Fabrication Methods of Sustainable Hydrogels

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List of Abbreviations

2D	Two dimensions
3D	Three dimensions/three dimensional
4D	Four dimensional
AA	Acrylic acid
AD	Adipocytes
ADSC	Adipose-derived stem cells
BMP-2	Bone morphogenetic proteins 2
CC	Cell coating
CLSM	Confocal laser scanning microscopy
DMEM	Dulbecco's modified eagle medium
ECM(s)	Extracellular matrices
EDC	Ethyl carbodiimide
EG	Ethylene glycol
EGDMA	Ethylene glycol dimethacrylate

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FBS	Fetal bovine serum
FN	Fibronectin
G	Gelatin
HEMA	Hydroxyethyl methacrylate
HUVECs	Human umbilical vein endothelial cells
IPN	Interpenetrating polymeric
iPS-CMs	Induced pluripotent stem cell-derived cardiomyocytes
LbL	Layer-by-layer
LCA	Life-cycle assessment
LECs	Lymph epithelial cells
MBSCs	Bone marrow stromal cells
MCS	Maleic chitosan derivatives
MMT	Montmorillonite
NHDFs	Normal human dermal fibroblasts
PAAm	Polyacrylamide
PBS	Phosphate buffer saline
PEG	Poly(ethylene glycol)
PEGDA	Poly(ethylene glycol) diacrylate
PLGA	Poly(lactic-co-glycolic acid)
PPGs	Polyacrylamide particle gels
PPO-PEO	Poly(propylene oxide)-poly(ethylene oxide)
PVA	Poly (vinyl) alcohol
PVP	Poly (vinyl pyrrolidone)
PVSA	Poly-vinylsulfonic acid
RGD	Arginine-glycine-aspartic acid
TPVA	Thiol-terminated poly (vinyl alcohol)
VAc	Vinyl acetate

1 Introduction

What is a hydrogel? Answering this seemingly simple question could appear easy but this is not the case. Using the SciFinder portal (https://scifinder.cas.org), the word “hydrogels” led to 114,105 references (70% published between 2007 and 2017) including 28 book chapters, 6761 reviews, 24,324 patents and 83,187 articles (Fig. 1). Except for book chapters, the number of research articles, reviews and patents per year has doubled in less than 10 years. Basically, hydrogels are three-dimensional, smart and/or hungry polymer networks extensively swollen with water. Their sizes are variable, and they are named recently micro- and nanohydrogels when their sizes are reduced to 1 μm and 1 nm respectively [1]. Depending upon the pore size between polymer networks, the structure of hydrogel can be classified as nonporous, microporous, or superporous [2]. These complex structures

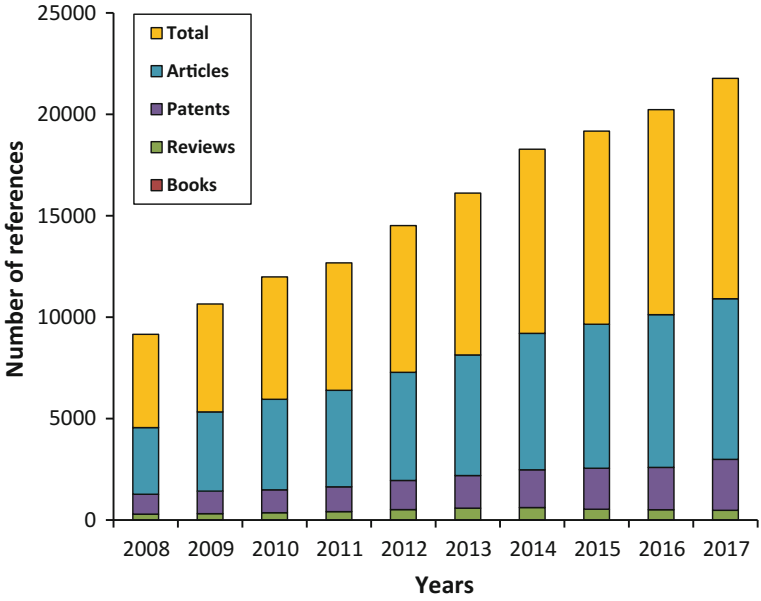


Fig. 1 Evolution of the scientific production relative to hydrogels between 2008 and 2017

are capable to absorb large quantities of water or other fluids such as biological liquids, but they do not dissolve in them. Owing to their varying compositions, hydrogels are classified into three categories for biomedical applications depending on their physical properties, i.e. liquid, semi-solid and solid [3]. They should be biocompatible, and non-toxic and can be biodegraded (or not) for specific applications. The most common hydrogels are cross-linked polymers generated by the polymerization of one or several monomers [4]. They can be also formed by the reticulation of synthetic or natural polymers [5]. Their hydrophilicity is mainly due to the presence of hydrophilic groups such as –OH, $–CONH_2$, –COOH, –CONH– or others [5]. Their ionic nature can be neutral, cationic or anionic, some of them having ampholytic behaviour. Hydrogels are sometimes named 'reversible' or 'physical' gels if molecular entanglements (ionic interactions, hydrophobic forces or hydrogen-bonding) play the main role in forming the network. It is sometimes possible to dissolve them by changing physicochemical environmental conditions, such as the ionic strength of the solution, light, magnetic field, pH, or temperature [6]. Hydrogels are non-reversible when a cross-linker leads to the formation of covalent bonds to build the network. All these families of hydrogels may have natural or synthetic origins. Novel hydrogels with specific properties made of natural and biodegradable polymers are in great demand. Nonetheless, during the 50 last years of scientific literature and patents speaking of hydrogels, the natural hydrogels have been gradually replaced by synthetic ones. Synthetic hydrogels are described in the literature as homopolymeric, copolymeric or multipolymeric

hydrogels. They have been found more versatile and diverse for biomedical applications owing to their tailorable designs or modifications. Hydrogels based on polyethylene glycol (PEG), poly (vinyl) alcohol (PVA), poly (vinyl pyrrolidone) (PVP) are examples of synthetic hydrogels. Natural hydrogels are produced using polymers (mainly polysaccharides and proteins) extracted from various biomass. Despite their "green" nature and biocompatibility, they have some disadvantages such as insufficient mechanical properties but also some variations depending on the production batch. The polysaccharides currently used in natural hydrogels are dextran, hyaluronic acid, alginate or chitosan [7–9] whereas the main protein employed is collagen [10].

The success of hydrogels in tissue engineering, agriculture, drug delivery, superabsorbent, wound dressing, sealing, coal dewatering, artificial snow, separation of biomolecules or cells, antiadhesive compound, biosensors, contact lenses and other is linked to their characteristics including gas (such as O_2) permeability, stability, biocompatibility, excellent mechanical properties, wettability and permeability to water, refractive index and light transmittance [3, 4].

This book chapter intends to clarify the classification of hydrogels, to describe the methodologies for making them and to synthesize all their applications in several scientific and industrial areas.

2 Classifying Hydrogel: What's the Bottom Line?

Fabrication methodology of sustainable firstly requires a strong and comprehensive understanding of hydrogel products involved in the preparation. Recently, Varaprasad et al. [11] published a decent mini review describing an updated hydrogels classification, regarding their cross-linking and physical states but also some associated developments in miscellaneous applications. Based on different aspects (Fig. 2), hydrogels can be classified in many ways, depending on (i) source, which is of main importance for a sustainable point of view, (ii) polymeric composition, (iii) physicochemical composition, (iv) type of cross-linkers used, (v) network electrical charge and finally (vi) physical appearance [4]. Today, life-cycle assessment (LCA) of hydrogels should be also considered as a seventh item. In an eco-designing point of view, the good knowledge of the environmental effect and generated hydrogels is of first importance. LCA should be considered here as a comprehensive methodology to estimate and evaluate the environmental impact of the whole fabrication methodology of hydrogels, but also allover its whole life cycle according to ISO 14044. This notion implicated not only one single parameter but a succession of analyses throughout the product lifecycle. Thus, the best typical crop of the environmental impact of a product must consider the environmental courses all over the whole product's life, including the emission to land, water and air as well as the energy and material balance of product resources [12–14]. A complete LCA from the extraction of polymers/materials following by their modification/transformation/designing/manufacturing into a "sustainable"

