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Hydrogel design strategies for drug delivery

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Abstract

Hydrogels are water-swollen three-dimensional networks made of polymers, proteins, small molecules or colloids. They constitute a versatile platform for drug delivery, because of their capacity to encapsulate and protect drugs and provide sustained and/or remotely programmable spatial and temporal release, and have thus generated a substantial amount of research for the delivery of either small active compounds or biopharmaceuticals. This article discusses the features that make hydrogels attractive as matrices for delivery and reviews a range of designs, focusing on studies from recent years, in particular: "smart" hydrogels (responding to temperature, light, magnetic fields, ultrasounds or combined stimuli); recent technologies: 3D printing and microneedles; and closes by discussing polymer-free drug delivery systems: peptides, small molecules and colloids.

Introduction

Hydrogels are water-swollen networks usually formed of polymers, sometimes smaller molecules or colloidal particles, either chemically or physically cross-linked. Their interest as drug delivery systems (DDS) keeps rising (1)(2) - ca. 20k publications found with the keywords "hydrogel", "drug" and "delivery", half of them in the last 5 years - including a marked focus for applications in regenerative medicine and cell therapy (3) (a field beyond the scope of this review). Hydrogels present a wide range of design options in terms of the nature of the constitutive molecules, their functionality (e.g. co-delivery of multiple drugs (4)(5)(6)(7), simultaneous imaging and therapy (8–10), programmable and controlled release (1,11,12), the hierarchy of micro- and nano-environments accessible (hydrophobic or hydrophilic), and a plethora of additional possibilities, such as attaching ligands, combining them with nanoparticles (NPs), attaching drugs etc; for all these reasons, they provide a versatile platform for drug delivery, and some have made it to the clinic (1).

Conventional drug delivery involves the repeated administration of an active compound to maintain therapeutic levels in the body; this compromises patient compliance, efficacy and can lead to side effects due to high doses. Research in drug delivery has therefore focused efforts on achieving controlled and local drug delivery, using nanostructured systems, such as liposomes, nanoparticles, membranes and hydrogels. Hydrogels mostly comprise of water, offering an environment similar to natural tissues, tunable mechanical properties matching soft to hard tissues, and a capacity to encapsulate drugs, slowing or preventing their degradation, aggregation, prolonging their lifetime, while providing sustained release, controlled by diffusion out of or degradation of the matrix, or remotely controlled by external/endogenous triggers. Most hydrogels offer a hydrophilic locus of solubilisation, and are thus particularly attractive for biopharmaceuticals, a rapidly increasing area of new drugs approved, such as recombinant proteins and peptides (13)(14), monoclonal antibodies and polynucleotides (15)(16)(17), including siRNAs, an area of particular focus in recent years (18)(19)(20). Depending on their architecture however, hydrogels may also solubilise hydrophobic drugs, for instance when combined with polymer nanoparticles in nanocomposite gels (21) (22).

In terms of their architecture, hydrogels can be made from a very large range of building blocks (e.g. polymers – usually classified as natural or synthetic -, peptides (13)(16)(23)(24)(17), proteins (13), surfactants (25), colloids (26)(27), small molecules (2)(28)(29)…), with different chemistries, different arrangement of the building blocks and different types of connections (cross-links), leading, effectively, to a myriad of macroscopic and nanoscopic structures, size range, physical properties, and function; these characteristics determine which drugs are encapsulated (e.g. small drugs (2), proteins (30) or cells (3)(31)) and how they are released. On the macro-scale, hydrogels can be either "bulk"/macroscopic gels (suitable for transepithelial route, insertion or injection in the body), or microgels (32) (micrometers in size, suitable also for pulmonary and intrabony delivery (1)) or nanogels (33)(34)(35) (10-100 nm, suitable for systemic administration and studied for intra-cell delivery (1)(34)). Within the hydrogels, the size of the pores affects their deformability (if they are microscopic) and the diffusion of cells, while the mesh size (in the range of 100s of nm) dictates the release of drugs through diffusion; this can be altered though degradation and swelling of the matrix, either time-dependent or triggered. On the smaller length scale, specific interactions between the gel matrix and the drug also impact release, whether drugs are covalently conjugated to the polymer or interacting via physical bonds (hydrophobic, van der Waals, electrostatic etc).

A particularly attractive feature of hydrogels is the possibility of injectability (36), either imparted by shear-thinning properties, or by in-situ gel formation, which can be triggered by physiological temperature or other external stimuli (so-called "smart" or "stimuli-responsive" gels, cf section 1), in contrast to implantation in the body through invasive procedures. Both strategies explain the attractivity of physical gels *vs*. chemical gels, also referred to as "supramolecular" gels or "self-healing" gels (37), i.e. gels which are sustained by physical interactions instead of covalent bonds; these include van der Waals, hydrogen bonds, electrostatic forces and host-guest interactions, typically with cyclodextrins (14)(19)(37)(38)(39), or curcubit[n]urils (40). This versatility and inherent dynamic nature of crosslinks in physical gels, in addition to the absence of toxic crosslinkers and free radicals used in many chemical crosslinking protocols, make them particularly suitable for drug delivery applications, and explains why a lot of recent research has focused on supramolecular gels, which also constitute the majority of the gel designs discussed in this article.

This review on hydrogels for drug delivery does not intend to provide an exhaustive synopsis of the field - which is vast - but focuses on advances and curiosities of the last few years, with an emphasis on gel structure and function. Accordingly, a large section is devoted to stimuli-responsive gels, with selected triggers, followed by two sections on recent technologies, namely, 3D printing of hydrogels and hydrogel-based microneedles. The last section discusses polymer-free hydrogels, namely, small molecules, colloids, and carrier-free gel drug delivery systems (DDS). While cell delivery is mentioned, hydrogels as biomaterials for cell therapy or regenerative medicine is not the subject of this article and a review on the topic can be found elsewhere (3).

1. Remote or endogenous triggers to control delivery: "smart" gels

Over the past decade, research into hydrogels has evolved from inert matrices to "smart" materials, namely, materials that change their behaviour in response to one or several stimuli, or their combination. While self-assembled surfactant aggregates offer an ideal platform to craft dynamically responsive gels (25), the majority of drug delivery devices are based on polymers, due to a larger solubilisation locus and safety profiles. Responsiveness is advantageous in the area of delivery, as it enables the controlled and targeted release of a payload (41); growing clinical evidence supports the value of more complex release profiles, such as patient-specific kinetics, on and off on-demand

release, pulsatile (11), or sequential release of different therapeutics (42). Conventional triggers include pH and temperature; the former, which has been known well before the concept of "smart" DDS was developed, is not covered here. The explosion of so-called "thermogels", mostly in tissue-engineering applications, but also for drug delivery, justifies a mention here. While substantial effort has gone into smart materials, it is worth noting that clinical translation remains in its infancy, with most clinical treatments still delivered passively at set times, and current challenges lying in the penetration of the activation signal, delivery and retention at the target site, control of the trigger in vivo, and inherent materials complexity (11). The most straightforward design relies on "nanocomposite gels" (21), a hydrogel matrix acting as the actuator (i.e. undergoing physical change), as well as potentially acting as the drug solubilisation locus, while embedded nanoparticles act as the transducing material (receiving the signal and converting it into a stimulus); however, other designs have been proposed too and, while the focus here is on macroscopic gels, stimuli-responsive injectable nanogels (33)(43) and microgels (32) are also emerging.

