Chapter 7
Hybrid Nanohydrogels: Design and Applications

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Abstract Hydrogels are composed of three-dimensional cross-linked polymer networks with hydrophilic nature, which can therefore absorb large quantities of water within the spaces available among the polymer chains. Hydrogels can provide good mechanical support and/or a hydrated environment that offer good cytocompatibility and controlled release of molecules. During the last decade, vast amount of research has been focused in the development of hybrid nanohydrogels which include the incorporation of a secondary nanosized component to the hydrogel matrix in order to provide additional reinforcement or tailor a specific application such as imparting biological functions in tissue engineering, drug delivery and gene therapies. This chapter provides a fresh insight into some of the recent developments in hybrid nanohydrogels, describing some physical and chemical cross-linking approaches to form strong networks. Moreover, the use of synthetic and biological molecules to impart desired properties is also described, focusing mainly in tissue engineering and drug delivery applications.

1 Introduction

Hydrogels are three-dimensional, cross-linked water soluble polymer networks which can adsorb a large amount of water or biological fluids without dissolving [1]. This is possible due to the polar hydrophilic groups in their structures that are hydrated when in contact with water, creating a primary bound with it. The high water retention capacity of hydrogels provides a similar physio-chemical environment to

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native extracellular membranes, and therefore, hydrogels exhibit high biocompatibility, which have made them a great deal of research focus during the last decades, especially for tissue engineering and drug delivery applications.

Recently, great attention has been centered toward the use of nanohydrogels, which, as the name stipulates it, are three-dimensional polymer networks that have embedded nanoparticles either acting as cross-linkers and therefore enhancing the mechanical robustness of the hydrogels or introducing functionality due to their high surface area and versatility of functionalization, as well as the possibility of encapsulating bioactive compounds. Within the scope of this chapter, it is not possible to cover all relevant aspects of hybrid nanohydrogels, and therefore, the focus will be to demonstrate some of the recently published works on hybridization of hydrogels toward advanced mechanical reinforcement and for tailoring specific functions for tissue engineering and drug delivery applications.

1.1 Design of Hybrid Nanohydrogels

Due to the ambiguity of the terms "hybrid" and "nanocomposite" and the wide misuse of these terms in the literature nowadays, it is necessary to begin this chapter by defining whether the materials fall into hybrids or not. The most accepted definition of a hybrid (from the material's chemistry perspective) is a material that combines two or more components which are blended on the molecular scale with chemical bonds between them [2]; In the way that the materials complement each other, acting synergistically to have new functions which the component materials do not possess individually.

Recently, hybrid nanohydrogels have gained significant interest, as they represent an excellent opportunity for the design and development of nanostructured materials. Different hybridization strategies can be used to provide mechanical reinforcement to a matrix, creating hybrid networks, where the secondary component is a nanoparticle chemically or physically bonded to the polymer network [3]. Moreover, hybridization of inert polymer networks with bio(macro) molecules can also provide physical support for cell growth and enhance the cell adhesion and cell proliferation, which is essential for tissue engineering applications for instance [4]. Also, specific functionalities can be tailored by hybridization of a hydrogel network with loaded nanoparticles, where high concentrations of active compounds can be encapsulated and released [5].

The physical properties and therefore targeted applications of the hybrid nanohydrogels essentially depend on two aspects:

- The composition of the secondary phase (nanocellulose, silica nanoparticles, graphene, etc.)
- The mechanism of network formation arising from the type of interaction between the polymer chains and the nanoparticles (chemically or physically cross-linked).

For physically cross-linked hydrogels, the gel is formed via hydrophobic, electrostatic or hydrogen bonding interactions, forming semi-permanent links among the polymer chains inside the network [6]. On the other hand, chemical cross-linking uses covalent bonding to prepare permanent hydrogels, which although it requires another level of chemical modification, it provides greater mechanical stability [3] and allows the tuning of variables such as gelation-time and gel pore size. Moreover, chemically cross-linked hydrogels guarantee adsorption of water/or bioactive compounds without any dissolution [6].

