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Review

Dual cross-linked hydrogels as promising materials for drug delivery

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ABSTRACT

Hydrogels have long found their place as versatile materials for drug delivery due to their biocompatibility, tunable properties and tissue-like mechanical behavior. Despite these advantages they suffer from a multitude of drawbacks, ranging from lacking injectability and low mechanical strength to short drug release times. These factors limit their potential clinical applications. Dual cross-link hydrogels are a versatile tool to address these shortcomings. By combining covalent with dynamic-covalent and physical cross-linking they create smarter, stronger and more versatile hydrogels, broadening their applicability. This review aims to bridge the gap between traditional hydrogels and emerging dual cross-linked hydrogels by providing an overview of the chemistries involved. We discuss the most popular cross-linking strategies and how these can be used to address specific challenges in hydrogel design. Furthermore we highlight how recent research has utilized these promising materials to enable the application of hydrogels in ever more demanding environments.

Contents

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1. Introduction

Over the last few decades hydrogels have, become a mainstay of biomedical, as well as broader materials research. They are applied from tissue engineering and drug delivery to soft robotics (López-Díaz et al., 2024) and battery research (Yang et al., 2022). As an excellent mimic of biological tissues, due to their high water content, they can be used for a diverse range of medical applications. Hydrogels are 3D materials composed of a cross-linked polymer network swollen by water (Alemán et al., 2007). They are soft materials with highly tunable stiffness, which enables them to mimic human tissue (Geckil et al., 2010). Furthermore hydrophilic drugs can be easily incorporated and released in a controlled manner (Li and Mooney, 2016). The polymer component can be chosen from natural polymers, often polysaccharides such as alginate or hyaluronic acid, to semi-synthetic polymers like chitosan, to fully synthetic polymers, for instance polyethylene glycol (Bao et al., 2019; Germershaus et al., 2015; Bakaic et al., 2015).

Due to this versatility hydrogels have found a diverse range of applications. They can be used as wound dressings, drug delivery devices and sensors (Liang et al., 2021; Li and Mooney, 2016; Peppas and Van Blarcom, 2016). All these applications rely on their ability to fine tune the physico-chemical properties. To control these, the choice and amount of polymers, as well as the most suitable cross-linking approach, have to be identified.

Hydrogels can be used to deliver payloads with distinct properties. These range from small molecules up to protein drugs (Ziegler et al., 2021a), nucleic acids (Zhong et al., 2023) and in some cases nanoparticles (Mietzner et al., 2024) and living cells (Wang et al., 2017). As a result, an equally diverse range of hydrogels is needed to provide control over the release of these drugs. Using different polymers and cross-linking mechanisms is one such way to provide control over the release of these substances.

Traditional hydrogels can be limited in their clinical applicability due to drawbacks stemming from their cross-linking approach. These limitations include long gelation times, which complicate in-situ gelation and reduce injectability (Gregoritza and Brandl, 2015), low mechanical strength, which can lead to hydrogel disintegration, and environments that are hostile to cells, thereby hindering the delivery of cell-based therapeutics. Furthermore a single cross-linking mechanism may be insufficient to provide adequately strong hydrogels for highly dynamic environments such as the myocardium (Zheng et al., 2022). Another key challenge is the ability to achieve controlled and sustained release of therapeutics, which is often limited in conventional hydrogels due to rapid diffusion or premature degradation. Dual cross-linked hydrogels offer a promising strategy to overcome these challenges. Introducing a physical cross-linking mechanism can accelerate gelation and enhance mechanical strength through sacrificial bonds (Nakajima, 2017). In addition, the combination of two distinct cross-linking mechanisms can be tailored to modulate network architecture and degradation kinetics (Distler et al., 2020), thereby enabling more precise control over drug release profiles. Stimuli-responsive mechanisms can also be incorporated to enable on-demand release while preserving the macroscopic stability of the hydrogel (Sun et al., 2019a).