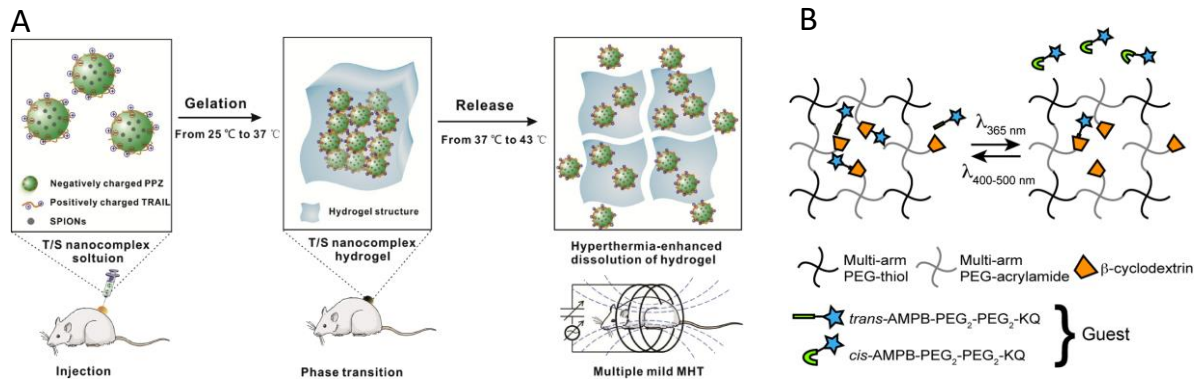

Figure 1. (A) Schematic diagram illustrating temperature-induced gelation and further dissolution of nanocomplex hydrogels based on the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), a homotrimeric type 2 transmembrane protein-ligand belonging to the TNF cytokine family, and superparamagnetic iron oxide nanoparticles SPIONs (T/S). The T/S nanocomplex solution, containing negatively charged poly(organophosphazene) (PPZ), positively charged TRAIL, and hydrophobic SPIONs, turns into a hydrogel at physiological temperature (37°C). Multiple magnetic hyperthermia therapy (MHT), a technology based on the energy conversion of SPIONs under an alternating magnetic field (AMF) can enhance the release at mild temperatures (43°C). Reproduced from (27) **(B)** Example of light as a trigger: the irradiation at λ = 365 nm induces the isomerization of the azobenzene (Azo) attached to a model drug, weakening the binding affinity between Azo and β-cyclodextrin (β-CD), releasing Azo from the cavity of β-CD, which is tethered to a tetra-PEG hydrogel network, making the release rate photoresponsive. Reproduced from (14)

1.1. Thermogels

Thermally triggered drug delivery is the most traditional and easily implemented stimulus and the literature utilising this trigger is vast (44). Typically, thermogels rely on the existence of a phase-transition between room temperature and physiological temperature, e.g. a lower critical solution temperature (LCST), such as poly(N-isopropylacrylamide) (PNIPAM) or poly(oligoethylene glycol methacrylate) (POEGMA), or a volume phase transition temperature (VPTT) (45). This transition is usually actuated by the change in temperature occurring from contact of the material with the body, e.g. after injection, enabling in practice the in-situ gelation of the material, thus used as a depot formulation. The field of thermogelling polymers is thriving, for a range of biomedical applications not

limited to drug delivery, in particular tissue engineering and cell therapy (3)(46)(47)(48), and are not covered here. More recent developments, as discussed in the next sections, rely on encapsulating, within the thermo-responsive hydrogels, a material that locally generates heat, in response to an external trigger, thus inducing a phase transition; NIR, for this purpose, is attracting a lot of interest, based on the surface plasmon resonance effect (SPR), typically of gold nanoparticles or other metallic NPs, such as platinum NPs (49) or copper sulfide (50)(51). In this case, the external trigger that induces a phase transition may be a gel-sol transition, which enables the release of a cargo.

An original application of a thermogelling polymer based on PPG, PEG and tetraphenylethene (TPE) – a typical chromophore with aggregation-induced emission (AIE) - was proposed for the in vivo drug release monitoring of drug concentration and matrix erosion, based on the concept of AIE (52). AIE relies on aggregation-dependent fluorescence emission, allowing the non-invasive monitoring of drug concentration to maintain dosage in the therapeutic window.

An original thermogelling construct was proposed by Zhang et al (27) (**Figure 1A**), combining the thermally-triggered gelation of poly(organophosphazene) (PPZ), and the multiple magnetic hypothermia (MHT)-induced release of TRAIL (tumour necrosis factor-related apoptosis-inducing ligand), a promising monotherapy strategy for cancer, but limited by its short biological half-life. The design involved positively charged TRAIL and oleic acid-coated SPIONs (superparamagnetic iron oxide nanoparticles) nanoparticles, interacting with negatively charged PPZ. The construct assembled into weak gels upon injection at body temperature, while the release of TRAIL was enhanced by MHT-mediated gel dissolution at higher temperature during hyperthermia (**Figure 1A**).

Focusing on the role of chirality to design thermogelling polymers, Mao et al (53) explored the stereocomplexation of complementary chiral blocks, with constructs based on an enantiomeric mixture of poly(*D*-lactic acid((PDLA)/PEG diblock and poly(*L*-lactic acid(PLLA))/PEG; the polymers exhibited multiple gel-sol-gel transitions upon heating, which were rationalised by small- and wide-angle X-ray scattering, and used to tune the release of the cancer drug doxorubicin (DOX).

Using heat-induced phase transition as the response of another trigger, a flexible patch for transdermal delivery was developed by Evanghelidis et al., combining PNIPAM with a microstructured heater based on an electrospun polymer fiber network covered with a thin gold layer and attached to flexible PET substrates (45). When submitted to a 3V current, the patch heated up and released a model drug from the gel matrix.

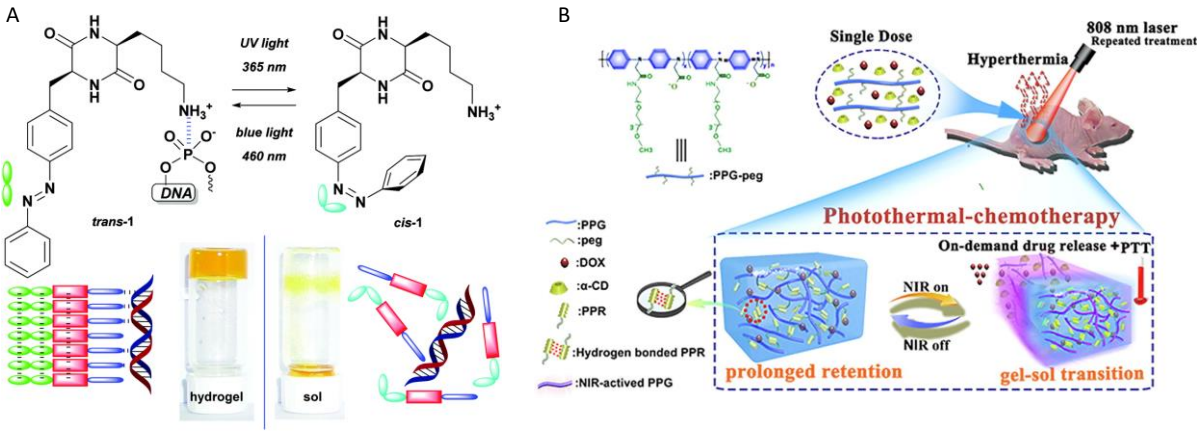

Figure 2. (A) An azobenzene (Azo)-containing cyclic dipeptide (PAP-DKP-Lys) acts as a photoresponsive low Mw gelator (LMWG), based on known 2,5-diketopiperazine-based gelators, but replacing the phenyl rings with *trans*-Azo. The hydrogel undergoes a gel-sol transition upon irradiation at λ = 365 nm due to the photoisomerisation of Azo; the gel reforms upon irradiation with blue light. Polyacids, such as DNA, may further stabilise the fibres and be released upon irradiation. Reproduced from (17)**(B)** Schematic illustration of the fabrication of supramolecular gel responsive to NIR irradiation

and its application for repeated photothermal-chemotherapy with one-dose injection. The gel is based on the conjugated polymer (poly(*N*-phenylglycine) (denoted here as PPG) grafted with poly(ethylene glycol) (PEG) side-chains, which complex with α-cyclodextrin, forming pseudopolyrotaxanes (PPR) that act as cross-links for the network. Under NIR irradiation, the conversion of light into heat leads to the melting of the gels, due to weakening of the inclusion complexes, inducing the release of an encapsulated drug (DOX). Reproduced from (54).

