrated here to provide a clear vision of the polymerizing constituents of the hydrogels. The gels are also formed from the blend of two or more polymerizing materials that polymerize simultaneously with the curing agents. Thus, based on its preparation methods, one can classify hydrogels into four classes as follows:

Homo-polymeric hydrogels

Homo-polymeric hydrogels are formed by the polymerization of a single monomer species [35]. The intensity of cross-linking depends on the monomer and polymerization technique used. Monomer poly-HEMA (2-hydroxyethyl methacrylate)-based cross-linked homopolymeric hydrogels find use in drug delivery system and in films as contact lenses. It is also used in artificial skin manufacturing and burn dressing, owing to the wound healing conditions that it provides. The polyHEMA-based homo-polymers are further used for bone marrow and spinal cord cell regeneration and in artificial cartilage manufacturing [36–38]. The mechanical properties of homo-polymers can be attuned and improved by introducing the hydrophobic compound into its structure, giving birth to an amphiphilic material [39]. Certain of these hydrogels swell or shrink in response to external stimuli. Homo-polymers based on polyethylene glycol (PEG) are responsive to external stimuli such as fluctuations in pH, temp, electric field and concentration of enzymes, thus finding use in applications like drug delivery system [40, 41]. Glycol (PEG)-based hydrogels are responsive towards external stimuli, and hence these smart hydrogels are widely used in drug delivery system. Chemically cross-linked PEG hydrogels are used as scaffolds for protein recombination and functional tissue production. It is a suitable biomaterial for the efficient and



Scheme 1 Types of polyacrylamide hydrogel based on its ionic structure.

controlled release of drugs, proteins, biomolecules and growth factor [41, 42]. Several methods for the preparation of hydrogel based on desired properties have been tested. In order to obtain good mechanical properties in PEG hydrogels, a new method called 'Click' chemistry was proposed by Lin and Anseth [41], based on a growth mechanism that is characterized by its rapid and specific reaction. Another method of obtaining high mechanical strength in hydrogels is by alternatively freezing and thawing repeatedly. Polyvinyl alcohol (PVA) hydrogels can also be obtained by using UV radiation as the cross-linker, but this method results comparatively in a lower mechanical strength. Yet another technique to obtain homo-polymeric hydrogels for wound healing applications is by irradiation using a radiation source. Benamer et al. [43] irradiated polyvinyl pyrrolidone (PVP) hydrogels with a 60 °C source at a dose rate of 3.2 Gy/minute.

Co-polymer hydrogels

Co-polymeric hydrogels are composed of two types of monomers of which one or both of them are hydrophilic in nature. Figure 1 shows the difference between homo-polymers and co-polymers.

PEG-based hydrogels with methacrylic acid (MAA) as copolymer are tested in feasibility for drug delivery system [42]. Polyvinyl alcohol (PVA)-based hydrogel prepared with a suitable modifier such as gelatine, dextrin, hyaluronic acid or collagen can be used as a scaffold for tissue engineering [44]. This process required cycles of freezing (253 K/1 h) and thawing (RT/30 min) leading to the formation of PVA crystals which 'cross-link' the polymer chains. PVP hydrogels are obtained from different radiation doses (5–15 KGy) and different additives such as PEG (MW 600, 6000) and polyethelene oxide (PEO) (40,000). PEO reduces the PVP networks' cross-linking density, whereas PEG enhances the elasticity

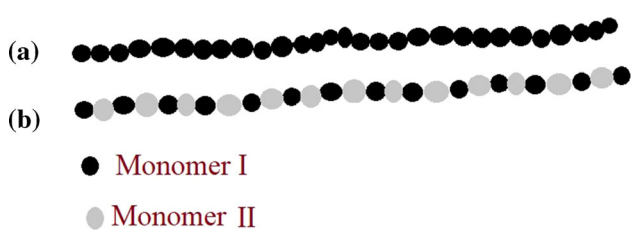


Figure 1 **a** Homo-polymer **b** co-polymer hydrogels (with alternatively different monomers in a chain).

(plasticizing effect) [45]. Wang et al. [46] suggested the use of cellulose or carboxymethyl cellulose (CMC) in the synthesis of PVP-based hydrogel. CMC is water-soluble and biocompatible. Its low cost and high abundance were also the reasons for its blending with PVP. The PVP/CMC blend yields a hydrogel with good mechanical property (mechanical strength better than pure CMC and flexibility superior to that of pure PVP hydrogels). Its high water uptake capacity, enhanced bio-degradability and non-noxious quality translated it as perfect hydrogel dressing material. For drug delivery system, Gong et al. synthesized biodegradable co-polymeric hydrogel: triblock(ethylene glycol)–poly(ε-caprolactone)–poly(ethylene glycol), for drug delivery system [47]. Co-polymeric hydrogels can also be synthesized by free-radical co-polymerization of two monomers. Thomas et al. used acrylamide and acrylic acid as the two monomers, N,N-methylenebisacrylamide as the cross-linker and potassium persulphate as the initiator. On embedding silver nanoparticles into this gel, a hydrogel–silver nano-composite with antimicrobial activity is obtained. Co-polymeric hydrogel based on γ-benzyl L-glutamate (BLG) and poloxamer and synthesized by polymerization of BLG *N*-carboxyanhydride shows thermoplastic properties. The initiation occurs by diamine groups located at the ends of poly(ethylene oxide) chains of the poloxamer. This hydrogel was pH- and temperature-sensitive and developed for drug delivery application [48].

Semi-interpenetrating network

A semi-interpenetrating network consists of a linear polymer that penetrates another cross-linked network without bonding chemically (Fig. 1) [46]. Due to the absence of restricting interpenetrating elastic network, they can provide a rapid kinetic response to pH or temperature. Gum arabic and a cross-linked copolymer of pHEMA form a semi-IPN synthesized in the presence of ammonium persulphate as an initiator and N,N-methylenebisacrylamide as a cross-linking agent [49]. The hydrogel was placed in sliver nitrate which was later reduced using trisodium citrate. The composite of hydrogel and silver nanoparticles exhibits good antibacterial properties. Polycationic semi-IPN hydrogels show properties suitable for drug delivery in the stomach [50]. Cross-linked chitosan and PEO-based semi-IPN hydrogels showed excess swelling in acidic conditions. Thus, it

has been tested for the treatment of *Helicobacter pylori* by delivering antibiotics such as amoxicillin and metronidazole in the stomach. A semi-IPN hydrogel of guar gum (GG) and poly(methacrylic acid) was prepared at room temperature using water as solvent. 5-aminosalicylic acid (5-ASA) was loaded in the hydrogel, and the entrapment efficiency was above 85% [51]. It exhibited minimum swelling in acidic pH due to the formation of a complex hydrogen-bonded structure and maximal swelling due to the electrostatic repulsion due to the ionization of the carboxylic groups in pH 7.4 medium. This results in a minimum release of 5-ASA at pH 2.2. In vitro study reveals that the degree of degradation depends on the concentration of cross-linking agent and content of GG. The enzymatic degradation of hydrogels by cecal bacteria can accelerate the release of 5-ASA entrapped in the hydrogel at pH 7.4. PVP-based hydrogel has been attempted as a very promising thermo-sensitive material [52]. PVP hydrogel does not exhibit thermosensitivity under normal condition. The volume phase transition temperature (VPTT) of the semi-IPN hydrogel prepared from PVP and CMC was determined by swelling behaviour and differential scanning calorimetry (DSC). The results showed a dependence of VPTT on CMC content. Experiments carried out using bovine serum albumin (BSA) as a model drug, which was loaded, and in vitro released in different buffer solutions, suggesting that PVP/CMC semi-IPN hydrogels could help in protein drug delivery in the intestines.

Interpenetrating network

Interpenetrated network (IPN) hydrogels are formed by the intimate combination of two polymers. One or both polymers are synthesized or cross-linked in the immediate presence of the other (Fig. 2) [53]. IPNs have a permanent interlocking of network segments that helps overcome thermodynamic incompatibility and results in limited phase separation. Further, it is believed that interlocked structures also ensure the stability of the bulk and surface morphology [53]. IPNs form relatively dense hydrogel matrix, which exhibits stiffer and tougher mechanical properties, controllable physical properties and more efficient drug loading compared to conventional hydrogels [54]. IPN pore sizes and surface chemistries can also be controlled to obtain the desired drug release kinetics, interaction between the hydrogel and the surrounding tissues with better mechanical properties [55]. Because of their ability to restrict the equilibrium swelling of either or both of the interpenetrating phases according to the elasticity (i.e. cross-linking density), the encapsulated drugs burst release. As investigated by Chivukula et al., a highly cross-linked interpenetrating hydrogel network sensitive to pH fluctuations restricts the typical rapid swelling response of a pH-responsive hydrogel. It exhibits a linear swelling followed by an abrupt pH change from pH 7.4 to 2 [56]. IPNs can also enhance biocompatibility of hydrogels. One such example is polyethylene glycol diacrylate (PEGDA) hydrogels modified with β-chitosan which has improved biocompatibility. Polyurethane (PU) is another classic biomaterial. An attempt was made by Kim et al. [57] to extend the application of PU hydrogels. The IPN of polyurethane (PU) and polyacrylamide (PAM) was obtained by mixing them together with their respective cross-linking agents (vinylpyrrolidone and methylenebisacrylamide) followed by exposure of the mixture to UV radiation. This was an effort by Kim et al. [57] to enhance the applicability of PU hydrogels. This IPN of PU hydrogels is used for drug delivery systems, wound dressing material, artificial muscles, sensor systems and bio-separators. Liu et al. used IPN hydrogels to impart sensitivity towards temperature and pH fluctuation [58].