2 Hybridization of Hydrogels Toward Advanced Mechanical Reinforcement

Despite the many advantages aforementioned, in most hydrogels, a high water-uptake comes with an inherent fragility, which limits their usability in many applications [7]. Different strategies have been developed in order to produce hydrogels with high mechanical performance, such as (i) double network hydrogels [8], (ii) hydrophobic association [9], (iii) composite hydrogels using microparticles [10] and (iv) hybridization of hydrogels. Among them, there has been a growing interest in hybrid nanohydrogels during the last decade, where the incorporated nanoparticles can act as cross-linkers through covalent bonding or physical interactions, resulting in hybrid nanohydrogels that overcome the limitations related with conventional cross-linked hydrogels, such as structural heterogeneity and mechanical fragility [7]. The improvement in their performance related to mechanically stiff and highly elastomeric network in the nanocomposite hydrogels networks is attributed to the interactions between the polymer chains and nanoparticles [11], which enables the transfer of mechanical force within the cross-linked network resulting in enhanced mechanical strength and toughness [11].

Carbon-based nanomaterials such as graphene and carbon nanotubes (CNTs) have been the most promising and widely studied candidates for mechanical reinforcement of hydrogels. Graphene in its purest form exists in a single 2D monolayer of sp^2 carbon atoms arranged in a hexagonal arranged crystal lattice. The carbon–carbon sigma bonds in the graphene structure give rise to exceptional properties that are appropriate for reinforcement of hydrogels. Faghihi et al. [12], have combined the advantages of graphene oxide (GO) and poly(acrylic acid)/gelatin in the fabrication of nanohydrogels, and the results exhibited that the addition of GO significantly increased the Young's modulus and maximum stress of hydrogels. Regarding CNTs, this type of fillers, classified in multi-wall (MWCNT) or single-wall (SWCNT), is very effective in terms of high specific surface area and excellent mechanical properties, especially toughness [13]. Zhang et al. [13], synthetized high strength MWCNTs/cellulose hydrogels from NaOH/urea aqueous solution cross-linked by epichlorohydrin. The swelling testing showed that the equilibrium swelling ratio decreased with the increment of MWCNTs content. Additionally, the incorporation of

MWCNTs into cellulose hydrogel networks improved both thermal and mechanical properties.

Another important reinforcement additive of hydrogels is naturally occurring aluminosilicate clays, such as halloysite (HNTs). These nanotubes have a diameter of ca. 50 nm and length between 500 and 1000 nm [14]. Their inner surface is composed of aluminol groups (AL–OH) positively charged to capture the negatively charged molecules in the lumen, whereas the outer surface contains silanol groups (Si–OH), negatively charged to facilitate adhesion of positively charged molecules [15]. Park et al. [16], prepared hybrid nanohydrogels composed of HNTs and hyaluronic acid (HA) via photo-cross-linking of HA and HNTs modified with vinyl groups. The compressive mechanical properties of the hybrids revealed that the hydrogels exhibited a nonlinear behavior attributed to the strain stiffening of the polysaccharide-based hydrogels and the fracture stress increased with increment of HNTs content up to 10%.

Another important kind of nanofiller for hydrogels is nanocellulose, including both cellulose nanocrystals (CNC's) and cellulose nanofibers (CNF's). CNCs are rod-like crystalline structures that have a diameter between 5 and 30 nm (depending on the source and extraction method) and length >100 nm. Due to its characteristics, such as high aspect ratio, low density, outstanding mechanical properties and highly reactive surface, CNCs have been considered as one of the most important candidates to modify the mechanical behavior of hydrogels. Yang et al. [17] obtained and evaluated nanohydrogels reinforced by CNCs from two different sources and therefore different aspect ratios. They found from uniaxial tensile measurements that the values of aspect ratios and non-permanent interactions between the fillers and matrix dominated the reinforcement. Also, they argue that the improvement in modulus of the hydrogels is correlated to the volume of the constrained polymer, where the CNCs impart significant enhancement to the entanglement network. Yang et al. [18] also carried out the mechanical reinforcement using CNCs in hydrogels based on poly(acrylamide) (PAM) with multiple cross-links. They observed that the hybrid CNC-PAM hydrogel exhibited higher Young's modulus and higher fracture strength than the PAM reference, without CNC's; and the nanohydrogel suffered greater deformation by increasing the content of CNCs were the effective physical interactions in the network promoted an increase in the fracture strength.