1.2. Photo-controlled release: light and NIR

Light offers a number of advantages as a trigger: low-cost, ease of tunability of wavelength and intensity, spatiotemporal control, and a wide range of chemistries available to design photo-responsive hydrogels, as reviewed elsewhere (44). Light in the UV (10-400 nm) and visible (390-700 nm) range however has very low penetration (due to high absorption) and can damage tissues as much lower power than NIR; it is therefore limited to near-surface tissues, transdermal delivery (55), or following a surgical procedure using a standard clinical blue light (400-500 nm, 400-600 $mW \cdot cm^{-2}$), for instance to induce clinically relevant fast gelation (56). The principles of light as a trigger often relies on the use of photo-actuated bond-isomerisation, typically with coumarins, spiropyrans, azobenzene, (44). For instance, the UV-dependent host-guest complex formation between azobenzene and β-cyclodextrin can be exploited to tune gel formation or breakage, and thus the release of a hydrophilic payload from a PEG-based, such as a short peptide, as demonstrated by Anseth et al. (14) (**Figure 1B**). The photoisomerization of azobenzene was also exploited in the design of low molecular weight gelator (LMWG) based on the 2,5-dikitopiperazine motif (17), which rely on the hydrogen bonds provided by the heterocycle and π-π stacking of non-polar rings. Replacing the phenyl with trans-azobenzenes retains the gelation mechanism, binding long dsDNA oligomers inside the fibrous network, but can be switched with light when isomerised into the polar and non-planar cis-azobenzene, thus releasing DNA (**Figure 2A**). An original design was proposed by Wang et al (57), who developed a photoresponsive gel based entirely on a recombinant protein, by stitching together the photoreceptor C-terminal adenosylcobalamin binding domain ($CarH_c$) proteins. The polymeric $CarH_c$ proteins assemble into a gel in the presence of adenosylcobalamin in the dark and disassemble upon exposure to light, providing a facile mechanism for recovery/release of stem cells and proteins. Finally, light actuation can also rely on the incorporation of metallic NPs that generate heat upon light irradiation and can induce a volume transition in a thermoresponsive polymer, as mentioned in the previous section. This approach was adopted by Kim et al. in transdermal patches based on gel nanocomposites of poly(N-isopropylacylamide-co-vinyl-2-pyrrolidinone) beads and magnetite in an alginate template, which were actuated by blue light of 47.5 $mW \cdot cm^{-2}$ (55); the light-triggered release could be modulated by adjusting exposure time and light intensity.

For in vivo applications, NIR is more attractive than other ranges of wavelengths from the photochemical spectrum due to deeper tissue penetration (ca. 2 mm through skin) and higher biosafety. For cancer therapy in particular, where localised therapeutic approaches with high efficacy and specificity and low adverse effects are needed, NIR-light responsive drug-loaded hydrogels are attractive. NIR-responsiveness typically relies on the use of nanocomposite gels with metal-based nanoparticles displaying NIR plasmon resonance, such as platinum, copper sulfide (50)(58)(59) or carbon-based materials. Recently, 2-dimensional NIR phothermal agents, such as graphene oxide (60), black phosphorus (BP) (61) and MoS_2 (62), have also received attention due to their excellent NIR absorption and large specific area. For instance, Qiu et al (61) reported the precision delivery of cancer drugs to a tumour site by NIR-induced decomposition of a nanocomposite agarose gel containing BP. BP presents a high photothermal conversion efficiency and a tunable, direct energy band gap. By converting light to energy, the gel could reversibly undergo on-demand hydrolysis and softening,

releasing a loaded drug (DOX) from the matrix at a specific site, with gel melting being highly dependent on the power of the laser (between 1-3 $W \cdot cm^{-2}$). Wu et al. developed a NIR responsive gel based on a short thermoresponsive peptide (NapGFFYD) with embedded PEGylated 2D niobium diselenide ($NbSe_2$) as the NIR photothermal agent, in a move towards increased biocompatibility (23).

Leaking of nanoparticles out of hydrogel matrix or their aggregation compromise the efficacy of photothermal therapy (PTT). Zeng et al. addressed this issue by modifying gold nanorods with polydopamine, inspired by the adhesive properties of mussel (59), thus tethering the gold nanorods within the thermoresponsive matrix comprised of β-glycerolphosphate-bound chitosan and dopamine-modified alginate. An alternative strategy, which circumvents the use of nanocomposite gels, is the use of conjugated polymers (CPs) in the gel structure. CPs are versatile materials that are attracting increasing interest in particular for bioimaging applications (63)(64)(65). Liu et al for instance exploited the well-known host-guest interaction between PEG and α-cyclodextrin to build hydrogels (66), where PEG chains were grafted on a CP backbone (poly(*N*-phenylglycine, PNPG), endowing the gel with high photothermal conversion efficiency (η=52.6%) (54) (**Figure 2B**), which allowed the triggered release of DOX. The host-guest complexes acting as cross-links to the network impart shear-thinning properties and thus injectability. The same building blocks were used by Ruan et al (67), using nanocomposites of PNPG and PEG (where PEG may be simply tethered by PNPG polymers via hydrogen bonds and physical entanglements), subsequently incorporated in a gel by the addition of α-cyclodextrin. The gels had a broad NIR-I (650-900 nm) and NIR-II (1000-1700 nm) absorption and showed high photothermal conversion efficiency (ca. 40%); the chemotherapeutic cisplatin could be repeatedly released upon subsequent cycles of NIR irradiation. CP can also be prepared as nanoparticles (64), and incorporated into a thermoresponsive gel matrix, as in the example by Wu et al (68), where NPs or films based on poly(diketopyrrolopyrrole-*alt*-3,4-ethylene-dioxythiophene) were incorporated into a PNIPAM gel and were able to release a drug on demand via NIR irradiation.

Many of the designs described in this section rely on the use of thermosensitive polymers, which shrink upon NIR-triggered heat generation. A different approach was adopted by Anugrah et al, who exploited the capacity of indocyanine green (ICG) to generate reactive oxygen species (ROS) when irradiated by NIR, which can then cause oxidative damage on weak covalent bonds such as redox-sensitive diselenides (Se-Se) (69). The gel, based on alginate, involved the functionalisation of alginate with norbornene groups and the introduction of diselenide-tetrazine (Se-Tz) crosslinkers to produce NIR-responsive linkages through a click reaction. NIR-irradiation triggered the rupture of Se-Se bonds, enabling the modulated release of encapsulated DOX, based on power density (1-2 $W \cdot cm^{-2}$).

While the systems presented in this section show promise, they remain proof-of-concept studies. Amongst the challenges is the development of photochemical reactions and processes that are fast, efficient, and activated by low-energy (long) wavelengths.

1.3. Magnetic gels

Magnetic fields represent another method for external activation of drug release, usually relying on the incorporation of superparamagnetic NPs into the hydrogels, and the use of either static or alternating magnetic fields. Classically, SPIONs, NPs of 5-20 nm in size, have been extensively used for this purpose, due to their biocompatibility, precisely controllable composition and size, and degradation into nontoxic iron species. The application of a static magnetic field can be employed to remotely mechanically deform a ferrogel, resulting in fluid convection and release of a payload. For instance, Mooney et al. demonstrated that they could regulate release rates from a ferrogel by tuning the magnetic signal; specifically, they developed a SPION-containing biphasic alginate gel (42,70)

(**Figure 3A**) to induce the triggered release of a payload, after a delay of 5 days, and achieved a payload 690- to 1950-fold higher than the unstimulated baseline values; the design proved particularly efficient to achieve a sequential payload release, by tuning the frequency (42). The optimization of pulsatile profiles may be particularly beneficial in chemotherapy to maximise anticancer toxicity, reduce off-target side effects and address adaptive resistance, as shown recently by Kennedy et. al (12), who systematically investigated the timing and rate of the magnetic stimulation with the same biphasic alginate gels (42,70)(**Figure 3A**), incorporating the chemotherapeutic mitoxantrone, and comparing for instance the impact of continuous vs. pulsatile delivery on the survival of melanoma cells (**Figure 3B-C**). An enhancement of the effect of magnetic fields can be achieved by incorporating macropores, for instance by introducing gelatin particles which melt at physiological temperature, which result in an increased deformation induced (71).