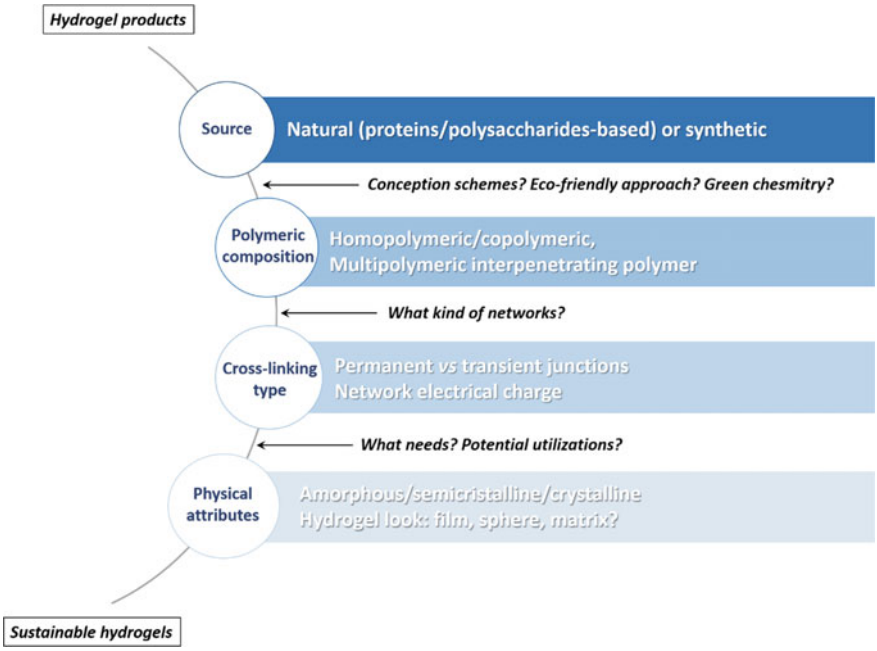


Fig. 2 The overall bottom line for classifying hydrogels

hydrogel, through the practical use of the product and finally the end of life circumstances, such as disposal or recycling, should be considered [15]. It was found that engineered bio-sourced materials should prospectively play an increasingly major role in our consumer society which is in perpetual search of sustainable and environmentally friendly materials. It was particularly reported that in comparison to petroleum-based materials, biopolymer materials could significantly reduce the energy/environmental balance impact. The use of biomass feedstocks and byproducts (polysaccharide-based composition for example) for making hydrogels is also not negligible and could contribute to trapping carbon thanks to this concept.

Hydrogels can be separated depending on their natural or synthetic origins. Thus, the hydrogel can contain natural polysaccharides and/or proteins such as chitosan, cellulose, alginate, starch, gelatin, or collagen. The list of synthetic polymers is longer, and the most common synthetic monomers used, especially in the pharmaceutical field, are probably PEG and its derivatives (PEG acrylate, methacrylate, diacrylate, dimethacrylate), ethylene glycol (EG), acrylic acid (AA) or hydroxyethyl methacrylate (HEMA). Table 1 gives an overview of these polymers commonly used for the preparation of hydrogels.

The type of polymer network generating during the fabrication method also greatly affects the classes of hydrogels [16]. From a single species of monomer, it is possible to obtain homopolymeric hydrogels which may have cross-linked skeletal structure, as reported by Takashi et al. [17]. The use of two or more different

Table 1 Some natural and synthetic monomers used for making hydrogels

Natural polymers	Number of publications[a]	Synthetic polymers	Number of publications
Chitosan/ chitin	218/82	Poly(ethylene glycol) (PEG)	370
Alginate	336	PEG-acrylate PEG methacrylate PEG diacrylate PEG dimethacrylate	27 38 118 33
Dextran	55	Methacrylic acid	72
Cellulose	105	Ethylene glycol (EG)	319
Gelatin	262	Hydroxyethyl methacrylate (HEMA) and derivatives	59
Fibrin	72	Ethylene glycol dimethacrylate (EGDMA)	29
Collagen	252	Vinyl acetate (VAc)	2
		Polyvinyl alcohol (PVA)	101
		Acrylic acid (AA)	141

[a]Based on Scopus, with the keywords combination "polymer name AND hydrogel AND fabrication"

monomer species can be used to prepare copolymeric hydrogels, which needs at least a hydrophilic component and are characterized by a specific configuration in the chain of the polymer network [18]. Note that this kind of hydrogel can include a natural polymer in its structure [19]. The last type according to polymeric composition classification, i.e. the so-called multipolymer interpenetrating polymeric (IPN) hydrogels, is made of two independent natural and/or cross-linked synthetic polymers. The semi-ipn hydrogel is also reported in the literature and is composed of a cross-linked and a non-cross-linked polymer [20]. The kind of cross-linked interactions is also considered since it is possible to prepare hydrogels with chemically cross-linked networks (e.g. grafting, radical polymerization, condensation/enzymatic reaction, high-energy radiation) but also physically cross-linked networks. The cohesion of the last one is in general based on ionic and/or hydrophobic interactions, hydrogens bonds, polymer chain entanglements, stereo-complex formation, thermo-reversible gels, maturation due to heat-inducing aggregation, freeze-thawing [4, 11, 21]. The physical and chemical structure plus the physical appearance of hydrogels give birth to supplementary classes, e.g. non-crystalline, semi-crystalline, crystalline as well as gels (macro/micro/nano), matrix, film or microsphere. Generally speaking, some authors also report three main classes based on physical properties, i.e. solid, bio-adhesive and liquid-based hydrogels [11]. The preparation process is mainly involved for obtaining these looks (see Sect. 3). Finally, as reported by Ahmed [4], four groups describe the importance of electrical charge into hydrogel network on the cross-linked chains, i.e. neutral, ionic, amphoteric electrolyte and zwitterionic.

3 Methodology for Making Hydrogels and Sustainable Hydrogels

3.1 Goals and Technical Features

As described above, talking about hydrogels involves working on highly hydrophilic polymer networks presenting high swollen properties with water and aqueous media. Lot of works in the literature described hydrogels as a hydrocolloid gels material in which one, the dispersion medium is water [4, 22]. One of the most important applications of hydrogels largely described during the last decade is probably their uses as polymeric matrices for: (i) controlled releases of pharmaceutics drugs and and (ii) living cells entrapment/encapsulation [23–25]. Therefore, from the past 30 years, hydrogels continue to be a technology booming thank to their very high flexibility degree closely like human tissues [4, 26, 27]. A lot of studies was published for the optimization of hydrogels synthesis aiming to increase the technical features and improve their efficiency in pharmaceutical and biomedical applications [3, 4, 28]. In fact, the perpetual search for new biomaterials (e.g. artificial organs or tissues, filling materials, pharmaceutical release, diagnostic system) such as hydrogel is a fundamental notion in the biomedical sector. This requires a multidisciplinary approach involving physicians, biologists, chemists, and physicochemical. Hydrogels thus constitute a group of polymeric biomaterials having a hydrophilic structure allowing them to retain large quantities of water per area unit in a complex three-dimensional network. Moreover, thanks to the cross-links between the chains of the network, these biomaterials are highly resistant to dissolution in aqueous media. Consequently, as related by lot of authors [22, 23, 29, 30] we can easily list different functional features to characterize a most favorable hydrogel material for industrial applications such as: (i) highest biocompatibility, (ii) lowest solubility, (iii) highest swelling properties in water and in saline media, (iv) highest re-wetting ability depending on the desired applications, (v) highest biodegradability, (vi) highest stability and robustness in swelling surrounding, (vii) highest durability during storage before use, (viii) lowest releaser of toxic compound, (ix) odorless and/or colorlessness, (x) highest temperature, pH and photostability before and after swelling formation and, (xi) highest porosity to allow the fluid circulation and the best swelling properties. In general, it is well established that according to the use of the hydrogels, the main technical features to be developed must be optimized to consider a genius balance between the properties of the biomaterials and the targeted applications [3, 30]. Moreover, as very well related by Ahmed [4], it was clearly established that according to the nature, the intrinsic properties, the distribution and the density of compounds used (e.g. natural or synthetic polymers, cross-linkers, adhesives, adjuvants, extracellular matrices), hydrogel macrostructures could include diverse amount of water in swelling state in the application medium leading to higher water mass fraction in scaffold than polymers mass fraction itself. Therefore, if we focus particularly on the case of entrapment living cell application, another innovative technology is the cell coating