On the other hand, cellulose nanofibers (CNFs) are also promising reinforcement additives for hydrogels. Varying depending on their biological origin, CNF shaves a high aspect ratio 4–20 nm wide and >1 μm of length, consisting of alternating crystalline and amorphous domains of cellulose [19]. CNFs can form a rigid network in different matrices, subsequently benefiting their mechanical properties. Wang et al. [20], mechanically reinforced hydrogels of gelatin with the incorporation of CNFs, where the reinforcement was associated to the formation of a stiff three-dimensional network of CNFs, physically cross-linked with gelatin via electrostatic interactions and entanglement. CNFs have also been used as a reinforcement additive of polyvinyl alcohol (PVA) hydrogels. PVA chains are strong, tough and highly stretchable polymer chains, which can entangle cellulose nanofibrils, CNF acting as physical cross-linker to maintain mechanical integrity [21]. Likewise

when the hydrogels were stretched, the fracture of PVA and disintegration of the hydrogen bonds occurred, dissipating great amount of energy, and maintaining the stretchability, yielding excellent mechanical properties to the nanohydrogels [22].

3 Hybrid Nanohydrogels for Tissue Engineering Applications

Tissue engineering is the combination of cells, engineering and materials science which aim to restore, preserve or enhance tissue functions. Tissue can be engineered in different ways, one of the most convenient methods is to use three-dimensional tissue scaffolds for the formation of new viable tissue. Here, cells from the type of tissue that needs to be regenerated are incorporated to the scaffold for their delivery in vivo, in the way that the scaffold provides a space for new tissue formation and controls its structure and function. This technique is used to fabricate soft tissues such as cartilage, ligament, tendon, artery or hard tissues such as bones.

During the last years, nanohydrogels have demonstrated to be a promising option for the fabrication of polymer scaffolds for tissue engineering [23] because of their high water content, swellability and permeability. These specific characteristics provide a good media that benefit the diffusion of oxygen, nutrients and waste inside the structure of the scaffold, which is necessary as an environment for cell encapsulation and a successful tissue regeneration [24]. However, it is still a challenge to find the most suitable composition of the material, as it has to mimic the role of the extracellular matrix in a way that the body reacts as if it was real tissue [23].

3.1 Chemically Cross-Linked Hybrid Nanohydrogels for Tissue Engineering

There are different approaches to chemically cross-linking hydrogels, where a typical method involves the addition of a cross-linking agent consisting of small reactive molecules that promote the network formation, such as glutaraldehyde, glyceraldehyde, formaldehyde, gossypol, tannic acid, among others [25]. For instance, Tanpichai et al. [26] successfully prepared poly(vinyl alcohol) (PVA/CNCs hydrogels using glutaraldehyde (GA) as a cross-linker. In this case, GA induced the cross-linking reaction of the hydroxyl groups in PVA chains and CNCs. As a result, the addition of CNCs decreased the creep elasticity due to restriction of the polymer chains, but without affecting the swelling ratio and thermal stability. The hydrogels exhibited promising properties for tissue engineering, such as high strength, elasticity and water-holding capacity.

