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Self-assembly in magnetic supramolecular hydrogels

Cristina Gila-Vilchez[a,c], Laura Rodriguez-Arco[a,c], Mari C. Mañas-Torres[b,c], Luis Álvarez de Cienfuegos[b,c] and Modesto T. Lopez-Lopez[a,c]

Abstract

Most recent advances in the synthesis of supramolecular hydrogels based on low molecular weight gelators (LMWGs) have focused on the development of novel hybrid hydrogels, combining LMWGs and different additives. The dynamic nature of the noncovalent interactions of supramolecular hydrogels, together with the specific properties of the additives included in the formulation, allow these novel hybrid hydrogels to present interesting features, such as stimuli-responsiveness, gel-sol reversibility, self-healing and thixotropy, which make them very appealing for multiple biomedical and biotechnological applications. In particular, the inclusion of magnetic nanoparticles in the hydrogel matrix results in magnetic hydrogels, a particular type of stimuli-responsive materials that respond to applied magnetic fields. This review focuses on the recent advances in the development of magnetic supramolecular hydrogels, with special emphasis in the role of the magnetic nanoparticles in the self-assembly process, as well as in the exciting applications of these materials.

Addresses

[a] Universidad de Granada, Departamento de Física Aplicada, C. U. Fuentenueva, E-18071 Granada, Spain
[b] Universidad de Granada, Departamento de Química Orgánica, Unidad de Excelencia Química Aplicada a Biomedicina y Medioambiente, C. U. Fuentenueva, E-18071 Granada, Spain
[c] Instituto de Investigación Biosanitaria Ibs.GRANADA, Spain

Corresponding authors: Lopez-Lopez, Modesto T. (modesto@ugr.es); Álvarez de Cienfuegos, Luis. (lac@ugr.es)

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Magnetic hydrogels, Supramolecular hydrogels, Magnetic nanoparticles, Smart materials, Magneto-responsiveness, Drug delivery, Tissue engineering.

Introduction

Hydrogels are solid-like materials composed mainly by water or biological fluids entrapped in a filament network. Their microstructural and mechanical properties, as well as their chemical composition, can be tailored in an attempt to closely mimic the extracellular matrix of living systems. Thus, these materials have found interesting and useful applications in the biomedical and the biotechnological fields [1]. Hydrogels can be prepared by natural or synthetic components, such as, carbohydrates, proteins, peptides, surfactants and/or synthetic polymers. In addition, hydrogels can be designed to have a dense reticular network stable in time made by covalent cross-links between polymeric chains (chemical hydrogels), but also, to be more fluid-like and reversible, by cross-linking the chains through noncovalent interactions (physical hydrogels). Supramolecular gels belong to this last group [2]. Usually, these hydrogels are constituted by LMWGs that interact with each other by noncovalent interactions, such as electrostatics, hydrogen bonds, π-π interactions, etc. [3]. Their self-assembly is anisotropic giving rise to 1D polymers (fibers) of higher aspect-ratio. The intertwining of these fibers throughout the whole volume affords a 3D fibrillar network that can macroscopically immobilize the liquid, thus forming the gel. Conventional polymer networks cross-linked by covalent bonds, cannot be dissolved, are thermally irreversible and usually too tough to experience large changes of properties under external stimuli. On the contrary, the dynamic, reversible and weaker nature of the noncovalent interactions in supramolecular hydrogels make it feasible to modify their properties by the application of external stimuli, such as changes of temperature, pH, solvent, light, etc. [4,5]. Stimuli-responsive soft materials offer the possibility of developing complex systems capable of interacting with the environment and performing specific functions under spatio-temporal control. These materials are highly sought after as they can have many biomedical and technological applications.

An interesting strategy to develop stimuli-responsive soft materials implies the inclusion of magnetic nanoparticles (MNP) within a hydrogel matrix to afford magnetic hydrogels or ferrogels [6,7]. Common

synthesis routes of MNP and characterization methods are summarized in Scheme 1 -for more details see refs. [8–12]. The inclusion of magnetic nanoparticles in a hydrogel can make these systems sensitive to external magnetic fields. This property, called magneto-responsiveness, offers many advantages since this stimulus can be applied externally or remotely, in a time-controlled way, is not invasive, neither harmful, and therefore can be ideal for advanced biomedical applications, such as controlled drug delivery and cell growth, hyperthermia therapy, or as contrast agents in magnetic resonance imaging, among others [13]. Based on the type and amount of MNP and their interaction with the hydrogel organic matrix, the magnetic stimulus can produce micro- and macroscopic structural changes in major or minor degree. By itself, the inclusion of MNP in a hydrogel can modify its structure and mechanical properties due to the new interactions created between both components (*i.e.*, particles and hydrogel fibers). This interaction is an essential parameter to control or modify the properties of the magnetic hydrogels and to avoid MNP precipitation and leakage from the hydrogel matrices. In relation to the latter, magnetic hydrogels prepared by simple encapsulation of MNP in the hydrogel network (blending method) are vulnerable to MNP leakage and precipitation [14]. A strategy to maximize the attractive interaction between MNP and hydrogel fibers, is the adequate functionalization of the MNP with different molecules or coatings, so that they can bind, covalently or noncovalently, to the hydrogel organic matrix (grafting-onto method) [14]. In this case, if the attractive interaction between MNPs and gelators is dominant, the stability of the magnetic hydrogels against leakage should be guaranteed. For example, Barczak et al. [15] found that amine groups on the surface of magnetic particles resulted in well-formed and stable alginate-based magnetic hydrogels, likely due to strong attractive interactions between alginate and amine groups. On the contrary, for particles functionalized with phenyl or glycidoxy groups, repulsive interaction with the negatively charged groups of alginate are expected, and in agreement they obtained alginate-based magnetic hydrogels that exhibited phase separation and leakage of magnetic particles [15]. Furthermore, nanoparticle functionalization improves colloidal stability by reducing particle aggregation, which is crucial to achieve a good distribution of the nanoparticles within the hydrogel matrix. It also protects against oxidation, thus prolonging the shelf life of the final product [15]. In the case of metal (iron, cobalt, nickel) and metal oxide-based nanoparticles, functionalization can be done by (i) adding the ligand during or after the synthesis of the nanoparticles, or (ii) by ligand exchange [16,17]. In the first case, ligands such as sodium citrate [18], oleic acid [19,20], cetyltrimethylammonium bromide (CTAB), dopamine or other amine compounds [21–24,20] are used. Polymers like polyethylene glycol (PEG) [25–27,19,28], dextran, chitosan, polyvinyl pyrrolidone (PVP), poly (ε-caprolactone) (PCC) [25], or polyacrylic acid (PAA) can also be employed [29]. PEG for example, is widely used in biomedical applications because it protects the nanoparticles from clearance by the immune system. Some of the ligands listed above can be later exchanged with molecules bearing groups such as amines, carboxylates, phosphonates, or thiols [15], with high affinity for the metal oxide surface. Biomolecules such as lipids [18,30], nucleic acids [31], or peptides/proteins [32,21,33] are also useful to provide with biomimetic features. As for the binding mechanism, grafting is achieved by a combination of physical and chemical adsorptions, the latter taking place through coordinative binding of bidentate

Scheme 1

Method of synthesis	Particle composition	Typical particle size	Relevant reference	Characterization methods
Phase transformation from solid precursors	Ferrites in general, typically Fe_3O_4	30 – 1100 nm	[8]	• Energy-dispersive X-ray spectroscopy (EDS) → **Chemical characterization** • X-ray diffraction analysis (XRD) → **Crystallographic structure** • Dynamic Light Scattering → **Hydrodynamic size and electrophoretic mobility** • Electron microscopy → **Particle size and shape** • Magnetometry → **Magnetic properties**
Co-precipitation	Fe_3O_4	~ 10 nm	[9]	
Reaction in gas phases	Metals (Co, Ni,...) and metal oxides (Fe_3O_4)	2 – 100 nm	[10]	
Polyol process	Metals (Co, Ni, Fe, alloys)	20 – 2000 nm	[11]	
Decomposition of organo-metallic compounds	Metals (Co, Fe)	5 – 50 nm	[12]	

Common synthesis routes of magnetic nanoparticles and characterization methods.

or multidentate functional groups to the hydroxyl groups on the metal oxide surface. This is the case, for example of carboxylates when binding citric or oleic acids, or amines in the case of dopamine (a bidentate ligand). Other materials such as silica [15,28], gold [34], or graphene oxide [35,36] can be also grown on the surface of magnetic nanoparticles, leading to core-shell structures which enable multiple functionalities in a single nanoparticle platform.