(CC). Generally, classic in vitro cultures in two dimensions (2D) can only present monolayer structures even after reaching cells confluency in the culture dish. One of the explanations might be the lack of extracellular matrices (ECMs) expressed by cells when they are maintained in 2D culture, which is necessary to switch into three-dimensional (3D) structure tissues. To overcome this issue, artificially addition of ECM surrounding the cells can be performed. This is called CC, which means nanometer- or micrometre-sized polymer thin films around cells, to induce their biological activities. This coating is performed using protein or polymer and can control for instance cell adhesion [31], growth direction [32, 33], or even killing specific bacteria [34]. Different coating methods exist, one of them is called "Layer-by-Layer" (LbL) formerly developed by Decher in 1981 to coat polymer and proteins onto substrate surfaces by dipping or spraying [35, 36]. This approach has been more and more used for cell surface modification, due to its easy preparation and tunable composition on cell surfaces under physiological conditions. The aim is to use specific ECM as coating components, known for their interactions with integrin receptor on the cell membranes. Many different types of ECM are found in our body, the most represented being collagen, laminin, hyaluronic acid, fibronectin or elastin. By selecting appropriate natural ECM components cytotoxicity is avoided while inducing specific cell-adhesive properties on molecules like RGD (arginine-glycine-aspartic acid) [37]. Among the cell membrane proteins, integrin receptors are important, determining the specificity for extracellular ligands as well as inducing intracellular signaling processes [38, 39]. Specifically, the $\alpha 5\beta 1$ integrin receptors can recognize the ECM component fibronectin (FN) since it contains the RGD sequence [40]. Gelatin (G) is a mixture of peptides and proteins produced from partial hydrolysis of collagen extracted from the skin, bones, and connective tissues. FN and G can interact with each other due to the collagen-binding domain found in FN, leading to nanometer-sized cell-adhesive surface films on cell surfaces, like the natural ECMs for multilayered structures without any cytotoxicity.

3.2 Technologies Developed for Their Preparation

A lot of strategies has been described in the literature to synthesize diverse forms of hydrogels. As recently mentioned in a very interesting review [30], hydrogels can be prepared by using several methodologies such as (i) polymerization grafting; (ii) chemical or physical cross-linking and (iii) radical cross-linking (Fig. 3). Conventionally, polymerization and radical processes are well defined as a good technology to generate varied hydrogels with controlled size, composition, particles distribution and morphologies [41–43]. Generally, the chemical method is the most common process related in literature for the preparation of hydrogel biomaterials with very good mechanical strength [23]. Nevertheless, the main drawback of chemical cross-linking is the use of toxic cross-linker such as for example

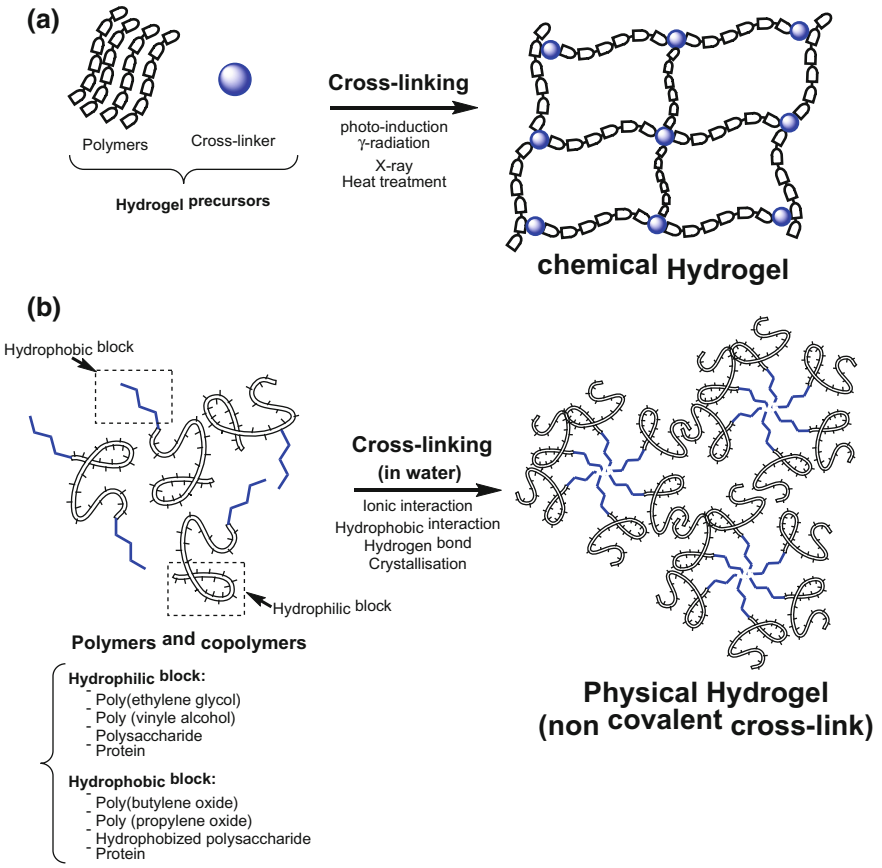


Fig. 3 The mains strategies to prepare hydrogels. **a** Chemical cross-linked polymers, **b** physically cross-linked polymers

glutaraldehyde and epichlorohydrin which must be removed for industrial and/or human applications. Consequently, a healthier alternative is the physical cross-link method [4, 22].

In a classic way, for the production of hydrogels (from macro- to nanogel 3D-networks) lot of cross-linking reactions have been performed (Table 2) such as: (1) the photo-induction reaction, (2) the Schiff-base reaction, (3) the thiol/disulfide reaction, (4) the carboxyl/amine reaction, (5) the amide/amine reaction and, (6) the click chemistry reaction [4, 23]. Furthermore, to perform the best hydrogel synthesis with controlled cross-link density and molecular sizes, studies traditionally recommend multi-steps procedure from polymerization to cross-link multifunctional mono/polymers having very reactive groups/functions [3, 4, 23]. As clearly mentioned by Mahinroosta et al. [30], the most important challenge for the preparation of hydrogels is the crucial control of the particle size distribution

Table 2 Examples of cross-linking reaction performed to prepare hydrogels

Methods	Mechanisms/cross-linker	Polymers/blocks	References
Chemical cross-linking	Gamma radiation	Cellulose, tara gum, acrylic acid	Alla et al. [81], Amin et al. [82]
	Aldehyde-amine reaction/ glutaraldehyde	Chitosan, polyvinyl alcohol	Zu et al. [83]
	Addition reaction/ 1,6-hexanedibromide	Scleroglucan	Coviello et al. [84]
	Condensation reaction/*N*,*N*-(3-dimethylaminopropyl)-*N*-ethyl carbodiimide (EDC)	Gelatin	Kuijpers et al. [85]
	Photo-polymerization	Acrylated lactic acid, poly (ethylene glycol)	Hubbell [86]
Physical cross-linking	Photo-clickable polymerization	Maleilated chitosan, poly (vinyl alcohol)	Zhou et al. [52]
	Amphiphilic graft	Polystyrene, poly (vinylpyridine)	Forster and Antonietti [87]
	Hydrophobic modification; self-aggregation	Cholesteryl, modified pullulan	Taniguchi et al. [88]
	Ionic interaction/calcium ions (Ca^{2+})	Alginate	Gacesa [89]
	Melt polycondensation	Poly(butylene terephthalate); Poly (ethylene glycol)	Bezemer et al. [90]
Enzymatic cross-linking	Transglutaminase reaction	Lysine-containing protein, poly-(ethylene glycol) glutaminamide	Sperinde and Griffith [44]
	Horseradish peroxidase reaction	Silk fibroin proteins, hyaluronic acid	Raia et al. [46]
	Alcalase reaction	Sucrose, acrylate, metacrylate	Chen et al. [45]
	Transglutaminase reaction	Hyaluronan	Broguiere et al. [54]
	Transglutaminase reaction	Gelatin	Yang et al. [91]

modulated by synthesis processes such as the regulation of monomer/polymer/cross-linker ratio, the perfect adjustment of experimental conditions (e.g. pH, ionic strength, temperature). To accomplish this aim, other cross-linking alternative methods using enzymes were proposed to generate specific hydrogels [23]. As for example, Sperinde and Griffith [44] synthesized original hydrogels with cross-linking between a lysine-containing protein and a functionalized PEG by using transglutaminase (a human tissue enzyme). In their study, authors showed the catalyzed reaction between the amine group of lysine and the γ-carboxamide group