Recent progress (2019–2022) of polyacrylamide-based hydrogel composites

Due to the presence of solvent molecules during the gel formation process, most of the polymeric hydrogels are brittle in nature. Therefore, they are more prone to fracture when handled in a swollen state and break even at low strain and low extendibility. Hence, with the requirement of hydrogels with high mechanical strength, extensive research has been made in the field of nano-composite gels. Due to the simplicity in synthesis and multi-functionality of nanoparticles and reversibility of self-assembly and cheap cost, they make the best choice in applications like cartilage replacement and artificial tissues. Altering the properties of polyacrylamide gel by using suitable additives makes it versatile for a wide range of applications. Improvement in mechanical properties can be obtained by using reinforcing

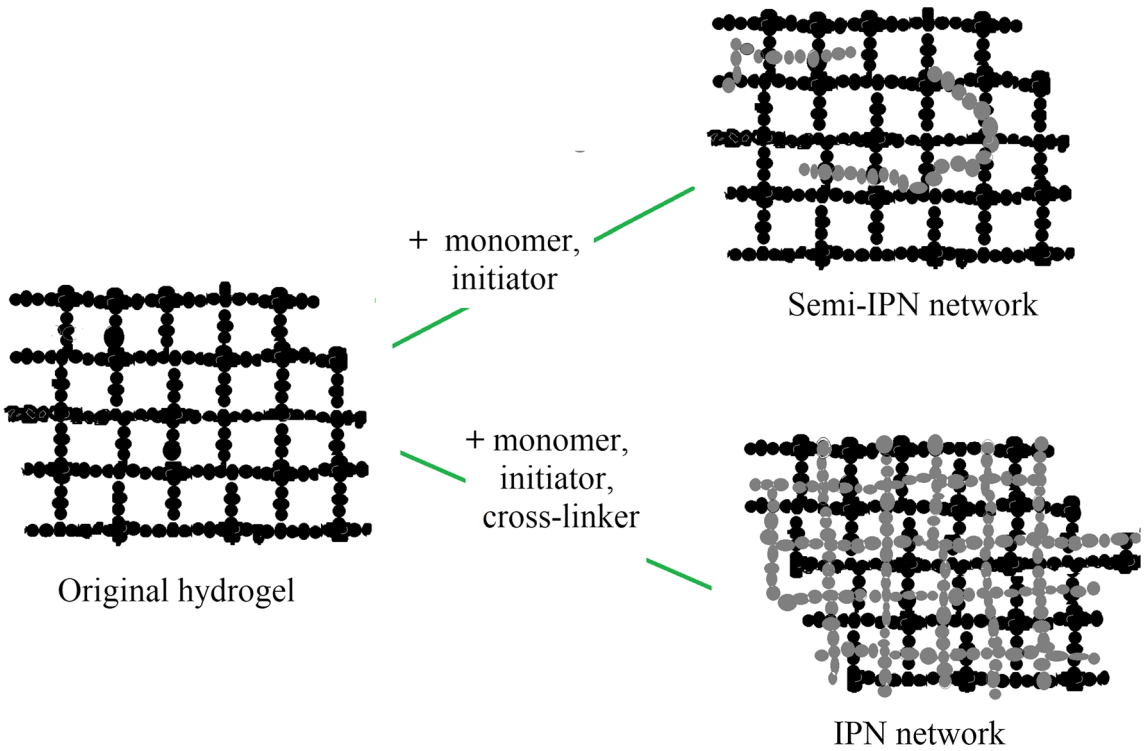


Figure 2 Schematic representation of semi-IPN network and IPN network hydrogels. Concept adapted and redrawn from [59].

agents that create strong interfacial and mechanical interlocking between the matrix and reinforcing agents.

Compared to polymer gels, molecular gels have greater flexibility for one-to-one correspondence in their defined chemical structures (polymer materials have disparity in their molecular weights). By mixing well-designed low molecular weight gelators with different alkyl chains, the quality of the network structure constructed in molecular gels is altered. Cellulose nanocrystals (CNC) are more interested and investigated biomaterial [60]. The enzymatic or acidic hydrolysis of cellulose fibres produces CNCs. The geometric features of CNCs depend on the acid hydrolysis and the source of cellulose microfibrils. CNCs having porous network, biodegradability and environmental profits, can be used as potential additive in polymeric composites [61]. Contrary to bulk cellulose, CNCs show high surface area, modulus, strength and distinctive liquid crystalline properties. Networks are formulated based on CNC and acrylamide as starting materials, and the free-radical polymerization occurs in an aqueous solution with propagating polyacrylamide macro-radical on the surface of modified CNCs. The resulting nanocomposite hydrogels possess excellent elastomeric properties that allow extensive stretching up to a 1000%. The effect of CNC on PAM indicates that the resulting hydrogel has a greater tensile property with high elongation ratios and is more viscoelastic than the chemically cross-linked polymer counterparts. Hydrogels used in bio-related applications are typically surrounded by excess liquid, as the mechanical properties of hydrogels are largely dependent on the concentration of polymer or polymer volume fraction of the hydrogel network. The noteworthy properties of the PAM hydrogel are conferred subsequently.

Swelling and degradation behaviour of PAM hydrogels

Hydrogels are stable in conditions of strong and fluctuating temperatures. Depending on the properties of the polymer and the density of the network joints, hydrogels in equilibrium can contain up to vast amounts of water. The typical swelling kinetics for hydrogels can be idealized as the Fickian swelling kinetics [62] where the swelling ratio is a function of square root of time and the swelling ratio of different hydrogels can be fitted to a Fickian model.

$$\text{Swelling percentage W(t)}\% = \left(\frac{M_t - M_o}{M_o}\right)\% = K_s t^{0.5} \quad (3)$$

where K_s, M_t are the swelling rate (s^{-1}) and weight of the hydrogels after swelling for time t, respectively. M_o is the mass of the sample (at zero swelling or $t = 0$). A non-Fickian (anomalous) model was also introduced to fit the swelling ratio.

$$F = \frac{M_t}{M_\infty} = Kt^n \quad (4)$$

where M_∞ is the equilibrium mass. For the Fickian diffusion, the value of n is 0.5. (It can be 0 to 1 in range). The numerical values of K and n were calculated by using $F = Kt^n$ (at different times). The value of n_i can be estimated for ith sample using the following equation, and F_{2i}, F_{1i} are calculated at times t_2 and t_1, respectively.

$$n_i = \frac{\log \frac{F_{2i}}{F_{1i}}}{\log \frac{t_2}{t2}} \quad (5)$$

Hydrogels are capable of swelling, de-swelling and retaining large amounts of water. In the swollen state, hydrogels are soft and rubbery, resemble a living tissue, and have excellent biocompatibility. The swelling of the hydrogels is important to assess the cross-linking degree, degradation rate, mechanical properties, etc. The initial uptake of the water by hydrogels hydrates the most hydrophilic and polar groups and is termed as primary bound water. After the hydrophilic group hydration, the water molecules expose to hydrophobic linkages of hydrogels, resulting in secondary bound water [63]. The primary and secondary bound water are called total bound water.

Swelling behaviour is the distinct feature of hydrogels, utilized in several applications like sensors, actuators, bone tissue engineering, drug delivery and metal/dyes adsorption [64–66]. The polymer volume fraction in a hydrogel may be altered if the hydrophilic polymer network imbibes liquid over time. Hydrogels with high percentages of polyacrylamide generally showed the least amount of swelling.

Jayaramudu et al. [67] prepared cellulose nanocrystal/polyacrylamide (CNC/PAM) hydrogel by free-radical polymerization. The swelling ratio was calculated by the weights of dry and wet samples. The dried hydrogels were dipped in deionized water, and the water-absorbed hydrogels were further weighed at different time intervals until equilibrium. The swelling ratio was calculated by

$$\text{Swelling ratio}\left(S_{g/g}\right) = \frac{W_t - W_o}{W_o} \quad (6)$$

where W_t and W_o are the weight of swollen hydrogels at different time intervals and weight of dried hydrogels, respectively. The swelling ratio was studied as a function of time and CNC concentration (0, 1, 3, 5 wt%). The swelling ratio of PAM was reported to be 11.69%, which was reduced with CNC addition till 3 wt% of (10.33%) due to the reduced porosity by cross-linking in the hydrogel. Further, the swelling ratio started increasing again with the CNC content of 5 wt% (14.14%).

The swelling behaviour of poly(acrylamide-co-acrylic acid) potassium salt and sodium polyacrylate was evaluated by Mahon et al. [68] with varying temperature (25–100 °C), pH (6.5–12) and salinity (0–85,000 ppm). The maximum swelling was obtained between pH 6.5 and 9 at 25 °C for 2 h. Further, the NaCl concentration reduces the swelling capacity for both hydrogels due to the additional cations resulted in a reduced anion–anion electrostatic repulsion. The swelling performance of the hydrogels was decreased with high temperatures due to the crumple of the hydration shell. The temperature range between 50 and 75 °C was observed to be optimum for 2–6 h periods. The degradation behaviour of the hydrogels can be calculated by the remaining mass of the gels using the following equation.

$$\text{Remaining gel}(\%) = \frac{W_0 - W_t}{W_o} \times 100 \quad (7)$$

where W_o is the weight of hydrogels after 48 h (equilibrium swelling) and W_t is the weight after time t.

Mechanical properties of PAM hydrogel composites

Mechanical properties of hydrogels are to be attuned carefully based on their application in the pharmaceutical and biomedical field. Various biomedical applications, viz. ligament and tendon repair, wound dressing material, matrix for drug delivery, tissue engineering and cartilage replacement, require evaluation of the mechanical property in accord. The mechanical properties of hydrogels should maintain

for the specific period before which the therapeutic moieties are released and the physical texture of the hydrogel is retained. Without using additives, one way of obtaining desirable mechanical properties is by altering the degree of cross-linking. The higher the degree of cross-linking, the stronger the hydrogel obtained owing to the decrease in percentage elongation, enhancing brittleness. Hence, only an optimum degree of cross-linking gives relatively strong and elastic hydrogel. Copolymerization with comonomer may result into hydrogen bonding within the hydrogel, which has also been utilized by many researchers to achieve desired mechanical properties. By increasing the degree of cross-linking, a stronger hydrogel can be obtained, but the higher degree of cross-linking can cause the hydrogel to become more brittle. Hence, there is an optimum degree of cross-linking to achieve a relatively strong and elastic hydrogel.

The human tissue mimicking hydrogel must also correspond to the strain-dependent elastic modulus of tissues (Fig. 3). The low strain (0% to 35%) behaviour can be represented by a lower Young's modulus (E_{low}) compared to that at high strain (65% to 99%).