Another key factor that controls the behavior of the magnetic hydrogel is its chemical constitution, that is, if it is a chemical or physical hydrogel. Chemical magnetic hydrogels were first developed. These materials showed the capacity to modify their mechanical properties, and even their macroscopic aspect, upon application of an external magnetic field, paving the way to develop on demand drug delivery vehicles, as beautifully exemplified in the seminal work by Zhao et al., who used covalent cross-linked alginate hydrogels [37]. Excellent reviews have been devoted to these types of polymeric magnetic materials [7,13]. More recently, physical magnetic hydrogels based on the self-assembly of LMWGs have started to appear [38]. These systems offer a higher degree of interpenetration between the MNP and the hydrogel organic matrix. The formation of the hydrogel implies the self-assembly of the LMWGs to afford polymeric fibers. If this process is triggered in the presence of MNP, these can be engulfed by the organic fibers. Moreover, since the organic matrix is self-assembled in the presence of MNP, the application of a magnetic field can modify the arrangement of the particles which, in turn, can modify the organic matrix giving rise to anisotropic gels [32]. The topic of the present short review is focused on the recent development of magnetic supramolecular gels, with special emphasis on their self-assembly. Given the importance of applications of these materials, after a first section on the role of magnetic particles on the integrity and mechanical properties of these materials, this paper is split in different sections and subsections depending on their applications. Note also that Table S1 presents in a concise way information about gelators, type of MNP and applications of the magnetic hydrogels reviewed here.

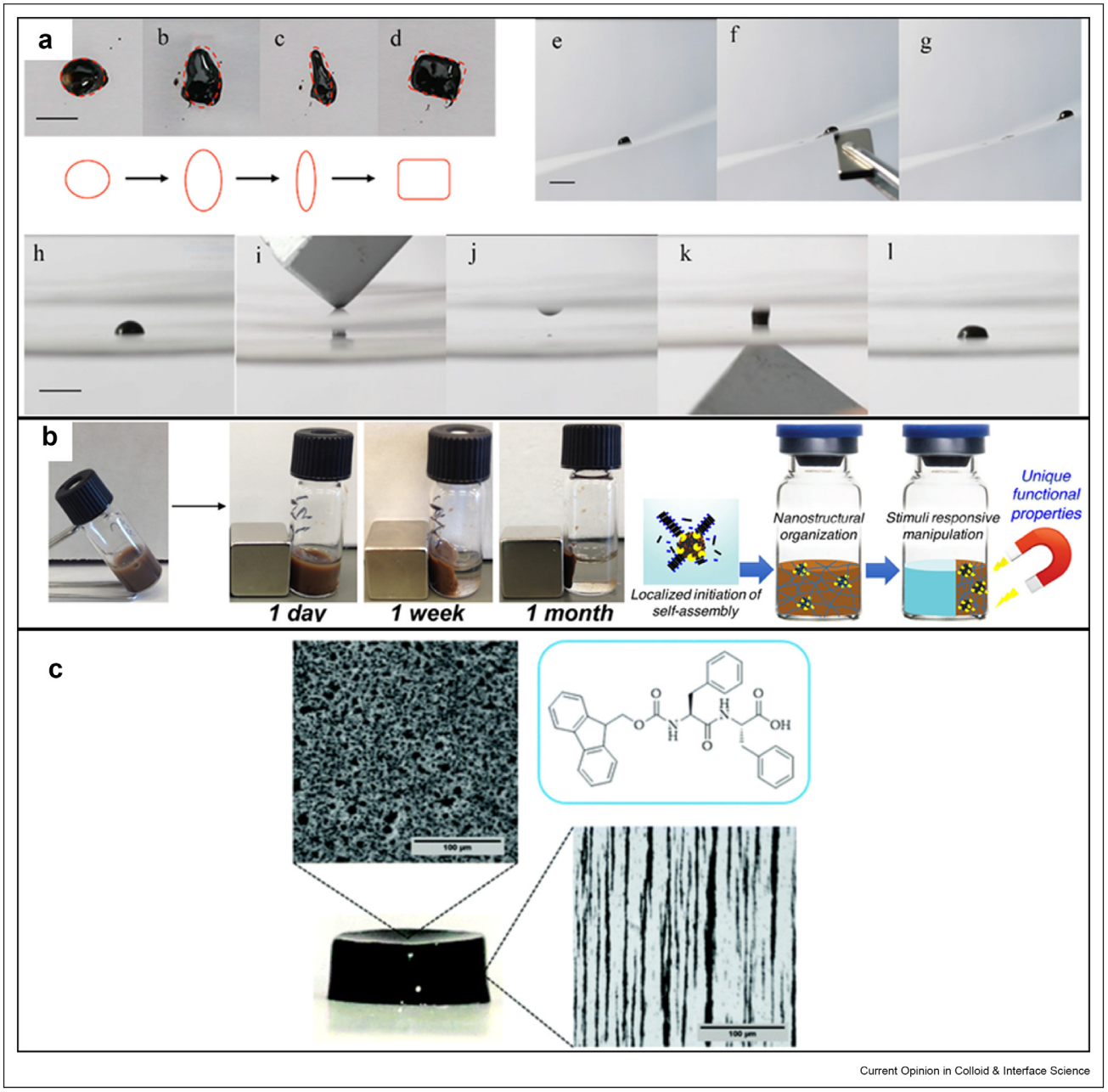
Role of magnetic particles on the macroscopic integrity and mechanical properties

An appropriate integration of the magnetic particles (MP) within the 3D fibrous structure of the hydrogel is critical to obtain homogenous hydrogels that do not suffer from phase separation or lack of water immobilization, which would hamper applications. When the magnetic hydrogel is prepared by the self-assembly of gelators in the presence of an aqueous suspension of particles, stabilization of this suspension and proper functionalization of the particle surface is important to guarantee homogeneity [32,15,25,21]. For example, Yang et al. [21] demonstrated that for the successful self-assembly of hydrogel hybrid nanofibers consisting of MNP and the dipeptide derivative Nap-FF [Nap = 2-(naphthalen-2-yloxy)acetyl)], an adequate functionalization of the MNP surface was required to get supramolecular interaction (*i.e.*, π-π interaction and hydrogen bonding) of the functional groups on the surface of the MNP with the gelators. Similarly, Ma and Zhang [25] employed a biocompatible poly (ethylene glycol)—poly (ε-caprolactone) (PEG—PCL) block copolymer to stabilize magnetite nanoparticles that were later used in combination with α-cyclodextrin (α-CD) for the preparation of magnetic hydrogels by supramolecular complexation between α-CD and PEG-PCL. Another example involves the well-established ability of nitrilotriacetic acid (NTA) to ligand metal ions, which was used to integrate nickel nanoparticles in supramolecular hydrogels [39]. With this aim, gelators containing NTA were designed based on highly efficient self-assembly motifs, and solutions of them were reversibly self-assembled and disassembled in the presence of nickel nanoparticles by a heating/cooling procedure to produce thermally reversible magnetic supramolecular hydrogels. TEM observations demonstrated that the gelators self-assembled to form networks of entangled nanofibers with the nickel nanoparticles attached to them, whereas circular dichroism (CD) spectra indicated β-sheet like structures. In another work, DNA strands were covalently attached to MNP that were afterwards mixed with a Y-scaffold resulting in non-aggregated suspensions [31]. MNP and Y-scaffolds in suspensions were eventually self-assembled by DNA hybridization when double stranded DNA linkers were added, resulting in homogeneous magnetic hydrogels (Figure 1a). In a more recent work, Contreras-Montoya et al. [32] prepared magnetic supramolecular hydrogels consisting of iron MNP dispersed in a supramolecular network of Fmoc-FF dipeptides (Fmoc = Fluorenylmethoxicarbonyl). They found that pre-treating the particles with the Fmoc-FF peptide was required to obtain homogeneous gels.

