Applications of Hydrogels

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Abstract

Hydrogels offer multiple unique properties in terms of their porosities, mechanics, interfacial dynamics, and biological responses that make them highly relevant to a broad range of potential applications. Herein, we review how hydrogels can address key challenges in biomedical, personal care, cosmetic, bioseparations, environmental (including natural resource extraction), catalytic, and agricultural applications, with an emphasis on how hydrogels can be rationally engineered in each case for optimal performance. Biomedical applications of hydrogels in drug delivery, tissue engineering, cell encapsulation, wound healing, and biological barrier materials are particularly highlighted in the context of how various

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approaches to hydrogel synthesis and fabrication influence hydrogel performance in such applications.

Abbreviations

AAc	Acrylic acid
AAm	Acrylamide
AAS	Atomic absorption spectroscopy
AgNPs	Silver nanoparticles
AMPS	2-Acrylamido-2-methyl-1-propanesulfonic acid
APO-1	Apoptosis antigen-1
APTMACl	(3-Acrylamidopropyl)trimethylammonium chloride
CD95	Cluster of differentiation 95
CMC	Carboxymethyl cellulose
CRF	Controlled release fertilizer
ECM	Extracellular matrix
EHS	Engelbreth-Holm-Swarm
FDA	US Food and Drug Administration
GAG	Glycosaminoglycan
HA	Hyaluronic acid
HPMA	2-Hydroxypropyl methacrylate
HPMC	Hydroxypropylmethyl cellulose
Hydrogel-M	Hydrogel-embedded metal catalyst
MMPs	Metallomatrix proteinases
MW	Molecular weight
NPs	Nanoparticles
PA	Peptide amphiphile
PAA	Poly(acrylic acid)
PAAm	Poly(acrylamide)
PAGE	Poly(acrylamide) gel electrophoresis
PCL	Poly(ϵ-caprolactone)
PDADMAC	Poly(diallyldimethylammonium chloride)
PEG	Poly(ethylene glycol)
PEO	Poly(ethylene oxide)
PGA	Poly(glycolic acid)
PHEMA	Poly(hydroxyethyl methacrylate)
PLA	Poly(lactic acid)
PLGA	Poly(lactic-co-glycolic) acid
PNIPAM	Poly(N-isopropylacrylamide)
PPO	Poly(*p*-phenylene oxide)
PU	Poly(urethane)
PVA	Poly(vinyl alcohol),
RGD	Arginylglycylaspartic acid
SAPs	Superabsorbent polymers
SDS	Sodium dodecyl sulfate
SPHs	Superporous hydrogels

SPIONs	Superparamagnetic iron oxide nanoparticles
SRF	Slow release fertilizer
TNFRSF6	Tumor necrosis factor receptor superfamily member 6
UV	Ultraviolet
VEGF	Vascular endothelial growth factor

1 Introduction

The diversity of backbone polymer compositions, crosslinking strategies, and morphologies accessible with hydrogel-based materials opens a broad spectrum of potential applications for hydrogels. In general, applications of hydrogels tend to exploit one or more of three key properties that are unique to hydrogels relative to other types of materials. First, the capacity of hydrogels to imbibe large amounts of water (in many cases multiple times their dry weight) and bind that water inside the gel network by hydrogen bonding/water structuring is often leveraged for dewatering applications (e.g., in natural resource extraction), water retention applications (e.g., drought-resistant agricultural additives), or sorbency applications (e.g., wound dressings for absorbing exudate or personal care products such as sanitary pads or diapers). Second, the controllable porosity of hydrogels can be used to limit access to chemicals entrapped within the gel phase (e.g., controlled catalysis, selective biosensing, xenograft cell encapsulation), regulate the release of entrapped cargoes within the gel phase (e.g., drug delivery, agricultural release), and/or absorb targeted chemicals from the gel environment (e.g., environmental remediation, bioseparations); all such interactions are highly tunable (and, in the case of environmentally responsive hydrogels, dynamically tunable) based on both the size of the pores and the chemical affinity of the gel phase for the encapsulated species. Third, the soft mechanics of hydrogels strongly mimic those of biological tissues, leading to applications in tissue engineering and biological barrier materials in which a hydrogel can provide appropriate mechanical signals to surrounding cells.

In this chapter, we will outline the main applications of hydrogels across multiple fields, including biomedical engineering, personal care products and cosmetics, bioseparations, environmental applications, natural resource extraction, catalysis, and agriculture. Emphasis is placed on the mechanism by which hydrogels can address key application needs in each area and how hydrogel properties can be effectively engineered to optimize the performance of hydrogels in each application.

2 Biomedical

The use of hydrogels in biomedical applications was first demonstrated by Wichterle and Lim in 1960 via the crosslinking of hydrophilic poly(2-hydroxyethyl methacrylate) (PHEMA) polymers into a network to form a contact lens [1]. Contact lenses remain a key application of hydrogels, with the more recently developed long-wear

contact lenses based on interpenetrating polymer networks between silicone and PHEMA that provide significantly improved oxygen transport relative to PHEMA lenses only of particular note [2]. However, since this initial demonstration, hydrogels have been applied in a wide variety of biomedical applications, the key applications of which will be summarized in the following section.

2.1 Tissue Scaffolds

The number of papers pertaining to the use and/or design of hydrogels for use as scaffolds in tissue engineering applications has dramatically increased since the earlier work in this field in the 1990s, and the interested reader is referred to critical reviews on the development of tissue-engineered hydrogels by Zhu and Marchant [3] and Brandl et al. [4]. In general, hydrogels are attractive candidates as scaffolds for tissue engineering applications since they are naturally hydrated and porous networks that can be engineered to have unique architectures and mechanical properties that mimic native soft tissues to a greater extent than other polymeric biomaterials [3], providing cells with the mechanical and topographical cues required to develop into functional tissues.

Hydrogel tissue engineering scaffolds have primarily been designed by drawing inspiration from the organization of the native extracellular matrix (ECM) of cells [3]. Natural ECM offers mechanical support to cells in addition to containing many essential cell signaling molecules, fibrous proteins (primarily based on collagen, elastin, and laminin), and proteoglycans (glycosaminoglycans) [5]. Cells can respond to biochemical or mechanical cues from their ECM; alternately, cells can actively restructure their ECM by releasing enzymes to direct its dynamic degradation and remodeling; in this latter case, cells effectively signal each other through these dynamic ECM restructuring processes [6]. An effective tissue scaffold should mimic these key properties of native ECM, including a capacity to support cell adhesion/growth; provide biomimetic physical, mechanical, and chemical cues to direct cell behavior; and facilitate effective exchange of nutrients, gases (e.g., O_2 and CO_2), metabolic waste, and biological signals to and from the cells [7].

The use of hydrogels as ECM mimics for tissue regeneration requires a combination of control over hydrogel chemistry and structure. From a chemistry perspective, scaffolds should ideally mimic specific functions of the natural ECM such as cell adhesion [8, 9], proteolytic degradation [10–12], growth factor/cytokine binding [13, 14], and matrix protein binding [15, 16]. Most useful hydrogel chemistries are either injectable [17, 18] or can be formed via ultraviolet (UV) photopolymerization [19, 20] since the use of mild synthesis conditions is required in the presence of cells. From a structural perspective, the macroporosity and fibrous nanostructure of native ECM is mimicked by a variety of methods to make macroporous hydrogel scaffolds including salt or porogen templating, bicontinuous emulsion templating, gas foaming, cryogelation techniques, electrospinning, and additive manufacturing techniques like 3D printing, all aiming to provide space for cells to grow, proliferate, and signal other cells (Fig. 1) [21]. Hydrogel structure can also be manipulated spatially