Dual cross-link hydrogels are a promising method to address these challenges. This review focuses hydrogels that employ two orthogonal mechanisms with significantly different equilibrium constants (Fig. 1a). These include the combinations of covalent with dynamic-covalent or physical cross-linking mechanisms. In some cases where the dynamic-covalent or physical mechanisms possess an equilibrium constant similar to irreversible covalent mechanisms it may replace it as the high strength component. Hydrogels in which two cross-linking mechanisms with similar equilibrium constants are employed are beyond the scope of this review.

2. Cross-linking mechanisms

Hydrogels are water swollen polymer networks (Alemán et al., 2007). Synthetic hydrogels are often created by cross-linking macromolecular precursor molecules. This cross-linking can either take place between two functional groups that are part of the precursors or via the introduction of a dedicated cross-linking agent.

These can employ a wide range of functional groups. For the purpose of this review these will be broadly categorized into physical, dynamic-covalent and covalent linkages (Fig. 1a).

Physical cross-links rely wholly on non-covalent interactions. Dynamic-covalent bonds are an intermediary step. They form covalent bonds which can break and reform. Covalent bonds form permanent bonds which can be broken under strain, but do not reform. For the rational design of hydrogels relying on these interactions, two factors can be used to gauge the behavior of the hydrogels. Firstly, the equilibrium constant (K_{eq}). It is a measure of the ratio of associated to dissociated cross-links and thus by extension a measure of their stability (Appel et al., 2012). At the high end this can come close to covalent bonds (Shi et al., 2019). Secondly, the association (k_a) and dissociation (k_d) constants. These are a measure of the association and dissociation rates of the cross-link. High association and dissociation rate constants indicate a more dynamic network (Webber and Tibbitt, 2022) that is, for example, able to relax faster under applied stress or self-heal more rapidly. The equilibrium constant can be defined as $K_{eq} = k_a/k_d$. This equation shows that bonds with the same equilibrium constant can have widely different dynamic behavior. Thus emphasizing the importance of considering bond dynamic in their entirety.

These constants can be determined via a variety of methods. All of them rely on determining the ratio of product to educt and the rate of conversion. Thus the most suitable method highly depends on the chosen cross-linking approach. The equilibrium constant can be measured using fluorescence spectroscopy (Brooks et al., 2018), UV–Vis spectroscopy (Lascano et al., 2016) and 1D-NMR (Morgan et al., 2024). Rheology and density functional theory (DFT) can also provide insights into bond dynamics. When elucidating the equilibrium constant via rheology, the high frequency plateau modulus is measured. With the help of phantom network theory the equilibrium constant can then be calculated (Tang et al., 2018). This is only possible if the assumptions for phantom network theory are fulfilled. DFT can be used to calculate the Gibbs free energy of the bond which in turn can be converted into the equilibrium constant (Zhang et al., 2024). The rate of association and dissociation can be measured using the previously mentioned methods (Thordarson, 2011). Rheology and DFT first determine the Gibbs enthalpy and entropy of activation, which can then be converted. Marco-Dufort et al. (2020) applied several methods to link the molecular behavior of the cross-link junction to the macroscopic hydrogel behavior. They found the methods that extrapolated from micro- to macroscale to be in good agreement with the inverse. This emphasizes that, for ideal highly swollen polymer networks, the influence of microscale dynamics on the performance of hydrogels is of paramount importance.

