Chapter 4
Nanobased Biodegradable Hydrogel for Biomedical Application

P. K. Sandhya, M. S. Sreekala, and Sabu Thomas

Abstract Recently, the design of hydrogels using bio-based materials has been increasingly developed for application in pharmaceutical technology. The incorporation of nanoscale structures is useful for tuning the cell behaviour and responses through optimization of mechanical properties or an enhancement in the stability of hydrogels. A considerable progress can be observed in the synthesis and technology of biodegradable nanocomposites hydrogel in the design of controlled and sustained drug delivery systems. The great interest of researchers to produce biodegradable hydrogels is due to the rich resources and huge potential to reduce the fabrication costs. Nowadays, some of the nanoparticles that are used for the preparation of the hydrogels are synthesized by green methods. The current chapter gives an idea about the preparation, characterization, various nanofillers used for the preparation of nanocomposite hydrogels and the application of biodegradable hydrogels in different fields.

1 Introduction

Nanotechnology is an interdisciplinary field which bridges the recent advances in the chemical, physical, and biological fields combined with the rising needs in the pharmaceutical and biomedical sectors. This upcoming technology has led to new developments in nanocomposite hydrogels for many applications in drug delivery, sensors, regenerative medicine, stem cell engineering, and other biomedical devices. In fact, owing to small size, drug loading capacity, surface functionality, and stability, the nanoparticles have gained increased attention for potential applications in biomedical fields [1]. Nanoparticles exist in different shapes like

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spherical, cubical, triangular, rodshaped, ellipsoidal, and so on. Some of the examples of nanomaterials are carbon-based nanomaterials (carbon nanotubes, graphene, nanodiamonds), metal/metal oxide nanoparticles (iron oxide, silver, and gold), polymeric nanoparticles (dendrimers and hyper-branched polymers) and inorganic or ceramic nanoparticles (silicates, calcium phosphate, and hydroxyapatite) [2]. On the basis of dimension, the nanoparticles are classified as one dimensional (clay), two dimensional (graphene, nanotubes), and three dimensional (metallic nanoparticles) [3].

Hydrogels are three-dimensional, highly hydrated porous networks of interconnected natural or synthetic polymer chains to produce a hydrophilic material with macro-molecular structure of a gel [4]. Due to the high water content, permeability, controllable porosity, structural similarity to extracellular matrix and tunable physical, chemical, and biological properties make hydrogels as a promising material for biological applications [1, 5]. In addition to these features, the hydrogels possess some short comings such as low strain, low thermal stability, and poor mechanical strength. Hydrogels have many applications, especially in immunomodulation, stem cell engineering, wound dressing, drug delivery systems, cancer research, cellular, contact lenses, orthodontic applications, and molecular therapies because of its biocompatibility [6, 7]. Multiple functionalities of the hydrogel network and dynamic interactions between the surrounding matrices and cells are the important demand of these applications [8]. In order to meet the requirements, a range of innovations in biomolecular engineering, polymer chemistry, micro- and nanofabrication technologies were introduced for better functionalization [8]. Recently, an increasing trend is observed in the development of nanocomposite hydrogels for different biomedical application.

The low mechanical strength is one of the disadvantages of hydrogels, and it makes them difficult to handle and load in various parts of the body, especially when used as tissue engineering scaffolds [9]. Now, various approaches are introduced in the field of optimization of mechanical and chemical properties of hydrogels for specific biomedical purposes. The limitations of hydrogels can be reduced by the addition of nanoparticles, where these nanostructures undergo physical or covalent interaction with the polymeric chains to create the novel properties in hydrogels [10]. The properties of nanoparticles such as a high surface area-to-volume and aspect ratio made them a suitable candidate for use in the network of polymeric materials [11]. For example, the surface area-to-volume ratio increases the bioavailability, surface reactivity, mechanical properties, and release of loaded bioactive agents. Moreover, the nanoparticles can penetrate tissues via capillaries and epithelial lining, and they can influence the transport properties which ultimately lead to an effective delivery of therapeutic agents to target the cells [12–14].

Nanocomposite hydrogels are also known as hybrid hydrogels, and they are crosslinked three-dimensional water-swollen networks in the presence of nanoparticles. The physical and chemical interactions of polymeric chains with nanoparticles lead to the formation of network with new exclusive properties [6]. The inclusion of the nanoparticles provides unique properties like thermal behaviour, optical activity, barrier resistance, mechanical resistance etc. [15]. The limitations of conventional

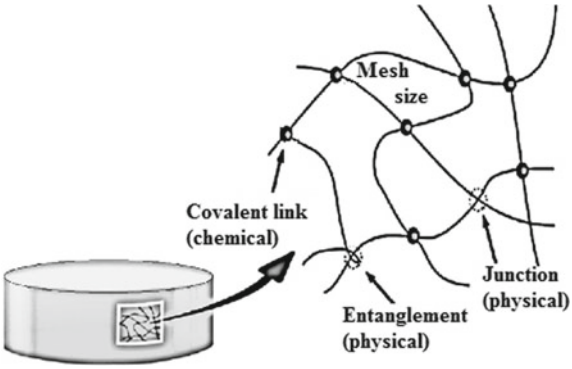

Fig. 1 Structural chemistry of a hydrogel [21]

hydrogels can be overcome by extraordinary features of nanocomposite hydrogels. For instance, in order to make the hydrogels mechanically stronger than conventional hydrogels, clays are used as catalyst, absorbents, metal chelating agents as well as polymer nanocomposites [16]. For wound dressing, the water absorption is controlled with the inclusion of clay nanofillers [17]. The nanofillers such as graphene and carbon nanotubes are used in hydrogels for tissue engineering, drug delivery, and coating the electrodes in solar cell operated medical devices [18, 19]. While considering the increased requirements of nanocomposite hydrogels for biomedical use, various strategies have been explored to conquer its drawbacks but at the same time maintain the advantages of nanoparticles and hydrogels [20].

A three-dimensional network of crosslinked polymer chains constitutes the solid portion of the hydrogel and is usually referred to as a mesh with the spaces filled up with a fluid like water. The fluid present in the meshes exerts an elastic force that leads to the expansion and contraction of the hydrogel [21]. These processes are responsible for the solidity of the hydrogel. Ionisable groups bound onto the polymer chains, and a number of mobile ions are present in the ionic phase of hydrogels. The mobile ions include counter-ions and co-ions due to the presence of the electrolytic solvent, which surrounds the hydrogel. Figure 1 represents the structural chemistry of the hydrogel.

2 Preparation of Biodegradable Hydrogels

The nanocomposite hydrogels prepared from natural polymers are biodegradable, possess good mechanical strength, and highly hydrophilic. The natural polymers commonly used to fabricate nanocomposite hydrogels are starch, cellulose, chitin, alginate, gelatin, and carrageenan. The stiffness and water absorbing capacity of the nanocomposite hydrogels can be increased by the presence of alcohols, amides, and carboxylic acid as hydrophilic moieties in the structure of nanocomposite hydrogels. Under extreme conditions of pressure, temperature, and pH, the stability of

nanocomposite hydrogels can be increased by the addition of cross-linker during their synthesis [15].