Another way to chemically cross-link hybrid nanohydrogels is via photo-cross-linking, in which a photoinitiator decomposes when exposed to UV light, generating

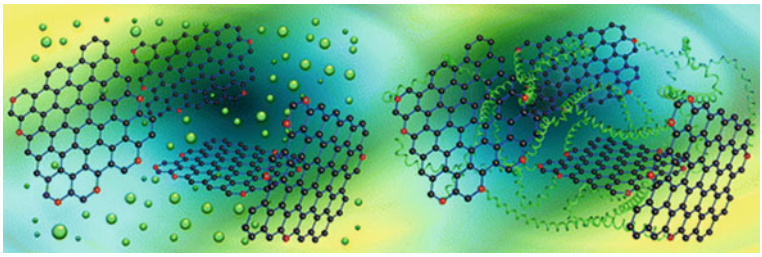

Fig. 1 Schematic model of GPO hydrogel formation. Left: before polymerization. Green balls are the monomer molecules. Right: after polymerization. The green spirals are the polymer chains, and the red balls are the peroxyl groups [28]

free radicals that react with the hydrogel displaying polymerizable groups such as acrylate or methacrylate, which can be cross-linked. The mild conditions necessary to trigger this type of cross-linking make it advantageous in tissue engineering [4].

One example of this approach is the preparation of chitosan-based hydrogels reinforced with nano-graphene oxide (nGO). Feng et al. functionalized chitosan and nGO with photocurable methacrylategroups to produce mechanically enhanced hydrogels that were cross-linked using BAPO-OH as photoinitiator, which is active at wavelengths longer than 350 nm, avoiding any possible damage of cells within the scaffold structure. The mechanical performance was increased as the content of M–*n*GO increased, and therefore, it was demonstrated that the low mechanical properties of chitosan-based photocured hydrogels can be improved via hybridization [27].

Liu et al. [28] functionalized GO/PA sheets by radiation-induced peroxidation to obtain graphene peroxide (GPO). This functionalization enhanced the interactions between GPO and PAM. In this work, the hybrid nanohydrogels were obtained via in situ free radical polymerization using GPO as polyfunctional initiator and cross-linking center between the polymer chains and the GO sheets. This combination resulted in a mechanically stiff and elastomeric hydrogel, which potentially can be used in tissue engineering. A schematic model of GPO hydrogel formation is shown in Fig. 1.

3.2 Physically Cross-Linked Nanohydrogels for Tissue Engineering

Secondary interactions, such as hydrophobic, electrostatic or hydrogen bonding interactions, form the network in physically cross-linked hydrogels, where semi-permanent junction among the polymer chains is obtained without the need of additional cross-linkers or initiators. Nevertheless, a major drawback is the lower mechanical robustness of the physically cross-linked hydrogels, as well as their easy dissolution, and strong response to stimuli such as pH, temperature and ionic strength.

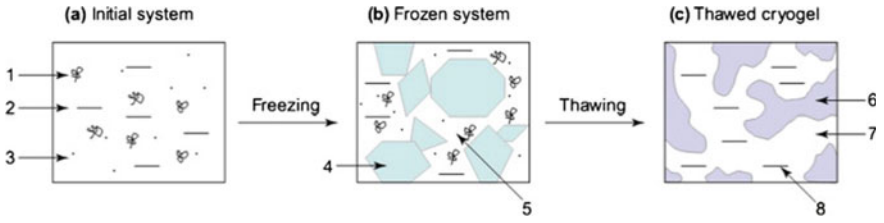

Fig. 2 Different stages that the hydrogel undergoes during the freeze/thaw process. The initial system consists of (1) polymer macromolecules in the solution, (2) solvent and (3) low molecular solutes. The frozen system contains (4) polycrystals of frozen solvent and (5) unfrozen liquid microphase. After thawing, the system includes a polymeric network (6), macropores (7) and solvent (8) [30]

Physical cross-linking of hydrogels can be carried out via crystallization induced by freeze–thaw cycles, where the cross-linking occurs due to the presence of crystalline regions. The polymer solution undergoes gelation reactions, resulting in a hydrogel with a heterogeneous phase that is formed due to the freezing (crystallization). The solubility of the polymer changes when the water converts into ice, which generates regions rich in polymer and regions lacking polymer [29]. The polymer-rich regions eventually turn into polymeric chains, joined by hydrogen bonds, which structure remains after thawing [30]. The different stages that the hydrogel undergoes during the freeze–thaw process are represented in Fig. 2.