A compression test can be carried out to test the stress–strain behaviour of hydrogels and their composites. Awasthi et al. [13] in their attempt to design a polyacrylamide-based composite with TiO_2 nanoparticles and/or CNT for cartilage replacement

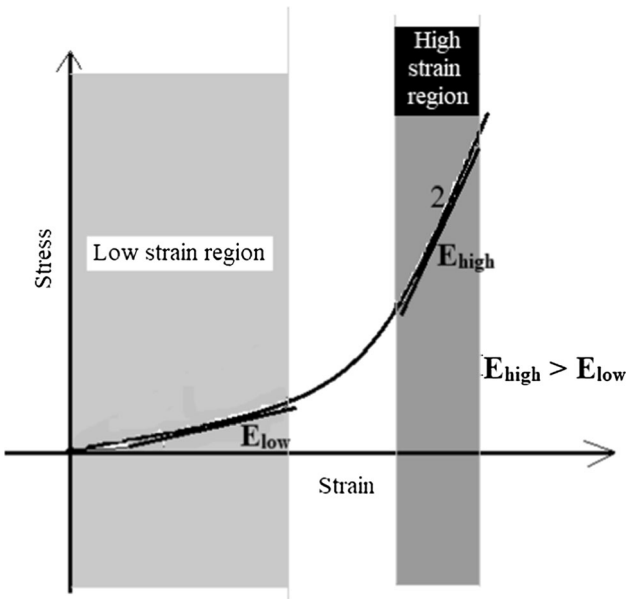


Figure 3 Typical stress–strain curve for cardiovascular tissue.

carried out compression tests [13]. The compression is carried out by compressing a prismatic sample of the gel between two flat plates approaching at constant velocity. The composites with both TiO_2 nanoparticles and CNT exhibited the closest to the human tissue-like behaviour with the highest strength. The compressive strength and elastic modulus were increased (> 0.43 and 2.340 MPa) significantly for the composition of polyacrylamide with TiO_2 and CNT (PAM–TiO_2–CNT). Furthermore, in addition to the mechanical testing, the needle insertion test was performed to investigate the puncture resistance of the materials. The needle insertion technique is useful in the aspect of accidental injuries in cartilage by any sharp object or during surgery. This technique is not fully explored for hydrogels in the literature. For the PAM–TiO_2–CNT composite, the authors reported a higher puncture resistant with only one shallow crack (Fig. 4) when compared to the other composites (PAM–TiO_2, PAM–CNT and bare PAM). The increased mechanical properties for PAM–TiO_2–CNT composite hydrogel were offered due to the synergistic effect and strong interfacial bonding (calculated using density functional theory) between TiO_2 and CNT with PAM.

Shi-Neng Li et al. [69] fabricated PAM/chitosan hydrogels, cross-linked by hyperbranched polysiloxane (HSi). HSi was functionalized with bi-functional vinyl and epoxy groups. Contrary to the single vinyl and epoxy group in HSi, PAM/chitosan hydrogel with bi-functional cross-linking exhibited improved mechanical properties. The enhanced tensile strength (302 kPa), elongation at break (2263%) and toughness (3.85 $Mj.m^{-3}$) were achieved for PAM/chitosan

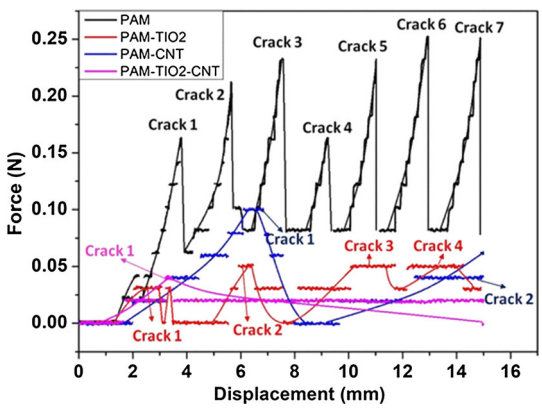


Figure 4 Force–displacement curves for hydrogel samples during the needle insertion test. 'Reproduced with permission from reference [13]. Copyright [2021], [American Chemical Society]'.

hydrogel. This increment in the prepared hydrogel was due to strong interaction between networks.

Pourjavadi et al. [70] prepared an alginate/PAM double-network hydrogel with reversible Schiff-base reaction of glycidyl methacrylate, modified by ethylenediamine (DAGM) and oxidized sodium alginate (OSA, first network) and irreversible cross-linking of PAM (OSA–DAGM–PAM). The mechanical testing was performed by the estimation of tensile and compressive properties of the samples with 500 N and 2000 N load, respectively. The tensile testing was carried out at a different concentration of OSA, and it was observed that the enhanced concentration of OSA (0.9 wt%) resulted in enhanced tensile stress, strain and fracture strain (2200%) due to the configuration of reversible imine and hydrogen bonds in the structure of prepared hydrogel. The stretchable behaviour of the hydrogel was 2500% with 1.5 wt% OSA (1.5 times more than PAM). A further increase in OSA concentration leads to a reduction in the tensile stress of the material. The higher elastic modulus (85.9 kPa) was noted with 0.9 wt% OSA concentration. Nonetheless, the compressive strength of the hydrogels was also higher (16 MPa) at 95% strain with 0.9 wt% of OSA concentration. Thus, the results conclude that the prepared double-network hydrogel with superior mechanical properties can be applicable for various clinical fields mainly for wound dressing.

Voronova et al. [71] worked on PAM/cellulose nanocrystal composite hydrogel (PAM/CNC), formed by the solution casting process. The CNC content was varied from 4.6, 10.3, 15.2, 19.7, 29.8 and 40.1 wt%. The tensile testing displayed the higher value of Young's modulus (2740 MPa), tensile strength at break (70.4 MPa) and ultimate tensile strength (70.4 MPa) for PAM/CNC composite with 40.1 wt% CNC content. Thus, the CNC particles with PAM can be useful as compatibilizers and emulsifiers.

Tribological and rheological properties of PAM composites

For applications like bio-sensing, the durability of the device is an essential requirement. Hydrogel composites should have high wear resistance for use in bio-sensors. The coefficient of friction is a measure of wear resistance. The lower the coefficient of friction, the lower the wear of hydrogel surface on rubbing against a hard surface. A ball on plane kind, reciprocating tribometer with a mild steel ball, is used for calculation of the coefficient of friction.

The wear rate is measured from the radius of the wear mark formed at the contact site after 1500 oscillations. If a is the radius of the wear mark and R is the radius of the counter body (ball), then

$$\text{Wear volume } (W_v) = \frac{\pi}{3}\left(2R^3 - 2\sqrt{(R^2-a^2)^3} - 3a^2\sqrt{(R^2-a^2)^3}\right) \tag{8}$$

$$\text{Wear rate } (W_r) = \frac{\text{Wear volume}}{\text{no. of cycles} \times \text{stroke length} \times \text{load}} \tag{9}$$

Thus, wear resistance is inversely proportional to the wear rate. The main applications that require such testing are those like magnetic biosensors where the durability is to be enhanced. Awasthi et al. [72] used polyacrylamide-based nano-composites with CNTs and Ni nanoparticles that are chemically infused. A wear test under a reciprocating ball on plane for 1500 cycles and 0.5 to 1 N load showed that the composite containing CNTs and Ni nanoparticles are most wear resistant with lower coefficient of friction, when compared to the pure gel. This can be due to the lubricating effect of CNTs dispersed in the composites, reducing friction. Further, the reinforcing effect of the CNTs and dispersed Ni nanoparticles reduces wear.

Shi et al. [73] reported tribological performance of polyvinyl alcohol/polyacrylamide (PVA/PAM) double-network hydrogel. For this experiment, two distinct set-ups were designed to explore the migrating and stationary contact for hydrogel lubrication (Fig. 5). The hydrogel sample (4 mm

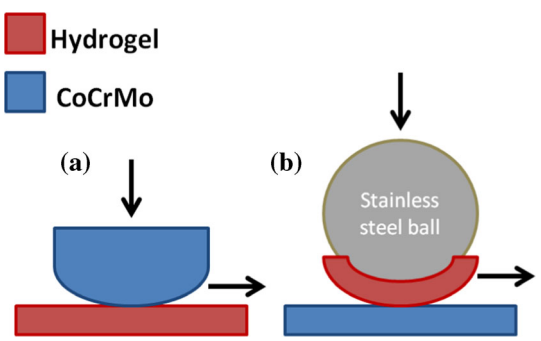


Figure 5 Schematic diagrams of **a** migrating contact and **b** stationary contact configurations. Concept adapted and redrawn from reference [73].

thickness) was tested against the CoCrMo ball (8 mm diameter) to evaluate the migrating contact, while for the condition of stationary contact, a hydrogel sample of 2 mm thickness was joined with a stainless steel ball (6 mm diameter). The hydrogel sample with stainless steel ball was tested against the counter body of the lower CoCrMo plate (Fig. 5).

The friction of coefficient (COF) was found lower for PVA/PAM hydrogel. The COF was increased (0.113 and 0.095, respectively) with the increased concentration of acrylamide (15 wt%) in both migrating and stationary contact conditions, respectively. The optimum friction performance was observed for 5 wt% acrylamide content.

Deng et al. [74] fabricated polyacrylic acid–polyacrylamide (PAA–PAM) hydrogel coating on Ti6Al4V substrate by the charged group adsorption. The friction test was performed using a ball-on-disc tribometer with stainless steel ball as a counter body, deionized water as lubrication and 1.0 N load at room temperature. The reduced dynamic friction was obtained (Fig. 5a,b) for Ti6Al4V–PAA–PAM (0.085) than that of Ti6Al4V–PAA (0.104) and Ti6Al4V (0.429). The dynamic friction of Ti6Al4V–PAA–PAM was fluctuating significantly with velocity (0.05–0.15 m/s). The dynamic friction was demonstrated to be 0.082, 0.087 and 0.097, respectively, with the mentioned velocities. The scratches formed during wear testing were shallow with the scratch width of 0.42 mm in Ti6Al4V–PAA–PAM. The double network in Ti6Al4V–PAA–PAM prevents the water, and due to these water molecules, the tribological and anti-shearing properties of the hydrogel were improved and can be used for artificial joints. The rheological properties of the PAM hydrogels are of quite interest for various applications like biomedical and flexible sensors. The TOCN–CNT/PAM hydrogel (TOCN is 2,2,6,6-tetramethylpiperidine-1-oxyl oxidized cellulose nano-fibre) was prepared by Lu et al. [75] for flexible sensors, and its rheological properties were investigated to execute strain sweep and frequency sweep. The storage modulus G′ was increased after the addition of CNT in TOCN/PAM network. The G′ was reported highest (101.18 kPa) with 2% CNT addition in TOCN/PAM when compared to pure PAM (6.99 kPa) or TOCN/PAM (17.59 kPa). Further assessing other rheological parameters, it was concluded that TOCN–CNT/PAM with 2% CNT content showed the best rheological properties and could resist different mechanical deformations like folding, stretching, and curling. Thus, TOCN-2.0% CNT/PAAM hydrogel with significant viscoelasticity, flexibility, stretchability, mechanical integrity and damage resistant of the material can serve as multifunctional sensor for the applications in electronic skin and healthcare tools.