The naocomposite hydrogels can be made through the combination of nanoparticles and hydrogels by various mechanisms. The simplest and widely used method for the preparation of a variety of nanocomposite hydrogels containing various nanoparticles is the gelation of a suspension of pre-ready nanoparticles in a solution of hydrogel forming monomer. For example, Sershen et al. [22] prepared gold nanoparticle hydrogel composites by adding nanoshell gold particles into a solution of monomers followed by addition of gelation initiator and an accelerator. The aggregation of the nanoparticles in monomer solution before and during the gelation process and the leaching of nanoparticles out of the hydrogel matrix if the cross-link density is low limits the wide application of this method of preparation [23, 24]. The other method used for the preparation of nancomposite hydrogels is the physical introduction of nanoparticles into a hydrogel networks after gelation. This method is suitable for hydrogels that can highly swell in water but dramatically shrink in aprotic solvent acetone. Repeated swelling–shrinking process is employed for the introduction of naoparticles into this kind of hydrogels [25, 26]. Pardo-Yissar et al. [25] incorporated gold nanoparticles into polyacrylamide gel after the electropolymerization formation of the hydrogel. The next method of preparation of nanocomposite hydrogels involves the loading of nanoparticle precursors into a gel [27]. Marcelo et al. [28] used redox active catechol side chain in acrylamide-N-isopropylacrylamide (NIPAAm) to form nanoparticle hydrogel composite from gold precursor, and great reinforcement of mechanical property was observed for the resulting hydrogel. The use of crosslinker groups on the outer surface of nanoparticles is an interesting method for the preparation of nanocomposite hydrogels. Further developments in the field of using nanoparticles as cross-linking agent were introduced by Rose et al. [29] for adhesion between two hydrogels. This method depends on certain factors such as the ability of the nanoparticles to adsorb onto the polymer gels, to act as a connector between the polymer chains and the ability of the polymer chains to recognize, and dissipate energy under stress when adsorbed onto the nanoparticles. By using the interactions among the nanoparticles, polymers, and distinct gelator molecules, nanocomposite hydrogels can also be prepared [30]. For instance, Wu et al. [30] has reported the incorporation of silicon (Si) nanoparticles into a conducting polymer hydrogel for Si-based anodes. These different approaches for the preparation of nanocomposite hydrogels have introduced new chances in manufacturing advanced biomaterials for various applications in the field of biotechnology and biomedicine. Figure 2 illustrates the schematic representation of formation of nanocomposite hydrogels in different ways.

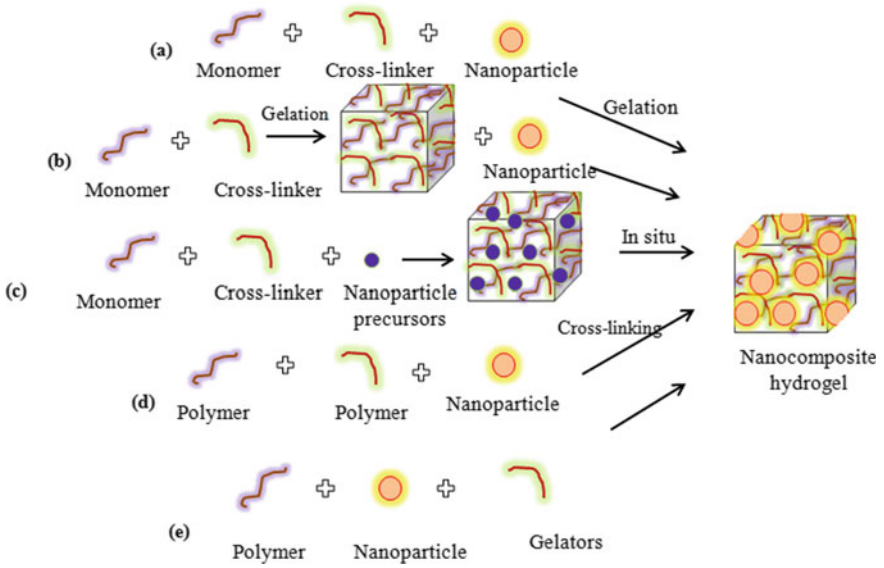

Fig. 2 Schematic representation of formation of nanocomposite hydrogels by different methods **a** gelation of a suspension of pre-ready nanoparticles in a solution of hydrogel forming monomer **b** physical introduction of nanoparticles into a hydrogel networks after gelation **c** loading of nanoparticle precursors into a gel **d** use of crosslinker groups on the outer surface of nanoparticles **e** using the interactions among the nanoparticles, polymers, and distinct gelator molecules

3 Characterization Techniques

Physicochemical properties of these materials depend on the type of compound used for a hydrogel matrix preparation. The most commonly used characterization techniques for studying the morphology of the nanocomposite hydrogels are scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) [31, 32]. UV–visible spectroscopy and Fourier transform infrared spectroscopy are used to determine the chemical composition of the nanocomposite hydrogels [31]. Light scattering provides information about the structure and molecular dynamics of nanoparticles as well as their size distribution [33]. This technique is essential for the characterization of soft material. Viscosimetry technique involves the preparation of dilute solutions of nanogels to determine viscosity. If the intrinsic viscosity of the solution is known, the average molecular weight can be determined and can be used for monitoring the size changes of the nanogels during their synthesis. Gel permeation chromatography (GPC) determines the molecular weight of the nanogel particles [31]. Differential scanning calorimetry (DSC) is used for determining the heat absorbed or released by a substance. It measures the melting, phase transition, crystallization, and glass transition temperatures of the polymers constituting the nanogels. It also finds the degree of swelling of the nanogels by analysing the presence of associated and non-associated water in the nanogels.

Depending on the applications and nature of the hydrogels, the other characterization techniques used are the response of nanoparticles to the changes in temperature and pH, biocompatibility studies and in vitro dissolution and release of drugs [34].

4 Nanofillers in Nanocomposite Hydrogels

Many organic and inorganic nanofillers are being incorporated in hydrogel matrices to overcome the drawbacks like poor mechanical strength, tensile strength, and elastic modulus. Recently, the researchers are focused on the incorporation of many nanoparticulate systems such as carbon-based nanomaterials (graphene, carbon nanotubes), ceramic nanoparticles, metal/metal oxide nanopatrticles, and polymeric nanoparticles into the hydrogels for preparing nanocomposite hydrogels. The addition of these nanoparticles may reinforce the starting hydrogels and result in nanocomposite hydrogels with responsiveness to mechanical, magnetic, electric, and thermal stimuli [35].