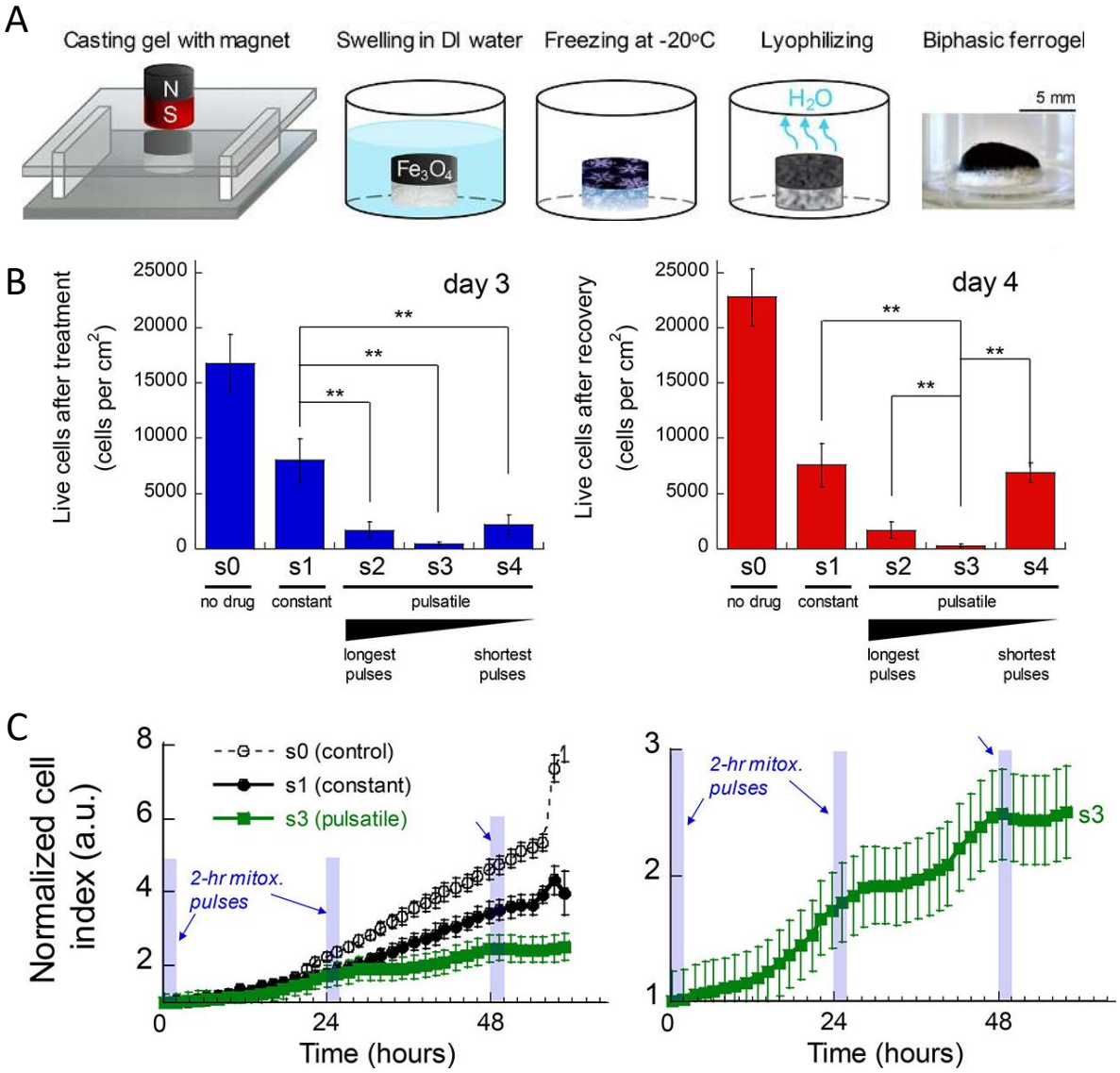

Figure 3. Magnetically responsive hydrogels enabling pulsatile chemotherapeutic delivery profiles **(A)** A schematic of the biphasic ferrogel fabrication process. The biphasic ferrogels were made of alginate crosslinked with 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDC) contain iron oxide powder, which is concentrated to one side of the gel, with the use of magnets. The gels were then left to swell, frozen at −20 °C to form ice crystals, and finally lyophilized to evaporate the ice crystals, leaving pores. Pulsatile temporal delivery profiles enhance the toxicity of mitoxantrone exposure when compared to

constant delivery profiles: **(B)** quantification of live cells after constant (s1) or various pulsatile (s2-s4) delivery profiles immediately after treatment (left, blue) and after a day of recovery (right, red). **(C)** Left: Normalized cell index (melanoma cell population) vs time when exposed to no mitoxantrone (dashed black), constant mitoxantrone concentration (s1, solid black), and a pulsed mitoxantrone profile (s3, solid green). Right: Zoomed-in index vs time for cells exposed to pulsatile schedule s3. Blue rectangles indicate where the mitoxantrone pulses are "on" for the s3 condition. Reproduced from (12).

Injectability being an attractive feature, SPIONs have also been embedded in nano- or micro-gels; shortcomings, however, are linked to fast release - even in the absence of activation - and the rapid sequestration of gel particulates by the lymphatic system (72). To overcome this leakage, microgels have been incorporated into in-situ forming hydrogels, together with SPIONs. Campbell et al. for instance developed thermoresponsive microgels prepared by the co-polymerisation of NIPAM and *N*-isopropylmethacrylamide that undergo a 90% decrease in volume when heated; AMF pulses increased the release rate of 4 kDa FITC-dextran by a factor of 4, with an enhancement that persisted over days (72). Departing from the widely used SPIONs, Yassine et al used microfluidics to incorporate anisotropic iron nanowires (FeNWs, with dimensions 500 x 45 nm) into PNIPAM microgels; these gelled in situ and achieved 70% drug release using repeated pulses of 20 kHz and a power 5-fold lower than conventional AFM, exploiting frictional heat generation (73), therefore demonstrating a better potential for translation to the clinic where magnetic fields are in the few kHz/MHz range and with a lower power than fields typically used in research. Exploiting other heating mechanisms, gold NP films have also been used in PNIPAM hydrogels, where the heat is generated via the induction of eddy currents, resulting from the collective conductivity of the supra-molecular gold film structure (74); the long-term stability of gold in-vivo is advantageous (compared to SPION which can degrade and oxidise over time), while AMF overcomes the depth penetration issue linked with NIR-activation.

1.4. Healing sound: ultrasounds as a trigger

Compared to light, ultrasounds (US) offer highly effective penetration into soft tissues and can trigger drug release either through thermal or mechanical effects generated by cavitation phenomena or acoustic convection forces. US activation is usually irreversible, i.e., it does not enable the on-off control offered by other triggers (75). For this reason, self-healing polymers are advantageously used with this trigger. Huang et al. for instance proposed Fe^{3+}-[PEG-Dopa] hydrogels based on mussel-mimetic metal-catechol coordination bonds, offering intermediate bond strength, balancing robust mechanical properties with the possibility of disruption by US (76). Sun et al. exploited double-network hydrogels, where one network provides mechanical stability, while the other is disrupted by US, inducing the triggered release of drugs linked to the polymers by dynamic covalent bonds (77). The weak physical connections formed in host-guest complexes (a strategy previously mentioned, e.g. **Figure 1B**) have also been exploited in a construct based on PEG end-modified with either adamantane (Ada) and β-cyclodextrin (78). The mechanical distortion of the β-CD cycle results in the break-up of the Ada: β-CD inclusion complexes, hence the break-up of the gel connections and the release of proteins embedded in the gel structure.