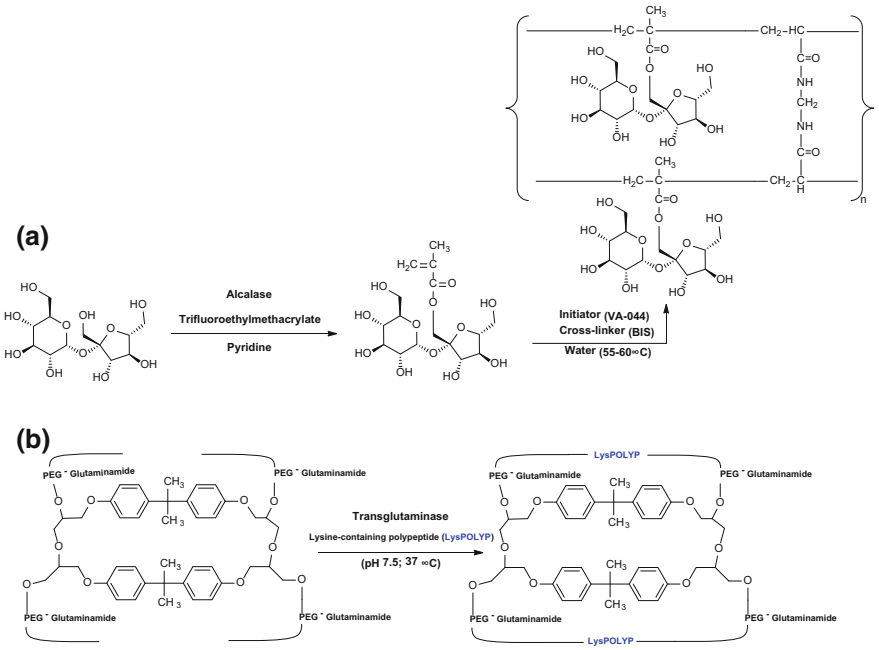


Fig. 4 Two mains examples of enzymatic cross-linking for the preparation of hydrogels. **a** Chemoenzymatic synthesis of poly-sucrose-methacrylate)-hydrogel (adapted from Chen et al. [45], **b** enzymatic cross-linking of glutaminamide polyethylene glycol (PEG) with lysine-containing polypeptide using transglutaminase

of PEG resulting in an attractive biomaterial allowing highly hydrated 3D-networks for living cells. In another enzymatic strategy, Chen et al. [45] developed chemo-enzymatic and enzymatic approaches to prepare a sugar-based hydrogel such as poly-sugar acrylate/methacrylate with highly water absorbents and drug delivery systems properties. As a final point, not to mention that recently, an enzymatic crosslinked silk fibroin proteins-hyaluronic acid hydrogel was produced by using horseradish peroxidase resulting in a highly elastic hydrogel with the application as scaffolds in tissue engineering [46]. The main enzymatic cross-linking way to prepare hydrogels are presented in Fig. 4.

Concerning the LbL coating (see Sect. 3.1), this "cell accumulation technique" technology provide around 6 nm thick FN-G films around cell surface, fabricated by FN and G coatings alternatively for 9 steps. Till now, over 100 μm thick 3D-tissue models with capillary networks [47, 48] were successfully constructed for further advanced studies as drug delivery systems, cancer cell invasion mechanism observation, or even manufacturing a biosensor chip [49]. Some tissues, for example, cartilage tissues [50], require a higher amount of ECMs, cell-cell distance in the tissues being in micrometre-sized level, and LbL FN-G coating methodology providing only nanometer-sized level. Another novel approach called "collagen

coating method" and "multiple coating methods" was thus developed to construct 3D-tissue models with lower cell density and more ECM content using micro-coating technologies [51]. For this method, collagen type I, the most widely used material in biomedical and tissue engineering, was directly used. The method lies in the specific recognition abilities between another integrin receptor, α2β1, and the collagen I fibers.

3.3 Preparation and Optimization: Few Examples

In view of the above concerning the technologies used (chemical, physical and enzymatic cross-linking) to prepare hydrogels, a lot of optimization processes have been recently developed in order to synthesize improving hydrogel biomaterials with higher application performances. As for example, in their study, Zhou et al. [52] produce a very interesting maleilated chitosan/thiol-terminated PVA hydrogel by using photo-clickable thiol-ene polymerization process with and thiol-terminated poly (vinyl alcohol) (TPVA) and maleic chitosan derivatives (MCS) activated under UV light source (60 mW/cm^2) by a photo-initiator such as the 2-hydroxy-1-[4-(hydroxyethoxy) phenyl]-2-methyl-1-propanone (Darocur 2959). In this case, the author has clearly shown the potential of this new photocrosslinked MCS/TPVA hydrogels as tissue engineering scaffolds biomaterial due to the efficient L929 cells attachment and proliferation.

Moreover, we can mention the work of Lu et al. [53] on the specific preparation of a new tissue adhesive phenolic glycol chitosan hydrogel using an optimized photo-cross-linkage process activated by blue-light illumination. In this study, author particularly showed that this biomaterial possesses hemostatic properties and very good tissue adhesiveness. Moreover, the encapsulation of antibiotic such as gentamycin into these hydrogels gave very advantageous antibacterial ability.

Recently, Broguiere et al. [54], proposed a new hyaluronan hydrogel synthesized by an optimized enzymatic cross-linking strategy using a transglutaminase activity from the activated blood coagulation factor XIII. Authors related that this hydrogel possesses higher significant ability for 3D neuronal network tissue engineering (strong synaptic connection, dendritic and axonal specification, faster neurite outgrowth) than classical hyaluronan gels. Last technological advances in the hydrogel biomaterial fields were performed lately (Fig. 5). First, we can cite Yan et al. [55] who developed a multiscale modeling approach to synthesize an extracellular matrix mimetic hydrogel with sequestered recombinant human bone morphogenetic protein-2 (rhBMP-2). This novel synthetic bone scaffold prepared by an optimized carbohydrazide/aldehyde cross-linking strategy was efficiently validated as by in vivo assay with rat ectopic model. Secondly, Kim et al. [56] designed a very smart heparin mimetic hydrogel to improve and stabilize bone morphogenetic proteins 2 (BMP-2) properties which are well known as one of the most important bone formation stimulators. In this study, authors prepared a hydrogel biomaterial surface model with an efficient photo-crosslink process using heparin and

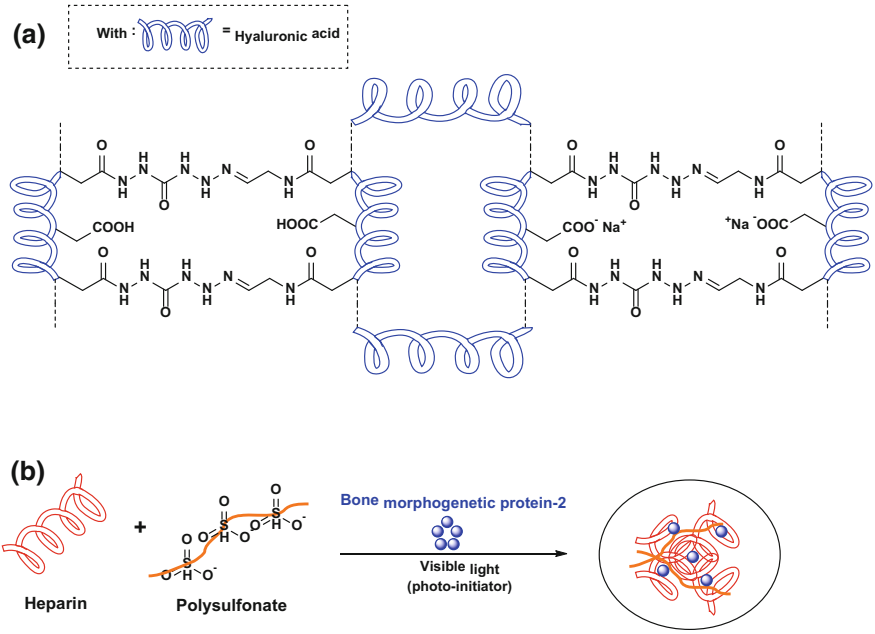


Fig. 5 Last technological advances in the hydrogel biomaterial fields. **a** An extracellular matrix mimetic hydrogel with cross-linked hyaluronic acid (adapted from Yan et al. [55]), **b** a new hydrogel biomaterial surface model with an efficient photo-crosslinking process using heparin and polysulfonate derivatives to encapsulate bone morphogenetic protein-2 (adapted from Kim et al. [56])

polysulfonate derivatives such as poly-4-styrenesulfonic acid (PSS) and poly-vinylsulfonic acid (PVSA). These sulfonated hydrogels were successful used to bind/encapsulate BMP-2 to increase osteogenesis and osteoinductive properties of bone marrow stromal cells (MBSCs) for bone tissue engineering.