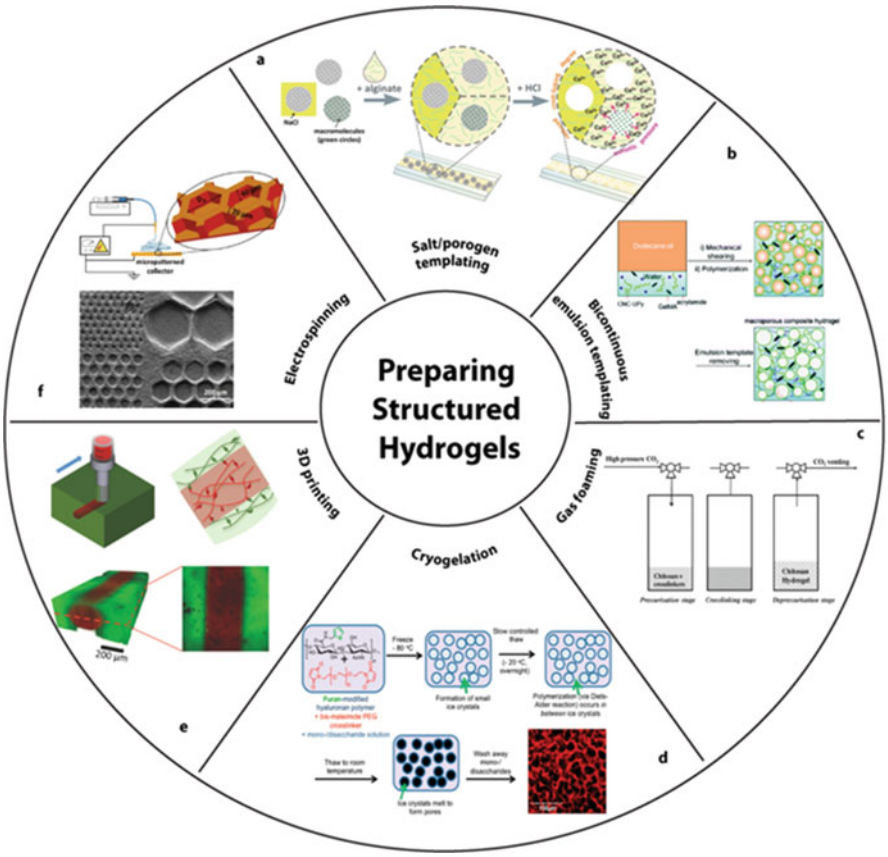

Fig. 1 Conventional methods of preparing structured hydrogels: (**a**) salt/porogen templating. (Reproduced with permission from [24], copyright Wiley 2015), (**b**) bicontinuous emulsion templating. (Reproduced with permission from [25], copyright Royal Society of Chemistry 2017), (**c**) gas foaming. (Reproduced with permission from [26], copyright Elsevier 2011), (**d**) cryogelation. (Reproduced with permission from [27], copyright American Chemical Society 2016), (**e**) 3D printing. (Reproduced with permission from [28], copyright Wiley 2015), and (**f**) electrospinning. (Reproduced with permission from [29], copyright Elsevier 2015. Overall image reproduced with permission from [21])

within the gel to promote desired cell responses by structured signaling. For example, gradient hydrogels with spatially defined mechanical gradients, typically prepared by locally altering the monomer and initiator concentrations of photopolymerizable precursors, have been demonstrated to direct cell spreading or expansion in a particular direction [22]. The addition of cell signaling chemical gradients (e.g., cell-adhesive peptides) into the scaffold can further control the spatial distribution of cells on or within a hydrogel [23].

Natural polymers are commonly used to fabricate tissue engineering scaffolds due to their inherent biodegradability and the potential for their degradation products

to modulate the native biological system. The four main types of natural polymers used include natural proteins (e.g., collagen, elastin, fibrin, gelatin, or silk [3], the first three of which are found in native ECM), genetically engineered proteins such as calmodulin [30, 31], polysaccharides (e.g., hyaluronic acid or dextran [32, 33]), and DNA [3]. Collagen has been particularly broadly used since it is the key native structural protein in many tissues and can be degraded by metallomatrix proteinases (MMPs) such as collagenase, allowing for controlled matrix degradation. Additionally, gelatin is popularly used since it naturally contains arginylglycylaspartic acid (RGD) residues which promote cell adhesion, migration, differentiation, and proliferation while also showing capacity for in situ thermogelation. Some carbohydrate-based building blocks also have native biological properties that can be leveraged for functionality. For example, hyaluronic acid (HA) is a non-sulfated glycosaminoglycan (GAG) that plays a key role in regulating the mechanics and hydration of the extracellular matrix as well as promoting cell spreading [8, 34, 35]. The combination of both proteins and polysaccharides together, inspired by the structure of native ECM, can overcome any deficiencies associated with either building block alone, with collagen/HA [36], laminin/cellulose [37], and fibrin/alginate [38] interpenetrating networks among the many examples reported. With DNA, it is common to add arms and/or "sticky" (i.e., self-assembling) ends to DNA's polynucleotide chains that can be specifically tailored for relevant applications [39, 40] while still taking advantage of the native self-assembly of complementary DNA under physiological conditions.

Naturally secreted ECMs can also be recovered from cells in vitro for use as hydrogel tissue scaffolds. The most common of these systems is Matrigel™, a protein mixture secreted from Engelbreth-Holm-Swarm (EHS) mouse sarcoma cells. The collected protein mixture from these cells contains critical ECM proteins such as laminin, collagen type IV, elastin, and growth factors [41]; reconstitution of these proteins into a gel has thus shown beneficial properties in various cell and tissue studies [42]. Similar gelatinous mixtures of proteins can be constructed in the lab using chemical crosslinkers (e.g., glutaraldehyde or epichlorohydrin), although the possible cytotoxicity of unreacted crosslinker must be considered if this latter approach is pursued.

Synthetic polymers have also been applied to tissue engineering applications since they offer more tunable and reproducible physical and chemical properties. Nonbiodegradable synthetic polymers are most widely used, with hydrogel scaffolds based on 2-hydroxyethyl methacrylate (HEMA), 2-hydroxypropyl methacrylate (HPMA), acrylamide (AAm), acrylic acid (AAc), N-isopropylacrylamide (NIPAM), poly(ethylene glycol) (PEG), Pluronic or poly(ethylene oxide) and poly (*p*-phenylene oxide) PEO-PPO block copolymers, and poly(vinyl alcohol) or PVA most frequently used [43]. On the other hand, biodegradable synthetic polymers have displayed distinct advantages for tissue scaffolds since the rate of polymer degradation can be tuned to match the healing/regeneration rate of the damaged tissue [44]. However, these polymers are mostly not water-soluble and thus cannot be used directly to form hydrogels. Many hydrophobic biodegradable polymers (including poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ϵ-caprolactone)

(PCL), and their respective co-polymers [44, 45]) can though be grafted to water-soluble polymers to enable the formation of hydrophobically-associative physically crosslinked hydrogels that can degrade at a rate related to the degradation rate of the degradable hydrophobic graft. Hybrid hydrogels based on combinations of synthetic polymers with natural polymers can also be applied to exploit benefits of both types of polymers to precisely engineer scaffold properties. Functionalization of synthetic polymer building blocks before or after hydrogel formation with bioactive moieties such as cell-adhesive sequences [46, 47], enzyme-sensitive linkages [48–50], and/or growth factors [51] can also introduce the desired biological properties of the scaffold in an all-synthetic hydrogel system, with the work of Anseth's group in creating dynamically biofunctional PEG hydrogels being particularly notable on this topic [52].

Significant effort has also been invested to try to reproduce the fibrous network structure of natural ECM (Fig. 1). Synthetic self-assembling peptides such as self-complementary peptides and peptide amphiphiles (PAs) have been extensively used to create fibrous hydrogel networks [53], exploiting the native fiber formation of such materials. Electrospinning of hydrogel nanofibers via either rapid UV photo-polymerization of extruded fibers [54] or rapid in situ gelation upon extrusion [55] can create nanofibrous structures directly. However, biofabrication strategies that apply additive manufacturing techniques to form complex three-dimensionally structured tissue constructs with high shape fidelity have attracted particular recent interest for the augmentation, replication, or replacement of native tissues of interest. By combining computer-aided manufacturing approaches with biomaterials and cellular components, scaffolds with applications in tissue engineering [56] as well as drug screening [57] and in vitro disease models [58] can be designed with prescribed structures and thus functions. Commonly used bioprinting techniques for hydrogels include inkjet, laser-assisted, extrusion, and stereolithographic bioprinting, as shown schematically in Fig. 2 [59].

The mechanisms available for hydrogel biofabrication inherently limit the types of hydrogels that can be used. The final matrix must facilitate cell migration, growth, and proliferation [60], but the materials must be printable in a manner appropriate for each mechanism and be capable of rapidly forming stiff structures following printing to maintain shape fidelity; these are often conflicting properties from a hydrogel design perspective. Mixtures of bioinks with different molecular weights (e.g., high and low molecular weight or MW alginate) can offer benefits in this regard, with the low molecular weight component reducing the viscosity of the ink (to enable printing) but the high molecular weight component enabling rapid gelation to maintain shape integrity [61]. In addition, while optimal shape fidelity is attained with stiff hydrogels with high crosslinking densities, this stiffness can also limit cell migration, growth, and differentiation [62, 63]. On this basis, medium crosslinked hydrogels are often considered optimal for the biofabrication of tissues or tissue mimics, gaining improved cell responses within the scaffold at a cost of losing a degree of geometrical accuracy. As a result of this suite of required properties, relatively few bioinks are now available on the market, with most hydrogel-based commercial processes using the rapidly gelling calcium-alginate chemistry [64].