One advantage of the addition of MP reported in several works is that the presence of MP accelerates the kinetics of gelation, although different explanations to this phenomenon have been given [32,25,26,22]. For example, this acceleration of kinetics may be the result of an attractive interaction between the functional groups in the particle surface and the gelators [25]. Alternatively, MNP might work as fillers, reducing the volume that the fibers need to span to achieve the gel point [22]. Another reason can be the formation of columnar particle structures when gelation is performed under a magnetic field [32,26]. In this case, a sol-gel transition due to attractive magnetic forces between particles can induce immediate gelation. Remark that a sol-gel transition is the change of a dispersion of

colloidal particles or polymers from a liquid state (sol) to a solid-like (gel) state, in which the liquid is immobilized. Different mechanisms can be behind sol-gel transition, such as self-assembly of molecules mediated by physical (*e.g.*, electrostatic or hydrogen bonding) or chemical (*e.g.*, radical polymerization) interactions, or the attraction between colloidal particles due to electrostatic or magnetostatic interactions between permanent or induced electric or magnetic moments. In all cases, the formation of a three-dimensional network by the molecules or particles, which immobilizes the continuous liquid phase, is the basis of the sol-gel

Figure 1



(**a**) Remote controlling of the shape and movements of DNA-MNP hydrogels. (**b**). Schematics of the external manipulation of the formed hydrogel with a magnet and the localized initiation of self-assembly onto the magnetic NPs. (**c**) Macroscopic picture of the magnetic peptide (Fmoc-FF) hydrogel based on FeNPs@PEG@Fmoc-FF nanoparticles and optical images from the top and side views. (**a**) Reprinted with permission from [16]. Copyright 2017 American Chemical Society. (**b**) Reprinted with permission from [19]. Copyright 2018 American Chemical Society. (**c**) Reprinted by permission from Royal Society of Chemistry from [11].

transition. Note that for the application of a magnetic field during gelation or to the final hydrogel, it is common to use an electric coil or pair of Helmholtz coils, placed coaxially with the sample, and connected to a DC power supply [32,40]. According to Biot-Savart law, the electric current flowing through the coils generates a magnetic field. The field generated by the coils, especially Helmholtz coils is quite uniform in the central region, which is an advantage for applying a homogeneous magnetic field to the sample. The use of permanent magnets for magnetic field application is also quite common [31,33], although the resulting magnetic fields could be quite non-uniform.

The mechanical properties of the resulting magnetic hydrogels can also be enhanced by the presence of MNP because of at least two phenomena. Firstly, because of the increase of the degree of cross-linking due to the attractive forces between the functional groups on the particle surface and the gelators [15,25,33]. Secondly, by the reinforcement associated to the rigid inclusions that represent the MP or the structures made by them (Figure 1c) [32]. In this regard, Contreras-Montoya et al. [32] found that the application of an external magnetic field provoked the aggregation of MNP into columns aligned in the direction of the magnetic field, giving rise to hydrogels that showed anisotropic microstructure and mechanical properties. Indeed, the surface of the MP is an excellent substrate to attach different functionalities to affect the self-assembly of the gelators. For example, the gelation of peptide supramolecular hydrogels can be successfully controlled via the anchoring of catalytic enzymes on the particle surface, as they act as initiation nodes for the self-assembly of peptides into fibers, for example, as demonstrated by Conte et al. [33]. In that work, MNP were functionalized with thermolysin or chymotrypsin, and were used respectively to trigger the formation of Fmoc-TF-NH_2 and DFF-NH_2 gelators, starting from solutions of non-assembling precursors (Fmoc-T + F-NH_2 and DF-OMe and F-NH_2, respectively) to which the MNP were added for gelator formation. Then, the self-assembly of the gelators took place, giving rise to a "hub-and-spoke" morphology of the hydrogels, where MNP served as nuclei for self-assembly (Figure 1b).

However, when the particle surface is not properly functionalized to interact attractively with the gelators, their incorporation to the matrix can result in disruption of the network homogeneity at the microscopic level, phase separation, water losses from the matrix, and a weakening of the macroscopic mechanical properties [15,41]. Besides, Veloso et al. [22] also found a slight weakening of the mechanical properties when Mn and Mn-Ca ferrites functionalized with F or FF were incorporated to dehydrodipeptide (Nap-F-*Z*-ΔF-OH)-based gels. These authors demonstrated the co-assembly of the MNP with the hydrogel fibers already at the early stages of self-assembly, and an enhancement of the fiber elongation rate in detriment of nucleation when the nanoparticles were incorporated.

Particle size also plays an essential role in the formation and final properties of the magnetic supramolecular hydrogels. Gila et al. found that when gelation was carried out under a field, larger particles provoked a shorter gelation time and a faster increase of the storage modulus due to the stronger magnetic attraction between them (Figure 1c) [26]. However, once the magnetic field was switched off, the magnetic hydrogel based on micron-sized MP presented weaker mechanical properties as compared with a similar magnetic hydrogel based on MNP, since smaller particles were integrated more smoothly in the self-assembled fibrous structure, whereas larger particles may have disturbed the 3D self-assembly [26].