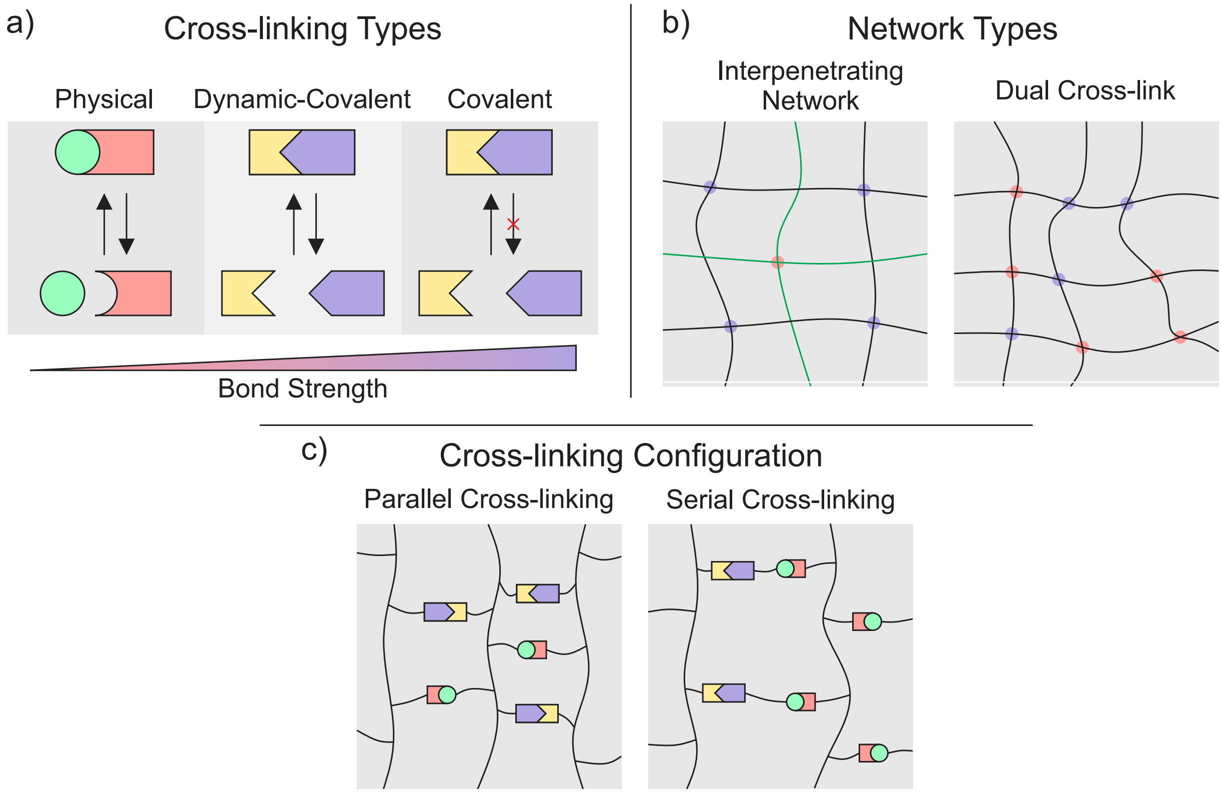

Fig. 1. (a) Schematic representation of physical, dynamic-covalent and covalent cross-linking mechanisms. While the first two are reversible, covalent bonds are generally not. Generally the bond strength increases from physical to dynamic-covalent to covalent. Though there are exceptions where physical cross-linking mechanisms show exceptional strength (Shi et al., 2019). (b) Interpenetrating networks consist of two different polymers cross-linked via two different cross-linking mechanisms. Thus two networks are formed, which are not interconnected. By contrast the papers surveyed in this review employ networks with two cross-linking mechanisms which are introduced into a single polymer backbone, or connect two different polymers. (c) Dual cross-linking can either be introduced in a serial or a parallel manner.

2.1. *Physical cross-linking*

Physical, or non-covalent cross-linking encompasses a wide range of mechanisms (Fig. 2). These range from weak hydrogen bonding interactions with bond energies on the order of tens of $kJ\,mol^{-1}$ (Oveissi et al., 2020) to metal coordination bonds between calcium and carboxylic acids with energies of about $20\,kJ\,mol^{-1}$ (Fang et al., 2007) and in extreme cases between iron and catechol with energies of $230\,kJ\,mol^{-1}$ (Avdeef et al., 1978). A special type of physical cross-linking is represented by DNA-based cross-links. They present the opportunity for highly tunable cross-linking behavior. For DNA and RNA delivery they present an interesting system due to specific interactions with the incorporated payload (Mo et al., 2021). As they possess a highly variable structure with design considerations of their own, DNA based cross-linkers are beyond the scope of this review.