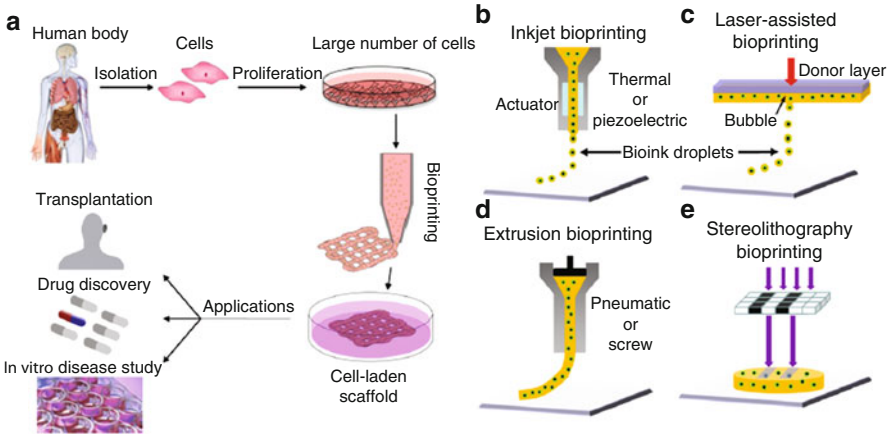

Fig. 2 Bioprinting processes for fabricating cell scaffolds: (**a**) the typical workflow of bioprinting involving the isolation and expansion of human cells prior to printing the desired cell-laden scaffold; (**b**) inkjet printers eject small droplets of cells and hydrogel via thermal or piezoelectric droplet generation strategies; (**c**) laser bioprinters use a laser heating to vaporize a region in the donor layer (top), forming a bubble that propels a suspended bioink to fall onto the substrate; (**d**) extrusion bioprinters use pneumatic or manual forces to continuously extrude a cell-hydrogel solution; (**e**) stereolithographic printers use projections of light to selectively crosslink bioinks plane-by-plane. In (**c**) and (**e**), colored arrows represent a laser pulse or projected light, respectively. (Reproduced with permission from [59])

Leveraging the properties of in situ covalently gelling hydrogels in this application is likely to lead to significantly more diverse (and thus biofunctional) tissue chemistries while still maintaining the key properties required for printability.

2.2 Cell Encapsulation

As a subset of tissue engineering, the encapsulation of a few or single cells inside hydrogel microparticulate gels has been extensively explored to create microscale matrices with the capacity to support cell viability (e.g., facilitating cell adhesion and supporting the diffusion of nutrients/oxygen into the encapsulated cells) while also excluding undesirable agents (e.g., inflammatory cells) [65]. Such an approach has been used to encapsulate cells of various lineages including islet cells (of particular interest as protected insulin-releasing materials), kidney cells, fibroblast, myoblasts, and various stem cell lineages [66]. Early work with cell encapsulation technologies aimed at the immunoisolation of cells producing therapeutic proteins for various diseases [65], requiring ideally nondegradable hydrogel matrices to enable the use of any cell from any lineage to produce the therapeutic protein. Now, while immunoisolation is still being explored, the principal interest in cell encapsulation lies in developing models for understanding cellular physiology and for cell delivery in vivo in regenerative medicine applications with musculoskeletal, neural, dermal,

hepatic, and cardiovascular applications. In this case, the degradation of the gel or gel microparticle at targeted times appropriate for the regeneration of the tissue of interest is essential for the proper function of the gel.

Hydrogels used for cell encapsulation must be cytocompatible, prepared using mild crosslinking conditions so the cells do not get killed or highly stressed during the encapsulation process, stable over the appropriate period of time, and contain sufficient porosity to ensure that the microstructure has enough space for cells to move/rearrange, communicate, respire/reproduce, and access nutrients [18]. Additional porosity can be introduced if required via the use of porogens or other methods described in Sect. 2.1 for fabricating macroporous bulk scaffolds.

Calcium-crosslinked alginate is by far the most frequently used biomaterial for cell microencapsulation based on its simple, rapid, and biologically friendly crosslinking mechanism and its safe degradation products [67]. However, the calcium-alginate system is prone to high levels of swelling and/or cation exchange to remove the calcium crosslinker in vivo, limiting the maximum long-term stability achievable [63]. Other divalent cations (e.g., barium) have been used to improve the stability of the gel microbeads [68]; the use of functionalized alginates such as perfluorinated alginate [69] can also improve the stability of the ionic complex formed. UV photopolymerizable systems have more recently been explored by using inverse emulsions, microfluidic processes (which can enable few or single cell encapsulation) [70], or other assembly techniques to template a microparticle form that is subsequently covalently crosslinked in place via photoinitiation with a cytocompatible initiator (e.g., Irgacure 2959). Cytocompatibility is maintained for most cell types provided the irradiation time remains relatively short. Cell adhesion to the matrix is also essential to ensure long-term cell viability. For hydrogels without inherent cell adhesivity (e.g., hydrophilic synthetic polymers like poly (ethylene glycol)), hydrogels are typically biofunctionalized with a peptide or ECM protein such as fibronectin or the RGD cell-adhesive peptide, with the peptide most commonly used since it is less expensive and easier to isolate and has less diverse functions [71]. Surface decoration of gels with antibodies including apoptosis antigen-1 (APO-1 or APT), cluster of differentiation 95 (CD95), and tumor necrosis factor receptor superfamily member 6 (TNFRSF6) [72] can also modulate the inflammatory response to the material, in particular to avoid the "walling-off" fibrotic response that would reduce transport in and out of the capsule.

2.3 Drug Delivery

Hydrogels have several properties that have made them widely exploited in drug delivery applications. The high internal porosity of hydrogels enables loading of drugs into the scaffold and the controlled diffusion of those drugs out of the scaffold at a rate dependent on the tortuosity (i.e., the combination of pore size and pore connectivity) of the hydrogel network, a parameter that can be tuned by the method of fabrication and the crosslink density [73]. The chemical flexibility of hydrogels can also be applied to introduce affinity sites for charged [74, 75], hydrophobic

[76, 77], or other specific types of small molecules to improve loading and/or prolong release kinetics. The high water content of hydrogels leads to generally low inflammatory responses due to low non-specific protein adsorption, at least compared to other types of biomaterials useful for drug delivery [78]. Biodegradability or dissolution may also be introduced via judicious selection of crosslinker and/or building block material.

The terms "controlled release," "sustained release," "extended release," and "long-term delivery" are largely used interchangeably in the literature to describe drug release from hydrogels. However, in any case, the main goal of most hydrogel-based drug delivery systems is to maintain the local concentration of the therapeutic agent between the limits of toxicity (upper limit) and the subclinical baseline below which the agent has no functionality (lower limit), termed the "therapeutic window" (Fig. 3) [79]. For long-term delivery profiles, the engineering goal is to prolong the amount of time in which release occurs in this window and to reduce the slope of the release profile leading up to a leveling off or a plateau region.

Many properties of both the hydrogel phase and the hydrogel environment contribute to determining the release kinetics from a hydrogel, including both the rate and magnitude of water penetration into the gel (i.e., swelling) and the effects of

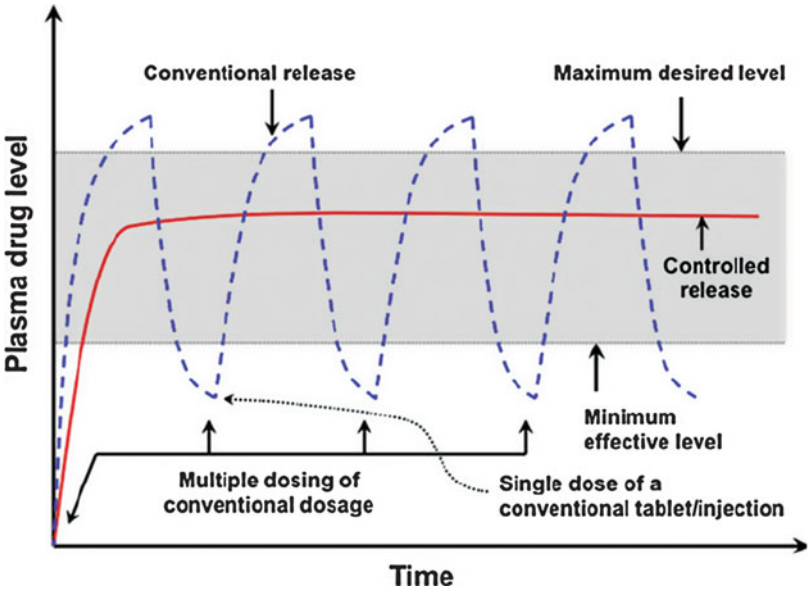

Fig. 3 An example of a drug release profile with the line indicated as "maximum desired level" being the toxic level and the line labeled as "minimum effective level" being the subclinical limit, while the grayed region in the middle encompasses the therapeutic window. The blue dotted line represents conventional release in which multiple administrations of a drug are required, while the red curve shows a standard zero-order kinetics curve for a controlled release vehicle in which the drug concentration is maintained long-term within the therapeutic window. (Reproduced with permission from [79])