4.1 Graphene-Based Nanocomposite Hydrogels

Graphene is a two-dimensional carbon atom monolayer with excellent electrical, mechanical, and thermal properties which makes it as a suitable candidate for improvement of many properties of composite materials [36–38]. It is easy to introduce hydroxyl, carboxylic acid, and epoxide groups in the plane of graphene, and it can be converted into graphene oxide (GO) and reduced graphene oxide (RGO). These graphene derivatives possess a combination of hydrophilic as well as hydrophobic (π–π interactions) which provides them dipole interactions, hydrogen bonding, colloidal stability, pH-dependent surface charges, and other surface reactions along with non-covalent functionalization. Graphene derivatives shows high drug entrapment ability with particular sensitivity for hydrophobic drug molecules due to their amphiphilic nature and ability to be functionalize [18]. In hydrogels, graphene acts as a gelator to self-assemble into the hydrogels and also as a filler to blend with small molecules and macromolecules for the preparation of multifunctional hydrogels [39, 40]. Graphene-based hydrogels attracted great attention in the field of tissue engineering because the water-rich graphene-based hydrogels is similar to natural soft tissues, in addition to high conductivity, biocompatibility, good mechanical strength, and non-covalent bonds between graphene derivatives and polymers (chitosan, poly(N,N′-dimethylacrylamide etc.).

Ligorio et al. [41] used GO as a nanofiller for the design of hybrid peptide hydrogel for the delivery of nucleus pulposus (NP) cells. There is a strong interaction between peptide and GO, promoting high cell viability and metabolic activity, mimicking the mechanical properties of the NP tissue. Liu and colleagues [42] developed a highly

efficient near-infrared (NIR) and pH-responsive carboxymethyl chitosan functionalized reduced graphene oxide/aldehyde functionalized polyethylene glycogel which shows excellent delivery performance of antitumor drug, doxorubicin hydrochloride (DOX).

Rasoulzadehzali and Namazi [43] prepared novel pH-sensitive bionanocomposite hydrogel beads based on chitosn and graphene oxide–silver nanohybrid particles for controlled release of anti-cancer drugs. Jing et al. [44] prepared chitosan/graphene oxide composite hydrogels by the incorporation of the mussel-inspired protein polydopamine (PDA) with self-adhesive and self-healing properties. The hydrogen bonds, covalent bonds, $\pi-\pi$ stacking, and supramolecular interactions allow the nanocomposite hydrogels strong mechanical behaviour, good adhesiveness, high stability, fast recovery ability, and self-healing properties. These hydrogels found application in the field of electroactive tissue engineering. Shin et al. [45] incorporated reduced graphene oxide in gelatine methacryloyl hydrogel matrix to improve the mechanical and electrical properties of the hydrogel which leads to a more natural microenvironment for the cardiomyocytes and improving the cardiac tissue morphogenesis and beating behaviour. The graphene/Ag composite hydrogel prepared by cross-linking reaction of graphene with acrylic acid and methylene bisacrylamide exhibited good biocompatibility and high swelling ratio, and it accelerates healing in the treatment of artificial wounds in rats [46].

4.1.1 Carbon Nanotube-Reinforced Nanocomposite Hydrogels

Carbon nanotubes (CNTs) are cylindrical nanostructure with hexagonal arrangement of sp^2 hybridized carbon atom. CNTs are formed by rolling the graphene sheets, and the wall of CNT discriminates it as single-walled carbon nanotubes (SWCNT) or multi-walled carbon nanotubes (MWCNT) [47]. SWCNTs show perfect quality control as drug carrier whereas MWCNTs occurred with defects in the nanostructure which are quite unstable and can be modified easily [48]. CNTs consist of carbon only, and they have superior biocompatibility, immunogenicity, and low toxicity which made them suitable for biomedical applications.

The properties of carbon nanotubes (CNTs) such as high tensile strength, chemical stability, electrical conductivity, and thermal stability encouraged the usage of CNT as a reinforcing agent in tissue engineering and drug delivery systems [49–52]. Kouser et al. [53] prepared biocompatible nanocomposite hydrogels through solution blending method using microporous multiwall carbon nanotubes (MWCNT) dispersed chitosan (CH)-acrylonitrile (AN), N,N′-methylenebisacrylamide (MBAAm) and linseed polyol. The addition of nanoparticle increases the swelling ability, biodegradability, modulus and tensile strength, and biocompatibility. By varying the concentration of MWCNT, the properties can be finely tuned, and these nanostructure hydrogel is found applications in the field of tissue engineering. Saeednia et al. [54] incorporated carbon naotubes into a thermosensitive and injectable hydrogel formed by chitosan and β-glycerophophate (β-GP), and the prepared hybrid hydrogel can be used as a potential breast cancer

therapy system for controlled delivery of methotexate (MTX). Choudhary et al. [55] studied the variation in the properties of tamarind gum hydrogels by incorporating CNT, OH–CNT, and COOH–CNT. The microscopic studies of the prepared nancomposite hydrogels showed that the alteration in the microstructure is due to the alteration in the interactive forces among the polymeric chains of the hydrogel, and it tailored the electrical and mechanical properties. These hydrogels can be used in the differential drug release patterns of the model drug, tigecycline. Multi-walled carbon nanotube-alginate nanocomposite hydrogels were developed by encapsulating COOH-functionalized MWCNT as a reinforcing phase within alginate [56]. The resulted nanocomposite hydrogels showed better handling characteristics, stability, enhanced cell clustering, improved stiffness, and they can act as a new substrate for mimicking cancer progression in a dish or for cell therapy and tissue engineering.

4.1.2 Ceramic Nanoparticle-Reinforced Nanocomposite Hydrogel

By combining inorganic ceramic nanoparticles with natural or synthetic polymeric hydrogels, it is possible to fabricate several advanced nanocomposite hydrogels. Synthetic silicate nanoparticles, silica, glass ceramic, hydroxyapatite (HAP), bioactive glass, b-wollastonite and calcium phosphate are examples of bioactive nanoparticles [35]. Ceramic nanoparticles are characterized by high mechanical and thermal stability, excellent biocompatibility, easy functionalization, and facile surface modification. Moreover, most of these silicon-based nanoparticles are already present in the body and are essential for the functioning of human tissues [57]. Silicon stimulates the osteogenic differentiation in human stem cells, and it promotes the collagen type 1synthesis. Apart from that silicon is very important in skeletal development. HAP is an essential ingredient of normal bone and teeth, and it is used as biomaterial for bone regeneration. They can promote new bone growth without causing any local or systematic toxicity, inflammation or foreign body response through osteoconduction mechanism [58, 59]. High mechanical strength and unique bioactive properties of silicon-based nanoparticles and nanoclays will be of great interest for the repair and regeneration of human tissues and body functions [60]. Nanoclays and their composites are nontoxic, and they are used for various biomedical applications such as drug delivery, wound healing, bone cement, and enzyme immobilization [61]. The effect of incorporation of clay nanoparticles on the mechanical and biological properties of photo-crosslinked triblock copolymer hydrogel PTMC-PEG-PTMC (poly (trimethylene carbonate)-poly (ethylene glycol)-poly(trimethylene carbonate)). The prepared hydrogels were enzymatically degradable by cholesterol esterase and by the action macrophages [62]. Entezam et al. [63] investigated the effect of modified nanoclay by chitosan on the physical, mechanical, and antimicrobial properties of poly (vinyl alcohol) hydrogels for wound dressing applications. Filipowska et al. [64] assed osteogenic potential of three groups of bipolymeric hydrogel-based surfaces made of plain collagen, chitosan, or collagen/chitosan modified with silica particles of two sizes. They analysed the biocompatibility and osteoinductive properties of the

resulting composites in the human bone marrow-derived mesenchymal stromal cells. New porous silicon-based gelatin hydrogel composites showed property enhancements such as mechanical stiffness, higher hydrolytic stability, and swelling capability attributed to the porous silicon microparticles capacity of producing multiple bonds within the hydrogel network [65]. Lima et al. [66] successfully developed hydrogel nanocomposites based on alginate and mesoporous silica with reduced release burst and enhanced elastic moduli using prednisolone as a model drug. The synthesized nanocomposites can be used as a tool for further physiological and pathological applications like drug delivery device.