Finally, other optimizations were done in the case of CC methodology, in order to evaluate coating effect on the construction of 3D-tissue models, cells without coating, cells coated with FN-G nanofilms or cells coated with collagen microfilms were seeded. Cells coated with collagen microfilms resulted at least 2-fold higher tissue than nano-coating (Fig. 6), with about 1/3 the cell number sufficient to fabricate equal-thick 3D-tissues. Collagen micro-coated cells led to tissues thickness up to 1871 μm. Also, cell-cell distances in these 3D-tissues were calculated as 15.6 ± 4.0 and 8.8 ± 3.1 μm, respectively. In comparison, cells without any coating resulted in compact distribution in some area and the very near distance between cells, about 3 times smaller than a cell with collagen micro-coating (data not shown). The difference in cell number also showed that the thickness of all samples increased according to the seeded cell number. The next step was the construction of functional 3D-tissue models. The development of 3D-vascularized thick tissues possessing high-density blood capillary networks is still an important

issue for tissue engineering. To get a vascularized model, a sandwich culture with one layer of Human Umbilical Vein Endothelial Cells (HUVECs) seeded between 4 or 10-layers of FN-G nanofilm coated Normal Human Dermal Fibroblasts (NHDFs) was used. After 1 week, a highly developed homogenous capillary network with the tubular morphology of HUVECs was observed (Fig. 6B1, B2). With micrometre-sized collagen fiber-coated cells, vascularized network structures were also observed, suggesting that collagen coating method can be used to construct vascularized thick 3D-tissues (Fig. 6A1, A2). Other functional tissue models with FN-G nanofilm coated cells, as induced pluripotent stem cell-derived cardiomyocytes (iPS-CMs) or lymph epithelial cells (LECs), were also successfully constructed. Strong beating phenomenon was assessed during incubation [57]. When using collagen microfilm coating method, the constructed 3D tissues showed stable and strong beating (80 times/min) and high cell viability (>90%) after 4 days of incubation in 800 μm thick 3D tissues. Immunostaining assays such like actinin antibody, troponin T antibody, connexin antibody, and Azan stains were also performed to confirm the good functionality of cardiac myoblasts in the 3D iPS-CM tissues [24]. The collagen microfilm coating method can thus be applied to various types of cells and different purposes.

4 Innovative Sustainable Hydrogels: What's New?

4.1 Utilization of Current and Classical Hydrogel Products

Also known as smart and hungry three-dimensional networks, hydrogels are still subject of numerous papers and patents because of their high-tech potential for applications in a large range of fields, from the biomedical, biotechnology, agriculture to the pharmaceutical, microelectronics industry, oil recovery or cosmetic [30, 58]. Today, hydrogels must respond to physicochemical parameters (electric/magnetic field, solvent, pH, ionic strength, temperature) in their surroundings, change their physiochemical properties and be able to return to their initial states. Thus, the use of hydrogel products is obviously reliant on their technical features. Overall, the following items correctly characterize the functional properties that hydrogels should achieve [4], i.e. (i) the lowest soluble content and residual monomer, (ii) the lowest price, (iii) most eco-friendly approach (LCA concept), (iv) the highest stability and durability in the swelling environment, (v) the highest behavior against storage, (vi) the best potential for biodegradation without formation of toxic species, (vii) a light-stability without any color, odor and toxicity, (viii) a re-wetting capacity, that is, the ability to release or maintain solution trapped in the hydrogel (high flexibility), (ix) the highest absorbency under load, (x) the highest absorption capacity but also the possibility to correctly control a desired rate of absorption. Different items and levels in these features must be considered for making an "ideal" hydrogel. Nevertheless, authors recognize that no hydrogel can

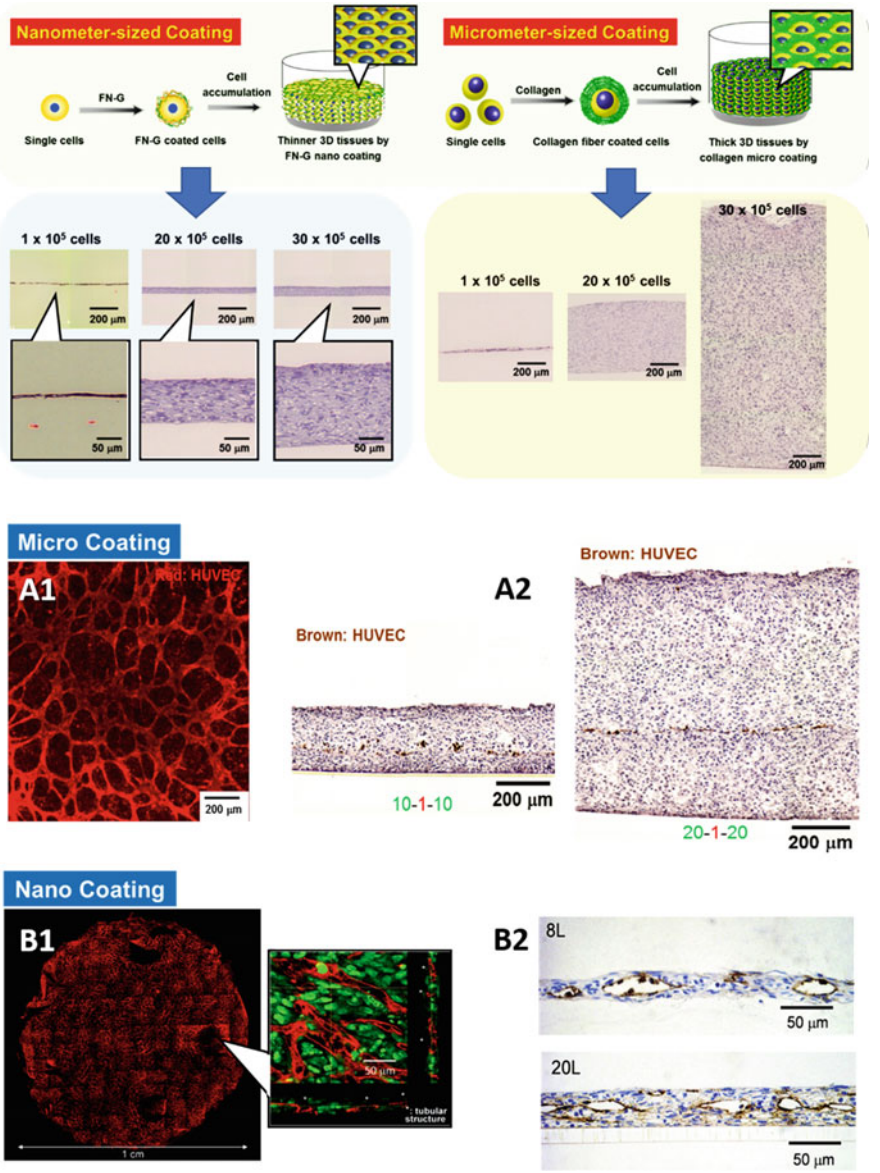


Fig. 6 Schematic illustration of fabrication of ECM layers on cell surfaces by (top left) nanometer-sized FN/G films and (top right) micrometre-sized collagen nanofiber matrices for construction of 3D-tissue models with higher and lower cell densities. Images of confocal laser scanning microscopy (CLSM) of vascularized 3D-tissue models constructed by **A1** nano- and **A2** micro-coatings by sandwich culture. Immunohistological staining images using anti-CD31 antibody of the 3D-tissue models by **B1** nano- and **B2** micro coating methods, adapted from Liu et al. [80]

simultaneously (and at maximum level) fulfil to each item. Thus, the applicative goals of hydrogels strongly impact the way for their fabrication, leading sometimes to porous hydrogel/aerogel (delivery drug system) [59] or superabsorbent capacity for (blood, hygienic) compress use [60] for example. Table 3 gives an overview of applications and performance of hydrogels in various fields before 2015.