The biomaterials, sensors and biomedicines applications are based on shape memory hydrogels. For this purpose, a TOCN/PAM hydrogel was prepared by Lu et al. [76] by varying the TOCN content in PAM matrix and the rheological properties were explored for all the samples. The G′ and thus viscoelasticity was increased (17.6 kPa) with higher TOCN content (3%) than that of pure PAM (7.0 kPa) or low TOCN contents (9.2 kPa to 13.3 kPa for 1 and 2% TOCN content, respectively). Thus, it was clear from the results that addition of more concentration of TOCN could enhance the viscoelasticity and mechanical strength of the prepared hydrogels due to the prominent cross-linking density and stronger interactions between TOCN and PAM. Thus, such types of hydrogels with improved rheological properties can be a potential candidate for actuators, sensors and biomedical applications.

Magnetic hydrogel composites

Hydrogel composites with magnetic characteristics are generally termed as ferrogels. In magnetic biosensors, non-toxic Fe_2O_3 nanoparticles encapsulated in the hydrogels. The magnetic nanoparticles dispersed in the polymer matrix form a superparamagnetic material. This means that the ferrogels show zero retentivity and coercivity in the magnetic hysteresis curve. The biocompatibility of the ferrogels was checked against the magnetic nanoparticles in the hydrogels by Blyakhman et al. [77]. The superparamagnetic (γ-Fe_2O_3) and diamagnetic (Al_2O_3) nanoparticles having similar properties (dimensions, morphology and water suspension behaviour) were embedded in PAM hydrogel by free-radical polymerization. The magnetism of the ferrogels and alumina-based hydrogels was characterized by using a varying concentration of the nanoparticles (0, 0.3, 0.6 and 1.2%). The higher content of the magnetic nanoparticles leads to a higher magnetic moment. The ferrogels and alumina-based hydrogels composites showed different magnetic behaviour, as gels with γ-Fe_2O_3 exhibited ferromagnetic properties, while hydrogels with Al_2O_3 nanoparticles revealed a

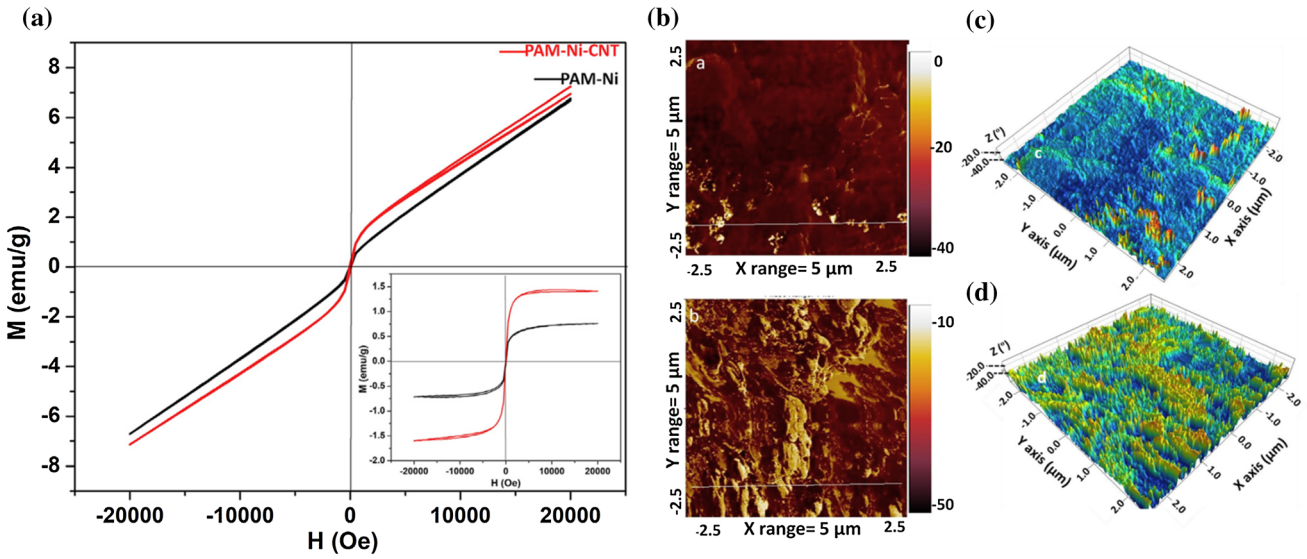


Figure 6 **a** Magnetic hysteresis loops (M-H), showing magnetic properties for PAM–Ni and PAM–Ni–CNT hydrogel composites (inset shows the magnetic saturation after paramagnetic corrections). **b** AFM topography images, **c**, **d** MFM phase images for PAM–Ni and PAM–Ni–CNT hydrogel composites, respectively. 'Reproduced with permission from reference [72]. Copyright [2020], [Elsevier]'.

diamagnetic nature. Furthermore, having different magnetic properties both gels composites showed the same proliferation of human fibroblasts cells. The higher content of nanoparticles resulted in higher amount of cell proliferation. Thus, it was concluded that the biological activity of the cells on the surface of hydrogels is independent of the magnetic behaviour of the nanoparticles.

Filho et al. [78] fabricated PAM hydrogels with the encapsulation of Fe_2O_3 nanoparticles. The sample of gel (4 g) was soaked with Fe^{2+} (5 ml, 0.1 mol/L) and Fe^{3+} (5 ml, 0.2 mol/L) for 15 min under vortex shaking followed by the addition of NH_4OH which resulted in the formation of magnetite by coprecipitation reaction.

$$Fe^{2+}_{(aq)} + 2Fe^{3+}_{(aq)} + 8OH^{-}_{(aq)} \rightarrow Fe_3O_{4(s)} + 4H_2O_{(l)} \quad (10)$$

The vibrating sample magnetometer was used to demonstrate the magnetic properties of the materials using 15 kOe magnetic field amplitude. The hysteresis loop was recognized as S-shaped with almost zero coercive field and remanent (0.01–0.03 kOe and 2 emu/g, respectively). The saturation magnetization was 65.9 emu/g for pure magnetite, but the saturation was decreased with an increase in PAM content due to the organic or non-metallic addition in the sample.

The magnetic nanoparticles in PAM can serve in various fields like magnetic biosensors, drug delivery, etc. For such applications, PAM nano-composite with Ni nanoparticles and CNTs were tested under a magnetometer [72]. The saturation magnetization for CNT and Ni composites showed a much higher saturation magnetization (85% increment) compared for composites only with Ni due to the grain refinement (28 nm) and spin-transfer mechanism (Fig. 6a). The domain size and domain wall width were further calculated using magnetic force microscopy and linked with higher magnetic properties of PAM–Ni–CNT composite (Fig. 6b).

Biological properties of the PAM hydrogel composites

Biocompatible properties of hydrogel are of immense importance in the biomedical field. In general, the term biocompatible describes the property of the material to be compatible with the living tissue [79–81]. Biocompatible materials do not produce a toxic or immunologic response when exposed to bodily fluids. Toxic chemicals used in the polymerization of synthetic hydrogels present challenges for biocompatibility; furthermore, initiators, organic solvents, emulsifiers, un-reacted monomers and cross-linkers used in polymerization and hydrogel synthesis may be toxic to host cells if they seep out to

tissues and encapsulated cells. To remove toxic chemicals from preformed gels, various purification processes are involved. The main purification methods of hydrogels embrace extraction into excess amount of water or dialysis, and this process could take many weeks to be finished [82]. Ba^{2+}–alginate hydrogel was purified by ethanol extraction, and then the hydrogel was dissolved in strong alkaline solution containing EDTA (ethylenediaminetetraacetic acid) [83]. Furthermore, the dialysis was done in order to remove Ba^{2+} ions followed by the precipitation of Na^{+}–alginate by the adding up of ethanol. The purified alginate was obtained after several filtration steps and charcoal treatment. Natural polymers have greater biocompatibility over synthetic polymers, but the presence of cross-linkers and initiators used in polymerizations of naturally derived monomers and pre-polymers is subject to the same level of toxicity concerts as are the purely synthetic hydrogels. The classification of hydrogels along with the significant properties of the hydrogels provides a clear perspective and description related to a broad range of hydrogels. The PAM hydrogels with some additives are the demanding candidates for various healthcare services like cartilage repair, wound healing, contact lenses and drug delivery [84].

Saygili et al. [85] prepared an alginate–PAM (PAM–Alg) double-network hydrogel loaded with transforming growth factor (TGF–β3, PAM–Alg–$NP_{TGF\text{-}\beta3}$) and poly(lactide-co-glycolide) (PLGA, PAM–Alg–NP) nanoparticles for cartilage repair. The prepared hydrogel composites were tested for in vitro biocompatibility using mouse fibroblast cells (L929) for 72 h, protein adsorption and in vivo cartilage defect model by male Sprague Dawley rats. The cell viability of the samples was more than 70%, confirming the cytocompatibility of the materials (no cytotoxic effect). The adsorbed proteins on the surface of the implants intercede cell adhesion on the implant surface [86]. The PAM–Alg–NP hydrogel exhibited a high protein adsorption ability due to the encapsulation of PLGA nanoparticles. Furthermore, the in vivo cartilage defect testing revealed an imperative cartilage reparability of PAM–Alg–$NP_{TGF\text{-}\beta3}$ hydrogel, proving a potential hydrogel composite for cartilage applications.

Torres-Figueroa et al. [87] reported an interesting work related to the controlled release of amoxicillin drug and inhibition of bacterial growth. Amoxicillin is used for the treatment of various infections as it can be served as prophylaxis for bacterial endocarditis in patients having dentistry and joint replacement [88]. The PAM/starch hydrogel composite was used for this study, and the amoxicillin was loaded in the hydrogel by swelling equilibrium process. The controlled release of the drug was evaluated in phosphate buffer saline (pH 7.4) and phosphate citric acid buffer solution (pH 3.0). The hydrogel with amoxicillin was dipped in buffer at 25 and 37 °C. The three bacterial species were used for the bacterial growth inhibition test as *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The drug release was more effective in pH 7.4 at 37 °C when compared to the acid medium delivery (pH 3.0). The PAM/starch composite was also able to show significant antibacterial activity against the bacteria of clinical interest (*E. coli* and *S. aureus*). Thus, the results from this study revealed that PAM/starch hydrogel can be a considerable material for drug delivery applications.