4.1.3 Metal and Metal Oxide-Based Nanocomposite Hydrogel

The unique characters of metal and metal nanoparticles that are not commonly found in polymer materials made them as reinforcing elements to prepare composite hydrogels with unique characteristic and tunable properties. Different types of metal and metal oxide nanoparticles are incorporated into the polymer hydrogels by covalent or non-covalent interactions to prepare nanocomposite hydrogels [20]. Metallic nanoparticle affects the hydrogel depend on the type of interaction, a weaker interaction improve the conductivity, stimuli responses and antimicrobial properties, but it has little effect on the mechanical properties of nanocomposite hydrogel. The improvement in swelling behaviour, localized surface plasmon resonance, sensitivity towards pH, electricity, and heat are the results obtained when there is a strong interaction between metallic nanoparticles and hydrogels. Natural polymers are good choice for the synthesis of nanocomposite hydrogel with metals because of its non-toxic and biocompatible nature.

Modification of hydrogels based on chitosan by inserting gold nanoparticles was done by Tyliszczak et al. [67], and the hydrogels act as an interesting material that affects the development in the fields of nanotechnology and polymer technology as well as they are the potential components for the preparation of modern wound dressing. The use of a covalent click chemistry strategy to cross-link chitosan hydrogels using functionalized gold nanoparticles (Au NPs) as multifunctional cross-linkers and the prepared nanocomposite hydrogels open a new avenue to bioengineering of pH-responsive surfaces or novel drug delivery systems [68]. Thermoswitchable electronic properties, enhanced electrochemical properties are the characteristics of gold nanoparticle based hydrogels and used as a light-responsive hydrogel for drug delivery, catalysts, tissue engineering, cancer therapy, and sensors [47]. A novel chitosan-Ag nanoparticle-reinforced hydrogels were successfully produced by a green and simple method with homogeneous porous network structures, better mechanical properties, and proper water-retention capacity [69]. The synthesized nanohydrogels found application in the field of wound dressing materials. Jing et al. [70] prepared stretchable gelatine/silver nanowires (GE-AgNWs) composite hydrogel with enhanced electrical conductivity, and mechanical properties has been developed through chemical grafting and physical cross-linking. The prepared nanocomposite hydrogels were biocompatible and can be used as a strain

sensor to detect multiple human motions. These hydrogels found application in the field of biosensors, electric skins, and health monitoring applications. It is found that the addition of silver nanoparticles into the hydrogels enhanced the antibacterial, antifungal, and electronic properties of the hydrogels [47]. Starch/CuO nanocomposite hydrogels were successfully prepared by in situ formation of CuO nanoparticles in the oxidized starch hydrogel matrix [71]. With increase in CuO nanoparticle content, an increase in sustained and controlled drug release was observed. Zhai et al. [72] fabricated porous keratin–chitosan/n-ZnO nanocomposite bandages by the inclusion of nano-ZnO into the keratin–chitosan hydrogel. The prepared nanocomposite hydrogels exhibit biological application due to its excellent mechanical, bactericidal, swelling, and bactericidal properties.

4.1.4 Polymer-Based Nanocomposite Hydrogels

A wide range of polymers like homo- and copolymers, branched polymers, cross-linked polymers, block copolymers, graft copolymers, and blends of two or more biopolymers are used as polymer matrix for the preparation of nanocomposite hydrogels [73–75]. Hydrogels can be divided into natural and synthetic polymer-based hydrogels on the basis of source of the polymer. Natural polymer-based hydrogels consists of natural hydrophilic polymers like gelatin, chitosan, cellulose, alginate, hyaluronic acid, peptides, agar–agar, and some of their derivatives [76–78]. Synthetic polymer-based hydrogels include poly(vinyl alcohol) (PVA), poly(ethylene glycol) (PEG), poly(acrylic acid) (PAA), polyacrylamide (PAAm), and poly(*N*-isopropylacrylamide) (PNIPAAm), and their copolymers [79–82]. The natural polymer-based hydrogels are drawing great attention in various fields like wound dressing, healthcare monitoring, biomedical daily care, and human–machine interfaces due to its biocompatibility, biodegradability and tissue mimicking consistency characteristics [83–87].

4.1.5 Cellulose-Based Nanocomposite Hydrogel

Cellulose is a natural polymer composed of β-(1–4) linked D-glucose units, and it is widely used for the synthesis of biocompatible hydrogels due to its properties like hydrophilicity, biodegradability, low-cost, biocompatibility, and non-toxicity [88]. The back bone of cellulose and its derivatives consists of large number of hydrophilic functional groups such as carboxyl, hydroxyl, and aldehyde groups which make them suitable candidate for the preparation of hydrogels for various biomedical applications. The specific applications of cellulose-based hydrogels include wound dressing, tissue engineering, drug delivery, bioimaging, and wearable epidermal sensors [88]. Using glutaraldehyde (GA) as a cross-linker cellulose nanocrystal (CNC)-reinforced poly(vinyl alcohol) (PVA) hydrogels were prepared with water content of ~92%. The prepared nanocomposite hydrogels can be used in the fields of biomedical and tissue engineering [89]. Javanbakht and Namazi [90] designed a novel hydrogel

nanocomposite film by the incorporation of graphene quantum dot as a nanoparticle into carboxymethyl cellulose hydrogel using doxorubicin as the drug model. The synthesized biodegradable nanocomposite hydrogel films act as a novel anticancer drug carrier. A green smart cellulose/black phosphorous nanosheet nanocomposite hydrogels were developed by a facile, green chemical cross-linking reaction in alkaline solutions [91]. Black phosphororus has recently emerged as an intriguing photothermal agent against cancer due to its biocompatibility, biodegradability, and high photothermal efficiency. Functional inorganic nanoparticle-reinforced cellulose hydrogels shows considerable potential in biomedical applications. A total biocompatibility within tissues, cells, and other components of the living body is shown by cellulose hydrogels with considerable amounts of water. With the addition of nanoparticles into cellulose hydrogel, it improves mechanical property, photoluminescence, conductivity, magnetic, catalytic, and mechanical properties [92]. For the preparation of cellulose-based hydrogels poly(vinyl alcohol) is a good candidate for the preparation of hydrogels which can be cross-linked by several methods such as irradiation, electron beam, chemical agents, and chemical thermal cycling. In the case biomedical applications, physical cross-linking is the most suitable method for the preparation of hydrogels than chemical or irradiation techniques because it avoids the residual amounts of toxic chemical cross-linker [93]. Freezing–thawing technique via physical cross-linking is the usual method used for the preparation of novel PVA/cellulose hydrogels [94].