Self-assembly of magnetic supramolecular hydrogels for biomedical applications

Magnetic supramolecular hydrogels as drug delivery vehicles

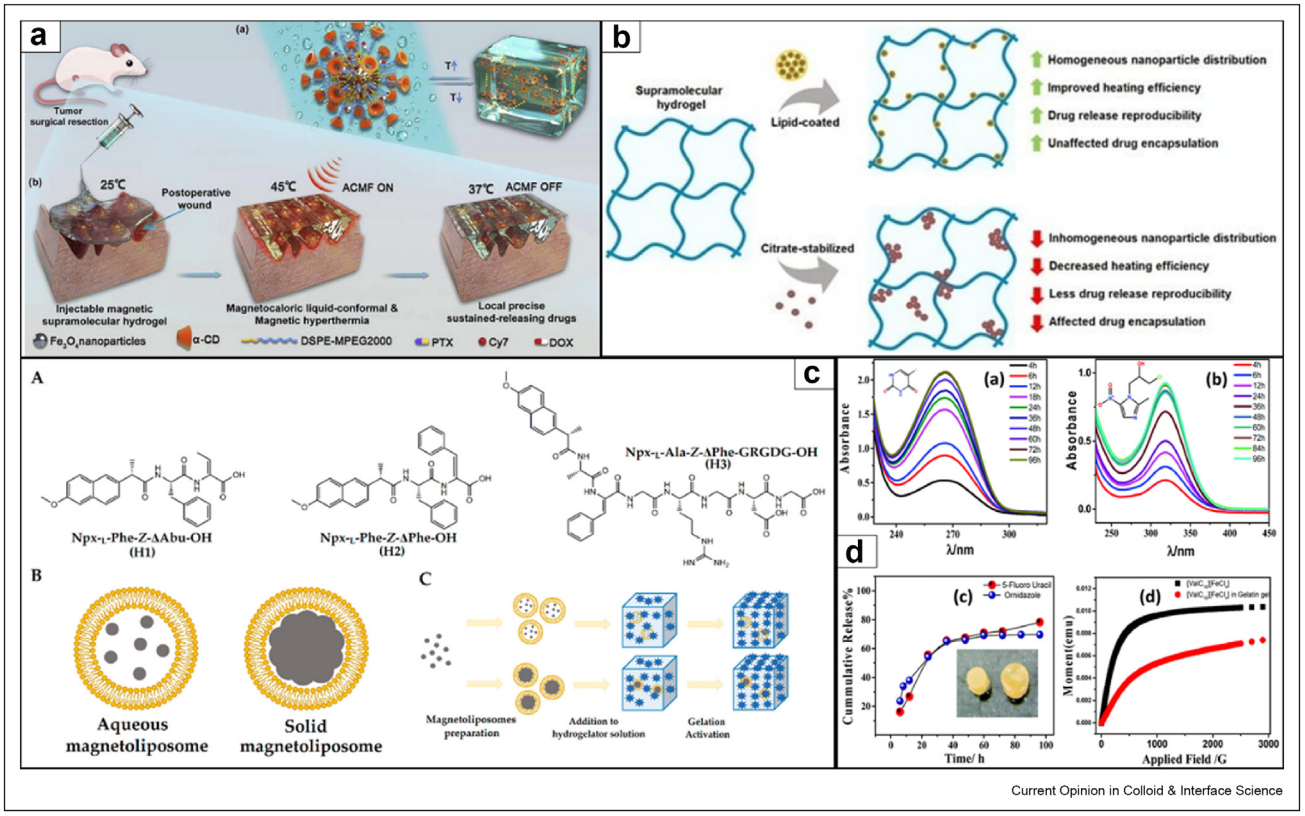
Recently, with the significant advance in the use of supramolecular chemistry to develop hydrogels with novel properties, magnetic supramolecular hydrogels have started to find applications as novel drug delivery systems. These systems offer the possibility to develop more sophisticated and versatile drug delivery systems. For example, drugs can be trapped into the reticular hydrogel structure, combined or attached to the MNP, or a by a dual combination of both processes [38]. Furthermore, the generation of heat by MNP under the application of alternating magnetic fields can enhance the drug release in supramolecular hydrogels, by completely disrupting the hydrogel matrix thanks to the generated heat, favoring a burst drug release, which could be combined with the death of cancer cells by the increase of temperature (hyperthermia) in cancer treatment. Magnetic stimulation is also capable of altering the porosity or mechanical properties of physical hydrogels thanks to their inherent reversible nature, thus favoring the development of on-demand drug release systems. Supramolecular gels also tend to exhibit shear-thinning and self-healing properties, both of which are necessary to develop injectable materials, thus allowing these hydrogels to be applied via a minimally invasive route of administration [22,27]. The capacity to shear under mild mechanical stimuli make them also ideal materials to administer extremely delicate cargos such as cells [27].

The multiple possibilities that the combination of MNP and supramolecular hydrogels can offer were first explored by Wu et al. [19] using a magnetic supramolecular hydrogel to prevent locoregional recurrence of breast cancer after tumor resection (Figure 2a). The

combination of pegylated MNP with α-CD that acted as inclusion complexation with the pegylated chains afforded a thermoreversible hydrogel presenting shear thinning behavior. The administration of the gel by injection in the postoperative wound region allowed a perfect distribution and fixation over the whole area. The application of external alternating magnetic fields induced MNP heat provoking the release of two types of chemotherapeutic drugs, doxorubicin (DOX) and paclitaxel (PTX), that presented a different release rate based on their hydrophilicity (DOX, faster release, PTX, slower release). Supramolecular hydrogels based on the self-assembly of aromatic short peptides have also been used in combination with MNP for the development of hybrid hydrogels with biotechnological applications. Yang et al. [21] were the first to develop a magnetic supramolecular hydrogel based on the combination of Nap-FF and MNP coated with FF. This system, which contained only small amounts of magnetic nanoparticles, showed a homogeneous distribution of the MNP in the hydrogel network that allowed a large magneto-rheological change (sol to gel transition) upon the application of an external magnetic field of low intensity. Das et al. [42] were also able to form a magnetic supramolecular hydrogel by the combination of polydopamine spheres coated with Fe_3O_4 nanoparticles and FF. The spontaneous formation of the supramolecular hydrogel by simply mixing the MP with the dipeptide made this system very attractive for biomedical applications. Recently, Carvalho et al. [43] developed dehydrodipeptide [Npx-Y-*Z*-ΔF-OH and Npx-D-*Z*-ΔF-OH (Npx = naproxen)] hydrogels loaded with superparamagnetic iron oxide nanoparticles (SPION) for theragnostic applications. The incorporation of the MNPs in the microstructure was evaluated, as well as the capacity to generate heat for magnetic hyperthermia, and as contrast agents for MRI. Hydrogels containing enough amounts of SPION showed significant dual T_1/T_2 MRI contrast, as well as the capacity to turn from gel to sol thanks to the heat generated by applying alternating magnetic fields.

Recently, Veloso et al. [34] studied the properties of novel magnetic hydrogels formed by the combination of a similar dehydrodipeptide (Npx-M-*Z*-ΔF-OH) with two different plasmonic/magnetic nanoparticles made of

Figure 2



(**a**) Schematic summary of the temperature induced reversible gel-sol transition of the magnetic supramolecular hydrogel and its application in cancer thermo-chemotherapy. (**b**) Schematic summary of the fabrication of supramolecular hydrogels with citrate and lipid-functionalized magnetic nanoparticles for drug delivery. (**c**) Schematic summary for the fabrication of magnetolipogels based on peptide hydrogels with magnetoliposomes. (**d**) Release pattern of drugs and magnetic behavior of the hydrogels. (**a**) Reprinted by permission from Elsevier from [22]. (**b**), (**c**) and (**d**) reproduced from [26,34,35] under a CC license.

core/shell manganese ferrite/gold (ca. 55 nm size) and gold-decorated manganese ferrite (ca. 45 nm size). Gels were evaluated as drug delivery vehicles containing curcumin as antitumor model drug. Release profiles were evaluated under photothermal conditions irradiating at the gold plasmon band of the samples. Although gold-decorated nanoparticles were more efficient in generating heat, hydrogels containing core/shell manganese ferrite/gold nanoparticles showed an enhanced drug release upon photoirradiation. Thus, these hydrogels can be excellent candidates for cancer therapy combining hyperthermia and controlled drug delivery. The same group also studied the influence of the coating of manganese ferrite nanoparticles and its impact on the generation of magnetic supramolecular hydrogels for drug delivery applications [18]. Two different coating, citrate-stabilized and lipid-coated nanoparticles were prepared (Figure 2b). Lipid-coated nanoparticles were distributed homogenously in the hydrogel, showing a lower heating efficiency and an improved drug release reproducibility. On the contrary, citrate-stabilized nanoparticles aggregated upon gelation and presented an enhanced heating efficiency. Nevertheless, the drug release profile of these nanoparticles was not reproducible. In both cases, the application of an external magnetic field increased the cumulative drug release. On another work, Nowak et al. [44] developed a magnetic hydrogel based on the combination of Nap-GFYE with Fe_3O_4 superparamagnetic nanoparticles. The inclusion of magnetic nanoparticles allowed gel to sol transition upon application of an external magnetic field. The on-demand drug release properties were tested using a fluorescent dye.