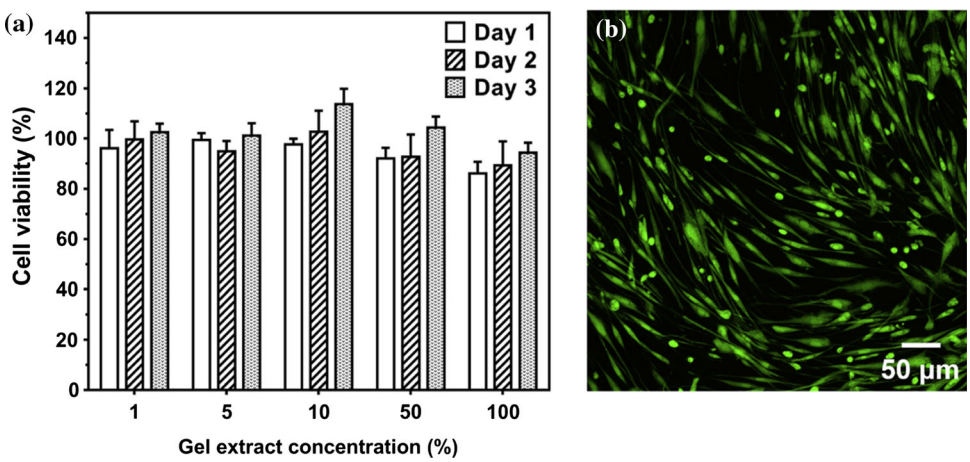


Figure 7 Cytotoxicity test of the CMC/DACNC/PAAm hybrid hydrogel: **a** Cell viability of hydrogel on day 1, day 2 and day 3. **b** Confocal fluorescent microscopy images of human primary dermal fibroblast cultured on the surface of hydrogel for three days. 'Reproduced with permission from reference [89]. Copyright [2019], [Elsevier]'.

Table 2 Concise outline of recent research work on PAM composite hydrogels

Hydrogel composites	Characterizations	Results	Reason	Reference
Cellulose nanocrystal/ polyacrylamide	Swelling behaviour of PAM hydrogels	Reduced swelling ratio of PAM with CNC addition till 3 wt%	Reduced porosity by cross-linking	[67]
Poly(acrylamide-co-acrylic acid) potassium salt and sodium polyacrylate	Swelling behaviour of PAM hydrogels	Maximum swelling between pH 6.5 and 9 at 25°C and reduced with high temperature	Crumple of the hydration shell	[68]
Polyacrylamide with TiO_2 and CNT nanoparticles	Mechanical properties of PAM hydrogel composites (compression test and needle insertion test)	High compressive strength, elastic modulus and puncture resistant with both TiO_2 and CNT	Synergistic effect and strong interfacial bonding	[13]
PAM/chitosan	Mechanical properties of PAM hydrogel composites (tensile test)	Improved tensile strength, elongation at break and toughness	Strong interaction between networks	[69]
Alginate/PAM with glycidyl methacrylate modified ethylenediamine and oxidized sodium alginate	Mechanical properties of PAM hydrogel composites (tensile and compressive test)	Enhanced tensile strength, fracture strain and elastic modulus with 0.9 wt% oxidized sodium alginate content	Configuration of reversible imine and hydrogen bonds	[70]
PAM/cellulose	Mechanical properties of PAM hydrogel composites (tensile test)	High tensile strength with 40.1 wt% CNC content	Strong interaction	[71]
PAM with Ni and CNTs	Tribology properties of PAM hydrogel (ball on plane)	Most wear resistant with both Ni and CNT in PAM	lubricating effect of CNTs	[72]
Polyvinyl alcohol/ polyacrylamide	Tribology properties of PAM hydrogel (ball on plane)	Optimum friction performance for 5 wt% acrylamide content	Strong bonding	[73]
Poly acrylic acid-polyacrylamide	Tribology properties of PAM hydrogel (ball on disc)	Higher wear resistant of Ti6Al4V–PAA–PAM	Double-network structure of hydrogels	[74]
TOCN-CNT/PAM	Rheological properties of PAM hydrogel	Higher storage modulus with CNT addition in TOCN/ PAM	Lubrication of CNTs	[75]
TOCN/PAM	Rheological properties of PAM hydrogel	Higher storage modulus and visco-elasticity with higher content of TOCN	Prominent cross-linking density and stronger interactions	[76]
PAM with γ-Fe_2O_3 and Al_2O_3	Magnetic hydrogel composites (comparison with biocompatibility)	Different magnetic properties of both gels composites showed the same proliferation of human fibroblasts cells	Biological activity of the calls on the surface of hydrogels is independent on the magnetic behaviour	[77]
PAM with γ-Fe_2O_3	Magnetic hydrogel composites	Decreased saturation with increase in PAM content	Organic or non-metallic addition in the sample	[78]
PAM with Ni and CNTs	Magnetic hydrogel composites	Increased saturation with addition of CNT in PAM–Ni	Grain refinement and spin-transfer mechanism	[72]
Alginate-PAM with transforming growth factor and poly(lactide-co-glycolide)	Biological properties of PAM hydrogel composites (cartilage repair)	High protein adsorption	Encapsulation of poly(lactide-co-glycolide) nanoparticles	[85]

Table 2 continued

Hydrogel composites	Characterizations	Results	Reason	Reference
PAM/starch hydrogel	Biological properties of PAM hydrogel composites (controlled release of amoxicillin drug and inhibition of bacterial growth)	Effective release of drug in pH 7.4 at 37°C	Good for drug delivery applications	[87]
Chitosan/cellulose nanocrystals/ polyacrylamide	Biological properties of PAM hydrogel composites (self-healing and MTT assay)	More than 86% cell viability for all the concentration of the gel	Biological active composite	[89]
Gelatine based PAM	Biological (transdermal drug release)	Non-toxic and clinically safe release medium	Biological active composite	[90]

Table 3 Criteria for making ideal contact lenses

Property	Suitable value for use as an eye lens	Remark
Refractive index	1.372–1.381	The eye cornea refractive index value and lens refractive index values should be in same range
Luminous transmittance (%)	> 95%	The more transparent the lens, the less it blocks the light due to its presence
Oxygen permeability(D*k*)	35 for open eye 125 for closed eye	Oxygen supply to cornea is proportional to the water retain ability of the lens. Prolonged lack of oxygen may damage the cornea tissue (anoxia)
Wettability and permeability to water	Initial contact angle value is 25°	Water permeability is strictly a function of the lens thickness and wettability. It is measured through advancing contact angle technique
Biocompatibility and mechanical property	Good biocompatibility	This is essential for the health of the wearer. The elastic modulus effects the comfort of the wearer

Huang et al. [89] proposed self-healing, cytocompatible hybrid hydrogel prepared by chitosan/cellulose nanocrystals/polyacrylamide. The carboxymethyl chitosan (CMC) and dialdehyde cellulose nanocrystal (DACNC) were used for the fabrication of composite hydrogel (CMC/DACNC/PAM). The self-healing phenomenon of the hybrid hydrogel was investigated by cutting in two parts and then brought together in contact immediately. The self-healing efficiency of the sample was described as the tensile strength of the healed hydrogel divided by the tensile strength of the original hydrogel. Additionally, the in vitro biocompatibility of the hybrid hydrogel was investigated by MTT assay using a human dermal fibroblasts cell line. The self-healing capacity was 8% after 24 h. The cell viability was recorded more than 86% for all the concentration of the gel (Fig. 7a). The fibroblast cells were grown and spread well on the surface of hybrid hydrogel (Fig. 7b) and can serve potentially for biomedical applications without and cytotoxic effects.

A highly stretchable and tough gelatine-based PAM hydrogel composite was prepared by Qiao et al. [90] for the application of transdermal drug release. For the evaluation of the application, four types of drugs (nicotine, lidocaine hydrochloride, diltiazem hydrochloride and diclofenac sodium) were used. The release rate of these drugs was correlated by the solubility of these drugs in water at pH 5.5. The order of the release rate of the drugs was observed as:

lidocaine > diltiazem > nicotine > diclofenac.

The linear and sustainable release of the drugs was deliberated by kinetic studies in the first 8 h. The cytotoxicity studies were done using a macrophage cell line, RAW 264.7 after 24 h of incubation period, and it was concluded that the release medium is non-toxic and clinically safe to the cells. The highlight of the above-mentioned research work is summarized in Table 2.

Applications of polyacrylamide hydrogels

Polyacrylamide hydrogels find many uses in biomedicals, owing to their biocompatibility, hydrophilicity and tissue-like mechanical behaviour. Although a real polymer network is never perfect, it has properties of extensibility and stretching. Some of the applications of polyacrylamide hydrogels are worth discussing. Polyacrylamide hydrogel can be used in water absorbent. Polyurethane (PU) and polyacrylamide (PAM) were mixed and exposed to UV radiation. These types of PU/PAM hydrogels are used in drug delivery systems, wound dressing materials, artificial muscles, sensor system and bioseparators [57, 91]. These days, inverse technique has been widely used for polyacrylamide-based hydrogels because of their easy removal and hazardous management. Nano-composites of polyacrylamide hydrogel with CNTs and TiO_2 serve as viable cartilage replacement material with non-toxicity, desired bio-activity and better mechanical properties over most existing replacement materials [13]. Developed nano-composite hydrogel based on CNTs, CNFs and polyacrylamide is used in the dispersion of CNTs in aqueous solution and for electrical devices [92]. In drug delivery, polyacrylamide-based hydrogel plays a vital role-anionic hydrogel is used in the design of intelligent controlled release devise for site-specific drug delivery of therapeutic proteins to the large intestine. Hydrogels are used as devices for controlled drug release in an organ. The PAM hydrogel has applications in stimuli-responsive and is known as smart polymers. The response is based on the network structure and chemical composition of the polymer. PAM hydrogel configured with $–CONH_2$ and –COOH groups is responsive to ionic strength and pH of the external medium [93]. The single-base difference in the sample can also be recognized by PAM hydrogel when it contains rationally designed single-strand DNA [94]. Furthermore, PAM hydrogels play an extraordinary role in extracorporeal toxin removal due to their inertness and chemical stability. The extracorporeal toxin removal device refers to a modality, which is placed outside the body of the patient where the blood diverted from the heart for the removal of toxic elements and afterwards returned to circulation. These devices must be efficient, economically cheap, non-infectious and easily availability [95]. PAM hydrogel is an attractive material for the applications in contact lenses [96–98].

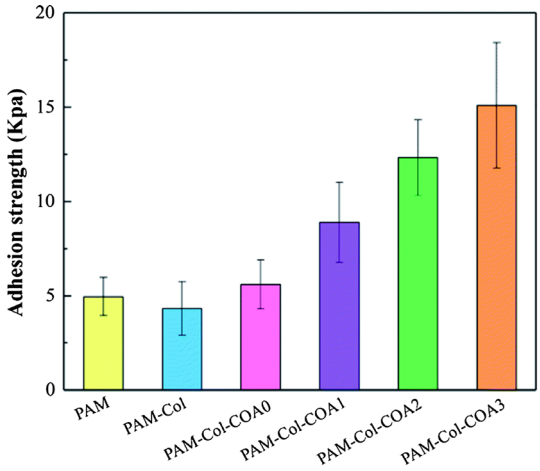


Figure 8 Adhesive strength of PAM hydrogels with collagen and various cross-linker concentrations. 'Reproduced with permission from reference [100]. Copyright [2018], [The Royal Society of Chemistry]'.