swelling on gel porosity, the degradation rate of the hydrogel, any change in pH of the gel matrix due to the degradation of polymers, the amount of drug present in the matrix, the diffusibility and solubility of that drug in the matrix and the release medium, the adsorption/desorption equilibria between the drug and the hydrogel building blocks, and the partitioning equilibria between the gel phase and the release media [80]. The complexity of these dynamic interactions is significant, and depending on the number of different contributors and the relative magnitude of those contributors to regulating drug release kinetics, different mathematical models have been developed to predict drug release rates. The most widely used of these models and equations for modeling drug release from gels include the following: (1) zero-order kinetics, relevant to reservoir-type vehicles (including reservoirs surrounded by hydrogels, which act as a membrane to mediate release) [81, 82]; (2) first-order kinetics, relevant for purely diffusion-controlled release of drug from hydrogels [83]; (3) the Baker-Lonsdale model, relevant for diffusion-based drug release from spherical matrices such as gel microparticles or micro-/nanogels [83]; (4) the Hixon-Cromwell model, relevant when drug needs to dissolve within the gel matrix prior to diffusion-based release [83]; (5) the Korsmeyer-Peppas model, relevant to account for drug-polymer affinity-retarded diffusion of drug through a hydrogel [83, 84]; and (6) the Hopfenberg model, relevant to describe hydrogels that undergo heterogeneous surface erosion during the release process [83]. Of these models and empirical formulae, the most prominent within the hydrogel community include zero-order kinetics for reservoir-type delivery systems (primarily for hydrogels incorporated into transdermal devices), first-order kinetics for hydrogels with no specific affinity to the drug (i.e., only diffusion-controlled release), and the Korsmeyer-Peppas model for hydrogels with non-specific affinity for the drug (i.e., both partitioning and diffusion-controlled release). Use of these models requires knowledge or measurement of the diffusion coefficient of the drug within a gel, which can be assessed using a diffusion cell in which a known thickness of hydrogel separates the source (the drug of interest dissolved in a suitable buffer) and receiver (containing only the buffer); the appearance of the drug in the receiver over time can be correlated to the diffusion coefficient of drug in the gel [85].

Hydrogel-based drug delivery vehicles have been successfully fabricated to deliver drugs via a range of different administration routes. While this is by no means an exhaustive list, it is meant to highlight the key areas in which hydrogels have been applied commercially for drug delivery.

2.3.1 Oral

Hydrogel-coated capsules, commonly referred to as GelCaps, have been widely used to deliver drugs orally. The gel capsule typically consists of a stiff gelatin-based hydrogel which surrounds either dispersed solid drugs or a liquid core containing drugs and some suitable dispersing agent (often non-crosslinked poly(ethylene glycol)). The presence of the gel layer enables facile swallowing via its lubrication effect as well as controlled release over time due to drug diffusion through the capsule and the slow degradation of the capsule in the digestive tract [86]. A variety of pH-responsive hydrogel coatings or delivery vehicles has also been designed in an

attempt to prevent or minimize release of a drug cargo in the stomach (pH 1–2) but promote release in the small intestine (pH 5–6), where most drugs need to be released and stable in order to be absorbed by the body in a bioactive form. Poly (acrylic acid) or PAA and related polymers have been widely used for this purpose based on their protonated/collapsed state at acidic pH but ionized/swollen state at near-neutral pH values characteristic of the intestine [87], with natural polymers such as pectin [88], chitosan [89], and carboxymethyl cellulose [90] that display the similar ionization equilibria also used. Some buccal hydrogel-based delivery vehicles (e.g., delivery vehicles immobilized in the mouth) have also been developed with mucoadhesive hydrogels based on chitosan or Pluronics [91], formulations that have the advantages of self-administration and more direct entry of the drug into the systemic circulation compared to conventional oral delivery methods.

2.3.2 Topical

Topically applied hydrogel formulations are most commonly used for wound healing applications, the fundamentals of which are covered in depth in Sect. 2.4. The combination of the beneficial properties of gels to absorb wound exudates and maintain local hydration [92] together with their capacity to control the release of drugs that can promote sterility at the wound site (e.g., antibiotics or antifungals) and/or active cues toward tissue regeneration (e.g., steroids and/or growth factors) [93] offers significant benefits in terms of facilitating more effective wound closure while avoiding infections.

2.3.3 Transdermal

While the hydrophobic stratum corneum lining the skin is a barrier to the use of hydrophilic hydrogels directly for transdermal delivery, hydrogels have still been used in two contexts for skin delivery. First, hydrogels can be used as carriers for nanoparticles that can penetrate into the skin via cellular transport mechanisms, prolonging retention of nanoparticles at the targeted site as well as extending the time period over which the drug is delivered [94]. Second, hydrogels can be used in the reservoir of a transdermal patch to prolong the release of drug through the porous membrane into the skin and/or improve the suspension of an insoluble drug inside the patch through the increased viscosity of the continuous phase [95]. The capacity of a hydrogel patch to continually hydrate the skin is also beneficial to avoid skin irritation, often observed with longer-term patches [96]. Hydrogel-based microneedles have also been recently developed that can penetrate through the outer layer of the skin and quickly form a continuous and unblockable aqueous conduit between the contents of the microneedle and the sub-dermal tissue, avoiding some of the inflammatory challenges often observed with conventional microneedle delivery vehicles [97].

2.3.4 Vaginal

Hydrogels have long been used as intravaginal delivery vehicles given their capacity for easy application, their favorable mechanical properties relative to viscous solutions that prevent or minimize leakage of the delivery formulation following

administration, and their capacity for mucoadhesion [98] to promote both retention and intimate contact with the vaginal tissue to improve drug absorption. Thermo-responsive gels that can selectively gel at the temperature of vaginal mucosal tissue (e.g., Pluronics mixed with mucoadhesive carbohydrates such as hydroxypropyl-methylcellulose (HPMC) [99] or chitosan [100]) have been particularly commonly applied. Liposome-containing hydrogels have also attracted attention due to their combination of improved drug delivery rates (particularly for hydrophobic drugs) and their provision of a physical barrier for infective agents to transfer through the vaginal wall [101]. Given the different pH values of vaginal fluid (pH 3.5–4.5 in healthy patients) and semen (slightly basic, pH 7–8), pH-responsive hydrogels have also been designed to either selectively gel to provide a dynamic biological barrier [102] or burst release an anti-infective drug only upon semen exposure [103], both of which have been shown to reduce transmission rates of sexually transmitted diseases.

2.3.5 Ophthalmic

Drug-eluting contact lenses that can facilitate longer-term and more effective delivery of drugs to the front of the eye relative to traditional eyedrops have long been a topic of research interest. While some benefits have been identified based on simply soaking commercial lenses in drug solutions and allowing then to release via simple diffusion on the eye [104], more advanced nanocomposite drug delivery strategies in which liposomes [105], nanoparticles (NPs) [106], or drug-loaded degradable films [107] have been integrated inside contact lenses have achieved significantly longer delivery times coupled with more desirable release kinetics (e.g., zero-order in the case of the degradable film, in which the hydrogel encasing the film effectively acts as a membrane) [107]. In situ gelling and/or highly shear-thinning hydrogel systems have also been used to increase residence time in the tear film, with Pluronic thermogelling hydrogels [108] or hydrophobic self-associative polymers (typically containing a highly hydrated backbone polymer coupled with hydrophobic grafts) [109] most commonly applied. Hydrogels have also been used for delivery to the back of the eye, following either implantation in the subconjunctival space or injection into the vitreous humor [110]. Particular recent efforts have focused on injectable hydrogels based primarily on hyaluronic acid (a major component of the vitreous humor) for the delivery of anti-vascular endothelial growth factor (VEGF) inhibitors, aiming to extend the efficacy of intravitreal injections for treating acute macular degeneration [111].

2.3.6 Intranasal

Intranasal delivery offers the advantages of capacity for self-administration, rapid absorption due to the high local vasculature, the avoidance of first-pass metabolism, and the capacity for direct drug delivery to the brain that circumvents the challenges of the blood-brain barrier [112]. However, practical hydrogels for use in this context must be in situ gelling and ideally mucoadhesive to ensure their facile delivery (via spray/aerosolization) and subsequent retention in the nose. Formulations including both mucoadhesive and thermogelling combinations such as chitosan/

hydroxypropyl methylcellulose [113] or gellan gum/Carbopol [114] (the latter a lightly crosslinked poly(acrylic acid)-based polymer with known mucoadhesion properties) have been among the more effective formulations according to these requirements. Self-assembled nanogels have also been successfully used for delivering both drugs and vaccines to the nose, exploiting the capacity of mucous to capture nanoparticles and the capacity of nanoparticles to penetrate through the mucous and into (or through) the nasal epithelium [115].

2.3.7 Rectal

While generally less used than some other routes, hydrogels have advantages in rectal drug delivery given the capacity of this route to increase patient compliance versus injections and improve bioavailability versus oral delivery. For example, mucoadhesive hydrogels such as chitosan-catechol have been successfully used for the treatment of colitis [116], while hydroxypropyl methylcellulose hydrogels have been used for delivery of anti-seizure drugs in children [117], a key target population for rectal delivery formulations due to the inability of children to swallow pills.

2.3.8 Injectables

Many of the in situ gelling hydrogels based on ionic interactions, hydrophobic interactions, supramolecular chemistry, or dynamic covalent chemistry [118] have been used for drug delivery, primarily following either subcutaneous or intramuscular injection if systemic delivery is the objective. However, in other cases, injection can be targeted to the desired site of action, including sites of local pain (local anesthetic delivery) [119], cancer tumors (chemotherapeutic delivery) [119], or arthritis (immunosuppressive drug delivery) [120].