The strongest promise of US perhaps lies in their use for transdermal delivery, as they have been shown to be particularly advantageous to enhance transdermal delivery, disrupting the intercellular lipid bilayer structures in the stratum corneum, thus improving the permeability of the skin. This effect was capitalized on in diclofenac sodium (DS) patches, where burst release was avoided by using the "nanocomposite gel" strategy, with the drug loaded in polyester microcapsules, themselves embedded in a four-armed PEG hydrogel patch (79). In this case, US work both as a penetration

enhancer and a trigger for the release. Hydrogels have been shown to enhance skin permeability when used as a coupling medium with low frequency ultrasound, resulting in increased localized transport regions (80).

1.5. Other stimuli

An original and less widely studied trigger for drug delivery relies on the response to mechanical forces (compression, tension or shear), either physiological or externally applied, and has been reviewed recently (81). Di et al for instance developed a microgel-embedded elastomer; DOX could be released from the microgels through stretching, as the spherical microgels become ellipsoidal in shape, increasing the surface, and thus the release rate (82). Bioresponsive materials represent another promising area of development; these hydrogels can be actuated by biological cues or pathological signals, with enzymes (83), glucose concentration (84)(85)(86), ATP/ATPase (87), and have been reviewed recently (88). Examples of bioresponsive gels are discussed in the following sections, and **Figures 4** and **6**.

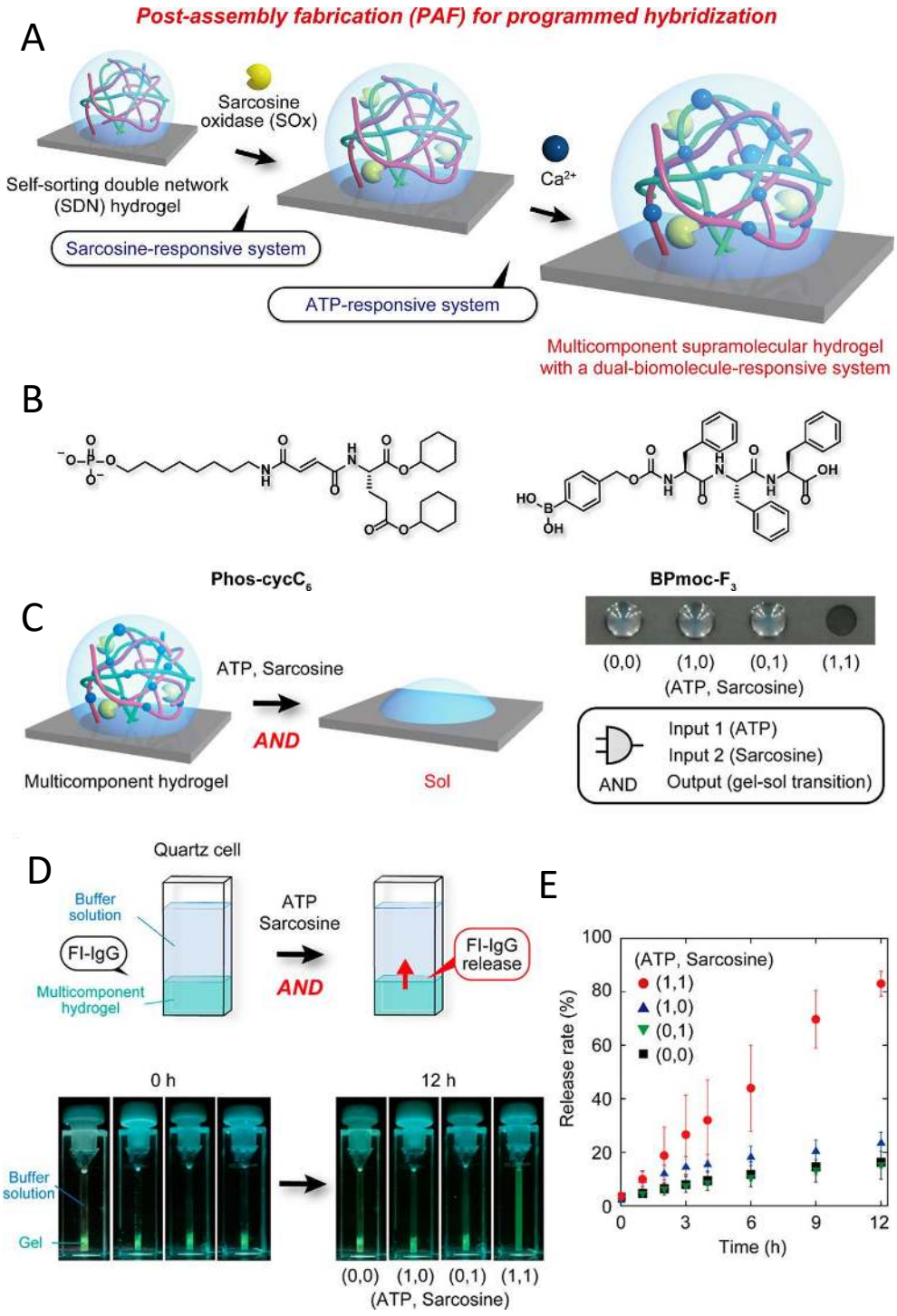

Figure 4. Illustration of the fabrication and properties of a dual responsive hydrogel based on a self-sorting double network (SDN), which responds both to adenosine triphosphate (ATP) and sarcosine. **(A)** Schematic representation of the post-assembly fabrication strategy for the construction of the SDN hydrogel. The additional components (sarcosine oxidase (SOx) and Ca^{2+} ions) are sequentially added to the SDN hydrogel composed of **(B)** Phos-cycC_6 and BPmoc-F_3. **(C)** AND logic gate-type response (gel–sol transition) of the multicomponent hydrogel to ATP and sarcosine. **(D)** Schematic representation of controlled fluorescein labelled immunoglobin G (Fl-IgG) release experiments. **(E)** Photographs of the multicomponent hydrogels encapsulating Fl-IgG before and after the addition of ATP and/or sarcosine (taken under UV light in a dark room). **(F)** Fl-IgG release profiles from the multicomponent hydrogel under various conditions. Reproduced from (89).

1.6. Multi-responsiveness

Responsiveness to more than one stimulus can give finer control over release kinetic profiles, enabling multiple delivery of different payloads, while also opening the way to theranostics, i.e. sensing/imaging combined with therapy (90). For instance Cao et al (91) reported nanogels comprising the hydrophilic poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) and hydrophobic photocleavable *o*-nitrobenzyl (ONB), which enabled the controlled co-delivery of a hydrophobic cargo from the lipophilic cores (via pH, UV and temperature) and a hydrophilic cargo linked to PDMAEMA via disulfide junctions (through redox activation). Tanaka and co-cowers (89) recently proposed an original design based on self-sorting double-networks (SDN) based on Phos-cycC_6/Ca^{2+} and BPmoc-F_3/So_x as the gelator pair, shown previously to orthogonally self-assemble (92). The hydrogel was dually responsive to adenosine triphosphate and sarcosine, programmable in an AND logic gate fashion, which enabled the controlled release of an antibody (89) (**Figure 4**). Combining light and biological triggers, Wang et al (90) fabricated carbon dots-embedded microgels, where carbon dots act as upconversion fluorescent probes; the delivery system can simultaneously detect glucose (using NIR light) and deliver insulin as a response.

A new level of multi-stimuli responsiveness was proposed by DeForest et al (24), who reported a modular framework based on a library of peptides which, through the connectivity of orthogonal stimuli-labile moieties acting as cross-links for the network, respond to a range of environmental cues (enzyme, reductant, light), inducing the sequential and spatiotemporally varied release of encapsulated cells or proteins. By controlling the molecular architecture, this platform provides biocomputational capacity through the combinations of Boolean YES/OR/AND gates, enabling the tailored, user-specific release of therapeutics triggered by environmental cues.

To conclude this section on “smart” hydrogels, it must be acknowledged that while the versatility and sophistication in designs and functionalities reported in the literature to date is admirable, the inherent complexity of the fabrication and control makes translation to the clinic challenging. While many of these gels have shown success in animal models, very few have proceeded to clinical trials. Further discussion of the successes, challenges and future directions of “smart” materials can be found in this review (11).