Butylina et al. [31] prepared hybrid nanohydrogels of PVA/CNCs via crystallization induced by freeze–thaw cycles. The resulting materials exhibited better compressive properties as a function of incorporated CNCs. On the contrary, the increase in number of freeze–thaw cycles from 3 to 5 negatively affected the compressive properties of materials. Zhang et al. [32], freeze-thawed PVA/GO hydrogels via physical cross-linking through hydrogen bonding between GO and PVA, demonstrate a significant improvement in tensile and compressive strength, compared to pure PVA hydrogels.

Abouzeid et al. [33] cross-linked TEMPO-oxidized cellulose nanofibers (TOCNF)/sodium alginate (SA) hydrogels using calcium chloride as ionic cross-linker prior to 3D printing. The hydrogels exhibited excellent compressive properties compared to pure SA and pure TOCNF showing promising properties for bone tissue scaffolds.

Gaharwar et al. [34] physically cross-linked poly(ethylene oxide)/silica nanoparticles to form hybrid nanohydrogels without the addition of a photo/chemical initiator. The nanohydrogels were vigorously mixed so that the silicate interacted with the polymer chains and formed a fully exfoliated network. Afterward, the swollen hydrogel was subjected to shearing and solvent evaporation. Dense films were obtained, with tunable mechanical properties depending on the silicate concentration. Moreover, a shear-thinning behavior was observed, which is potentially useful for injectable hydrogels for minimally invasive tissue engineering.

4 Hybrid Nanohydrogels for Drug Delivery Applications

Development of hydrogels for drug delivery applications has been extensively explored in the biomedical field during the last decades, growing at an accelerated rate since early reports [5, 35, 36]. Tumors as targets in cancer treatments, wound healing, ophthalmology and other similar applications have been a main focus in research related to nanohydrogels for drug delivery. Nanohydrogels are very promising structures due to the combination of great swelling capacity, elasticity and biocompatibility [37–39], which are inherent properties of all hydrogels but complemented via hybridization with loaded nanoparticles, where high concentrations of bioactive compounds can be encapsulated and released in a controlled manner upon biodegradation or by responding to external stimuli such as temperature [40], pH [41] or a magnetic field [42]. Moreover, nanosized hydrogel particles can be developed as well, which have higher possibility to transit through the different physiological barriers without being easily eliminated by the spleen or liver, for example, longer permanence in the blood stream, etcetera [43, 44].

4.1 Hybrid Nanohydrogels Based on Natural Polymers for Drug Delivery Applications

Natural polymers have been widely used in controlled drug delivery, due to their biocompatibility, biodegradability, nontoxicity and abundance of surface functional groups [45, 46]; being polysaccharides (such as cellulose, chitosan or dextran) and proteins (such as gelatin, collagen or fibrin) the main natural sources. Li et al. [47] reported the preparation of 5-fluorouracil-loaded nanohydrogels by using the sodium salt of the carboxymethyl cellulose (SCMC) and lysozyme (Ly), an antimicrobial enzyme, separately dissolving the drug and the SCMC, followed by mixing both solutions at different SCMC:Ly ratios at 80 °C. 5-fluorouracil-loaded spherical nanohydrogels were obtained with an average hydrodynamic diameter of 214 nm and a swelling ratio about 5. The in vitro release tests showed a slower release in a simulated gastric fluid (pH 1.2) than in a simulated intestinal fluid (pH 7.4), which implies a protection effect of the drug by the nanohydrogels in the stomach ensuring a sustained release in intestines. In a similar study, Li et al. [48] reported methotrexate-loaded nanohydrogels prepared from carboxymethyl cellulose (CMC) and Ly at different ratios following a similar procedure to that described above by Zhu et al., but in this case, the drug was dissolved in the Ly solution and added dropwise to the CMC solution. In this case, the nanohydrogles presented a regular spherical shape with an average hydrodynamic diameter of 123 nm. The in vitro release tests showed a much higher toxicity of the loaded nanohydrogels in HepG2 and MCF-7 cells than that of free methotrexate, which was attributed to the fact that loaded nanostructures could easily enter the interior of the cells by their small diameters and generate a cytotoxic effect on cancerous cells. Another contribution