2.3.9 Micro-/Nanogel Delivery Vehicles

Nanogels offer the advantages of nanoparticles in the context of drug delivery (i.e., long circulation times, capacity for targeting to specific tissues, capacity for cell uptake) with the advantages of hydrogels (low non-specific protein adsorption, capacity to load hydrophilic drugs, mechanical deformability to penetrate tight junctions). Of particular note, Akiyoshi's group has intensively investigated cholesterol-modified pullulan nanogels for delivering small molecules, peptides, proteins, and vaccines [121], with the high degree of control exerted over nanogel size coupled with the capacity of these nanogels to deliver both hydrophilic and hydrophobic payloads making this material particularly attractive. Smart thermoresponsive micro-/nanogels can also be used as an in situ gelation strategy for localizing delivery at a specific site [122]. Other micro-/nanogels have been developed to deliver drugs to treat a range of diseases including cancer, autoimmune disorders, or neurodegenerative conditions, among others [123] (Fig. 4).

2.3.10 Hydrogel-Mediated Smart Drug Delivery Vehicles

Environmentally responsive hydrogels or micro-/nanogels can be exploited both for promoting thermal in situ gelling responses (as described previously) and for enabling "smart" dosing of drugs in a disease-responsive [124] or doctor-/patient-

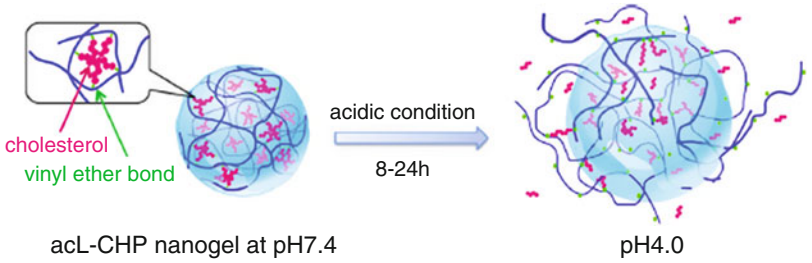

Fig. 4 Schematic describing the self-assembly of an acid-labile cholesteryl-modified pullulan (acL-CHP) used for glucose sensing and protein cargo release. (Reproduced with permission from [121])

responsive manner. Glucose-responsive hydrogels, gel microparticles, or nanogels for insulin delivery have been most commonly explored [125–128] although a range of other chemoresponsive hydrogels (e.g., antigen-responsive or molecularly imprinted hydrogels) have been similarly applied [129]. Thermoresponsive hydrogels have been applied to facilitate triggered burst release of drugs upon hydrogel heating based on the convective transport of water (and dissolved drug) from the hydrogel upon activation [130]. Alternately, hydrogels can be used as gates for the on-demand release of drugs from a reservoir in response to a particular chemical signal (e.g., insulin with glucose) [131] or remote signal (e.g., membranes featuring a combination of magnetically responsive super paramagnetic iron oxide nanoparticles or SPIONs and thermoresponsive nanogels that can be remotely heated via an oscillating magnetic field) [132].

2.4 Barrier Materials

Hydrogels have been frequently used as biological barrier materials by exploiting their high interfacial hydrophilicity and thus low bioadhesion to prevent undesired tissue adhesion following surgery due to fibrin deposition. The most common scenario in which hydrogels are used in this context is to prevent peritoneal adhesions following cardiovascular or abdominal surgery. Such adhesions between the peritoneal wall and underlying organs (most commonly the intestine) often become sites of postsurgical infection and account for 1% of all hospital admissions [133]. Relative to the viscous polymer solutions traditionally used for such applications [134], hydrogels have substantially longer residence times at the barrier site while also retaining more water per unit volume, facilitating longer healing times before the barrier degrades away; relative to lyophilized sheets or sponges of water-soluble polymers [135], hydrogels (and in particular injectable hydrogels) offer improved coverage of all possible adhesion sites due to the capacity of the precursor polymers to flow and fully wet the tissue interface prior to gelation. Kohane's group has contributed significantly to developing injectable hydrogels for this purpose, including hydrazone-crosslinked carboxymethyl cellulose (CMC)/dextran hydrogels [136],

hydrazone-crosslinked hyaluronic acid (HA)-based hydrogels [137], and highly shear-thinning physical hydrogels based on rheologically synergistic physical blends of hyaluronic acid and hydroxypropylmethyl cellulose (Fig. 5) [138]. Loading such hydrogels with drugs such as glucocorticoids, anticoagulants, fibrinolytics, antibiotics, or steroids can exploit the capacity of such hydrogels for drug delivery to treat the underlying biological causes of adhesion formation in addition to providing a transient physical barrier [133, 139]. The mechanical properties of such barrier of hydrogels are typically less important aside from the requirement that the gels are stiff enough to withstand the typical shear forces at the peritoneal wall over the required healing time (typically 1–2 weeks).

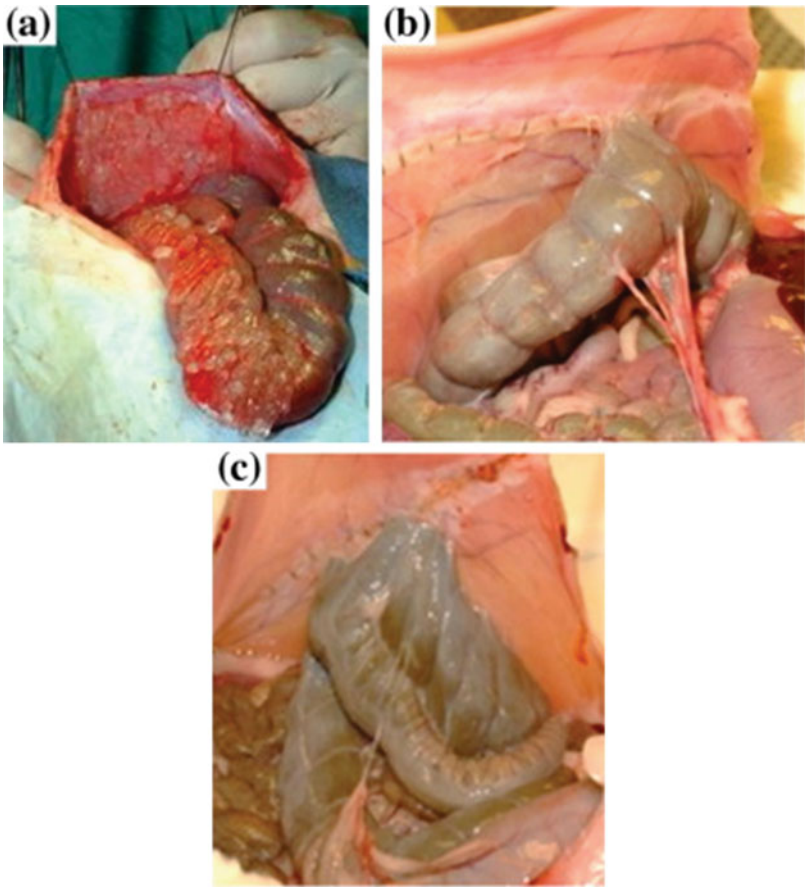

Fig. 5 In vivo assessment of adhesion prevention by hyaluronic acid/hydroxypropyl methylcellulose rheological blend hydrogels in a rabbit double injury model: (**a**) application of the hydrogel by extrusion immediately following the second injury, (**b**) adhesion formation 7 days after repeated injury following hydrogel treatment, (**c**) adhesion formation 7 days after repeated injury following treatment with saline, showing substantially higher adhesion between the intestine and peritoneal wall. (Reproduced with permission from [138])

Several commercially available hydrogels have been marketed for postsurgical adhesion prevention, including Oxiplex® (an ionically crosslinked hydrogel comprised of CMC, polyethylene glycol (PEG), and calcium chloride) [140], Intergel® (an ionically crosslinked hydrogel comprised of HA crosslinked by ferric chloride [141], although clinical trial results have been mixed [142]), Carbylan-SX (formed by disulfide crosslinking of thiolated HA) [143], and Spraygel® (an in situ gelling PEG hydrogel) [144]. Photopolymerizable hydrogels, predominantly based on gelatin [145] or methacrylated PEG or PEG-block-poly(lactic-co-glycolic acid) or PEG-PLGA polymers [146, 147], and thermogelling hydrogels, primarily based on Pluronic/Poloxamer PEO-PPO-PEO block copolymers, have also been demonstrated to have efficacy for reducing postsurgical adhesions. Self-assembled particle-based hydrogels based on bacterial cellulose have further been explored, with the capacity of such hydrogels to retain large amounts of water suggested to be effective for their role as a physical adhesion barrier [148]. Other in situ gelling chemistries such as Schiff base interactions (e.g., N,O-carboxymethyl chitosan/aldehyde-functionalized HA) [149] or thiol-ene click reactions (e.g., multi-thiol and multi-ene PEG) [150] have also been explored with early promise, although further investigation is required to confirm their utility relative to the other more widely investigated materials.