Besides using peptides to form supramolecular hydrogels, other biological or biomimetic compounds have also been used for the same purpose. For example, supramolecular hydrogels constituted by carbohydrates [45] and DNA [46] have also been reported. Like peptide-derived hydrogels, these hydrogels are interesting in biomedical applications due to their good biocompatibility [47–49]. For example, Song et al. [50] developed a supramolecular magnetic DNA hydrogel for enzyme encapsulation. The incorporation of the MNPs allowed the system to be collected and cleaned by the application of external magnetic fields. The inclusion of enzymes (glucose oxidase and horseradish peroxidase) in the hybrid hydrogel increased their stability, activity and reusability. Moreover, the hydrogel was also an excellent system to detect low glucose concentrations.

An interesting strategy to improve the efficiency of these magnetic supramolecular hydrogels as drug delivery vehicles is the incorporation of an additional drug delivery system in the hydrogel matrix. In this case two systems can exert a control over the release of the drug offering the possibility to fine-tune this process by a combined action. Veloso et al. [22,30] were able to form composite hydrogels by the combination of magnetoliposomes and peptide hydrogels. These authors used two types of magnetoliposome architectures, liquid and solid, loaded with curcumin and Nile Red fluorophore. The magnetoliposomes and their contents remained unaltered once the gel was formed. This system was able to load different types of drugs independently of their aqueous solubility since hydrophobic drugs can be contained within the liposome membranes and hydrophilic drugs in their interior, or trapped in the hydrogel network (Figure 2c). Very recently, the same group developed a similar system in which magnetic nanoparticles and liposomes were loaded independently in the dipeptide hydrogel matrix [22]. This combination of three components inhibited the passive diffusion of DOX allowing exclusively an on-demand release of the drug by the application of temperature variations or an external magnetic field. The coating of MNP favored their inclusion in the hydrogel matrix and significantly reduced their cytotoxicity. As a whole, this supramolecular system offered the possibility of modulating and controlling drug release, favoring the development of more efficient delivery systems. Kulshrestha et al. [51] followed a similar strategy of development of composite magnetic hydrogels, and tested them for drug delivery applications (Figure 2d). In their work, gelatin hydrogels containing vesicles of valine-based magnetic ionic liquid surfactant $[VC_{16}][FeCl_4]$ were prepared, characterized, and tested for the controlled release of antibiotic (ornidazole) and anticancer (5-fluorouracil) drugs. The inclusion of the magnetic vesicles produced a two-fold increase in the mechanical strength of the hydrogel. The loading of both drugs increased significatively from pure gelatin (ca. 8–10%) to magnetic (ca. 70–80%) hydrogels. The release profile of the magnetic hydrogel was studied and compared with the control $[VC_{16}][FeCl_4]$ vesicles. The magnetic hydrogel showed a slower release profile due to the entrapment of the vesicles in the hydrogel. Nevertheless, the release profile under the application of a magnetic external field was not investigated.

Note finally that the ability of MNP to respond to external magnetic fields have been recently explored to guide them through biological complex systems to exert a biomedical effect in a targeted area. These MNP can be functionalized with different therapeutics molecules but can also be coated with different polymers and embedded in hydrogels for this aim. The concept of this approach aspires to develop micro or nanorobots that can deliver a drug and repair, detoxify or perform a surgery in a small area inside the body [52]. Most of the examples have tried to validate these systems in biological complex mixtures *in vitro* and some of them have shown promising results *in vivo*. For example, Chen et al. have developed a microrobot with different morphologies based on MNP embedded in an alginate gel [53]. This

system has been designed to behave as targeted drug delivery to release its cargo in the intestinal area after its oral administration. MNP microrobots have been functionalized with urease being able to penetrate mucin gels [54] and with fluorophores to track and detect toxins secreted by *Clostridium difficile* [55]. A step further has been carried out by the group of Sitti, which functionalized MNP with bacteria (*Escherichia coli*) to *in vitro* targeted-delivery doxorubicin to 4T1 breast cancer cells under magnetic control [56]. Proof of concept that these magnetic micro/nanorobots can move in more complex systems have been validated *ex vivo*, in bovine eyeball [57], and *in vivo*, testing the thrombolysis enhancement in a rat embolic model [58] and as nanocatalyst for the bioorthogonal activation and local delivery of 5-fluorouracil in a mouse model [59].

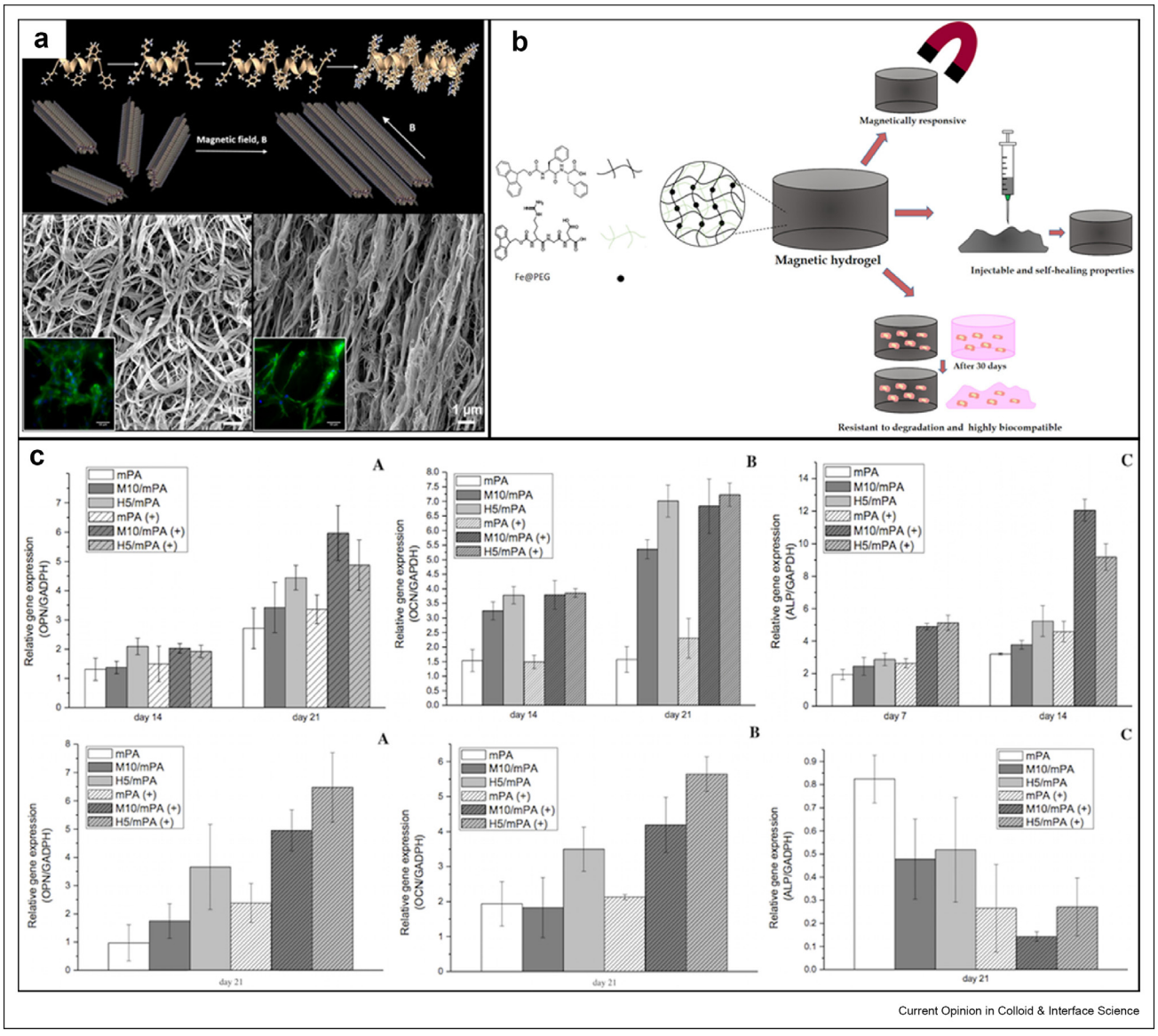
Magnetic supramolecular hydrogels in tissue engineering