The eye lenses are either hard or soft, depending on their elasticity. Hard lenses are relatively durable, but are less comfortable to the eyes. The human eye surface also has to be kept hydrated for the eyelids to slip over the eye surface or conjunctiva. The lacrimal and meibomian glands cover the conjunctiva with layer of mucous, oil and water. A material suitable for contact lens should be soft and not irritate the eye by drying it or by reacting with conjunctiva. Moreover, the refractive index value of the lens material should be close to that of cornea. Hard contact lenses are less flexible and primarily based on hydrophobic materials, whereas soft lenses are based on hydrogels [99]. For a hydrogel to be suitable to make lens, it should follow certain criteria such as enlisted in Table 3.

Furthermore, the PAM hydrogels are also applicable for wound healing [100, 101]. Wounds can be classified depending on the layers of skin involved as: superficial wounds (only upper most layer called epidermis is effected); partial-thickness wound (epidermis and deeper dermal layers are effected); and full-thickness wounds (subcutaneous fat and deeper tissue has been damaged) [102], while based on the degree of severity wounds are classified into 'acute' or 'chronic' wounds. Chronic wounds take longer and more resources like nursing care and cost to heal. The design of dressing for such a wound takes into account the healing process involved and the specific conditions in the patients' body such as allergies

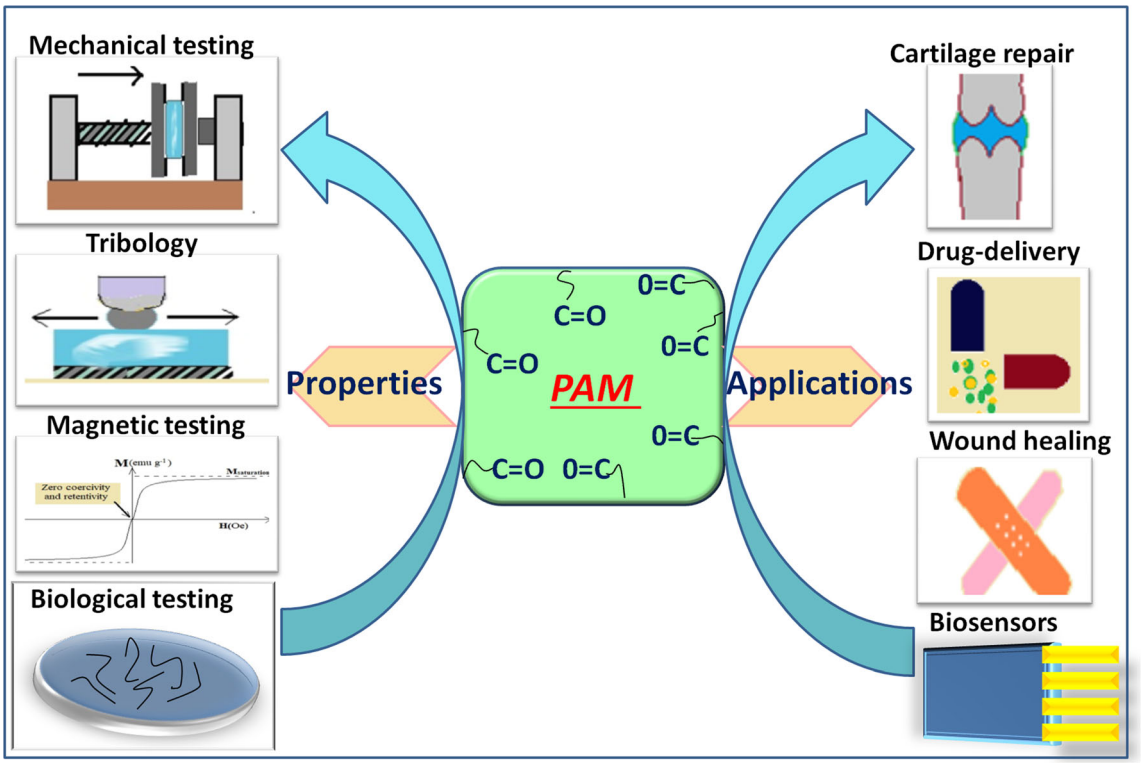


Figure 9 An overall representation of the properties and applications of the PAM hydrogel.

[102, 103]. A wound needs to be protected against infections from bacteria, pressure, trauma, maceration, necrosis and oedema. Thus, an idea wound dressing should consider these factors. It should also absorb excess pus and toxins from the wound and prevent it from drying as drying may cause further trauma [104]. Advanced dressing must not only isolate the wound to prevent infections but also provide moisture. Winter in 1962 observed that the healing process is accelerated by moisture [82]. PAM hydrogels are the constituents of moist dressing for wounds and act as 'moisture donor', helping autolytic debridement, increasing collagenase production and increasing the moisture content of necrotic wounds [105]. PAM also absorbs moisture, allowing transmission of vapour and oxygen to the wound. The adhesion property of the PAM is important for the wound repair, which prevents bleeding and promotes healing of the wound [100]. The addition of collagen and a cross-linker (dopamine with dialdehyde sodium alginate) with the PAM hydrogel (Fig. 8) can enhance the adhesion strength (~ 15 Kpa with 22% dopamine molar concentration; PAM–Col–COA3) when compared to that of pure PAM (~ 5 Kpa) [100].

Therefore, the above-mentioned discussions related to the various properties of polyacrylamide hydrogels including swelling, mechanical, tribological, magnetic and biological testing are extremely vital and explored by a number of researchers. Nevertheless, the brief depiction on the applications of PAM in different fields provides a clear insight of the magnitude of the PAM hydrogel and its composites. The schematic diagram presented in Fig. 7 shows the succinct content of this review report based on PAM hydrogels. It is clear from the scheme (Fig. 9) that the PAM hydrogel having various applications in cartilage repair, wound healing, contact lenses, drug delivery, etc., is significant material to investigate with different properties for producing an ideal composite, appropriate in desired utilization.

Conclusions

Polyacrylamide hydrogels are emerging polymers due to their unique properties, which have made them useful in fields like cartilage repair, wound dressing, contact lenses, drug delivery and biosensors. The PAM hydrogel can be prepared by a monomer unit along with a cross-linker mixed in a suitable quantity. The PAM composites were fabricated by introducing some nanoparticles and reducing them to change these cations/anions into metal ions. The present review described the introduction of hydrogels with their different types, based on the polymeric network structure. The PAM hydrogels along with different nanoparticles like TiO_2 and CNTs are turned with high strength (> 0.43 and 2.340 MPa compressive strength and elastic modulus, respectively) composites. However, the puncture resistant of the PAM was also enhanced with these nanoparticles, estimated using the needle insertion technique. The tribological and magnetic investigations (magnetic saturation 1.41 emu/g) revealed an improved performance of PAM with encapsulation of nanoparticles due to the fine-grained structure and lubrication effects (created by CNTs). Furthermore, the biological activity of PAM composites was remarkably important and ideal for the implementation in biomedical research. Thus, in short, this review report is an important highlight for PAM hydrogel composites and can provide a prominent direction to future research based on the PAM hydrogels for biomedical applications.

Scope for the future work

In drug delivery, magnetic bio-sensing, wound healing, bio-medicals and artificial tissues, research on polyacrylamide-based gels and composites have already expanded and gained attention. A considerable share of credit goes to better and novel experimental techniques. In research on fields like cartilage replacement materials, several biological and mechanical aspects of the material have to be tested and compared. Newer techniques like force measurement during needle insertion through PAM composites have made it possible to predict the internal damage to the replacement material and minimize it. The magnetic testing based on different techniques has been explored significantly in the literature, but the interconnection of magnetism to the domain wall width and magnetostatic energy (calculated using magnetic force microscopy) is still the lacunae in the literature. Therefore, this link can be an important study for PAM hydrogels. The comparison based on the main biomaterial additives (like CNTs, graphene, boron nitride) can also provides a crucial possibility to discover a potential composite for biological applications. The new-generation biosensors and drug release systems still have room for new findings. Further, computational and simulation techniques like density functional theory, simulations and ab initio modelling have enhanced the understanding of their chemical behaviour. This has opened a new arena for better understanding the effect of chemistry at molecular level on the macroscopic properties of the gel. Thus, an inter-linked research on theory and experiment for PAM hydrogels will seal the gap of persisting literature and can furnish an apparent visualization for future research.

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References

[1] Varaprasad K, Vimala K, Raghavendra GM, Jayaramudu T, Sadiku ER, Ramam K (2015) Cell encapsulation in polymeric self-assembled hydrogels, Elsevier Inc. https://doi.org/10.1016/B978-0-323-32889-0.00010-8.

[2] Laftah WA, Hashim S, Ibrahim AN (2011) Polymer hydrogels: a review. Polym - Plast Technol Eng 50:1475–1486

[3] Slaughter BV, Khurshid SS, Fisher OZ, Khademhosseini A, Peppas NA (2009) Hydrogels in regenerative medicine. Adv Mater 21:3307–3329

[4] Chung HJ, Park TG (2009) Self-assembled and nanostructured hydrogels for drug delivery and tissue engineering. Nano Today 4:429–437

[5] Wen J, Zhang X, Pan M, Yuan J, Jia Z, Zhu L (2020) A robust, tough and multifunctional polyurethane/tannic acid hydrogel fabricated by physical-chemical dual crosslinking. Polymers (Basel) 12:239–253

[6] Hamidi M, Azadi A, Rafiei P (2008) Hydrogel nanoparticles in drug delivery. Adv Drug Deliv Rev 69:1638–1649

[7] Tan H, Marra KG (2010) Injectable, biodegradable hydrogels for tissue engineering applications. Materials (Basel) 3:1746–1767. https://doi.org/10.3390/ma3031746

[8] Zhou F, Yang Y, Zhang W, Liu S, Shaikh AB, Yang L et al (2022) Bioinspired, injectable, tissue-adhesive and antibacterial hydrogel for multiple tissue regeneration by minimally invasive therapy. Appl Mater Today 26:101290. https://doi.org/10.1016/j.apmt.2021.101290

[9] Qin D, Zhang A, Wang N, Yao Y, Chen X, Liu Y (2022) Hydroxybutyl chitosan/ oxidized glucomannan self-healing hydrogels as BMSCs-derived exosomes carriers for advanced stretchable wounds. Appl Mater Today 26:101342. https://doi.org/10.1016/j.apmt.2021.101342