Chitosan-Based Nanocomposite Hydrogel

Chitosan is a potential candidate for the applications in the field of biochemical and biomedical fields due to the presence of numerous functional groups with peculiar properties like biodegradability and biocompatibility, high water absorption capacity, mechanical strength, long life, easy availability, and non-toxicity. Chitosan is a polysaccharide which mainly consists of β(1, 4)-linked 2-deoxy-2-amino-D-glucopyranose units and is obtained from alkaline hydrolysis of chitin [95–99]. Chitosan chain consists of a large number of amine groups (-NH_2), and hydroxyl groups (–OH) can be used as cross-linking agents for in situ chemical cross-linking [100]. In addition to that below pH 6.3, the amine groups can be easily converted into ammonium groups, which make them as a suitable candidate for the preparation of pH-responsive hydrogels. Moreover, non-toxic oligosaccharides are the products obtained from the degradation of chitosan and can be excreted or incorporated to glycosoaminoglycans and glycoproteins. By increasing the pH or by dissolving in a solvent, chitosan undergoes self-crosslinking. Song et al. [101] developed a complex physical hydrogel of cordycepin and chytosan through a one-step freezethaw operation, and the prepared complex gel exhibited outstanding antimicrobial properties and wound-recovering ability without side effects. These hydrogels displayed a quicker re-epithelization of skin wounds and

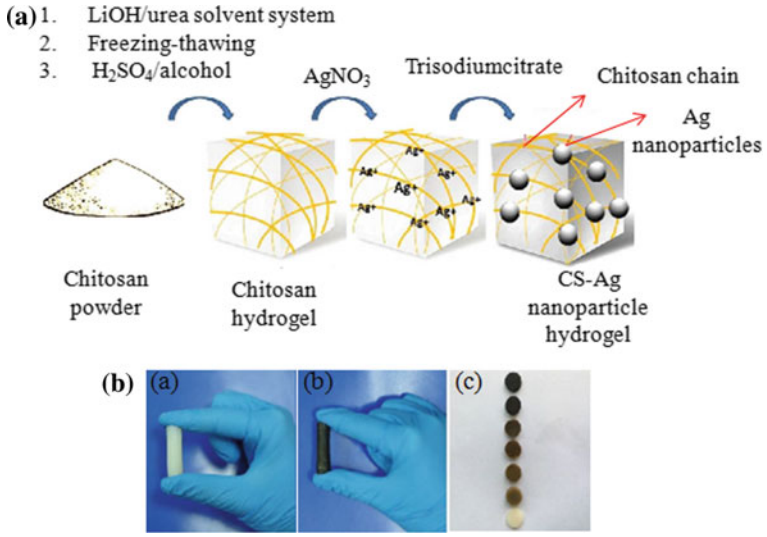

Fig. 3 **A** Schematically represents the formation of Ag nanoparticles in the chitosan hydrogel network. **B a** Chitosan hydrogels, **b** chitosan-Ag nanoparticles hydrogels, **c** hydrogels with different Ag content [69]

promoted collagen deposition. Santos et al. [102] reported the preparation and characterization of nanocomposite hydrogels with chitosan-embedded poly(lactic-co-glycolic acid) (PLGA) employed for the encapsulation of an enriched flavaniod fraction of Cecropia glaziovii Senthl. New photo-crosslinkable thermogels were prepared by photo-crosslinking of glycidyl methacrylate-modified hydroxypropyl chitin (GM-HPCH) under physiological conditions and in the presence of photoinitiator [103]. The synthesized hydrogels found applications in the field of tissue engineering. Smart polymeric hydrogels of chitosan and modified amino acid (acryloyl-phenylalanine)-based hydrogels were synthesized by in situ polymerization using ammonium persulfate as a redox intiator, and the synthesized hydrogels showed good intrinsic self-healing property [104]. Xie et al. [69] prepared chitosan hydrogels reinforced by silver nanoparticles with ultrahigh mechanical and high antibacterial properties for accelerating wound healing and Fig. 3A represents the steps involved in the formation of chitosan–silver nanocomposite hydrogel and 3B shows the photographic images of chitosan and chistosan-Ag nanoparticle hydrogels.

Carrageenan-Based Nanocomposite Hydrogel

Carrageenan (crg) is a naturally occurring anionic sulphated polysaccharide obtained from the red seaweeds of Rhodophyceae class, which consists of galactose and anhydrogalactose linked through glycosidic bonds [105]. The anionic nature of crg is due to the long linear chains of D-galactose and D-anhydrogalactose with

ester sulphates [106]. They exist in three types, kappa-crg-1 sulphate group, iota-crg-2 sulphate groups, and lamda-crg-3 sulphate groups, based on the number of sulphate groups per disaccharide. Crg is widely used in the fields of drug delivery, tissue engineering, and wound healing in addition to food, cosmetic, and pharmaceutical industries [107]. Thermoreversible gelation, ionic crosslinking, and ionic modification of Crg backbone with photo-crosslinking methacrylate moieties are the different methods employed for the formation of Crg hydrogels [108]. First study introducing a photo-crosslinked kappa-carrageenan with controllable elastic moduli, pore size distribution, and swelling ratios were conducted by Mihalia et al. [109]. In this study, methacrylated kappa-carrageenan was synthesized by reacting kappa-carrageenan with various amount of methacrylic anhydride. Bio-nanocomposite hydrogel beads based on kappa-carrageenan as hydrogel matrix and bio-synthesized silver nanoparticles as an antimicrobial agent were prepared and studied the swelling behaviour, cytotoxicity, and antibacterial activity [110]. This trend acts as a motivation for researchers in developing nanocomposite hydrogels with strong antimicrobial activity using green synthesized nanoparticles in hydrogels. Mahdaviniaet al. [111] developed ionically crosslinked and magnetic kappa-carrageenan/chitosan for in vitro release of the methotrexate drug using a facile and green route. They selected an in situ method of preparation for the synthesis of magnetic Fe_3O_4 nanoparticles in the presence of kappa-carrageenan and then crosslinked using the polycation chitosan biopolymer. Yegappan and colleagues [108] developed an injectable carrageenan nanocomposite hydrogel incorporated with whitlockite nanoparticles and an angiogenic drug, dimethyloxallylglycine with enhanced mechanical strength, physiological stability, thereby achieving sustained drug release and enhanced protein adsorption. Feng and co-workers [112] synthesized collagen–hydroxyapatite/k-crg composite material which can be used as a substitute for bone tissue. Gonzalez and Ossa [113] studied the injectability of bone graft substitutes based on carrageenan and hydroxyapatite nanorods. Pourjavadi et al. [114] developed an injectable hydrogel from biocompatible polysaccharides and poly-*N*-isopropyl acryl amide enriched with gold nanoparticles. The studies showed that the gels modified with gold nanoparticles showed significant enhancement in cell proliferation and adhesion and these hydrogels found application in tissue engineering.