4.2 An Innovative Strategy for Making Hydrogel Products

Since 2015, recent developments have been made in miscellaneous application fields. These works actually address few classes of hydrogels even if we can consider the growing interest for natural and sustainable hydrogels, i.e. (i) natural-based hydrogels, (ii) synthetic-based hydrogels, (iii) superabsorbent hybrid hydrogels or (iv) conducting polymer hydrogels. The properties of these innovative hydrogels will depend on several parameters such as concentration, type, and a number of ionizable groups, medium (and associated counter ion), hydrophilic/hydrophobic balance, charge, etc. As reported by Mahinroosta et al. [30], new intelligent hydrogels (Fig. 7) should be (i) sensitive to a wide range of external stimuli, such as temperature [61], enzymes [62], light [63] or pH (Aycan and Alemdar 2018), (ii) able to change their volumetric shape (expansion/contraction), (iii) swell and deswell (swelling ratio) biological fluids in particular for drug delivery applications and/or medical devices, etc. Recent developments especially involve the use of 3D printing for the fabrication of intelligent scaffolds. Tan et al. [64] published a cryogenic 3D printing method using the liquid to a solid phase change of a composite hydrogel. They successfully produced specific geometrical structures with compressive stiffness of O(1) kPa (0.49 ± 0.04 kPa stress at 30% compressive strain). Collagen type I, gelatin and other molecules were used to coat the 3D printed material before testing the systems on human dermal fibroblasts and other biomedical contexts, *e.g.* surgical training and tissue engineering. Besides, cross-linkable multi-stimuli responsive hydrogels were also prepared by direct-write 3D printing [65]. The behaviors of the new hydrogels were particularly interesting since they responded to shear-thinning, UV light but also temperature. This robust scaffold were made of poly(allyl glycidyl ether)-stat-poly(alkyl glycidyl ether)-block-poly(ethylene glycol)-block-poly(allyl glycidyl ether)-stat-poly(alkyl glycidyl ether) and synthesized by polymerization of glycidyl ethers. Bioelectronics platforms also gain attention and their fabrication can be performed using simple, flexible route by 3D bioprinting [66]. The authors confirmed the biocompatibility of the system against C2C12 murine myoblasts cell line. 3D printed hydrogels are in general programmable and responsive to environmental and fields signals, repeatable and stable over cycle/time, as reported by Lv et al. [67] for poly(ethylene glycol) diacrylate hydrogel microstructures which have excellent humidity responsiveness. New startups also try to take control of the cell microenvironment, e.g. Alvéole (http://alveolab.com, France) which develops innovative photopatterning solution (PRIMO) for 3D scaffold designing. This tool, using pseudo

Table 3 Overview of some hydrogel applications (before 2015)

Applications	Type of hydrogel	Properties/uses	References
Biomedical Biotechnology Pharmaceutical	Dextrin-based hydrogel/nanogel Dextrin-based hydrogel/urinary bladder matrix	Cell encapsulation and injectable nano/hydrogel	Silva et al. [92]
	Ionically cross-linkable (alginate) hyaluronate-based hydrogels	Drug (primary chondrocytes) delivery system for in vivo cartilage regeneration	Park et al. [93]
	Polyvinyl alcohol hydrogel/dextran copolymerization	Vascular grafting, high bio and hemocompatibility	Alexandre et al. [94]
	DNA hydrogel, DNA-capped gold nanoparticles	Enzymatic tool kit, adapter for protein detection, thermostable, plasmonics	Yang et al. [95]
	Fe3O4 nanoparticle/hydrogel magnetic nanocomposite	Excellent catalytic activity, sensitive toward H_2O_2 detection, environmental chelation	Gao et al. [96]
	Collagen/b-sodium glycerophosphate-carbodiimide hydrogel	Chitosan human-like assemblage, soft tissue defect filling, delivery system properties	Li et al. [97]
	TiO2/PEGDA hybrid hydrogel	Photodynamic therapy on tumour cells	Zhang et al. [98]
	Chitosan highly hydrated collagen hydrogel	Scaffold mimicking native extracellular matrix	Chicatun et al. [99]
	PVA/chitosan hydrogel	Swelling activity and antimicrobial potential, drug (sparfloxacin) delivery system	Abdel-Mohsen et al. [100]
	Poly(lactic acid)-poly(ethylene oxide) block copolymers	Nanoclusters as biosensors, enhance elastic modulus of the hydrogel, tissue engineering scaffold	Saffer et al. [101]
	PVA hydrogel	Arterial biomodelling	Kosukegawa et al. [102]
	Poly(*N*-isopropylacrylamide)/iron oxide magnetic hydrogel nanocomposites	Drug delivery system, hyperthermia for cancer treatment	Meenach et al. [103]
	Carboxy-methylated cellulose/chitosan hydrogel (irradiation)	Adsorption of heavy metal ions, water treatment	Zhao and Mitomo [104]
	Poly(acrylamide-co-acrylic acid)/chitosan nanostructured hydrogel	Drug (ascorbic acid) delivery system	Becerra-Bracamontes et al. [105]

(continued)

Table 3 (continued)

Applications	Type of hydrogel	Properties/uses	References
	Poly(ethylene glycol)/poly(e{open}-caprolactone)-based hydrogel	Cell delivery application, scaffold for cartilage formation (tissue collagen type II, aggrecan, SOX9, COMP gene expression)	Park et al. [106]
	PEG-PLGA graft copolymeric hydrogel	Molecular recognition for cancer treatment/imaging	Jeong and Gutowska [107]
	Methylcellulose-10%PEG Petrolatum-10%isopropyl myristate	Skin irritation (atopic eczema), a delivery system for allergens	Darsow et al. [108]
	PPO-PEO	Wound dressing and implant materials. Fill the spaces in a wound, isolate the area from bacterial infection	Corkhill and Hamilton [109]
Food packaging	Poly(*N*-isopropylacrylamide) nanohydrogel	Sensitive food packaging, heat capacity, delivery system, usable in w/o system	Fuciños et al. [110]
	Agar/κ-carrageenan/konjac glucomannan	Water and mechanical barrier properties, biohydrogel, antifogging, respiring hydrogel, antimicrobial property	Rhim and Wang [111]
	Poly(*N*-isopropylacrylamide) nanohydrogel Poly(*N*-isopropylacrylamide)(80%)/acrylic acid(20%)	Delivery system (pimaricin), antifungal, resistant to acidic conditions, thermal resistance	Fuciños et al. [112]
	Polyvinylpyrrolidone/ carboxymethylcellulose hydrogel	Biodegradable, eco-friendly material	Roy et al. [113]
	Carboxymethylcellulose/methacrylate hydrogel	Delivery system (by enzymes degradation), tool for detecting bacteria and fungi	Schneider et al. [114]
	Agar/silver nanoparticles hydrogel	Controlling microbial proliferation	Incoronato et al. [115]
	Collagen-based/dialdehyde starch hydrogel	Thermo-(ir)reversible gel, biodegradable, from waste proteins	Langmaier et al. [116]
Cosmetic	Carboxymethylcellulose hydrogel	Injectable, soft tissue filler, tunable hydrogel	Varma et al. [117]
	Poly(vinyl alcohol)/hyaluronic acid blends	Gelation time performance, high mechanical properties, blend hydrogel	Kodavaty and Deshpande [118]

(continued)

Table 3 (continued)