of Li et al. [49] was the encapsulation of doxorubicin in nanohydrogels prepared in a similar procedure than those described for 5-fluorouracil but in this case using SCMC/low density lipoprotein (LDL), a biological assembly responsible for transporting cholesterol around the body, as components. Spherical-shaped nanohydrogels were also reported with average diameter around 90 nm and a zeta potential of −35 mV. This last characteristic favored the loaded stage of the cationic anticancer drug resulting in a loading efficiency of 98%. The release of the drug from the loaded hydrogel was pH-dependent releasing faster at mildly acidic environments that under physiological pH conditions.

Chitosan, the second most abundant natural polymer, have also been extensively used for drug encapsulation in hydrogels. Zhang et al. [50] reported the preparation of chitosan-based luminescent/magnetic hybrid nanogels with average sizes about 160 nm by direct gelation of chitosan, cadmium telluride quantum dots and superparamagnetic iron oxide, which were loaded with insulin favored by the abundant amino groups from chitosan through conjugating via hydrogen bonds. Insulin release was promoted under physiological pH conditions (7.4) compared to mildly acidic conditions (5.3) explained by the more favorable solubility of insulin at pH 7.4. Zhou et al. [51] designed a nanohydrogel based on chitosan-poly(methacrylic acid) network containing immobilized cadmium selenide quantum dots with hydrodynamic diameters below 174 nm, for controlled drug delivery applications, among other applications like tumor cell imaging. Temozolomide was the anticancer drug loaded in these nanostructures, which was controlled released by a modification of the physicochemical environment of embedded quantum dots for converting chemical/biochemical signals to optical signals, this effect prompted by the pH-induced volume phase transition that can undergo the nanohydrogels.

Dextran is another important polysaccharide with multiple applications, most of them in the biomedical area, formed by a complex branched polysaccharide constituted by units of glucose with α-1,6 glycosidic linkages and with branches from α-1,3 linkages. Swain et al. [52] designed a novel biocompatible and stimuli responsive nanohydrogels constituted by polyacrylamide/dextran and decorated with 20 nm silver particles, which were efficiently dispersed throughout the nanohydrogel network. The function of silver nanoparticles was to increase the swelling and water retention properties of the nanohydrogels at specific pH values. The hydrogels showed the capacity to efficiently load ornidazole, an antibiotic drug. The nanohydrogels were prepared by polymerizing acrylamide in the presence of dextran, using methylene bis-acrylamide as cross-linker followed by incorporation of silver nanoparticles by treatment with silver nitrate followed by reduction reaction with sodium borohydride. The in vitro release of ornidazole was 98.5% at 6 h. Dou et al. [53] reported the preparation of dextran/polyacrylic acid (PAA)-based nanohydrogels with application in anticancer drugs delivery, using a redox sensitive disulfide group for cross-linking the chains. Doxorrubicine, as anticancer drug, was incorporated to ~98 nm nanohydrogels by conjugation through an acid-labile hydrazine bond. The in vitro and in vivo studies revealed that the hydrogels exhibited a dual pH/redox responsiveness on controlled doxorrubicine release, less toxicity of loaded nanohydrogels in comparison with free doxorrubicine, an excellent