2.5 Wound Healing

The skin is the largest organ on the human body and is prone to damage such as burns, wounds, and ulcers through exposure to the environment. The two most frequent challenges involve the treatment of burn or laceration victims [151] or the treatment of diabetic or pressure ulcers [152]. The level of treatment required for treating such damage depends on the depth of the wound into the epidermal and dermal layers, the location of the wound on the body, the amount of area covered by the wound, the longevity of the wound (i.e., chronic or acute), and the nature of the wound (i.e., open or closed). Common methods of addressing such injuries include auto-/allografts, tissue-engineered skin substitutes, simple wound closure (i.e., suturing), and wound dressings, the traditional woven versions of which are significantly limited by potential infection and adhesion to the wound site. In contrast, hydrogels offer an attractive option for wound healing/tissue regeneration [153]. A hydrogel can seal the wound to prevent exudate from leaking out (bioadhesive) and bacteria/fungi from accessing the wound (antibacterial/antifungal), keep the system hydrated, absorb exudate and inflammatory media (high swelling ratio), have sufficient mechanical strength to remain intact over the required period, resist the applied stresses faced (including physical handling), allow proper gas exchange, decrease the healing time compared to normal physiological process (gas permeable), and avoid provoking a large inflammatory reaction that would result in adhesion between the wound dressing and the underlying wound that could result in re-irritation of the site and/or patient discomfort (low protein adsorption) [154]. Compared to synthetic adhesives, hydrogels typically offer lower adhesive strength but also lower

inflammation and improved capacity to absorb exudate and/or deliver active agents to assist with the wound healing process [155–157].

Common types of hydrogels used for wound healing include synthetic polymer-based gels like poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), and poly (urethanes) (PU) as well as bio-based, polymer-based gels such as dextran, silk, gelatin/collagen, alginate, cellulose, and chitosan [158–160]. To address the key challenge of anti-infective properties, nanocomposite hydrogels incorporating silver nanoparticles (AgNPs) have been successfully demonstrated to inhibit bacterial and fungal growth [161], although the incorporation of copper ions, zinc oxide [162], and/or charged polymers (e.g., zwitterionic or quaternary ammonia grafts) [163] also assists in maintaining sterility. Multifunctional hydrogels can also be designed that combine the favorable properties of wound healing hydrogels with the release of therapeutic agents in order to accelerate healing and/or deliver anti-infective drugs, further controlling the microorganisms' growth at the site of the wound [164].

3 Personal Care Products and Cosmetics

A personal care product describes any substance used for the purpose of personal grooming and hygiene [165], while a cosmetic has been defined by the US Food and Drug Administration (FDA) as an "article an intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body. . .for cleansing, beautifying, promoting attractiveness of altering the appearance" [166]. Many commercial and household products can be classified as personal care products or cosmetics, including skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup, hair colors and dyes, deodorants, mouthwashes, and toothpastes [167]. Newer markets are being addressed as novel chemistries are developed, such as the use of smart supramolecular hydrogels [168] and/or hyaluronic acid-based gels [169] for anti-aging/anti-wrinkling products.

While many traditional cosmetics are based on creams, aerosols, and other hydrophobic and often colloidal delivery forms, hydrogels can play a role in such materials as viscosity enhancers to improve the delivery (i.e., the emollient feel of a cosmetic) and/or introduce additional viscosity to reduce the rate of emulsion or suspension instability [165]. Nanocomposite hydrogels containing liposomes [170], block copolymer self-assembled nanoparticles [171], and other nanoscale/microscale emulsions or particles capable of loading hydrophobic drugs [172–174] offer the dual benefits of prolonged drug delivery of molecules likely to penetrate into the skin (small hydrophobes) coupled with the capacity to retain moisture. Most hydrogel-based additives for these and other cosmetic applications apply polysaccharide-based gels since they are abundant in hydroxyl groups (and are thus moisturizing), are good rheological modifiers, produce inert degradation products, and promote sustainable manufacturing practices [175–177]. "Green" cosmetics based on replacing oil-based materials with hydrogel-based materials have also attracted interest (e.g., tamarind seed-extracted polysaccharides coupled with

hyaluronate and xyloglucan as a cosmetic formulation for skin creams [175]) based on consumer trends.

Hydrogels have been heavily used in the diaper and sanitary pad industry for over 30 years, with superabsorbent polymers (SAPs) particularly broadly employed due to their favorable water retention properties and thus capacity to absorb bodily fluids, wick moisture away from the skin, and prevent rashes or skin discoloration [178]. While Harper [179] and Harmon [180] filed patents for superabsorbent hydrogels in 1966, one of the earliest SAP hydrogels used for personal care products was based on starch-*g*-polyacrylate for use in feminine napkin/pad hygiene products [181]. The first use of SAPs in the diaper industry was proposed by Umicharm in 1982 in Japan, allowing the production of diapers with less leaks and a more ergonomic design that assisted also in suppressing the colonization of germs and the risk of fecal contaminations [181]; current leading diapers continue to use similar SAPs in their design [182]. More recently, to address the challenges associated with the ecological fate of disposable diapers, degradable SAP hydrogels based on carboxymethyl cellulose, hydroxyethyl cellulose, or starch derivatives have been explored [183], although the total capacity for water retention remains lower than the best nondegradable polymers reported. The coupling of hydrogels with fibrous fillers has also enabled improvements in the retention of absorbed fluids into the gel even under external pressures and/or forces. For example, the combination of strong synthetic fibers (polypropylene, polyesters, copolymers of polyesters and polyamides) and a highly swellable acrylamide hydrogel can absorb 1 g of a 0.9 wt% NaCl solution in an hour even after being subjected to loads of 21,000 dynes/cm^2 [184].

Other compositions of hydrogels have been applied in other personal care applications. Hydrogels made from polymers like Carbopol (lightly crosslinked poly(acrylic acid), a SAP hydrogel), hydroxypropyl (methyl)cellulose, methylcellulose, Poloxamers, carrageenan, and alginate have been used to create high hydrated ointments and creams to maintain moisture [181, 185, 186]. Combinations of hydrogels with lipids, often also containing glycerin and/or short alkylglycols as compatibilizing solvents, have also been explored, with the lipid component of the formulations serving to enhance adhesion of the formulation to the hydrophobic skin. Lipids such as palmitic acid, oleic acid, and ceramides, all of which are natively found in the epithelium of human skin, have been found to be particularly effective additives.

4 Bioseparations

Hydrogels have been applied to bioseparations since the 1990s, leveraging the capacity of hydrogels to swell/deswell in aqueous solutions and exhibit relatively low non-specific adsorption [187]. The most common application of hydrogels in bioseparations is gel electrophoresis, the standard technique used in biochemistry to separate and semi-quantitatively assess the type and amount of different proteins and/or DNA molecules within a complex mixture. Hydrogels based on polyacrylamide (polyacrylamide gel electrophoresis, or PAGE) are most commonly used due

to their controllable pore sizes and ease of manufacturing, with the surfactant sodium dodecyl sulfate (SDS) typically added to the test solution (SDS-PAGE) to equalize the surface charge of all proteins/DNA being analyzed and thus promote protein separation via size alone (i.e., the size of the protein relative to the hydrogel mesh size). The electric field is applied to direct the diffusion of the biomolecule and accelerate the separation process. For very high molecular weight proteins or larger DNA segments with thousands to millions of base pairs, agarose gels are often used instead due to their larger average pore sizes and thus capacity to separate larger molecules [188].

Hydrogels can also be used for the purification of biomolecules, generally using one of two possible techniques. First, bioconjugation techniques can be used to graft antibodies for the desired antigen target to the hydrogel and provide affinity sites to promote antigen binding to the hydrogel. This approach is generally effective provided the 3D conformation of the antibody and the access to the active site are both maintained during the grafting process; however, subsequent recovery of the bound antigen can be challenging, particularly for stronger antigen-antibody binding pairs. Second, stimuli-responsive hydrogels triggered by temperature or pH (most common) have been exploited in order to dynamically tune the size selectivity of the hydrogel (via swelling/shrinking transitions) and/or the affinity of the hydrogel for the target molecules (via hydrophilic/hydrophobic transitions) [188]. For example, Feil et al. used a poly(N-isopropylacrylamide-co-butyl methacrylate) membrane to separate a mixture of uranine (MW = 376 g/mol), low molecular weight dextran (MW = 44,000 g/mol), and high molecular weight dextran (MW = 150,000 g/mol) by changing the temperature to alter the overall mesh size and thus the separation selectivity. Smart hydrogel pore-filled membranes can be used in a similar way to successfully separate proteins, enzymes, small solutes, polymer latex particles, viruses, and other biological contents [189, 190]. Alternately, the sol-gel transition observed in many thermoresponsive hydrogels can be leveraged to recover bound target molecules and/or resolved bands of specific biomolecules following a separation step. For example, thermoresponsive gel electrophoresis matrices have been reported that can solubilize upon cooling to enable effective "de-gelling" following the separation and thus facilitate the recovery of each separated protein [191, 192] in a spatially controlled manner [193] depending on where the gel is heated/cooled.