[10] Schneider-Barthold C, Baganz S, Wilhelmi M, Scheper T, Pepelanova I (2016) Hydrogels based on collagen and fibrin - Frontiers and applications. BioNanoMaterials 17:3–12

[11] Zhang H, Cheng J, Ao Q (2021) Preparation of alginate-based biomaterials and their applications in biomedicine. Mar Drugs 19:1–24

[12] Khunmanee S, Jeong Y, Park H (2017) Crosslinking method of hyaluronic-based hydrogel for biomedical applications. J Tissue Eng 8:1–16

[13] Awasthi S, Gaur JK, Pandey SK, Bobji MS, Srivastava C (2021) High-strength, strongly bonded nanocomposite hydrogels for cartilage repair. ACS Appl Mater Interf 13:24505–24523

[14] Kazanskiĭ KS, Rakova GV, Kozlov SI, Stegno EV, Lapienis G (2004) Free-radical polymerization of poly(ethylene oxide) macromonomers with catalytic chain transfer in aqueous solutions. Polym Sci - Ser A 46:214–225

[15] Ali L, Ahmad M, Usman M, Yousuf M (2014) Controlled release of highly water-soluble antidepressant from hybrid copolymer poly vinyl alcohol hydrogels. Polym Bull 71:31–46

[16] Sajjad H, Lillie LM, Lau CM, Ellison CJ, Tolman WB, Reineke TM (2021) Degradable polyanhydride networks derived from itaconic acid. Polym Chem 12:608–617

[17] Sosnik A, Cohn D, Roman JS, Abraham GA (2003) Crosslinkable PEO-PPO-PEO-based reverse thermo-responsive gels as potentially injectable materials. J Biomater Sci 14:227–239

[18] Thoniyot P, Tan MJ, Karim AA, Young DJ, Loh XJ (2015) Nanoparticle-hydrogel composites: concept, design, and applications of these promising, multi-functional materials Praveen. Adv Sci 2:1400010–1400023

[19] Tangri A (2014) Polyacrylamide based hydrogels: synthesis, characterization and applications, Int J Pharm Chem Biol Sci. 4: 951–959. http://www.ijpcbs.com/files/volume4-4-2014/18.pdf.

[20] Olpan D, Duran S, Güven O (2002) Synthesis and properties of radiation-induced acrylamide-acrylic acid hydrogels. J Appl Polym Sci 86:3570–3580

[21] Guilherme MR, Reis AV, Takahashi SH, Rubira AF, Feitosa JPA, Muniz EC (2005) Synthesis of a novel superabsorbent hydrogel by copolymerization of acrylamide and cashew gum modified with glycidyl methacrylate. Carbohydr Polym 61:464–471

[22] Mihăilescu C, Dumitrescu A, Simionescu BC, Bulacovschi V (2007) Synthesis of polyacrylamide - based hydrogels by simultaneous polymerization/crosslinking. Rev Roum Chim 52:1071–1076

[23] Bajpai SK, Dubey S (2004) Synthesis and swelling kinetics of a pH-sensitive terpolymeric hydrogel system. Iran Polym J English Ed 13:189–203

[24] Wichterle O, Lim D (1960) Industrial research associations: some taxation problems. Nature 185:63–64

[25] Andrade JD, Nagaoka S, Cooper S, Okano T, Kim SW (1987) Surfaces and blood compatibility current hypotheses. Am Sot Artif Intern Organs 10:75–84

[26] Grinnell F (1987) Fibronectin adsorption on materials surfaces. In: Leonard EF, Turitto VT, Vroman L (Eds.) Blood in confact with natural and arfificial surfaces, New York Academy Science. New York, pp 280–290.

[27] Grinnell F, Feld MK (1982) Fibronectin adsorption on hydrophilic and hydrophobic surfaces detected by antibody binding and analyzed during cell adhesion in serum-containing medium. J Biol Chem 257:4888–4893

[28] Horbett TA, Waldburger JJ, Ratner BD, Hoffman AS (1988) Cell adhesion to a series of hydrophili–hydrophobic copolymers studies with a spinning disc apparatus. J Biomed Mater Res 22:383–404

[29] Owens NF, Gingell D, Rutter PR (1987) Inhibition of cell adhesion by a synthetec polymer adsorbed to glass shown under defined hydrodynamic stress. J Cell Sci 87:667–675

[30] Smetana K, Sulc J, Krcova Z (1987) Physicochemical aspects of the giant multinucleate cell formation. Exp Mol Pafhol 47:271–278

[31] Smetana K, Vacík J, Součková D, Krčová Z, Šulc J (1990) The influence of hydrogel functional groups on cell behavior. J Biomed Mater Res 24:463–470

[32] Smetana K, Vacik J, Součková D, Pitrova S (1993) The influence of chemical functional groups on implant biocompatibility. Clin Mater 13:47–49

[33] Peppas NA, Klier J (1991) Controlled release by using poly(methacrylic acid-g-ethylene glycol) hydrogels. J Control Release 16:203–214

[34] Macdonald DDMD (1977) The mathematics of diffusion, In: Transient Technical Electrochemistry, Plenum Press. New York, pp 47–67.

[35] Das N (2013) Preparation methods and properties of hydrogel: a review. Int J Pharm Pharm Sci 5:112–117
[36] Kalshetti PP, Rajendra VB, Dixit DN, Parekh PP (2012) Hydrogels as a drug delivery system and applications: a review. Int J Pharm Pharm Sci 4:1–7
[37] Syková E, Jendelová P, Urdzíková L, Lesný P, Hejčl A (2006) Bone marrow stem cells and polymer hydrogels - two strategies for spinal cord injury repair. Cell Mol Neurobiol 26:1113–1129
[38] Bavaresco VP, Zavaglia CAC, Reis MC, Gomes JR (2008) Study on the tribological properties of pHEMA hydrogels for use in artificial articular cartilage. Wear 265:269–277
[39] Cretu A, Gattin R, Brachais L, Barbier-Baudry D (2004) Synthesis and degradation of poly (2-hydroxyethyl methacrylate)-graft-poly (ε-caprolactone) copolymers. Polym Degrad Stab 83:399–404
[40] Gong C, Shi S, Dong P (2009) Synthesis and characterization of PEG-PCL-PEG thermosensitive hydrogel. Int J Pharm 365:89–99
[41] Lin CC, Anseth KS (2009) PEG hydrogels for the controlled release of biomolecules in regenerative medicine. Pharm Res 26:631–643
[42] Kim B, Peppas NA (2003) Poly(ethylene glycol)-containing hydrogels for oral protein delivery applications. Biomed Microdevices 5:333–341
[43] Benamer S, Mahlous M, Boukrif A, Mansouri B, Youcef SL (2006) Synthesis and characterisation of hydrogels based on poly(vinyl pyrrolidone). Nucl. Instrum Methods Phys Res Sect B Beam Interact Mater Atoms. 248:284–290
[44] Cascone MG, Lazzeri L, Sparvoli E, Scatena M, Serino LP, Danti S (2004) Morphological evaluation of bioartificial hydrogels as potential tissue engineering scaffolds. J Mater Sci Mater Med 15:1309–1313. https://doi.org/10.1007/s10856-004-5739-z
[45] Lugão AB, Rogero SO, Malmonge SM (2002) Rheological behaviour of irradiated wound dressing poly(vinyl pyrrolidone) hydrogels. Radiat Phys Chem 63:543–546
[46] Wang M, Xu L, Hu H, Zhai M, Peng J, Nho Y et al (2007) Radiation synthesis of PVP/CMC hydrogels as wound dressing. Nucl Instrum Methods Phys Res Sect B Beam Interact Mater Atoms 265:385–389
[47] Gong CY, Shi S, Dong PW, Kan B, Gou ML, Wang XH et al (2009) Synthesis and characterization of PEG-PCL-PEG thermosensitive hydrogel. Int J Pharm 365:89–99. https://doi.org/10.1016/j.ijpharm.2008.08.027
[48] Oh SB, Choi YK, Cho CS (2003) Thermoplastic hydrogel based on pentablock copolymer consisting of poly(γ-benzyl L-glutamate) and poloxamer. J Appl Polym Sci 88:2649–2656
[49] Gils PS, Ray D, Sahoo PK (2010) Designing of silver nanoparticles in gum arabic based semi-IPN hydrogel. Int J Biol Macromol 46:237–244
[50] Ju HK, Kim SY, Kim SJ, Lee YM (2002) pH/temperature-responsive semi-IPN hydrogels composed of alginate and poly(N-isopropylacrylamide). J Appl Polym Sci 83:1128–1139
[51] Singh K, Ohlan A, Saini P, Dhawan SK (2008) composite – super paramagnetic behavior and variable range hopping 1D conduction mechanism – synthesis and characterization, Polym. Adv. Technol. 229–236
[52] Erukhimovich I, de la Cruz MO (2004) Phase equilibria and charge fractionation in polydisperse polyelectrolyte solutions, 48: 1749–1756. https://doi.org/10.1002/polb.
[53] Lipatov YS (2002) Polymer blends and interpenetrating polymer networks at the interface with solids. Prog Polym Sci 27:1721–1801
[54] Mohamadnia Z, Zohuriaan-Mehr MJ, Kabiri K, Jamshidi A, Mobedi H (2007) pH-sensitive IPN hydrogel beads of carrageenan-alginate for controlled drug delivery. J Bioact Compat Polym 22:342–356
[55] Yin L, Fei L, Cui F, Tang C, Yin C (2007) Superporous hydrogels containing poly(acrylic acid-co-acrylamide)/O-carboxymethyl chitosan interpenetrating polymer networks. Biomaterials 28:1258–1266
[56] Chivukula P, Dušek K, Wang D, Dušková-Smršková M, Kopečková P, Kopeček J (2006) Synthesis and characterization of novel aromatic azo bond-containing pH-sensitive and hydrolytically cleavable IPN hydrogels. Biomaterials 27:1140–1151
[57] Kim SC, Klempner D, Frisch KC, Frisch HL (1977) Polyurethane interpenetrating polymer networks. V. Engineering properties of polyurethane–poly(methyl methacrylate) IPN's. J. Appl. Polym. Sci. 21:1289–1295
[58] Liu M, Su H, Tan T (2012) Synthesis and properties of thermo- and pH-sensitive poly(N- isopropylacrylamide)/polyaspartic acid IPN hydrogels. Carbohydr Polym 87:2425–2431. https://doi.org/10.1016/j.carbpol.2011.11.010
[59] Hoare TR, Kohane DS (2008) Hydrogels in drug delivery: Progress and challenges. Polymer (Guildf) 49:1993–2007
[60] Oyeoka HC, Ewulonu CM, Nwuzor IC, Obele CM, Nwabanne JT (2021) Packaging and degradability properties of polyvinyl alcohol/gelatin nanocomposite films filled water hyacinth cellulose nanocrystals. J Bioresour Bioprod 6:168–185
[61] Deeksha B, Sadanand V, Hariram N, Rajulu AV (2021) Preparation and properties of cellulose nanocomposite fabrics with in situ generated silver nanoparticles by

bioreduction method. J Bioresour Bioprod 6:75–81. https://doi.org/10.1016/j.jobab.2021.01.003