Applications	Type of hydrogel	Properties/uses	References
	Nanostructured lipid carriers-based hydrogel	Skin hydration, entrapment of oil (argan), easy formulated	Tichota et al. [119]
	Polyacrylamide-based hydrogel	Lip enhancement, widespread facial infections, potentially risky for health	Wang et al. [120, 121]
	Calcium hydroxylapatite-based hydrogel	Injectable, long-lasting un-permanent filler, highly biocompatible, dermal filler, potential body reactions (risk)	Pavicic [122]
	Palmitoyl glycol chitosan hydrogel	The delivery system (magnesium ascorbyl phosphate), UV protection, an inhibitor of tyrosinase	Wang et al. [120, 121]
	P(MAA-co-EGMA) hydrogel microparticles	Smart carrier, high skin permeability, pH-sensitive release behaviour	Lee and Kim [123]
	Xanthan/lignin hydrogel-epichlorohydrine	Thermal stability, hydrophobicity, decent biocompatibility	Raschip et al. [124]
	Xyloglucan-chitosan complex hydrogel	Non-toxic, antimicrobial and texture properties, thermal stability	Simi and Abraham [125]
Agriculture	Guar gum-g-polyacrylate-based hydrogel	Water retention and swelling behavior, application in moisture stress agriculture, pH-sensitive	Chandrika et al. [126]
	Fertilizing hydrogel	Work for establishing poplar	Böhlenius and Overgaard [127]
	ι/κ-carrageenan-agar/xanthan hydrogel blends	Coating seed, increase water holding capacity, increase gel strength	Hotta et al. [128]
	Chitin hydrogel	Biodegradable, plant growth regulator, excellent water uptake ability	Tang et al. [129]
	Nanocomposite PAAm/methyl cellulose/ montmorillonite hydrogel	Nutrient carrier vehicle, increase water absorption speed	Bortolin et al. [130]
	Poly(acrylamide-co-acrylic acid)/ $AlZnFe_2O_4$ hydrogel	Superabsorbent, improve wheat plant growth and establishment, enhance the moisture retention	Shahid et al. [131]
	Pectin-based polymer hydrogel	Remover of Cu^{2+} and Pb^{2+}, the release of fertilizers, help to conserve water, able to macromolecular relaxation	Guilherme et al. [132]

(continued)

Table 3 (continued)

Applications	Type of hydrogel	Properties/uses	References
Separation Oil recovery	Crosslinked dextran hydrogel-epichlorohydrin-toluene	Separation of liposome and drugs, water swelling property, high separation performance, decent sphericity and distribution	Bao et al. [133, 134]
	Dimethylamino ethyl methacrylate hydrogel	Thermo and pH-controllable, superhydrophilicity, superoleophobicity, o/w separation	Cao et al. [135]
	Clay nanosheets, *N,N*-dimethylacrylamide and 2-acrylamide-2-methylpropanesulfonic acid	The high-strength freestanding elastic hydrogel, selectively separation of Pb^{2+} and Cu^{2+}, recycle membrane	Bao et al. [133, 134]
	PEG-laponite XLG-acrylamide particle gels (PPGs)	3D dense network, mobility control, fracture-plugging applications, long-term thermal stability	Tongwa and Bai [136]
	Polyacrylamide/montmorillonite (Na-MMT)-chromium hydrogel	Enhance oil recovery, in-depth profile modifier, oil displacing agent, strong thermal stability	Zolfaghari et al. [137]
	Polyacrylamide/poly(vinyl alcohol)-chromium triacetate hydrogel	Gelation and swelling behaviour, enhance oil recovery	Aalaie et al. [138]
	PAM inverse emulsion/acrylamide	In-depth permeability control, fluid diverting, oil driving, increase oil productivity	Lei et al. [139]
	Xanthan/Zr^{4+} flowing gel	Enhance oil recovery, strongly resistant to shearing	Wang and Zhang [140]
	Conventional bilayer lipid membranes-hydrogel salt-bridge	pH and ion sensors, sensors for ligand-reception interactions, drug testing, enhance oil recovery	Tiena and Ottovaab [141]

hydrogel solution, allows the absorption of specific proteins on illuminated areas then cells to these proteins, respecting a defined micropattern, and thus 3D construction, for biomedical and tissue engineering for example. Finally, recent works highlighted 4D fabrication using shape-morphing hydrogel [68]. Alginate and hyaluronic acid were used as biopolymers for the conception of the hydrogel, and mouse bone marrow stromal cells for the biocompatibility tests. The authors were able to generate average internal tube diameters (20 μm), comparable to the smallest blood vessels without any loss of cell viability. Their statements are strong since this 4D (four-dimensional) biofabrication strategy aims to produce dynamically reconfigurable architectures, with tunable functionalities, as reported in Fig. 7. Wang et al. [69] recently published a comprehensive review concerning new development and biomedical applications of these hydrogels. This paper illustrates the work already done but mainly to perform in the fabrication processes which absolutely need to be (i) inexpensive, (ii) from and/or using nontoxic/non-hazardous materials and techniques and (iii) fine and easily-tuning possibilities. Thus, a wide range of papers are nowadays available in the literature and natural polymer (DNA, protein, polysaccharide) based-hydrogels take benefit from the situation [70–72].

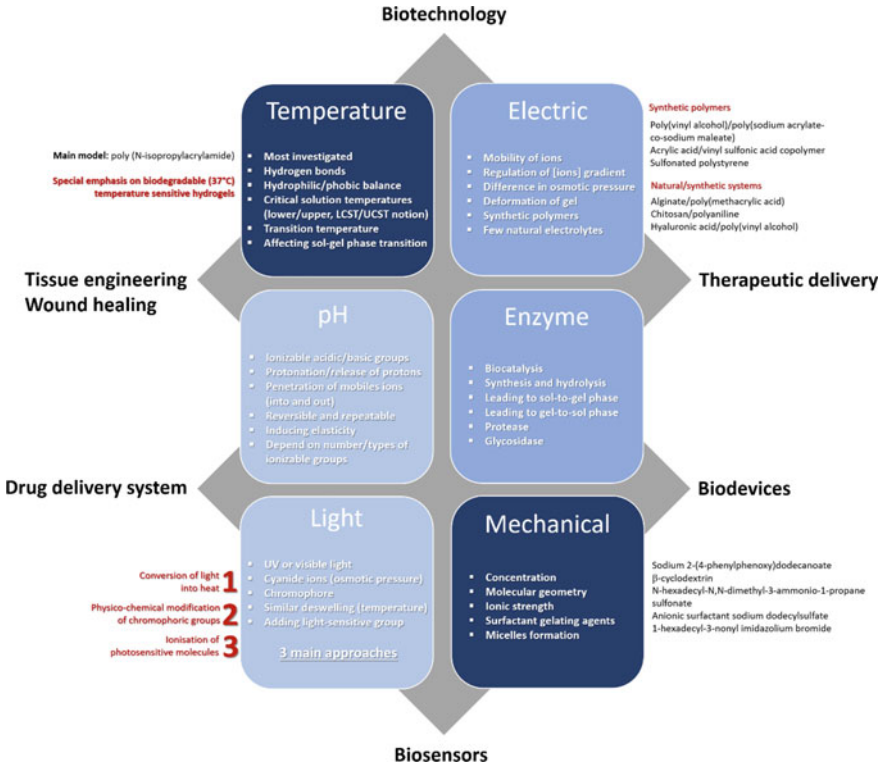
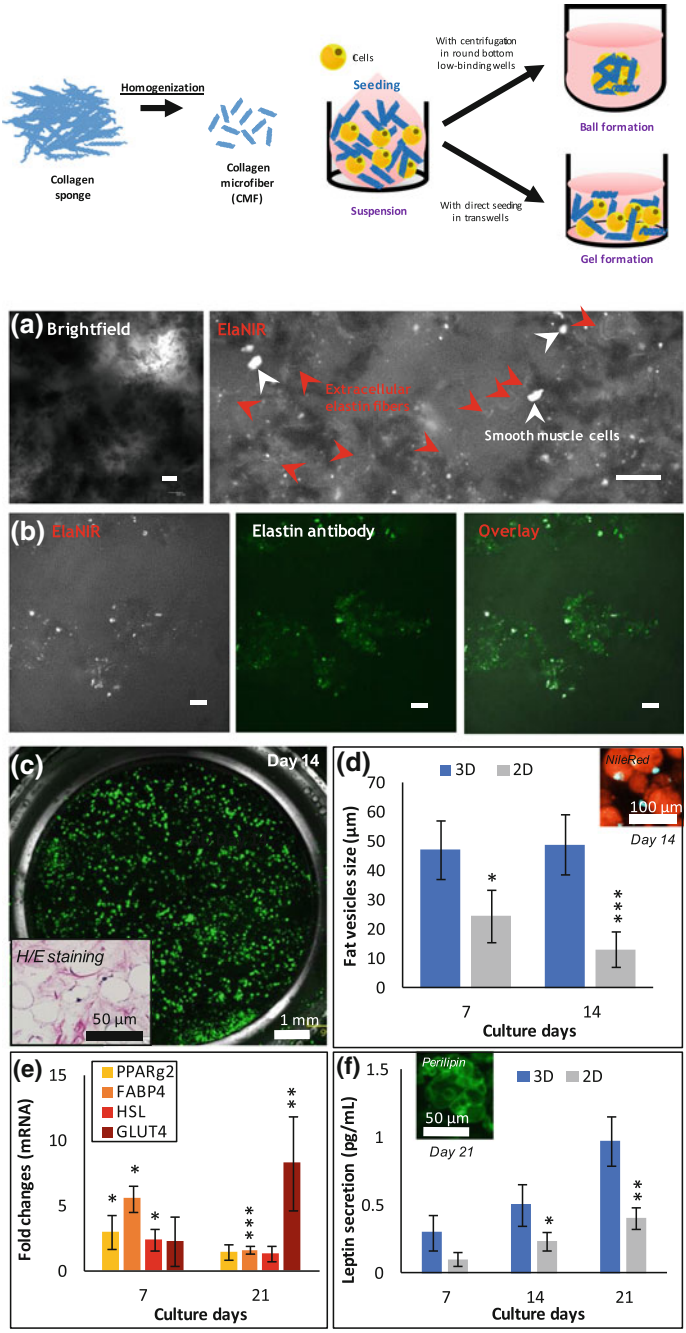