Due to their ability to quickly break and reform, physical cross-links impart properties of self-healing and thixotropy to hydrogels.

2.1.1. *Metal coordination*

Metal coordination is a versatile method for the cross-linking of hydrogels. Large ranges of elastic moduli can be realized through the choice of metal, ligand and their respective concentrations (Lee et al., 2000). For cations the modulus generally decreases in the order $Fe^{3+} > Cu^{2+} > Sr^{2+} = Ca^{2+} > Zn^{2+}$ (Malektaj et al., 2023), hydrogels based on other metals such as Mg^{2+} (Liao et al., 2024), Co^{3+} (Kwon et al., 2024) and Al^{3+} (S. Menyo et al., 2013) are also possible. The modulus can be further adjusted via the choice of ligand. These can be anionic such as carboxyl groups or neutral as with catechol groups.

Equilibrium constants from 10^3 up to 10^{40} are possible through the choice of ligands and ion (Shi et al., 2019). A common application for metal coordination cross-linking is in the production of alginate hydrogels. Alginate possesses naturally occurring carboxyl groups which are capable of complexing metal ions, most commonly calcium (Augst et al., 2006). Though most metal coordination cross-links lead to self-healing networks, this is not the case with alginate hydrogels (Tseng et al., 2015).

Metal coordination hydrogels can exhibit stimuli responsive behavior due to redox activity of the coordinated metal. This relies on a loss or gain of cross-linking in response to the oxidation state of the metal. In the case of Co^{3+} and Fe^{3+} a reduction of the metal leads to a loss of cross-linking. If metal coordination is the sole cross-linking mechanism, this in turn leads to a gel-sol transition for example in Co^{3+}-histidine cross-linked gels (Wegner et al., 2016). In dual cross-linked gels this can be mitigated via the second cross-linking mechanism, resulting in a reduction of Young's modulus while still retaining gel structure (Auletta et al., 2015).

In some cases, the coordinated metal is partially responsible for the therapeutic effect of the hydrogel. Examples of this are gels incorporating Mg^{2+} in combination with polyhedral oligomeric silsesquioxane (POSS) for enhanced osteogenesis (Zhang et al., 2021b) and Sr^{2+} for wound healing (Lu et al., 2020). The inverse effect must also be considered as some of the metals are toxic at the concentrations needed for hydrogel cross-linking. Though this effect is mitigated by the slowed release from the hydrogel (Popov et al., 2022). Thus, the toxicity must be evaluated on a gel-by-gel basis.

2.1.2. *Hydrogen bonding*

Many polymers exhibit hydrogen bonding between polymer strands. Though these interactions can lead to gelation at sufficient concentrations, the interactions are usually too weak to resist quick dissolution of