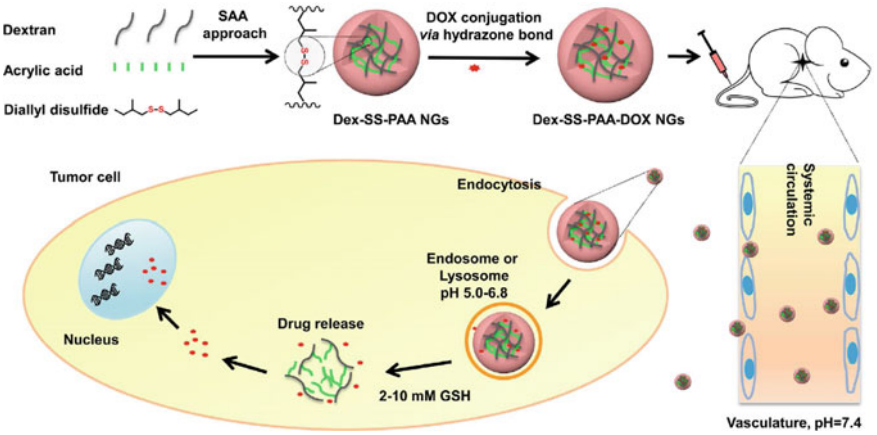

Fig. 3 Schematic illustration depicting the fabrication of the nanohydrogels, as well as their subsequent loading with doxorrubicine and their tumor-microenvironment sensitive drug release behaviors

growth inhibition of MDA-MB-231 tumors. Figure 3 shows the schematic illustration of nanohydrogels formation, the subsequent loading with doxorrubicine and their tumor-microenvironment sensitive drug release behaviors.

Some natural gums have also been used to design nanohydrogels with drug delivery applications. In this sense, Ghaemy et al. [54] designed a hydrogel based on tragacanth gum, incorporating functionalized multi-walled carbon nanotubes as secondary component and indomethacine as the drug loaded, while Torchilin et al. [55] prepared a hydrogel based on gellan gum, integrating through chemical links the prednisolone, an anti-inflammatory drug, and physically entrapping the paclitaxel, an anticancer drug, for obtaining a multi drug delivery nanohydrogel based on gellan gum.

4.2 Hybrid Nanohydrogels Based on Synthetic Polymers for Drug Delivery Applications

Synthetic polymers are also very important in biomedical applications, as they can offer similar properties to natural polymers, but also providing the possibility to tailor-specific properties for specific applications, for example, controlling the molecular weight, cross-linking degree and precise control of functional groups. Popular synthetic polymers for the synthesis of hydrogels are acrylamide, the *N*-isopropylacrylamide (PNIPAm), acrylic acid, methacrylic acid and derivatives of both, which have the ability to respond to an external stimulus. Rashidi et al. [56] reported the preparation of nanohydrogels from the in situ polymerization of *N*-isopropylacrylamide in a solution containing magnetic nanoparticles (Fe_3O_4), using

APS as initiator and a hybrid starch-maleate as cross-linker. The thermo- and pH-sensitive magnetic nanohydrogels were then loaded with mitoxantrone, an anti-cancer drug. Figure 4a shows the schematic representation for the preparation of the magnetic nanohydrogels, while Fig. 4b shows digital images of starch-maleate magnetic nanoparticles stable ferrofluid, magnetic nanohydrogels dispersion and magnetic response of nanohydrogels.