Natural extracellular matrices have a well-defined ordered structure at the nanoscale that can modulate cellular behaviors, and that are essential for particular functions, including cell motility, mass transport, surface lubrication, and force generation. By contrast, supramolecular hydrogels are prepared by the self-assembly of molecular components that dissolve homogeneously in aqueous media, and thus the resulting disordered networks are usually isotropic. Magnetic fields, alone or in combination with magnetic particles, can be used to affect the self-assembly of gelators, imprinting a certain structural order at the nano and micro-scale that can be beneficial in tissue engineering applications of supramolecular hydrogels. In this sense, Radvar et al. [60] found that magnetically aligned nanofibrous supramolecular membranes used as scaffolds for culture of mesenchymal stem cells, demonstrated better attachment of cells and cell elongation in the direction of anisotropy, suggesting the potential of these anisotropic membranes for tissue engineering applications (Figure 3a). Most methods reported in the literature for the alignment of fibers in supramolecular hydrogels by magnetic fields are based on the application of strong fields in the absence of magnetic particles in the composition. For example, Wallace et al. [61] demonstrated that strong magnetic fields can be used to align the fibrillar structures present in aqueous solution of Nap-FF. The key for achieving this alignment is the formation of worm-like micelles at high pH by Nap-FF, which can be spontaneously aligned by the strong magnetic fields prior to gelation. Then, gelation was triggered, while the orientation of the structures was retained on gelation by the applied field. Furthermore, according to the similarity in the FTIR spectra for aligned and unaligned structures, the supramolecular packing was unaffected by the magnetic field. This approach does not seem to be restricted to Nap-FF, but to be valid for any LMWG that forms worm-like micelles. More recently, Radvar et al. [60] used strong magnetic fields for the alignment of nanofibers during the self-assembly of peptides with hyaluronic acid (HA) to generate anisotropic supramolecular membranes (Figure 3a). They tested HA of different molecular weights and different peptides containing a block of four F residues at the C-terminus and another block consisting of a positively charged domain of K residues, connected both blocks by a linker with a variable number of amino acids. The charged domain ensured electrostatic interaction with HA, whereas the F residues drove self-assembly and allowed magnetic alignment in the field direction due to their high diamagnetic anisotropy. Strong magnetic fields, between 1 T and 12 T were applied during membrane formation for up to 24 h. Results demonstrated that both exposure time and magnetic field strength affected the final structure, the better alignment obtained for the strongest field and longest time of exposure. CD analysis demonstrated that the magnetic field had an important effect on the secondary structure of peptides, especially at pH 11 (with respect to pH 7), where π-π stacking is stronger, suggesting the orientation of aromatic rings with the field-disturbed β-sheet configuration. The authors further demonstrated that similar membranes prepared with an amphiphile peptide not containing aromatic residues did not present nanofiber alignment, which corroborated the role of the high diamagnetic anisotropy of the F residues.

Much smaller magnetic fields suffice for inducing anisotropic microstructures when magnetic particles are included in the formulation, since, in this case, anisotropy is easily obtained because of magnetic field-induced particle self-assembly [32,62,23,63]. However, for these magnetic fields no alignment of the fibers constituting the 3D network is in general expected. In this sense, Contreras-Montoya et al. [32] did not find any significant changes in the secondary structure of supramolecular magnetic hydrogels consisting of chains of iron nanoparticles embedded in a fibrous network of Fmoc-FF peptide even though the gelation was carried out under a magnetic field of about 20 mT. The key seemed to be the absence of peptide fibrous orientation at this low magnetic field.

Magnetic fields in combination with magnetic particles can also be used to self-assemble building blocks towards the development of complex structures for tissue engineering applications [62–64]. For example, in the work by Takeuchi et al. [64], a method for the magnetic self-assembly of hydrogel-based toroidal microstructures into tubes of large shape was reported. Briefly, toroidal shaped hydrogel microstructures with ferrite particles on their surface were fabricated and magnetized afterwards. Then, the magnetized toroids were placed into a dish that was shaken. For optimal shaking speeds and duration, toroids self-assembled into tubes because of

Figure 3



(**a**) Sketch of the self-assembly model, SEM images and cell behavior for the hydrogels. (**b**) Sketch of the properties of short-peptide supramolecular magnetic hydrogels. (**c**) Gene expressions as a function of time for hydrogels under, respectively, static and moving magnetic fields. (**a**) Reprinted with permission from [36]. Copyright 2020 American Chemical Society. (**b**) and (**c**) were reproduced from [21,43] under a CC license.

magnetic attraction. The authors cultured cells encapsulated in the hydrogel structures resulting in 3D cell-aggregated structures. This tube-shaped structure is advantageous for cell culture, since the tubular hole can be used to exchange required nutrients and wastes produced during cell growth. This same idea of self-assembly by magnetic forces might be used to self-heal magnetic hydrogels after damage.

Another feature of magnetic hydrogels is that they can be manipulated and moved by magnetic forces, which may be an advantage for tissue engineering applications. For example, shear-thinning magnetic hydrogels might be implanted *in vivo* by injection, and dragged to fill a defect, or modified by magnetic forces afterwards [27,19]. Moreover, this strategy may be used for the delivery by a minimally invasive route of delicate cargoes embedded within hydrogels, in places of difficult access. In connection to this, Mañas-Torres et al. [27] developed magnetic supramolecular hydrogels consisting of MNP and Fmoc-FF and Fmoc-RGD short peptides, self-assembled by pH switch, that demonstrated magnetic responsiveness and self-healing after injection through a syringe. Self-healing in this work was a consequence of the reversibility of the supramolecular interactions between peptides, responsible of the self-assembly. The

authors demonstrated that these hydrogels could be used as a platform for the delivery of cells by injection, followed by dragging by a magnet (Figure 3b). Furthermore, these hydrogels demonstrated excellent biocompatibility, together with enhanced stability vs. degradation both *ex vivo* and *in vivo* [21]. In a more recent study, Tran et al. [65] demonstrated that for RADA-16I-based supramolecular hydrogels containing iron microparticles (FeμP), alignment of fibers under a magnetic field of 10 mT was feasible after injection. In that work, self-assembly of RADA-16I peptide was achieved by adding DMEM *in vitro* and by injection into physiological pH *in vivo*. The authors found that below a minimum threshold concentration of FeμP of 0.1 wt%, only alignment of FeμP into chains was observed, whereas for this concentration fiber alignment also took place. This fiber alignment was corroborated both *in vitro* and *in vivo*, and it was found that it favored axon orientation of neural cells in the direction of magnetic field, by contrast to random orientation in unaligned hydrogels, demonstrating the benefits of magnetic alignment in magnetic hydrogels for regenerative medicine applications.