Gelatin Based Nanocomposite Hydrogel

Gelatin is derived from collagen and it is abundantly available, low cost, biodegradable, biocompatible and low antigenicity. Due to these properties it is widely used in the field of tissue engineering. Gelatine contains peptide sequences for the recognition of integrin receptors in the cells which is very essential for the cell adhesion in wound dressing materials [115]. Moreover, the nanofiber formation ability of gelatin can be used for skin generation. Pristine gelatin is seldom used for skin regeneration so that chemical modification or physical blending has been adopted for improving the gelling condition of gelatin. Grafting and crosslinking of gelatine and poly(ethylene glycol) diglycidyl ether in the presence of chitosan and hydroxyethyl

cellulose lead to reproducible and mechanically robust hybrid hydrogels showed superb performance for human foreskin fibroblasts cell line [116]. These biodegradable/resorbable hydrogel can promote cell growth, viability and proliferation. El-Feky et al. [117] prepared chitosan gelatine hydrogel loaded with timolol maleate (TM) for intraocular pressure (IOP) lowering was successfully developed by utilizing the semisynthetic biocompatible oxidized sucrose as crosslinker. A facile approach without chemical modification to construct injectable gelatin-based hydrogels with excellent shear-thinning as well as self-recovering for wound healing was introduced by Zheng et al. [115] The addition of gelatin and bioactive glass to chitosan hydrogels produce enhanced properties can be used as injectable systems for biomedical applications [118]. Song et al. [119] introduced a muco-adhesive ophthalmic drug delivery system, developed using chitosan–gelatin that crosslinked with β-glycerophosphate disodium salt hydrate (β-GD) and genipin. A new method to photopolymerize gelatine methacryloyl (GelMA) using a visible light curing unit with parameters similar to those used in the dental office were developed and can be directly established in regenerative procedures in dental care [120]. Bacterial cellulose and gelatine-based composite hydrogels were successfully prepared with glutaraldehyde as a crosslinking agent and they are considered as good candidates for drug delivery systems [121]. Maharana and co-workers [122] reported a study on the fabrication of filled hydrogels using gelatin, tamarid gum and carbon nanotubes for various biomedical applications such as tissue engineering, wound healing and drug delivery. The prepared hydrogels showed cytocompatibility with human keratinocytes. Glycerol phosphate crosslinked to chitosan–gelatin hydrogel base ocular drug delivery systems are reported and these hydrogels exhibited low cytotoxicity, prolonged precorneal retention time, high drug loading capacity [123, 124]. Bakravi et al. [125] prepared a series of gelatin-based hydrogel nanocomposites containing CuO nanoparticles by immersion of gelatin hydrogel in $CuCl_2$ solution with different concentrations and the prepared nanocomposite hydrogels were used as drug delivery agent.

Starch-Based Nanocomposite Hydrogel

Starch is widely used for the purpose of wound dressing because it is biodegradable, biocompatible, cheap, possess ease of physical and chemical modification and good physical properties. The poor mechanical properties of starch can be reduced by starch blends or composites with polymers like PVA. The PVA/starch hydrogels found application in the field of wound dressing because of its excellent mechanical, hydrophilic, biocompatible and non-toxic properties [126, 127]. Batool et al. [128] synthesized silver nanoparticles from fruit extract and used for the preparation of starch-based nanocomposite hydrogel and investigated their mechanical as well as antimicrobial activity. Successful preparation of a new drug delivery approach for the preparation of starch/CuO nanocomposite hydrogels was reported and the drug release studies revealed that CuO nanoparticles extend the release of drugs from the oxidized starch hydrogels [71]. New oxidized starch/ZnO nanocomposites hydrogels

were effectively synthesized by in situ oxidation of Zn^{2+} ions in the oxidized starch hydrogel medium and find applications in biomedical field [129].

5 Biomedical Applications of Biodegradable Nanocomposite Hydrogels

Nanocomposite gels combine the advantages of both hydrogel and nano-fillers. With the addition of nano-fillers with its properties such as mechanical, electrical, magnetic, and optical would endow the nanocomposite gel with extraordinary functionalities made them great potential in biomedical practice.

5.1 Drug Delivery

The process of transferring a drug into the body over a period of time at a specific rate with the desired drug concentration is called drug delivery. Nanocomposite hydrogels have many attractive physical properties like diffusion coefficient, swelling ratio, and mesh size, swelling ration) can be modified and tuned to improve performance of nanocomposite hydrogels of both water-soluble and insoluble drugs for drug delivery applications. The particular properties of hydrogels made them to be used as ideal drug delivery systems because they are similar to body's tissues, rubbery consistency, and high water content. Hydrogels are capable of handling both dry and swollen networks for drug loading and releasing. Physical entrapment method is generally used for the incorporation of drugs into hydrogels [125].

The incorporation of metal oxides like ZnO and CuO nanoparticles into the polymeric matrix improved the drug loading and drug release profiles of nanocomposite hydrogels. Gelatin/copper oxide hydrogel nanocomposites, a physical interaction between cephalexin and gelatine exists and carboxylic acid and amine groups in cephalexin are converted to carboxylate and ammonium group [125]. Starch/CuO nanocomposite hydrogels were used for drug delivery, a sustained and controlled drug releases were observed with increases in CuO nanoparticle content [71]. The hybrid hydrogel composites can discharge the drugs from polymer matrices in measured and more persistent manner. The particular characteristics of these materials are they can accurately and precisely control the duration, drug delivery timings, and the amount of drug to be delivered. The delivery of atenolol drug using gum dammar crosslinked polyacrylamide and zirconium-based biodegradable hydrogel composites are reported elsewhere [130]. Hydrogels based on carboxymethyl chitosan-poly (vinyl alcohol) containing Ag nanoparticles showed sustained and controlled drug releases that increased with increase in Ag nanoparticles content which can lead to prolong the release of the drug [131].

Graphene quantum dots possess large surface area with delocalized electrons, solubility in the variety of solvents, high fundamental fluorescence, chemical inertness, ability of drug loading by $\pi-\pi$ interactions and easy variability of size and shape, local functional groups at the edges made them applied for cellular imaging and drug delivery. Easy functionalization through the oxygen groups or through $\pi-\pi$ interactions provides graphene quantum dots as a drug delivery platform. In chemotherapy, a typical anticancer drug used is doxorubicin (DOX), which kills cells by incorporating with DNA. Moreover, it prevents the cell division and the DNA replication process [132, 133]. So it is necessary to prepare a drug carrier which is capable of releasing anticancer drugs effectively in the location of cancer cells and direct delivery of drugs into the cancer cells. Carboxymethyl cellulose/graphene quantum dot nanocomposite hydrogel films loaded with DOX were prepared and nanparticles could efficiently conjunct with DOX then deliver it to the cancer tissues and dramatically enhance cytotoxicity of DOX [90]. An antibacterial chitosan/graphene oxide-Ag bio-nanocomposite (CH/GO-Ag) hydrogel beads were used for controlled release of doxorubicin [43] and the Fig. 4 shows the drug release behaviour of the DOX-loaded CH/GO-Ag nanocomposite beads containing various amount of GO-Ag nanohybrid particles in the different pHs of 1.2 and 6.8. The release time of doxorubicin from DOX-loaded CH/GO-Ag nanocomposite beads were prolonged by increase in the GO-Ag nanohybrid content. This is due to the existence of GO-Ag nanohybrid particles into prepared nanocomposite beads make a longer path for the