2. 3D printing of hydrogels

With the increasing focus on individualised medicines with tailored doses, there has been a rising emphasis on bespoke methods of preparing medicines at the point-of-care. In this context, 3D printing (3DP, also referred to as “additive manufacturing”) is an emerging technology that allows the fabrication of complex, three-dimensional objects from computer-aided design (CAD). The structure is built layer-by-layer from a series of thin horizontal cross-sections, circumventing the use of moulds, thus giving a high degree of flexibility in the design. In 2015, the FDA approved SPRITAM, a rapidly dissolving levetiracetam tablet for oral suspension, demonstrated the power of 3DP technology to rapidly manufacture dosage forms on-demand, fuelling interest in this technology (93). The use of hydrogels with 3DP is emerging, and, similarly to the use of microfluidic techniques to generate microgels (30)(31), has been particularly focused on applications in regenerative medicine, for the manufacture of complex tissues where different cell types can be deposited within a single construct; there are however some examples of 3D printed gels for drug or gene delivery. The use of 3D printing has been quite notable for instance in the field of wound healing to design hydrogel-based skin substitutes with complex nanostructured layers (94), which can incorporate growth factors (46) or NSAIDS such as lidocaine (95).

Polymer solutions can be used as “bioinks”, provided that they are shear-thinning, and that gelation can be triggered post-extrusion, either by chemical cross-linking or a physical trigger (such as temperature). This technology has been envisaged for instance in ophthalmic drug delivery, to build drug delivery devices that can address the challenges of delivery to the back of the eye, e.g. with implantable pump systems (96), or Micro-Electro-Mechanical Systems (MEMS), with drug-infused hydrogels (96). 3DP is also being employed to manufacture micro- and nano-robots, or “microswimmers”, which could find applications in future diagnostic and targeted delivery applications, for instance to reach confined inner compartments of the body. Microswimmers belong to the class of “Active Matter”, a novel class of non-equilibrium materials, which consume energy and generate directed motion. Biodegradable microrobots have been made using 3DP from the two-photon polymerisation of photocrosslinkable hydrogel gelatin mathacryloyl (GelMA), decorated with magnetically responsive nanoparticles (97), which can be designed to respond to pathological concentrations of metalloproteinase-2 (MMP-2) by swelling (due to gelatin target cleavage sites), thus releasing an embedded cargo (8,97) (**Figure 5**). In addition to printing a drug matrix, 3DP technology can also be employed to construct moulds for casting the drug delivery device using soft lithography techniques (96).

Recent examples of hydrogel drug matrices using 3DP include the printing of lactose-crosslinked gelatin scaffolds for the sustained release of dexamethasone (98), a printed pill formed by the reaction between two complementary 4-arm PEG polymers with crosslinkable end-groups to load prednisone and bovine serum albumin (99), and discs from thermogelling Polaxamer 407 for the delivery of paclitaxel and rapamycin (100). In the latter example, the thermogelling sols were extruded into thin solid discs, then dehydrated, enabling convenient handling, storage and insertion into the peritoneal cavity post-surgery, for the prevention of postoperative peritoneal adhesion (100).

While the use of 3D printing technology for tissue engineering falls outside the scope of this review, artificial tissue mimics can indeed be created to overcome the challenge of precise spatio-temporal delivery of signalling molecules; 3D printing for cartilage and osteochondral tissues engineering have been recently reviewed (101). The gene of interest and its delivery vector can be incorporated into a hydrogel-based bioink, offering a promising platform for the localized, precise presentation of biotherapeutics. A recent example of such a gene-activated bioink (GAB) was achieved by engineering pore-forming methylcellulose/agarose-based bioinks to modulate the delivery of vector-plasmid complexes to stem cells (102). This bioprinting strategy is promising to generate a wide range of complex tissues, organs, and organ-on-a-chip (OoC), which are seeing an increased interest as alternatives to animal testing. An OoC is a multi-channel microfluidic device that allows continuous perfusion of chambers containing multiple cellular microenvironments, thus mimicking a physiologically relevant in vivo environment (103). These models have become extremely useful for high throughput screening and drug toxicology (93) and are often based on hydrogels which best mimic the cellular environment (104,105).

Host-guest supramolecular chemistry has been combined with 3D printing by the group of Burdick, who proposed a platform based on a mixture of hyaluronic acid modified with either adamantane or β-cyclodextrin to achieve injectable, self-healing gels that can be used as bio-inks. Improved mechanical properties can be attained by modifying HA with methacrylate and UV-induced photopolymerisation in the presence of a radical-generating photoinitiator (39,106).

The fabrication of 3D hydrogels is conveniently combined with two-photon polymerization microfabrication (TPPM), a highly precise manufacturing technology, to obtain 3D microstructures with high resolution on the nanoscale, and has been reviewed elsewhere (107).

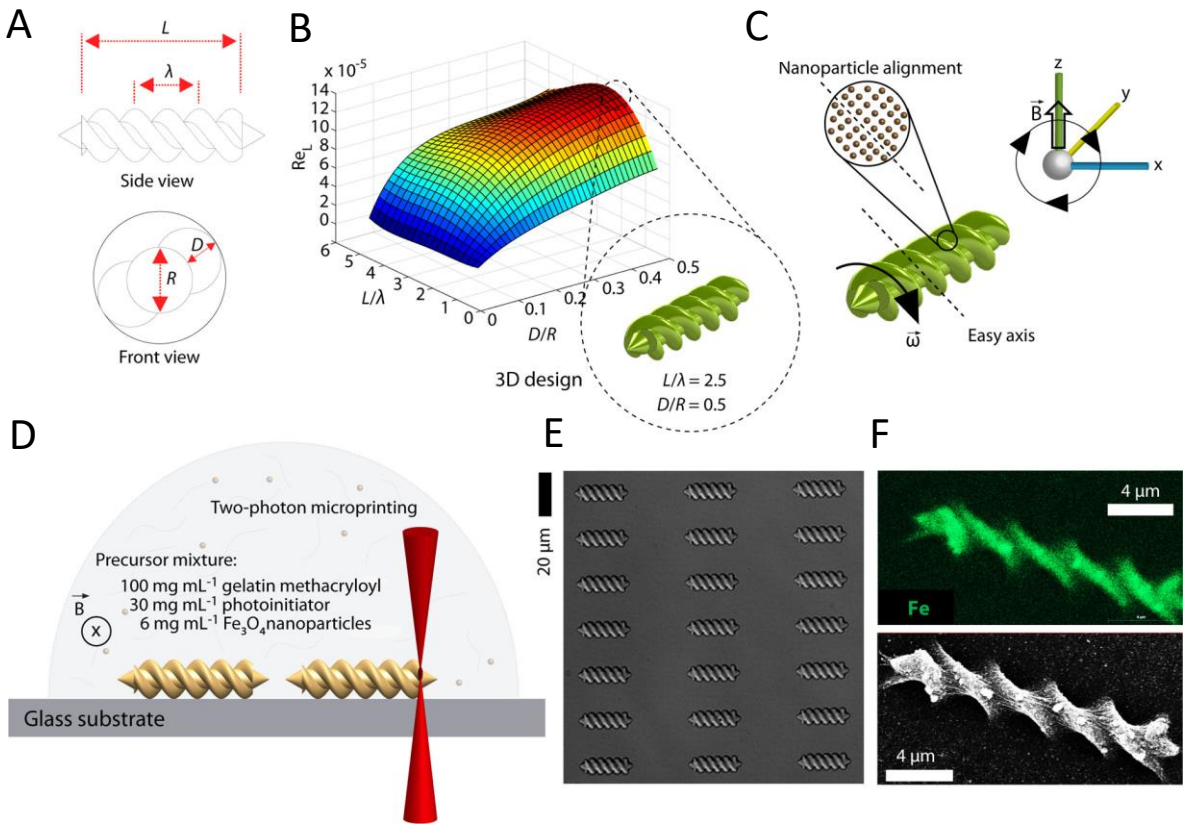

Figure 5. Design and 3D fabrication of biodegradable hydrogel microrobotic swimmers based on gelatin methacryloyl. **(A)** Empirical design of the double-helical microswimmer. **(B)** Computational fluid dynamics simulation for Reynolds number with respect to *L*/λ and *D*/*R* ratios, calculated for water at room temperature. The maximum forward swimming velocity was found with *L*/λ = 2.5 and *D*/*R* = 0.5 for the given design space sweep study. **(C)** Alignment of the iron oxide magnetic nanoparticles that defines an easy axis normal to the helical axis, thereby allowing rotational motion under rotating magnetic fields. **(D)** 3D fabrication of the microswimmers using two-photon polymerization. During the fabrication process, a continuous magnetic field was applied to keep the nanoparticles aligned. **(E)** Optical microscope differential interference contrast (DIC) image of a microswimmer array. **(F)** Energy-dispersive X-ray spectroscopy mapping of iron confirming the homogeneous embedding of the iron oxide magnetic nanoparticles inside the microswimmer body. Reproduced from (8).