Another advantage of the incorporation of magnetic particles in hydrogels intended for applications as scaffolds in tissue engineering is that they can be used to subject the growing cells to forces and stresses at the microscale. This is especially important for cells of the musculoskeletal systems, since these forces and stresses simulate the mechanical conditions at the microscopic level to which cells are subjected to in natural tissues, and can be considered as biomechanical cues for cell differentiation. For example, Huang and Chu [66] demonstrated that application of a magnetic field (either a static or moving field) to osteoblast cultures in polypeptide hydrogels containing MNP resulted in a positive enhancement of osteoblast differentiation (Figure 3c). These injectable magnetic hydrogels were prepared by sol-gel transition led by a temperature increase of suspensions of hydroxyapatite (HAP) and magnetite nanoparticles in thermo-responsive aqueous solutions of methoxy (polyethylene glycol)-polyalanine. The incorporation of the nanoparticles was found to decrease the gelation temperature, and results of analysis of secondary structure also demonstrated that the incorporation of HAP nanoparticles was disruptive and decreased the proportion of random coils and α-helix.

In another work [24], it was demonstrated that magnetic fields in combination with MNP could be used to trigger cellular response by releasing drugs from gel-phase vesicles. To be precise, magnetite nanoparticles functionalized with *N*-Biotinylated dopamine were self-assembled with dipalmitoyl phosphatidylcholine vesicles containing the desired drug, by the addition of avidin. The resulting magnetic nanoparticle-vesicle assemblies (MNPVs), together with cells, were immobilized in an ionically self-assembled calcium alginate hydrogel. Under the application of an alternating magnetic field, the heat generated by the MNPs was transferred to the vesicles, provoking the release of the encapsulated drug to the medium, resulting in responses from the cultured cells. For example, when ascorbic acid-2-phosphate was encapsulated in the vesicles and chondrocytes were cultured, strong enhancement of production of extracellular collagen was reported, with respect to control samples.

Self-assembly of magnetic supramolecular hydrogels for technological applications

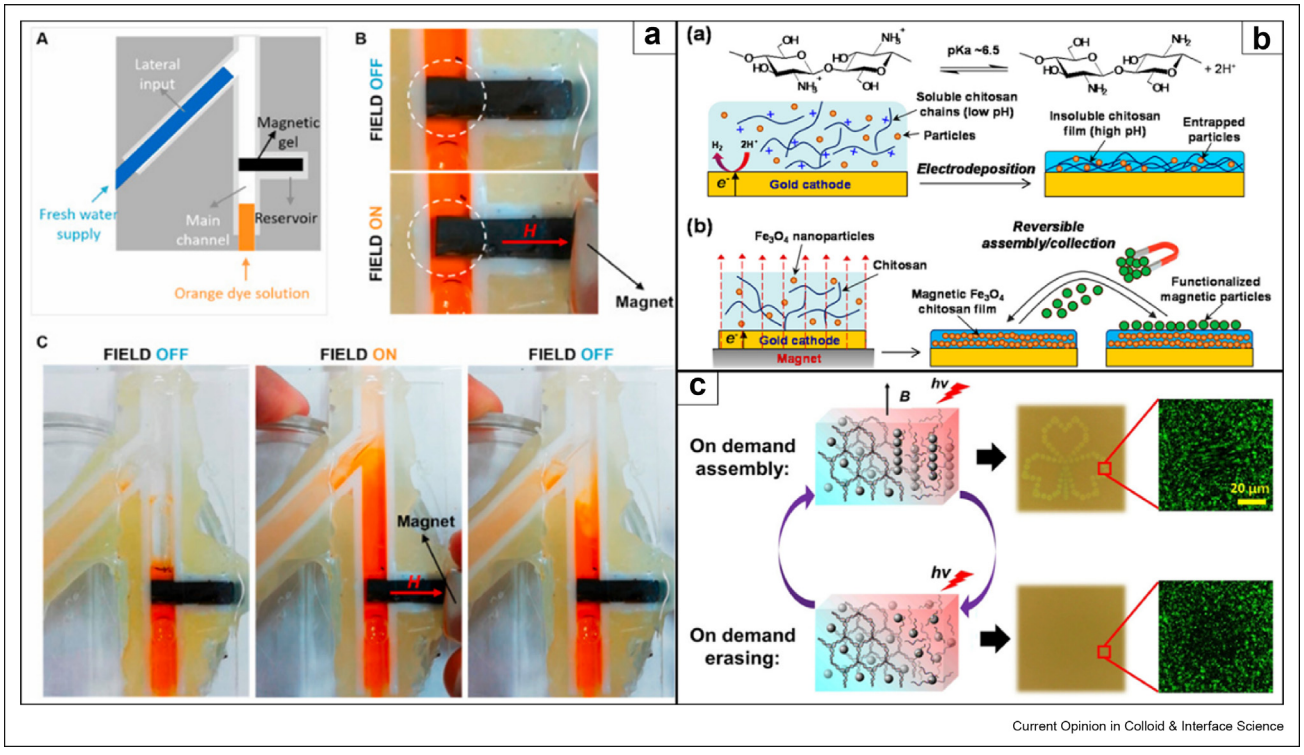
Soft materials able to modify their properties in response to magnetic stimuli are the base for applications in the field of magnetic soft robotics (sensors and actuators). Sensors are mainly based in changes of optical, mechanical, and electrical properties, whereas actuators rely on shape and size changes and locomotion under external stimuli. Connected to the latter, magnetic hydrogels commonly display rapid and reversible changes in mechanical properties under magnetic stimuli [20,40]. This physical phenomenon is known as the magnetorheological effect, and it has its origin in the magnetic attraction between particles magnetized by the applied magnetic field. An interesting work on supramolecular magnetic hydrogels that showed magneto- and photo-responsive mechanical properties was reported by Nowak and Ravoo [20]. They prepared magnetic hydrogels by the co-assembly of arylazopyrazole (AAP) modified pentapeptide gelator Nap-GFFYS, and β-cyclodextrin vesicles (CDVs) of 100 nm of diameter with superparamagnetic $CoFe_2O_4$ nanoparticles of 10 nm of diameter immobilized in the membranes of CDVs. Self-assembly of the LMWGs was achieved by lowering the pH (pH switch) by hydrolysis of glucono-δ-lactone (GdL), and additional non-covalent cross-linking of the self-assembled AAP-modified Nap-GFFYS gelators with the magnetic CDVs was also assumed for low concentration samples. CD spectra evidenced β-sheet secondary structure for both unmodified and modified Nap-GFFYS nanofibers. These hydrogels demonstrated reversible increases of the stiffness (storage modulus) of about 100% under application of a 0.78 T magnetic field because of the magnetic interaction between magnetic CDVs, and smaller reversible decrease of about 10% of this magnitude under UV irradiation. Furthermore, a hydrogel rod demonstrated bending actuation under a magnetic field [20]. Shape changes of magnetic hydrogels under a magnetic field can also be exploited for soft actuators [31,67]. For example, Vazquez-Perez et al. [67] reported high and reversible length changes during the process of magnetization of magnetic hydrogels consisting of iron microparticles embedded in self-assembled alginate networks swollen by water (Figure 4a). Gelation was triggered by ionic bonding between alginate chains mediated by

calcium ions. A proof-of-concept valve application based on the reversible length changes under a magnetic field was also constructed [67]. On another work, Ma et al. [31] reported magnetic DNA hydrogels that demonstrated remote shape changes, as well as displacement and even jumping against gravity in response to magnetic fields. Similarly, Conte et al. [33] found for magnetic hydrogels based on Fmoc-TF-NH_2 and DFF-NH_2 gelators, that magnetic particles and peptide fibers attached to them were pulled together when an external magnetic field was applied, giving rise to the folding of the entire hydrogel by up to 6-fold (Figure 1b).