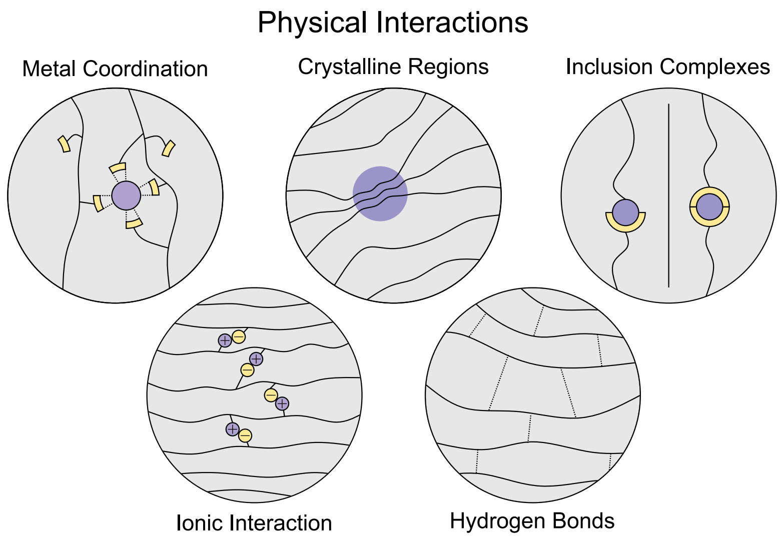

Fig. 2. Schematic of different physical cross-linking mechanisms.

the gel networks (Haglund et al., 1996). Hence hydrogen bonds can either be used in addition to other, stronger, cross-linking mechanisms or the amount of interactions has to be increased to a larger number. One strategy to achieve this, is the introduction of self-complementary 2-ureido-4[1H]-pyrimidinone (UPy). Each functional group provides four hydrogen bonding donor and acceptor sites. Thus sufficient strength is achieved to formulate a hydrogel (Dankers et al., 2012; Mol et al., 2019).

Due to the reversibility of hydrogen bonds, they also impart rapid self-healing behavior on the formed hydrogels (Cui and del Campo, 2012). Furthermore, free hydrogen bonds can be used to facilitate material-drug interactions. Cai et al. (2023) observed that this leads to slowed release kinetics that depend on the strength of the hydrogen bonding interaction between the incorporated drug and the cross-linker.

As the skin surface provides an abundance of hydrogen donors as well as acceptors hydrogels based on hydrogen bonding show skin adhesion properties (Yu et al., 2022).

2.1.3. Ionic interaction

Two different approaches can be taken to create an ionically cross-linked hydrogel. Either two polymers with different charges are combined, often alginate and chitosan, or zwitterionic polymers are created.

Zwitterionic polymers are characterized by the close proximity of the cationic and anionic functional groups. Hydrogels formed through these interactions show super hydrophilicity due electrostatically induced hydration (Jiang and Cao, 2010). They are also less susceptible to a foreign body response, reducing cellular overgrowth and making them attractive candidates for long-term implantation (Liu et al., 2019). Zwitterionic charge is commonly realized through carboxylic or sulfonic acids and quaternary ammonium ions (Liu et al., 2022b).

Alginate polymers naturally carry one acidic residue per monomer (Yang et al., 2011). Chitosan can readily be derivatized into a polycationic polymer by quaternization of the amino groups (Andreica et al., 2020). Hoang et al. (2022) combined the ionic cross-linking between these polymers with inverse electron demand Diels–Alder (iEDDA) based cross-linking. This led to hydrogels with a high loading capacity for the hydrophobic drug ketoprofen. After oral delivery of the hydrogel, it showed low release in the acidic environment of the stomach and high release in the neutral pH of the intestine. Due to the persistence of the iEDDA linkages a sustained release behavior could be achieved inside the intestine.

2.1.4. Crystalline regions

The creation of crystalline regions is an inherent property of some polymers used for the backbone of hydrogels. Foremost polyvinyl alcohol (PVA) is used for this application. Due to the abundance of hydrophilic functional groups, it can form a semi-crystalline structure (Bodugoz-Senturk et al., 2009). Crystalline regions in PVA are created via the "freeze–thaw" method, where the gel precursors are repeatedly brought below freezing. The more often this process is repeated the higher the degree of crystallinity and the higher the mechanical strength of the resulting hydrogel (Hassan and Peppas, 2000).