3. Hydrogel-based microneedles

Microneedles represent another emerging technology platform for the delivery of therapeutics, which was originally investigated to enhance the penetration of drugs to the stratum corneum; there is now a growing interest to extend their use to other organs and tissues. Placed on a supporting base or within an injection system, MNs can puncture the skin seamlessly, due to their microscale dimensions, and deliver a range of active compounds of varying size. Microneedles can broadly be classified into five types: solid removable, dissolving, hollow, coated and hydrogel-forming (108); hydrogel-based microneedles represent the newest type, and capitalise on the biocompatibility and biodegradability of hydrogels (109).

Hydrogel-forming microneedle arrays (MNs) are fabricated from aqueous blends of polymers via a micromoulding process in silicone moulds (110). They do not contain drugs, but swell in the skin,

creating porous aqueous microconduits through which drugs contained in a reservoir layer can diffuse and reach the dermal microcirculation; they have been shown to enhance the transdermal delivery of a variety of molecules for systemic absorption, as reported elsewhere (110). Donnelly et al. presented a transdermal patch combining lyophilised drug reservoirs of the high-dose antidiabetic drug metformin HCl with hydrogel-forming MN array to enhance the transdermal delivery of metformin (110). The MN, based on a mixture of PEG Gantrez®, a poly(methylvinylether/maleic acid) with molecular mass 1,500,000 Da, presented high enough mechanical strength to penetrate skin in vivo and in vitro, and may provide an alternative mode of delivery to help minimize gastrointestinal side effects associated with conventional oral delivery.

Taking this concept further, Gu and co-workers developed a patch of MNs with a core-shell structure for H_2O_2 and pH-cascade triggered rapid insulin release for the treatment of diabetes mellitus (84,85). For this purpose, insulin was entrapped into degradable polymeric micelles and glucose-oxidase (GOx) in non-degradable micelles, which were then loaded in the crosslinked gel composing the MNs. The gel-based device partially dissociates, releasing insulin, when triggered by H_2O_2 generated during the oxidation of glucose by GOx, covalently tethered in the gel. The thin sheath structure embeds catalase, a H_2O_2-scavenging enzyme, to minimize the risk of inflammation caused by H_2O_2 to normal tissues (**Figure 6A**).

GelMA combines the advantageous properties of a natural polymer (gelatin), modified with methacrylamide or methacrylate groups, which can be crosslinked by UV light or in the presence of photoinitiators, and has been used widely as a versatile material for tissue engineering and a bioink for 3D printing, as already mentioned above with 3D printed microswimmers (8)(97). Khademhosseini and co-worked recently used GelMA as the matrix to prepare MNs where DOX was loaded by one step moulding, thus showing the promise of this material to manufacture dissolvable MNs; drug release occurred both through swelling and enzymatic-degradation (111) (**Figure 6A**). Compared with the burst release often observed with MNs, the GelMA-based MNs patch achieved a gradual release of the drug, which was a function of the crosslinking degree (longer UV exposure times), and demonstrate the potential of this GelMA MNs as a platform for the non-invasive delivery of a range of therapeutics.

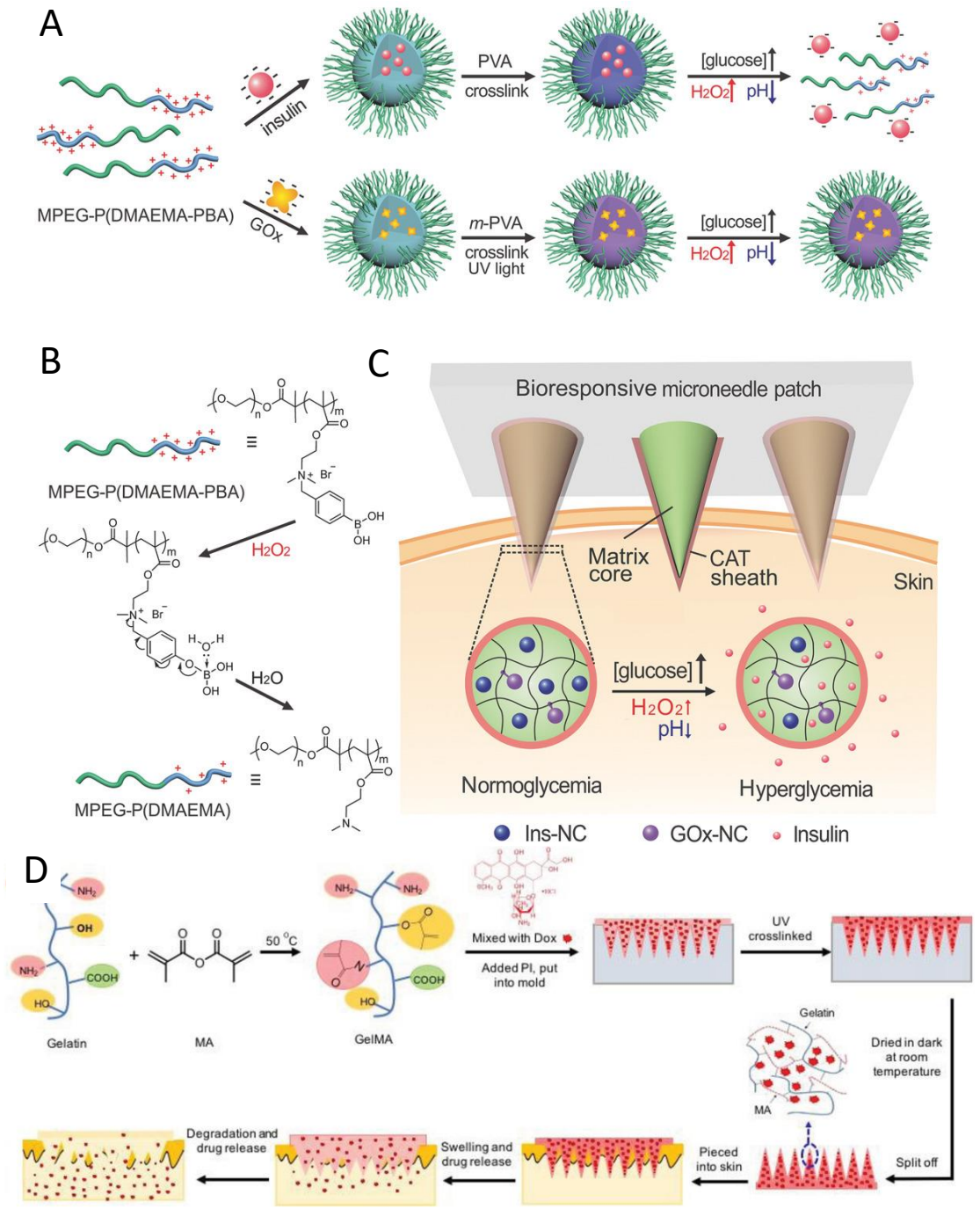

Figure 6. (A)-(C) Schematic of a glucose-responsive insulin delivery system utilizing H_2O_2 and pH cascade-responsive MN-array patch based on nano-sized complex micelles (NCs). **(A)** Formation of insulin-loaded-NCs (Ins-NCs) and glucose oxidase (Gox)-NCs and mechanism of glucose-responsive insulin release. **(B)** Schematic of H_2O_2-triggered charge reduction of the polymer. **(C)** Schematic of the NC-containing MN-array patch with a catalase (CAT) sheath structure for in vivo insulin delivery. Insulin release is triggered under a hyperglycemic state. Reproduced from (84) **(D)** Schematic of GelMA-based MNs for sustained drug delivery. Gelatin was modified with MA to generate GelMA polymers, then DOX was mixed with the GelMA prepolymer solution and casted into the micro-moulds. DOX-loaded GelMA MNs were then crosslinked by UV irradiation. After drying and curing, the MNs were peeled off from the micro-moulds. The dissolvable and degradable MNs are sharp enough

to penetrate the skin barrier and can thus release the loaded DOX into the transdermal space. Reproduced from (111).