Hydrogels based on graphene oxide are also of special interest due to their self-assembling capacity. For example, Peng et al. [35] managed to create self-assembling magnetic hydrogels as smart motors for the removal of toxic metals. For this purpose, they used graphene oxide (GO) as it has a wide range of functional groups such as epoxy, hydroxyl and carboxyl, providing strong hydrophilic properties. Then, they added aniline to a GO/$MnFe_2O_4$ solution, inducing the aggregation and gradual self-assembly of these materials into 3D millimetric hydrogels. The interesting adsorption capacity of GO sheets combined with magnetic Janus-like $MnFe_2O_4$ nanoparticles, led to magnetic motors with directed movement that can be controlled by external magnetic fields. This, in combination with their capacity of chemical self-propulsion via oxygen bubbles from Fenton-like reactions, allowed them to perform oriented movements in order to reach the target area to be decontaminated. Similarly, other authors used graphene oxide hydrogels in combination with magnetite (Fe_3O_4) nanoparticles to create smart materials for their use in catalysis, water treatment or enzyme immobilization [68,36]. For example, Fe_3O_4 and palladium (Pd) nanoparticles can be embedded into hydrogels previously formed by the self-assembly of reduced GO nanosheets with a 3D porous network, ideal for the diffusion of reactants in a catalytic reaction [68]. Then, the hydrogel was calcined and a magnetic aerogel with an interconnected porous structure was obtained, exposing the catalytic surface of the nanoparticles. This aerogel showed high catalytic performance when the reduction of 4-nitrophenol (4-NP) was evaluated, and the catalytic activity was mostly maintained after 4 cycles of reduction. Moreover, the presence of the magnetic particles made it possible to magnetically separate the aerogel from the reaction solution in order to be reused.

Magnetic fields can be used not only to interact with the previously formed magnetic hydrogels, but also can confer them interesting properties when applied during the gelation process, such as an organized structure with

Figure 4



(**a**) Magnetically-actuated valve based on hydrogel length changes. (**b**) Sketch of the formation and properties of the magnetic hydrogels with reversible assembly functions. (**c**) Mechanism of assembly of the magnetic particles into the reversible hydrogel and creation of color patterns. (**a**) Reproduced from [47] under a CC license. (**b**) Reprinted with permission from [39]. Copyright 2015 American Chemical Society. (**c**) Reprinted with permission from [51]. Copyright 2021 American Chemical Society.

specific magnetic properties, which can be of interest for technological applications. For example, Li et al. [23] created nanocomposite films combining chitosan and Fe_3O_4 with a patterned structure due to the application of a magnetic field during the hydrogel formation so that the magnetic particles self-assembled into hierarchical chains (Figure 4b). In this case, the magnetic particles conferred the hydrogel magnetic properties for their afterwards application in complex devices, the capacity to perform reversible assembly functions, and the possibility to be functionalized for further biosensing applications. For example, the authors demonstrated that cells can be captured via antibody functionalization of the magnetic particles, and then be collected from the hydrogels and analyzed, which makes these materials very interesting for pathogen detection. As the magnetic particles can be functionalized with a wide range of proteins and enzymes, along with the reversible collecting and assembling procedure from the hydrogel film, these composite hydrogels are very useful in a broad application area apart from biosensing.

In general, functioning of sensors relies in measurable changes of a physical or chemical property in the presence of the target substance. Among the different hydrogels, DNA hydrogels, which are usually prepared by the self-assembly of complementary single-stranded DNA molecules through base pairing (a process known as DNA hybridization), are of special interest for biosensors due to their programmable design and inherent biodegradability. Only a few supramolecular magnetic DNA hydrogels have been reported so far [31,50]. In the work by Song et al. [50] magnetic DNA hydrogels with encapsulated multienzymes were fabricated, and their biosensor ability for the detection of glucose was demonstrated, as commented before. Another strategy followed for the creation of sensing materials using DNA supramolecular hydrogels, is the building of reversible periodic structures by the magnetic nanoparticles embedded inside via external magnetic fields (Figure 4c) [28]. The formation of these structures into the hydrogel can display different colors due to Bragg diffraction depending on the periodicity of the magnetite particles structures. The hydrogels can disassemble under photothermal activity, giving the possibility to the particles to move to the target position while applying the magnetic field, and maintain afterwards their arrangement when the illumination stops and the hydrogels are cross-linked again. After that, the structure can be newly changed or totally removed by illumination. The coloration is achieved using a near-IR laser due to the strong absorbance of the magnetite nanoparticles.

Conclusions and outlook

This review summarizes the recent progress in the field of magnetic supramolecular hydrogels (vs. traditional chemical gels), with special focus on their self-assembly, as well as on their biomedical and technological applications. This area of research is relatively new and tries to combine the advantages of supramolecular gels, such as self-healing, reversibility, injectability and biodegradability, with the properties conferred by the incorporation of MNP such as magneto-responsiveness and hyperthermia, as well as the capacity to modify the microstructural and micromechanical properties of the composite hydrogel. In the last decade, the field of LMWG-based supramolecular gels has expanded considerably, offering the possibility of developing more complex structures and functions in which magnetic supramolecular gels are an exponent of sophistication by presenting the unique ability to remotely and externally modulate their mechanical properties with the intention of exerting additional control over cell growth, drug delivery, catalysts, actuators, biosensors, as well as in *in vivo* applications such as magnetic resonance imaging contrast agents and hyperthermia.

Nevertheless, there are concerns about the biocompatibility of MNP, in particular for long term applications, as well as their behavior inside the body, that is, their stability, biodistribution, excretion and toxicity. At this moment, SPION are the only MNP approved for human use as contrast agents and, although there are many bibliographic examples that show no toxicity of properly functionalized MNP, it is true that a long-term toxicological study is missing. In this sense, the immobilization of MNP into hydrogels can significantly improve the biocompatibility of these systems and thus, expand their fields of application. Additionally, the biocompatible scaffold provides a platform that can be used for biomedical and technological applications. Moreover, the combination of MNP and supramolecular hydrogels, allows the development of a new type of smart material, where drugs and other therapeutic molecules can be internalized, administered by injection, and their release profile on-demand controlled by external magnetic fields. The strengthening of the mechanical properties exerted by the MNP is also extremely useful for tissue engineering. Indeed, supramolecular hydrogels tend to be fragile and their applications as scaffolds for cell growth are rather limited. Mañas-Torres et al. [27] proved that the enhancement of the mechanical properties by the inclusion of MNP (an almost 7-fold increase of the values of the viscoelastic moduli) is crucial to maintain the integrity of the 3D matrix in cell culture experiments at longer periods. The inclusion of MNP in combination with the application of external magnetic fields can also modulate the microstructural order of the 3D matrix, giving rise to anisotropic materials difficult to obtain by other techniques. Anisotropic materials are also of great interest for cell growth since certain tissues such as skin and muscle show an anisotropic order. Besides these biomedical applications, the possibility of modulating the properties of the hydrogels by external magnetic

fields as well as the capacity to functionalize the MNP to collect or modify specific molecules have found applications in biosensing and catalysis.

Considering the synergy offered by the combination of MNPs and supramolecular hydrogels in terms of unique properties, we believe that novel magnetic supramolecular hydrogels with multifunctionality will be developed in the near future, pushing the field to the next level. A true advance in this field will be provided by the development of methodologies that allow a complete structural and functional control of the composite hydrogels. Additionally, it will be also important to gather more information of the behavior and fate of these composite hydrogels when implanted *in vivo*.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cocis.2022.101644.

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