2.1.5. Guest-host inclusion complexes

Guest-host interactions are created by cavitands or "hosts" and their respective guest-molecules. The guest-host complex is formed via hydrophobic and van der Waals interactions, with the size of the guest molecule being an important factor (Sinawang et al., 2020). Guest-host inclusion complexes can be formed in several different stochiometries: 1:1, 1:2 (Fig. 2) or as rotaxanes. The latter present a special case where a macrocycle encloses an axle, which in turn constricts the movement of the macrocycle. Due to this locking the complex loses the ability to dynamically interchange guests (Ghiassinejad et al., 2024). As rotaxanes have found little application in dual cross-linked gels to date, they are omitted in this review. Examples for 1:1 complexes are cyclodextrin-adamantane (Widener et al., 2023) or cyclodextrin-azobenzene (Liubimtsev et al., 2023) complexes. Before complexes can be formed, the polymer has to be modified with both partners. Here, a sequential approach, where the same batch is modified or a parallel approach, where two different batches are created, can be taken. If the hydrogel is to be modified with both components, a single pot approach is possible, where the guest-host inclusion complex is preformed and the gelation initiated when the inclusion complex is added to the polymer (Dhand et al., 2022). Otherwise, the polymers are prepared beforehand.

The other possible approach is the formation of a 2:1 inclusion complex. This strategy has been used with cyclodextrin and ellagic acid (Zhang et al., 2023b). Advantages of this method are, that the polymer only has to be modified with a single component and that the included substance can be released from the gel, though at the cost of structural integrity.

Curcubit[n]urils can be utilized as an alternative to cyclodextrin. Their inclusion complexes show higher association constants of up to

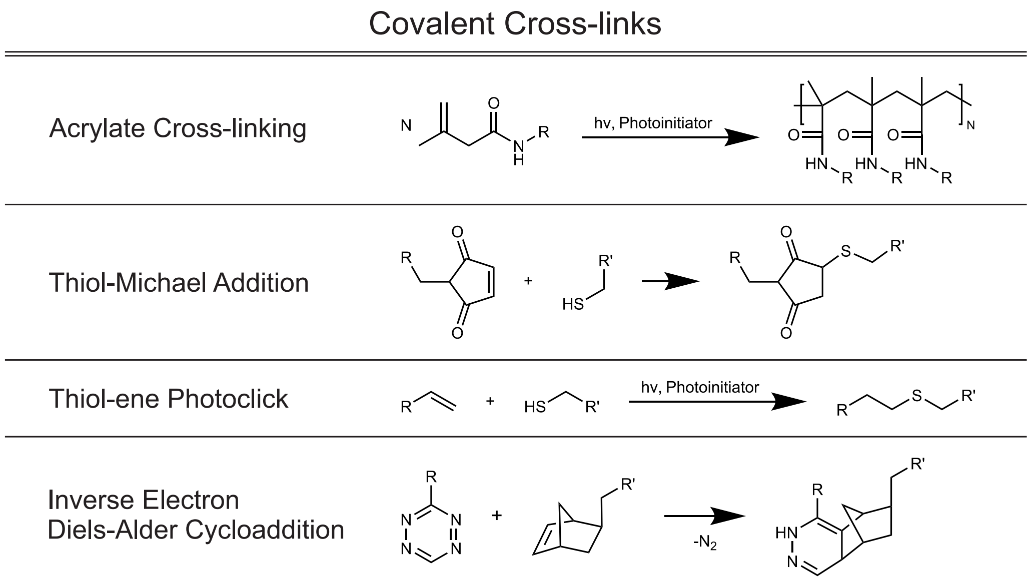

Fig. 3. Overview of the covalent cross-linking mechanisms discussed in this review.

10×10^{15} mol/dm^3 (Cao et al., 2014). Some of these most stable complexes are created by curcubit[8]urils which, due to its size, can create 1:2 inclusion complexes. These benefit from additional electrostatic interactions between the guest molecules (Cao et al., 2016).