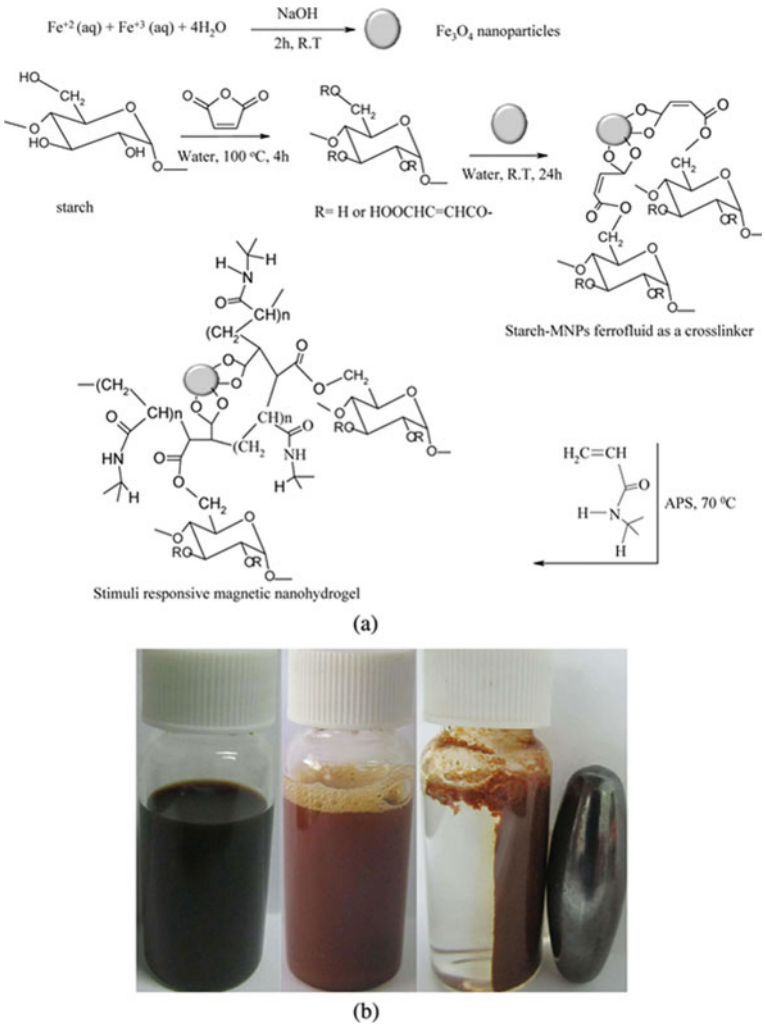

Fig. 4 **a** Schematic description for the preparation of magnetic nanohydrogels; **b** digital images of starch-maleate-magnetic nanoparticles stable ferrofluid, magnetic nanohydrogles dispersion and magnetic response of nanohydrogels (left to right)

Hamishenkar et al. [57] also worked with PNIPAm-based nanohydrogels containing Fe_3O_4 nanoparticles for loading anticancer drugs. In this case, the total components of the pH and thermal responsive hydrogels were a poly(*N*-isopropylacrylamide-*co*-itaconic anhydride) copolymer, poly(ethylene glycol) and the Fe_3O_4 nanoparticles. Doxorrubicine was the anticancer drug used in this study. The loaded nanohydrogels presented a regular spherical shape with an average diameter about 20 nm. The in vitro release studies revealed that the highest drug release was at 41 °C and a pH of 5.3, while at physiological conditions (37 °C and a pH of 7.4), the materials exhibited negligible release values. Moreover, doxorrubicine-loaded nanohydrogels presented higher cytotoxicity effects against HeLa cells than free drug, which was explained by the slow release of the loaded anticancer drug. Kim et al. [58] worked with polyacrylamide-based nanohdyrogels loaded with the 5-Fluorouracil as anticancer drug. The hydrogels were prepared through a in situ free radical polymerization including green tea extract (80% polyphenols) as secondary component, *N*, *N*′-methylenebisacrylamide as cross-linker and potassium persulfate as initiator. The presence of green tea molecules in the nanohydrogels improved their water–uptake ability and the stabilization of the magnetic nanoparticles in the networks. The nanohydrogels were subsequently loaded with iron ions (Fe^{2+}/Fe^{3+}) via a swelling method, followed by the conversion of iron ions into magnetic nanoparticles of about 10 nm in the nanohydrogel network via treatment with ammonia solution. The nanohydrogels were then loaded with 5-fluorouracil, showing encapsulation efficiencies ranging from 43 to 81% depending on the presence or absence of an external magnetic field, which was also studied as variant in the release tests resulting in a slightly higher percentage of drug release when the external magnetic field was used. These nanohydrogels present both superparamagnetic and biocompatible properties and are good candidates for drug delivery or other biomedical applications.

5 Concluding Remarks

The introduction of a secondary nanosized component into a hydrogel matrix, forming hybrid nanohydrogels, can provide mechanical reinforcement or the possibility to yield additional functionality such as imparting biological functions or encapsulation of bioactive compounds that can be encapsulated and released upon biodegradation of application of an external stimuli. Depending on the desired properties of the hydrogels, different hybridization strategies can be followed via chemical or physical cross-linking, allowing to tailor-specific applications. Some of the most prominent uses of nanohydrogels are in tissue engineering and drug delivery applications, which are further discussed in the following chapters.

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