5 Environmental

The major application of hydrogels in environmental applications relates to their use as sorbents for heavy metals [194] or ionic dyes [195], both of which are frequent contaminants in industrial wastewater/effluents and must be removed prior to return of the effluent to the environment. The capacity of charged hydrogels for ion exchange can be exploited to replace lower affinity counterions (e.g., sodium) with heavy metal ions and/or ionic dyes that must be removed from water effluent [196]. The high swelling ratio of many ionic hydrogels also provides

high accessible surface areas for ion sorption, with superabsorbent polymers that typically contain both high charge and high swelling ratios (Sect. 3) being particularly attractive in this regard. Superporous hydrogels (SPHs) that combine high swelling capacity with macroporosity (typically templated based on similar strategies to those used to make macroporous tissue scaffolds, Sect. 2.1) are also highly attractive for similar types of sorbent applications given their higher accessible surface area compared to traditional SAPs. The earliest examples of SPHs were based on acrylamide, salts of acrylic acid, and sulfopropyl sulfate [187], while newer compositions are typically interpenetrating networks (e.g., divinyl crosslinked poly(acrylamide) interpenetrated with calcium-alginate) that maintain high swelling capacity but with significantly improved elastic properties [197]. It is this capacity for swelling that allows hydrogels to effectively compete with, or in some cases exceed the performance of, other types of micro-/macroporous sorbents (e.g., activated carbon) on a per mass basis [198] while avoiding the disadvantages of those alternative materials (e.g., processing costs, disposal costs, etc.) [194]. The capacity of hydrogels to swell and deswell as a function of ionization (i.e., pH) also offers the potential to regenerate hydrogels following their saturation with target heavy metals and/or dyes, with reuse over multiple (albeit not infinite) cycles observed in many cases [195]. The hydrogels must be highly stable for reuse to be effective, with nanocomposite-reinforced hydrogels often applied to improve gel toughness and thus the potential for repetitive sorption/desorption cycles [199]. Based on these collective properties, hydrogels can effectively address all steps of the required sorption cycle for continuous heavy metal/organic dye removal (Fig. 6).

The most common types of hydrogels used for heavy metal removal are based on biomass sources grafted with polyanionic polymers, with cellulosics, starch, and clay the most common biopolymers and poly(acrylic acid) or 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) the most common polyanions [200]. Hydrogels based on neutral but highly water binding polymers such as poly

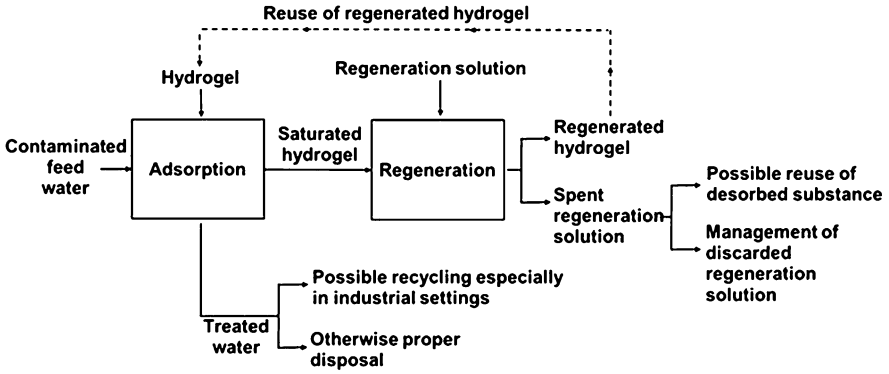

Fig. 6 Schematic of the use of hydrogels in the adsorption/regeneration process for binding heavy metal ions or organic dyes in wastewater. (Reproduced with permission from [195])

(vinyl alcohol) or polyacrylamide either grafted with polyanions [201] or derivatized to introduce anionic groups directly on the polymer backbone (e.g., sulfomethylation of polyacrylamide to form sulfonate groups) [201] have also been successfully used. Alternately, chelating grafts or even cationic grafts containing lone pair electrons can be used to bind cations through Lewis acid/base interactions, grafts that have been observed to offer the potential for higher selectivity for specific cations relative to simple ionic hydrogels [202].

For removing different types of organic dyes, the specific functional groups present on the hydrogel building blocks (e.g., –OH, NH_2, $–SO_3H$, –COOH, or $–CONH_1$) can be altered to control the affinity of the hydrogel for different targeted pollutants [200]. Cationic polymers such as poly(N,N-dialkylaminoethylmethacrylates), poly ((3-acrylamidopropyl)trimethylammonium chloride) (PAPTMACl), or poly (diallyldimethylammonium chloride) (PDADMAC) are widely used for the sorption of anionic dyes [195], while hydrophobic comonomers will also often promote dye sorption since many of these pollutants are highly aromatic [203]. Other additives are often incorporated into particularly micro-/nano-sized hydrogels to enable their effective removal from the water to allow for regeneration and reuse [198], with magnetic nanoparticles (enabling physical and low-energy separation of the gels from the wastewater via the application of a magnetic field [204]) particularly useful in this regard. Other nanoparticles have also been added to create active remediation hydrogels that have the capacity to actively bind *and* degrade organic dyes, with titanium oxide nanoparticles that can degrade organic compounds when UV-activated being the most common [205]). The excellent review by Khan and Lo is recommended for a broad-picture look at the various polymers and additives used to prepare hydrogels for environmental sorbent applications [195]. It should be noted however that truly selective removal of specific pollutants is typically challenging based on competitive binding and thus steric interference to the binding of the target molecule(s) in real wastewater samples [195].

The efficiency of pollutant removal depends on the kinetics, overall capacity, and pH activity range of a given hydrogel [195]. In a typical sorbent hydrogel, the degree of swelling (related to the crosslink density plus the solvent affinity of the gel building blocks) primarily controls the equilibration kinetics while a combination of the degree of swelling and the chemical nature of the backbone polymer and/or crosslinker used to prepare the hydrogel regulates the sorbent capacity of the hydrogel. Note that the use of micro-/nanogels instead of bulk gels can significantly enhance the kinetics of the response given the higher surface area to volume ratio and lower average diffusional path length to accessing all hydrogel binding sites (albeit at the cost of requiring a subsequent separation step to isolate these particles from the effluent) [198]. The pH must be equilibrated in a range that maintains the desired ionization of any ionic functional groups on the hydrogel important in driving heavy metal/dye uptake, with functional groups exhibiting very broad or indefinite pH ranges of ionization (e.g., sulfonates instead of carboxylates or quaternary amines instead of primary amines) offering benefits for maintaining high activity over a broad range of potential wastewater properties [195].

6 Natural Resources

The main application of hydrogels in natural resources lies in enhancing the recovery of oil from mature oil wells. Once easily accessible oil is pumped out, the well is typically flood with water in an attempt to utilize the hydraulic pressure of the added water to drive out residual oil trapped in the smaller pores of the reservoir. If a gel or a viscous polymer is co-injected with the water to fill a significant fraction (typically up to one half) of the now-empty part of the reservoir, the high viscosity and/or elasticity of the gel phase results in any additional water pumped into the well being specifically diverted through the (lower viscosity) residual oil-containing pores [206], based on the lower resistance to fluid flow through these pores. Such a process typically enhances the total oil recovered from a well by 5–30% [207].

Materials useful in this context must be low cost (~0.5 kg polymer required per barrel of additional oil production), highly water binding even in the presence of substantial salt concentrations, resistant to mechanical degradation, highly stable over time at high temperatures, and insensitive to oilfield chemicals [208]. As such, inexpensive and highly hygroscopic linear polymers such as partially hydrolyzed polyacrylamide or xanthan gum are most commonly used. However, relative to viscous polymer solutions, hydrogels have been demonstrated to improve this process in two ways. First, the capacity of superabsorbent hydrogels for binding water and resisting pressure (via the elasticity of the network) facilitates similar viscosity buildups and resistances to flow at substantially lower total polymer concentrations. Conventional superabsorbent hydrogels are limited in this context given that most depend on ionic interactions to drive swelling, interactions that are strongly suppressed in the high-salt oil well environment; furthermore, since the polymeric additive is often added to the well over the course of several years as more and more oil is removed (and thus water-filled pores form), the stability of conventional SAPs at high temperatures over this timeframe is non-ideal. Instead, a variety of clay-based superabsorbent nanocomposite hydrogels have shown promise in this context, with the clay component substantially improving the thermal stability of the gel [209]. Double crosslinking strategies combining covalent and ionic interactions have also been applied to this problem, allowing for increases in the mechanical resistance and stability of the gels to both pressure and degradation while maintaining superabsorbent swelling properties [210].