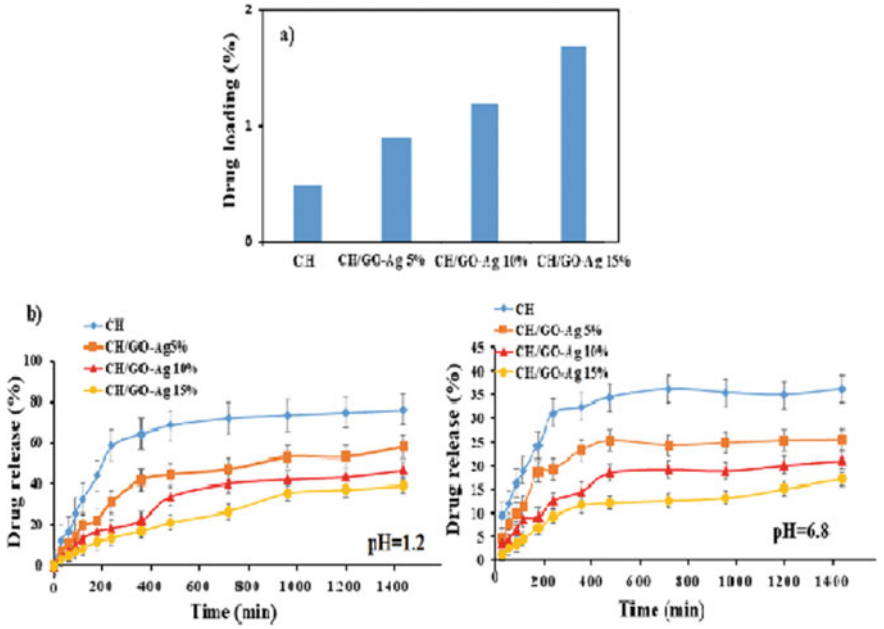

Fig. 4 Percentage of DOX loaded into **a** and released from b CH and CH/GO-Ag (5, 10 and 15%) nanocomposite hydrogel beads [43]

migration of doxorubicin from nanocomposite beads into the release medium and hydrogen bonding and electrostatic attraction interactions between doxorubicin and GO-Ag nanohybrid particles reduce the initial burst release of doxorubicin.

Addition of nanoparticles to nanocomposite hydrogels provides stability of drug as well as slower and continuous drug release, and reduces burst release effect [15]. Changes in temperature, magnetic field, pH, and electric field help to release drug from nanocomposite matrix. Nanocomposite hydrogels can act as reservoir of drug molecules with interaction between drug molecule and nanofiller is necessary for the delivery of drugs [134]. The electro-stimulated drug release behaviour is observed with PVA/CNT-based hydrogel using tetracycline as a model drug [135]. Fe_3O_4 nanoparticles reinforced with kappa-carrageenan, starch and cellulose base hydrogels were used for drug delivery applications reported elsewhere [20].

5.2 Tissue Engineering

For the regeneration or replacement of damaged tissues, tissue engineering is considered as a developing field. An appropriate scaffold that supports the recruitment, adhesion, proliferation, and differentiation of cells is necessary. Recently, hydrogels play the role of replacing defective tissues, but they have limited mechanical strength. To improve their properties, nanomaterials such as organic/polymeric and inorganic (hydroxyapatite, clay, graphene, and metallic nanoparticles) are embedded into the hydrogel's matrix. Those nanocomposites improve the properties of hydrogels and make them suitable in cartilage regeneration practices. The major challenges faced by the use of hydrogels for tissue engineering is the highly hydrated condition and poor mechanical properties in vitro and in vivo. The insertion of nanomaterials in the hydrogel's matrix during the crosslinking of scaffold, resulted in more homogeneous distribution and availability of much more particles for the same equivalent weight of carriers. In cell growth as well as tissue regeneration, the biomimetic properties of nanomaterials are important. . The direct interactions of nanostructured extracellular matrix with natural tissues and organs have nanometer dimensions [136].

In the case of thermally responsive hydrogels, the gelation and swelling behaviour can be triggered by temperature change, and they attracted great interest in the field of tissue engineering [137]. Other excellent materials for tissue engineering are chitin and chitosan due to their properties, such as high biocompatibility, biodegradability, nonantigenicity, antibacterial activity, and high adsorption [138]. PVA hydrogel shows high potential for cartilage tissue engineering due to its structure and material properties similarities with natural cartilage. Alginate is a biomaterial that has some properties like excellent biocompatibility, low immunological motivation, degradability, and flexibility and forms hydrogels tissue engineering [139].

The primary focus in the area of bone tissue engineering is the development of scaffolds and bone substitutes that provide structural and functional support in treating the bone defect. When incorporated with functional bioactive cues, carrageenan (crg) has the ability to allow apatite layer formation. The incorporation of kappa-carrageenan

into collagen–hydroxyapatite composite gel increased the compressive strength and improvement in mechanical property which justifies crg an efficient bone repair material [112]. Nano-hydroxyapatite (nHAP)-based bone substitutes have been widely used for their effective ion exchange, bioactivity, and biocompatibility [140].

The mechanical properties of silk fibroin (SF) can be improved by various strategies like combining SF with other biopolymers has a double network, showing an enhanced mechanical and biological property. Carboxymethyl chitosan (CMCS) is a biopolymer having the properties such as water-soluble, non-toxic, antibacterial and good degradability. The multiple functional chemical groups in CMCS effectively promote osteoblasts adhesion and proliferation. One of the essential features of bone repairing scaffold is osteoinductivity. SF has intrinsic abilities to regenerate bone, but it is insufficient to repair large areas of bone defects so that several bioactive ceramics like hydroxyapatite (HAp) have been used to make bone repair scaffolds by combing with SF [141, 142]. Strontium (Sr) can accelerate the regeneration and maturation of bone by promoting the differentiation of osteoblasts [143, 144]. Silk fibroin/carboxymethyl chitosan/strontium-substituted hydroxyapatite/cellulose nanocrystal composite scaffolds which can be used for bone tissue engineering [145].

5.3 Wound Dressing

One of the most attractive areas of research is the development of nanocomposite hydrogel in the field of tissue engineering and as wound dressings. The bacterial infections of wounds can be minimized with the help of wound dressings with antimicrobial effects. The difficulty of infection control in wound healing process is one of most serious challenges in wound care. The epidermal damages are common in our daily life so that dressing these damages could be useful for wound healing. The important characteristics of wound dressings are protecting the wounds from side infection, maintaining a moist environment for skin wound healing, penetration of microorganisms, and bacterial invasion [146]. Wound dressings can be used as bioactive agents and deliver to the wound sites for promoting epithelialization and treatment of severe injuries. Wound dressing in biomedical application should be fabricated into a three-dimensional (3D) architecture with a high porosity with oxygen and water vapour permeability, antibacterial properties, an appropriate pore size, high mechanical strength, and excellent biocompatibility [147, 148]. Silver, due to its polycationic nature, was used as antimicrobial agents since many centuries. Different types of wound dressings exist which depend on materials containing natural or synthetic polymers or their combinations. The microporous architecture of some natural polymers improves wound healing process by their antimicrobial activities [149]. Synthetic hydrogels composed of natural polymer collagen to obtain novel dressing materials for healing burns and wound dressing were introduced by Yannas's group [150]. The similarity of some polysaccharides (chitosan, gelatin, chitin etc.) to the human body macromolecules, they could be currently used to make different wound dressings. Chitin is one the natural polymers variety application including

drug delivery, tissue engineering, wound dressing, and other biomedical applications [149]. Biodegradable silk fibroin/chitin/silver nanoparticles 3D scaffolds can be used as a bandage for antimicrobial wound dressing [149]. Figure 5A shows the cell viability data, and it revealed that both silk fibroin and chitin had viability of below 25% for 24 h of incubation which reached to 36–39% after 48 h. DAPI or 4′, 6-diamidino-2-phenylindole was used as nuclear stain of the normal fibroblast (nHFFF2) cells attached on the bandages and was confirmed by the cytocompatible nature of the bandages as shown in Fig. 5B. From the images, it is clear that higher number of cells were attached on composite bandages containing lower concentration of Ag and vice versa.