[62] Porter TL, Stewart R, Reed J, Morton K (2007) Models of hydrogel swelling with applications to hydration sensing. Sensors 7:1980–1991

[63] Garg S, Garg A, Vishwavidyalaya RD (2016) Hydrogel: classification , properties , preparation and technical features, Asian J Biomater Res 2: 163–170. https://www.researchgate.net/publication/316075989%0AHydrogel:

[64] Varaprasad K, Jayaramudu T, Sadiku ER (2017) Removal of dye by carboxymethyl cellulose, acrylamide and-graphene oxide via a free radical polymerization process. Carbohydr Polym 164:186–194

[65] Wang L, Wang MJ (2016) Removal of heavy metal ions by poly(vinyl alcohol) and carboxymethyl cellulose composite hydrogels prepared by a freeze-thaw method. ACS Sustain Chem Eng 4:2830–2837

[66] Jayaramudu T, Raghavendra GM, Varaprasad K, Sadiku R, Ramam K, Raju KM (2013) Iota-Carrageenan-based biodegradable Ag0 nanocomposite hydrogels for the inactivation of bacteria. Carbohydr Polym 95:188–194

[67] Jayaramudu T, Ko HU, Kim HC, Kim JW, Kim J (2019) Swelling behavior of polyacrylamide-cellulose nanocrystal hydrogels: Swelling kinetics, temperature, and pH effects, Materials (Basel). 12.

[68] Mahon R, Balogun Y, Oluyemi G, Njuguna J (2020) Swelling performance of sodium polyacrylate and poly(acrylamide-co-acrylic acid) potassium salt. SN Appl Sci 2:1–15

[69] Li SN, Li B, Gong LX, Yu ZR, Feng Y, Jia D et al (2019) Enhanced mechanical properties of polyacrylamide/chitosan hydrogels by tuning the molecular structure of hyperbranched polysiloxane. Mater Des 162:162–170. https://doi.org/10.1016/j.matdes.2018.11.045

[70] Pourjavadi A, Tavakolizadeh M, Hosseini SH, Rabiee N, Bagherzadeh M (2020) Highly stretchable, self-adhesive, and self-healable double network hydrogel based on alginate/polyacrylamide with tunable mechanical properties. J Polym Sci 58:2062–2073

[71] Voronova MI, Surov OV, Afineevskii AV, Zakharov AG (2020) Properties of polyacrylamide composites reinforced by cellulose nanocrystals, Heliyon. 6.

[72] Awasthi S, Gaur JK, Bobji MS (2020) Advanced ferrogels with high magnetic response and wear resistance using carbon nanotubes. J Alloys Compd 848:156259–156269

[73] Shi Y, Li J, Xiong D, Li L, Liu Q (2021) Mechanical and tribological behaviors of PVA/PAAm double network hydrogels under varied strains as cartilage replacement. J Appl Polym Sci 138:1–12

[74] Deng Y, Sun J, Ni X, Yu B (2020) Tribological properties of hierarchical structure artificial joints with poly acrylic acid (AA) - poly acrylamide (AAm) hydrogel and Ti6Al4V substrate, J Polym Res 27.

[75] Lu Y, Yue Y, Ding Q, Mei C, Xu X, Wu Q et al (2021) Self-recovery, fatigue-resistant, and multifunctional sensor assembled by a nanocellulose/carbon nanotube nanocomplex-mediated hydrogel. ACS Appl Mater Interfaces 13:50281–50297

[76] Lu Y, Han J, Ding Q, Yue Y, Xia C, Ge S et al (2021) TEMPO-oxidized cellulose nanofibers/polyacrylamide hybrid hydrogel with intrinsic self-recovery and shape memory properties. Cellulose 28:1469–1488

[77] Blyakhman FA, Safronov AP, Makarova EB, Fadeyev FA, Shklyar TF, Shabadrov PA, et al (2021) Magnetic properties of iron oxide nanoparticles do not essentially contribute to ferrogel biocompatibility, Nanomaterials. 11

[78] Filho E, Brito E, Silva R, Streck L, Bohn F, Fonseca J (2020) Superparamagnetic polyacrylamide/magnetite composite gels. J Dispers Sci Technol. 0:1–9

[79] Mbituyimana B, Mao L, Hu S, Ullah MW, Chen K, Fu L et al (2021) Bacterial cellulose/glycolic acid/glycerol composite membrane as a system to deliver glycolic acid for anti-aging treatment. J Bioresour Bioprod 6:129–141. https://doi.org/10.1016/j.jobab.2021.02.003

[80] Madni A, Kousar R, Naeem N, Wahid F (2021) Recent advancements in applications of chitosan-based biomaterials for skin tissue engineering. J Bioresour Bioprod 6:11–25

[81] Fatima A, Yasir S, Khan MS, Manan S, Ullah MW, Ul-Islam M (2021) Plant extract-loaded bacterial cellulose composite membrane for potential biomedical applications. J Bioresour Bioprod 6:26–32. https://doi.org/10.1016/j.jobab.2020.11.002

[82] Caló E, Khutoryanskiy VV (2015) Biomedical applications of hydrogels: A review of patents and commercial products. Eur Polym J 65:252–267

[83] Klöck G, Frank H, Houben R, Zekorn T, Horcher A, Siebers U et al (1994) Production of purified alginates suitable for use in immunoisolated transplantation. Appl Microbiol Biotechnol 40:638–643

[84] Awasthi S (2021) A review on hydrogels and ferrogels for biomedical applications. Jom. https://doi.org/10.1007/s11837-021-04734-7

[85] Saygili E, Kaya E, Ilhan-Ayisigi E, Saglam-Metiner P, Alarcin E, Kazan A et al (2021) An alginate-poly(acrylamide) hydrogel with TGF-β3 loaded nanoparticles for cartilage repair: biodegradability, biocompatibility and protein adsorption. Int J Biol Macromol 172:381–393. https://doi.org/10.1016/j.ijbiomac.2021.01.069

[86] Liu H, Webster TJ (2007) Nanomedicine for implants: a review of studies and necessary experimental tools. Biomaterials 28:354–369

[87] Torres-Figueroa AV, Pérez-Martínez CJ, Del Castillo-Castro T, Bolado-Martínez E, Corella-Madueño MAG, García-Alegría AM, et al (2020) Composite hydrogel of poly(acrylamide) and starch as potential system for controlled release of amoxicillin and inhibition of bacterial growth, J Chem 2020.

[88] Kaur SP, Rao R, Nanda S (2011) Amoxicillin: a broad spectrum antibiotic. Int J Pharm Pharm Sci 3:30–37

[89] Huang W, Wang Y, Mcmullen LM, Mcdermott MT, Deng H, Du Y et al (2019) Stretchable, tough, self-recoverable, and cytocompatible chitosan/cellulose nanocrystals/polyacrylamide hybrid hydrogels. Carbohydr Polym 222:114977

[90] Qiao Z, Tran L, Parks J, Zhao Y, Hai N, Zhong Y et al (2021) Highly stretchable gelatin-polyacrylamide hydrogel for potential transdermal drug release. Nano Sel 2:107–115

[91] Abraham GA, De Queiroz AAA, Román JS (2001) Hydrophilic hybrid IPNs of segmented polyurethanes and copolymers of vinylpyrrolidone for applications in medicine. Biomaterials 22:1971–1985

[92] Chen C, Wang Y, Meng T, Wu Q, Fang L, Zhao D et al (2019) Electrically conductive polyacrylamide/carbon nanotube hydrogel: reinforcing effect from cellulose nanofibers. Cellulose 26:8843–8851

[93] Soppimath KS, Kulkarni AR, Aminabhavi TM (2001) Chemically modified polyacrylamide-g-guar gum-based crosslinked anionic microgels as pH-sensitive drug delivery systems: preparation and characterization. J Control Release 75:331–345

[94] Murakami Y, Maeda M (2005) DNA-responsive hydrogels that can shrink or swell. Biomacromol 6:2927–2929

[95] Schmidt B (1996) Membranes in artificial organs. Artif Organs 20:375–380

[96] Darnell MC, Sun JY, Mehta M, Johnson C, Arany PR, Suo Z et al (2013) Performance and biocompatibility of extremely tough alginate/polyacrylamide hydrogels. Biomaterials 34:8042–8048

[97] Fernández E, López D, López-Cabarcos E, Mijangos C (2005) Viscoelastic and swelling properties of glucose oxidase loaded polyacrylamide hydrogels and the evaluation of their properties as glucose sensors. Polymer (Guildf) 46:2211–2217

[98] Rosiak J, Burozak K, Pękala W (1983) Polyacrylamide hydrogels as sustained release drug delivery dressing materials. Radiat Phys Chem 22:907–915

[99] Lloyd AW, Faragher RGA, Denyer SP (2001) Ocular biomaterials and implants. Biomaterials 22:769–785

[100] Bai Z, Dan W, Yu G, Wang Y, Chen Y, Huang Y et al (2018) Tough and tissue-adhesive polyacrylamide/collagen hydrogel with dopamine-grafted oxidized sodium alginate as crosslinker for cutaneous wound healing. RSC Adv 8:42123–42132

[101] Xue H, Hu L, Xiong Y, Zhu X, Wei C, Cao F et al (2019) Quaternized chitosan-Matrigel-polyacrylamide hydrogels as wound dressing for wound repair and regeneration. Carbohydr Polym 226:115302

[102] Talu S, Talu S, Giovanzana S, Shah RD (2011) A brief history of contact lenses. HVM Bioflux 3:33–37

[103] Madaghiele M, Demitri C, Sannino A, Ambrosio L (2014) Polymeric hydrogels for burn wound care: advanced skin wound dressings and regenerative templates. Burn Trauma 2:153–161

[104] Stashak TS, Farstvedt E, Othic A (2004) Update on wound dressings: Indications and best use. Clin Tech Equine Pract 3:148–163

[105] Jones V, Grey JE, Harding KG (2006) ABC of wound healing: Wound dressings. Br Med J 332:777–780