Fig. 7 Main strategies for the conception of new smart hydrogels and recently associated polymers


Homogenization
Collagen sponge
Collagen microfiber (CMF)
Cells
Seeding
Suspension
With centrifugation in round bottom low-binding wells
With direct seeding in transwells
Ball formation
Gel formation
(a) Brightfield
ElaNIR
Extracellular elastin fibers
Smooth muscle cells
(b) ElaNIR
Elastin antibody
Overlay
(c) Day 14
H/E staining
50 µm
1 mm
(d) 3D 2D
NileRed
100 µm
Day 14
Fat vesicles size (µm)
Culture days
(e) PPARg2
FABP4
HSL
GLUT4
Fold changes (mRNA)
Culture days
(f) Perilipin
50 µm
Day 21
3D 2D
Leptin secretion (pg/mL)
Culture days

◂**Fig. 8** Schematic illustration of collagen microfiber hydrogels model construction. **a** Bright field (left) and ElaNIR signal in NIR channel (right). **b** ElaNIR signal was detected in NIR channel (left), the signal from an anti-elastin antibody (middle) and overlay imaging (right). Scale bar: 100 μm. **c** Live/dead assay attesting the good viability of mature adipocytes after 14 days in collagen microfibers hydrogels. **d** Adipose vesicles diameters measured each week using Nile red specific lipids staining. **e** Adipogenesis gene expression assessed by RT-qPCR on total RNA of ADSC (PPARγ2, FABP4, GLUT4 and HSL genes) expressed in fold changes regarding 2D condition. **f** Leptin secretion measurement by ELISA in the culture medium every week and normalized by DNA content. Perilipin immunostaining performed at day 21. Error bars represent SD. Tukey multiple comparison test (double-way ANOVA) was used with $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$

4.3 Focus on the Nano to Micro ECM Gel Coating System

Classic collagen hydrogels are still widely used for tissue engineering despite its limited collagen content of maximum 0.3%, remaining far away from the in vivo conditions. In this context, the use of collagen microfibers instead of classic collagen dilution can achieve higher density (until 20–30 wt%). The method relies on the immersion of porcine type I collagen in ×10 PBS (Phosphate buffer saline), followed by its homogenization for 2 min to create the microfibers (VH-10 homogenizer, As One Corp., Osaka, Japan). After centrifugation, the microfibers were washed in DMEM (Dulbecco's modified eagle medium) without FBS (Fetal bovine serum) before being mixed with the cells suspension.

4.3.1 Live-Staining of Secreted Elastin by Smooth Muscle Cells in All Tissues

Elastin is one of the major components of the extracellular and thus often assessed during tissue regeneration. For example, the aorta wall is constructed with an arrangement of elastin in concentric lamellae presenting smooth muscle cells between them [73]. A new fluorescent ElaNIR probe was used to visualize specific elastin secretion in smooth muscle cells 3D-tissue models. Human umbilical artery smooth muscle cells were seeded in ball microfibers collagen tissues. These ball tissues were made by centrifuging the mix cells-collagen microfibers in round bottom low-binding plate wells. Smooth muscle cells ball tissues displayed an increase of extracellular elastin fibers as stained by ElaNIR probes (Fig. 8a), confirmed by consistent elastin antibody staining (Fig. 8b). Overall, the specific ElaNIR probe along with the in vivo like smooth muscle tissue can be used as a model for observation of elastin production during tissue regeneration or for the screening of elastin-enhancing chemicals in cosmetics products [74].

4.3.2 Adipose Tissue Regeneration Inducing and Maintaining the Functionality of Both Pre and Mature Adipocytes in Long-Term Cultures

Adipose tissue regeneration is currently a competitive challenge for either cosmetic/pharmaceutical assays or plastic surgery purposes. Conventional in vitro two-dimensional (2D) cell cultures using directly mature adipocytes (AD) showed limited culture time by quickly dedifferentiating [75] while getting sufficiency matured AD by differentiating adipose-derived stem cells (ADSC) usually required more than one month [76]. The existing three-dimensional (3D) models accelerated the ADSC adipogenesis, but the mature AD still cannot be maintained more than one-week in vitro cultures [77]. In this context, the construction of a biomimetic 3D-tissue is determinant. Using collagen microfibers, high-density collagen (until 20–30 wt%, see H/E staining (Fig. 8c), similar to in vivo [78] artificial adipose tissues were performed mixing the homogenized type I collagen with a mature AD or ADSC and seeding in 24 well transwells. These 3D-tissues ensured the long-term maintenance of unilocular mature AD with a good viability of 95% at day 14 (Live/Dead image Fig. 8c). On the contrary, the 2D mature AD showed significantly 4 times smaller multiple vesicles (Fig. 8d). Concerning ADSC, 3D adipogenic genes expression was found at least significantly doubled throughout the differentiation (even 8.3 times higher for GLUT4 at day 21, Fig. 8e), along with up to almost 4 times bigger fat vesicles observed at day 14 (data not shown). Perilipin immunostaining, the protein stabilizing the fat vesicles, and leptin secretion, the well-known safety protein, finally attested the up to the twice better functionality of 3D adipocytes (Fig. 5e). The obtained long-term functional maintenance and the faster adipogenesis made this model relevant for screening assays and reconstructive surgery.

5 Conclusions

More and more hydrogels have been published and patented these last years for their specific properties leading to various applications. Some of them are widely present in commercial products. Their success is linked to their ability to swell in aqueous solutions or suspensions. This book chapter has done the state of the art of the different natural or synthetic hydrogels available and described the obtaining processes for different uses in numerous industrial fields. The potential of these macromolecular networks has not been fully explored at this time notably in therapy for tissue engineering and drug delivery, two fields where only a few products are on the market. Covalently cross-linked hydrogels made in the absence of solvents are the more popular for this kind of applications. Undoubtedly, methods from supramolecular chemistry applied to the synthesis in aqueous environments of new hydrogels having modifiable properties could open the way of new possibilities. Supramolecular chemistry is a domain of chemistry that focuses

on the building of macromolecular systems made up of non-covalently assembled molecular subunits. Current researches focusing on hydrogels for multidrug delivery by a single system and/or sequential delivery on demand with a high level of control by stimuli highlight also new opportunities. Another way of hydrogel improvement, notably for application in the human body, could be the control of their swelling capacity. Indeed, the swelling of hydrogels and/or their degradation after their implantation can alter surrounding tissues. This disadvantage can be limited by decreasing the polymer concentration but in this case, the time to form the hydrogel is too long. An interesting article recently published in Nature Biomedical Engineering proposed an original solution of a two-step gelation process of PEG hydrogels at low concentration [79]. In a first step, branched polymers clusters were generated but the crosslinking reaction was intentionally stopped just before the full gelation. The solution was then injected into the body at the required place and the clusters present in the co-crosslinked solution to form a gel in ten minutes. These hydrogels have low cytotoxicity and can act as an artificial vitreous body. So, the future of hydrogels in the therapeutic area will be probably linked to the development of innovative properties such as those described above but also to the reduction of costs for their obtaining.

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