4. Polymer-free gels and hybrids

Most of the hydrogels reported in this review have been based on polymer chains connected through cross-links forming a network. There are, however, an increasing number of hydrogels for drug delivery that depart from this traditional structure. In the field of low molecular weight gelators (LMWG), self-assembling short peptides, already mentioned in this article (13)(16)(23)(24)(17), have attracted a lot of interest, many examples of which can be found in a recent comprehensive review on LMWG (2). Peptide gels for drug delivery are usually based on peptides of two to seven amino acids, with unpolar moieties frequently attached to the peptide chain (2); they self-assemble into fibrous networks through a range of mechanisms, hydrogen bonds and π-π stacking (17), classically relying on β-sheets further assembling into fibres (16)(23)(112). A number of LMW hydrogelators which depart from peptides have also been explored for drug delivery (2). Pérez-García et al for instance developed a series of gels based on gemini dicationic (imidazolium) amphiphiles, which assembled into fibres in the presence of a small serine protease inhibitor, AEBSF-HCl (113).

A few examples of gels for drug delivery are based on the association of colloids (for instance in reference (27), illustrated in **Figure 1A**). Bastiancich et al. designed lipid nanocapsule (LNC)-based injectable hydrogels for the local chemotherapy of glioblastoma (26,114), which can be implanted straight after surgery and provide a sustained release of a drug. LCN were prepared using a phase-inversion process, and stabilised by non-ionic surfactants; the gel is formed by hydrogen bonds between the LCN when loaded with lauroyl-gemcitabine (GemC12) (26). Another example of a polymer-free hydrogel for drug delivery was based on mixing graphene oxide (GO) with metformin hydrochloride (60), an insulin sensitizer drug used in type 2 diabetes, usually administered transdermally by thermo-responsive microneedles or hydrogel-based microneedles (110), as discussed in the previous section. The gelation process is attributed to hydrogen bonds and electrostatic interactions between GO and metformin. The photothermal activation of GO induces the dissolution of the gels through irradiation with NIR light, triggering the sustained release of metformin (60). Another example of a particulate gel where sustained release can be triggered by ultra-sound was achieved with 10 nm magnetite nanoparticles (115). The iron oxide gels were obtained by direct gelation of a magnetite hydrosol, under the influence of a polypropylene oxide proton scavenger. The gel, based on Fe-O-Fe interparticle connections and comprising components that are FDA approved for parental administration, showed good biocompatibility and limited cytotoxicity at concentrations up to 207 $ug \cdot mL^{-1}$. The gels were loaded with selected organic dyes (methylene blue, to treat methemoglobinemia and eosin Y, an antimalaria agent, and alizarin for bone cancer treatment) and the drugs were released in burst mode upon ultra-sound application, due to the impact of the vibrations on the gel, which may be useful for fast and localised applications (115).

Another strategy used in carrier-free gels for drug delivery is to use the drug as the gelator; for this purpose, they may need to be combined to a small gelator (drug conjugates) or self-assemble spontaneously through their own amphiphilic properties (28). A number of gels based on this method over the last couple of decades have been reviewed here (2). Dastidar and co-workers proposed an approach based on the self-assembly of NSAIDs via salt formation, recently for instance with indomethacin-leucine reacting with the antiviral drug amantadine to yield primary ammonium monocarboxylate salts, which formed anti-inflammatory, injectable gels (116), or the combination of ibuprofen with a series of primary amines (117).

Alternatively, the spontaneous self-assembly of two drugs has been exploited, for instance where one is hydrophilic and the other hydrophobic, and both act simultaneously as the cargo and the carrier. With this approach, combination therapy was achieved by linking Taxol with the anticancer peptide tyroservatide (YSV). Taxol-EYSV spontaneously self-assembled into nanofibers upon hydrolysis with a high drug loading rate and controlled release behaviour, and enhanced cellular uptake (29).

Another approach consists in making a "prodrug" to induce self-assembly, as reviewed here (118), for instance by conjugating the active to a short gelator, such as self-assembling peptide (which could itself be a drug). This was the strategy adopted by Zhong et al who developed a redox-responsive supramolecular gel for the delivery of 10-hydroxy camptothecin (HCPT), a cell cycle-specific chemotherapeutic. In this case, the gel was formed by cleaving the disulphide bond in the peptide-drug conjugate (119). The anticancer pemetrexed (Pem) was converted to a molecular hydrogelator with inherent chemical exchange saturation transfer (CEST) MRI signal, and spontaneously assembled into filaments, thus forming an injectable theranostic supramolecular gel (10). The range of drugs studied to act as components of the gels is obviously limited, with a focus on flatter, aromatic structures. There are also issues with the high concentrations that may be required to form gels in some instances, and associated toxicity (118).

Hybrid peptide-polymer can also be used to form hydrogels and provide synergistic properties and new means of cross-linking. To end this section with a curiosity, Liu et al have proposed a nanomillipede forming self-assembling peptide as a cross-linker for dextran, through vinyl-sulfone reaction sites on dextran and thiol sites on the β-sheet forming peptide (120). The length of the nanomillipede can be controlled by exposure to ultrasounds for varying lengths of time, which, in turn, impacts the mechanical properties of the resulting hydrogel, thus providing a shear-thinning, self-healing hybrid hydrogel where properties are tuned without changing the components or they concentration.

Conclusion and Outlook

This review has provided a glimpse of the vast repertoire of hydrogel designs that exist for drug delivery and highlighted the versatility of supramolecular gels (vs. traditional chemical gels) for this purpose, which enable stimuli-responsiveness, injectability and tuning of the release profile. Looking back at a review in this journal on the same topic 20 years ago (121), it is clear that the field of supramolecular gels, in particular based on small gelators, has considerably expanded, and new technologies have emerged, such as 3D printing and microfluidics, and opened new avenues for the design of intricate, micro- and nano-scale structures, while the complexity of architectures and functionality (such as the type of stimuli to trigger release, and the control over release profiles) have greatly advanced.

Despite the exploding range of hydrogel designs, clinical translation has been lagging behind. The most impactful in terms of sales perhaps remains Medtronic INFUSE, a collagen-based gel that releases BMP2 for bone regeneration (1). Other products have since reached the clinic (1), but their number is limited, and they are usually based on simple designs and a limited library of polymers, many of natural origin. A number of challenges towards clinical translation are common to all DDS (costs, timescales of regulatory approval, etc) but the hydrated nature of hydrogels also poses additional challenges in terms of storage, degradation and sterilisation. The obvious question remains the trade-off between the complexity of the materials and subsequent regulatory hurdles, scale-up and cost.

In terms of developing new gels, design rules are still lacking - a large part of the published studies rely on trial and error, and there are not enough comparisons of different hydrogel matrices for the same drug, using the same methods, to start establishing a rationale for DDS design. In terms of modelling the release profiles also a lot of progress needs to be made, in particular with regard to in vivo release.

In conclusion, progress in technology and synthesis have broadened the arsenal of hydrogels available to tackle complex delivery challenges. The expanding field of biopharmaceuticals strongly suggests that this field will keep expanding, continuing to improve health.

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