Second, the use of particulate hydrogels and/or in situ gelling hydrogels can overcome the challenges associated with pumping highly viscous linear polymer solutions into narrow pores within oil wells, as both particulate gels and in situ gelation precursor polymers have substantially lower viscosities at the same overall mass concentration relative to bulk hydrogels [211]. In either case, the lower viscosity of the pre-gel materials can improve the plugging of alternate water flow pathways and thus promote more effective recovery of residual trapped oil while requiring less energy to administer. Hydrophobically functionalized polyacrylamides that can self-associate at rest but are shear-thinning on injection are of particular interest for this purpose, enabling facile injection but effective viscosification once inside the well [212]. Alternately, ionic interactions have been used

to crosslink partially hydrolyzed polyacrylamide/clay nanocomposites using a dynamic crosslinking mechanism that facilitates injection [213]. Microgels (again primarily based on polyacrylamides and derivatives) [214] have also been successfully used in this context, with high viscosities being achieved in the well either via latent crosslinking interactions or colloidal close packing at sufficient concentrations [215]. Microgel nanocomposites containing clay or other additives can provide similar benefits as observed on the bulk scale in terms of thermal resistance, swelling, and stability [216].

7 Catalysis

Hydrogels have been applied in both biological and chemical catalytic reactions due to their unique compositions and porosities. First, hydrogels can prevent the aggregation and thus maximize the accessible surface area of catalytic nanoparticles to the catalytic substrate [217], maximizing both the efficiency and the kinetics of the chemical reaction. Second, the porosity of the hydrogel (and thus the accessibility of the substrate for the catalytic surface) can be altered as the gel swells in a given solvent condition and/or responds to an external stimulus [218, 219], allowing for control of the rate of reaction by altering the diffusibility of both the reagents to and products from the active site. Third, specific functional groups integrated within the hydrogel matrix can serve as both chelating and capping agents for metal nanoparticles, promoting their stabilization and helping to protect them from potential oxidation/deactivation [220].

Hydrogel-embedded metal nanocatalysts (termed hydrogel-M, M for metal catalyst) are commonly implemented for improving the production of hydrogen gas via metal hydride-catalyzed hydrolysis (e.g., the hydrolytic dehydrogenation of ammonium borane) [221–224]. Nanoparticles may be prefabricated and entrapped within a gel or formed in situ following gel preparation, with several ex situ catalytic nanoparticle-hydrogel systems having been described in which nanoparticles are deposited and immobilized on hydrogel matrices [225]. As an example, NiNPs can be formed in situ within the hydrogels during the reduction of 2- and 4-nitrophenols and other nitro groups [222, 226, 227].

Nanoparticles can also be formed in situ inside hydrogels by pre-soaking the hydrogels in a solution of the appropriate metal salts and then adding a reducing agent (e.g., sodium borohydride ($NaBH_4$), hydrogen gas (H_2), citrate, or ethylene glycol, depending on the metal ions used) to precipitate the salts into metallic nanoparticles [220]. However, reduction of the metal into nanoparticles is not always required for catalysis. For example, 4-vinylpyridine hydrogels have been shown to form complexes with chromate ions that themselves can be used to catalytically oxidize benzyl alcohol to benzaldehyde or alkyl alcohols into carboxylic acids, the latter of which is a very useful reaction in carbohydrate chemistry [228]. Extrapolation of these hydrogel-M systems for the degradation of both organic and water-soluble dyes/pigments, pesticides, and herbicides for environmental applications is also possible.

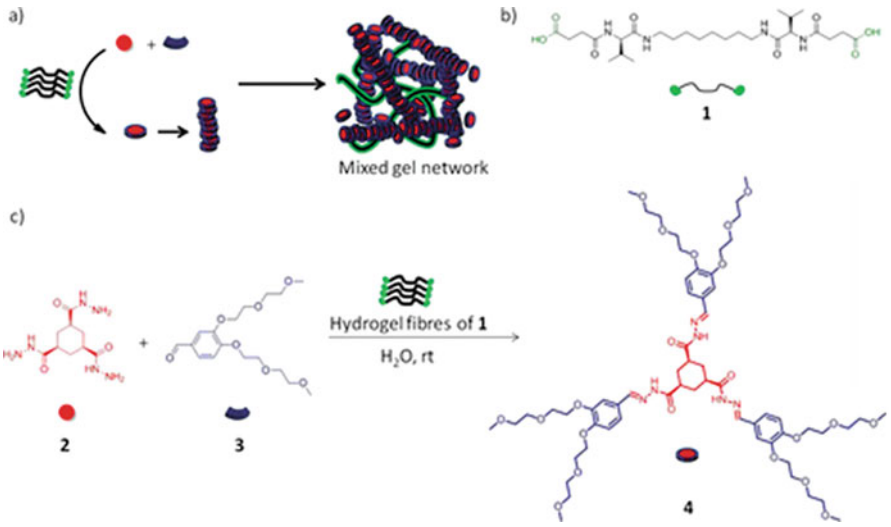

Fig. 7 Design scheme for the development of a double network supramolecular hydrogel in which the formation of the first network functions as a catalyst to drive the formation of the second network. (Reproduced with permission from [233])

Other hydrogels can serve complementary roles in catalytic reactions. For example, hydrogels have been used to coat anodes and cathodes to control the movement of ions for various electrochemical processes, with the role of the hydrogel in promoting the dilution of ions at the electrical source having been demonstrated to increase the overall efficiency of electrochemical reactions [229]. Additionally, enzyme-loaded hydrogels can be used to facilitate hydrogel crosslinking and self-healing [230, 231] and/or catalyze biochemical reactions; as an example of the latter, aptamer-crosslinked polyacrylamide hydrogels with molecular recognition have been used to immobilize glucoamylase on a paper substrate and support cascaded enzymatic reactions for signal amplification and subsequent sensor readouts for point-of-care diagnostic devices [232]. Catalytic activity can also be applied in the context of hydrogel synthesis. For example, in the case of double network hydrogels, the first network can be used to catalyze the formation of the second using orthogonal chemistries, as shown in Fig. 7 [233].

8 Agriculture

Finally, hydrogels have been applied in various agriculture and horticulture applications. The most basic of these examples involves the loading of hydrogels with active agrochemical agents, either directly (e.g., simultaneous drug loading and gel synthesis) or indirectly via passive diffusion/solvent evaporation/centrifugation following gel formation. A variety of agriculturally active agents such as pesticides [234], fungicides [235], herbicides [236], and fertilizers [237] have been formulated

in hydrogel delivery vehicles for field use. The most popular starting materials for preparing agricultural hydrogels include polysaccharides (facilitating high water retention and degradability) and superabsorbent polymers (SAPs) like poly(acrylamide) or poly(acrylic acid) [238, 239]. The use of SAPs is particularly of interest since the hydrogel can not only improve the release profile of the active agent but also promote a higher amount of water retention in the soil, beneficial to facilitate seedling emergence [240] and plant sustenance during drought conditions [241].

Controlled fertilizer release is the most common target of hydrogel formulations, enabling less frequent reapplication of fertilizer by farmers. Hydrogel coatings on fertilizer particulates are most widely used in slow release fertilizer (SRF)/controlled release fertilizer (CRF) formulations, with the coatings designed to protect the fertilizer from the soil microenvironment and release the contents over a time dependent on its degradation rate [242]. Alternately, to avoid any risk of loss of typically small molecule fertilizer compounds via leaching, oxidation, or evaporation, hydrogels can be designed that directly incorporate vital species for plants (i.e., N, P, K) into the hydrogel itself that can then be released gradually as the hydrogel degrades. As an example, Davidson and coworkers crosslinked a carboxymethyl cellulose (CMC) hydrogel with iron and calcium salts that degrades over time via ion exchange to allow for plant root-targeted delivery of various fertilizers [237].

Hydrogels can also be applied in other agricultural or horticultural applications. For example, Mori's group has developed hydrogel formulations for promoting seed germination. Plant seeds are placed directly on top of agar hydrogels to maintain an environment with controllably high water content in order to maximize the probability of seed emergence, avoiding the inconsistent and/or extreme wetness issues that can induce root burn or seed damage in soil [243]. The biodegradability of the natural polymer-based agar (and in other applications or chitosan [240]) hydrogels makes them useful either as a plant starter (after which the plant is transplanted in normal soil) or for growing full-sized plants in some applications [243]. Similarly, somatic embryoids have been encapsulated in alginate hydrogels and used as artificial seeds, with the design and functionality of such "synseeds" representing an alternative pathway to forming plants with a higher resistance to desiccation [244].

9 Conclusions

Hydrogels have tremendous potential to solve technological challenges across a broad range of applications. The diversity of building blocks and crosslinking strategies available for forming hydrogels leads to a broad range of accessible properties that can be rationally engineered according to the needs of specific end uses. Current research aiming to directly address the existing drawbacks of hydrogels – including the limited capacity of hydrogels to bear loads, maintain high hydration long-term in dry environments, prolong out-diffusion of loaded molecules, and further reduce protein adsorption – is expected to even further

broaden the applications of hydrogel-based materials. Furthermore, a growing understanding of how to process hydrogels to enable them to be printed both in 2D and 3D, structured internally by user-friendly, rapid, and highly controllable protocols, and delivered non-invasively (particularly for biomedical applications) will both improve the functionality of hydrogels in current applications and open new application areas. Fundamental modeling work to better predict the structure and physicochemical properties of nanostructured hydrogels also has significant potential to improve our understanding of structure-property correlations and thus design materials that still meet the key criteria of hydrogels but exhibit diverse physical, mechanical, and/or biological properties.

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