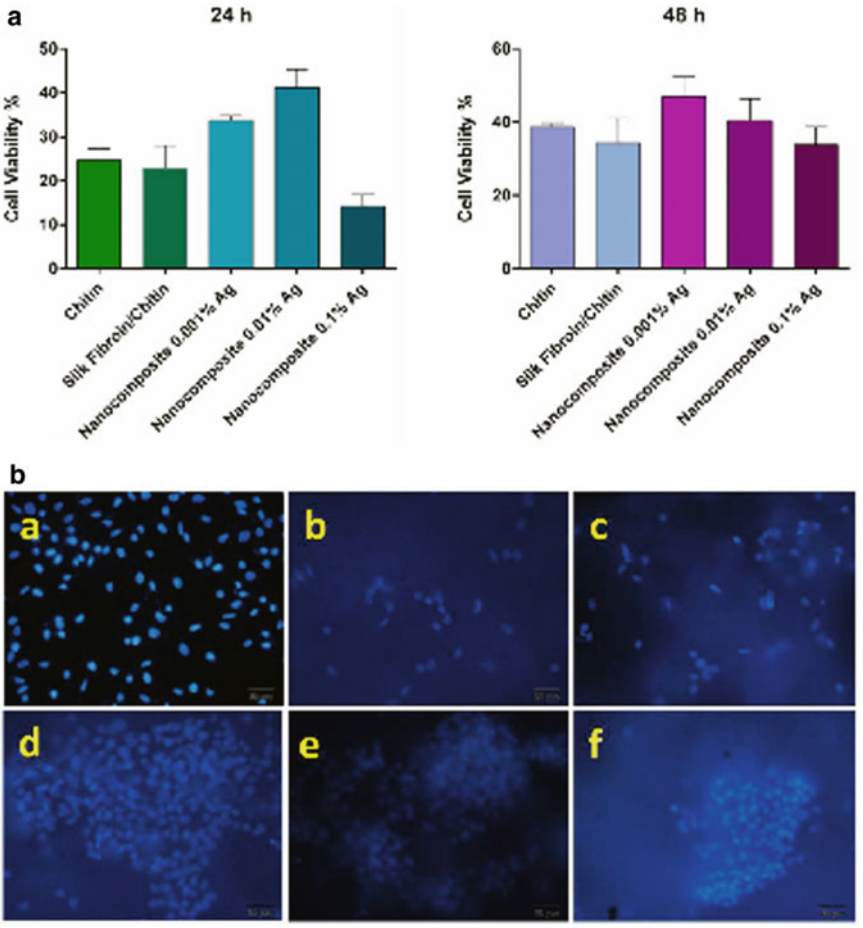

Fig. 5 **A** Proliferation and cell viability of nHFFF2 cell cultured on chitin, silk fibroin/chitin, and scaffolds with different Ag NPs contents after 24 and 48 h. **B** DAPI staining of the nHFFF2 cells attached on the chitin (**b**), silk fibroin/chitin (**c**), and nanocomposite scaffolds with 0.001% (**d**), 0.01% (**e**), and 0.1% Ag NPs (**f**). The cells with no samples used as a control (**a**) [149]

PVA is one of the most frequently used polymers and employed as wound dressings, wound management, and drug delivery systems. But the properties of PVA hydrogel such as stiff membrane, inadequate elasticity, and very incomplete hydrophilic characteristics which restrict its use alone as wound dressing polymeric membranes. Hydrogels prepared using PVA blended with some natural polysaccharides and some other synthetic ones are attractive. PVA/starch nanocomposites hydrogel membranes reinforced with silver nanoparticles demonstrate their potential to be employed for the wound dressing applications in dried as well as in the form of gel due to antimicrobial activity [128]. Sericin/poly(vinyl alcohol) hydrogel can be used as a drug delivery carrier for potential wound dressing application [151]. ZnO nanoparticles in the hydrogels are spherical and can be used in wound dressing applications. Hyaluronic acid-zinc oxide ((HA-ZnO) nanocomposite hydrogels (NCHs) was prepared by one-pot synthesis method and can be used for wound dressing [152]. Good biocompatibility and positive effects on wound healing were shown by chitosan, and it can accelerate repair of different tissues and facilitate contraction of wounds. A combination of heparinized PVA, chitosan, and nZnO was used to produce hydrogels using the freeze–thaw method which is applied for the preparation of wound dressings [153]. Heparinized nano-ZnO/poly(vinyl alcohol)/carboxymethyl cellulose bionanocomposite hydrogels are employed for wound dressing [154].

Carboxymethyl cellulose nanocomposite hydrogel containing ZnO impregnated mesoporous silica could serve as a kind of promising wound dressing with sustained drug delivery properties [155]. Carboxymethylcellulose hydrogel and mesoporous silica system can be used for wound dressing due to its water uptake properties which help in maintaining a moist environment and absorption of wound exudates, while releasing antibacterial agent preventing the wound against infections [147]. Due to the excellent biocompatibility, surface functionalizability, and mechanical properties, graphene oxide (GO) has attracted considerable interest. Large number of hydrophilic oxygenated functional groups on its surface enhances its hydrophilicity and miscibility within polymer matrices, potentially improving hydrogel swelling and mechanical property. Bacterial nanocellulose/poly(acrylic acid)/graphene oxide composite hydrogel uses two electron beam irradiation methods making them an effective wound dressing material [156].

6 Conclusion

The present chapter gives an outline of the increased usage of nanoparticle-reinforced biodegradable hydrogels for applications in various fields such as drug delivery, tissue engineering, and wound dressing with along with its advantages. By carrying out further research in this field, it is possible to develop hydrogels with specific properties by simple and cost-effective manner. In the designing of drug delivery systems as well as other biomedical applications, biodegradable hydrogels act as an alternative material of choice. Biodegradable nanocomposite hydrogels can act as a highly engineered platform for multiple biomedical applications, providing renewable and

permanent solutions to life sciences. Future studies in the field of nanocomposite hydrogels will focus on new fabrication technologies, understanding the interactions between polymeric chains and nanoparticles at different length scales and fabrication of multi-component network of hydrogels.

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