Both cyclodextrins and curcubit[n]urils, when covalently incorporated into the polymer, face the challenge of monofunctionalization of the host molecule. Several different procedures have been proposed for curcubit[n]urils (Vinciguerra et al., 2012; Yin et al., 2023) as well as for cyclodextrins (Kasal and Jindřich, 2021).

2.2. Covalent cross-linking

The formation of covalent bonds leads to non-reversible cross-linking. This in turn leads to highly stable polymer networks. For covalently cross-linked hydrogels the inclusion of a degradation pathway is of high importance. Due to the non-reversibility of the formed bond, a dedicated breaking point has to be introduced. Possible mechanisms include the introduction of hydrolytically cleavable linkers (Ziegler et al., 2022), enzymatic degradation moieties (Sokic et al., 2014) or photolabile groups (LeValley et al., 2020).

Covalent cross-linking mechanisms can be grouped in many ways. In the context of injectable materials the distinction between radical and non-radical reaction pathways is especially important. Acrylate based cross-linking and thiol-ene cross-linked hydrogels fall in the former category. This distinction can be important when proteins or cells are to be incorporated, as the radical needed for cross-linking can damage the cargo or covalently attach it to the polymer backbone leading to reduced release (Vermonden et al., 2012). A suitable radical initiator needs to be chosen for each application. Possible mechanisms are thermal initiation (Huang et al., 2017), redox reaction (Shin et al., 2004) and photo-initiation. Photoinitiators are a common choice due to the high degree of spatio-temporal control they offer (Li et al., 2019). Their drawbacks include the low penetration depth of UV- and visible light in biological tissues (Ash et al., 2017) as well as the risk of tissue damage due to UV exposure and initiator toxicity. Although this is dependent on the light intensity as well as the photoinitiator concentration and type (Sabnis et al., 2009; Xu et al., 2020). Examples of redox initiators are the combination of ammonium persulfate (APS) and tetramethyethyldiamine (TEMED) as well as the Fenton reaction. While the former shows good gelation kinetics this comes at the price of higher cytotoxicity, while the Fenton reaction is biocompatible, but can lead to weaker gels depending on the precursors used (Wilems et al., 2017). When developing a hydrogel system these factors have to be weighed against each other to choose the most suitable radical initiator for the intended application.

2.2.1. Acrylate

Acrylate hydrogels are formed via a radical cross-linking mechanism. The reaction proceeds via a chain growth mechanism (Roberts and Bryant, 2013). Gels can either be formed from acrylate monomers, most commonly acrylic acid or acrylamide (Sennakesavan et al., 2020), or a different polymer backbone, such as polyethylene glycol or gelatin, can be modified with acrylate endgroups (Yue et al., 2015; Roberts and Bryant, 2013). To create a network from the monomers, cross-linkers are needed. Often N,N′-Methylenebisacrylamide is used. When gels are formed from acrylic acid monomers the amount of cross-linker can be used to adjust properties such as cross-linking density and swelling behavior (Arens et al., 2019).

Due to its chain growth behavior, acrylate polymerization is more susceptible to interference from oxygen (O'Brien and Bowman, 2006). To stabilize the radical propagation catalysts such as N,N,N′,N′-Tetramethylethane-1,2-diamine can be added.

Polyacrylamide gels show good biocompatibility and can even be used as anti-fouling coatings on implantable devices. Through the choice of acrylamide monomer, these properties can be further augmented (Chan et al., 2022).

The carbon–carbon bond formed by acrylate cross-linking is not biodegradable. Thus, either degradable polymers are required or the cross-linker has to be replaced with a biodegradable alternative (Freedman et al., 2021).

2.2.2. Michael-addition

Michael-additions are base catalyzed reactions between a Michael-donor, an enolate or nucleophile, and a Michael-acceptor, an α, β-unsaturated carbonyl (Fig. 3). When thiols are utilized as the donor, additional base can often be omitted, though it still speeds up the reaction as the thiolate anion is the active species (Mather et al., 2006). It is a versatile reaction that has been used for a wide range of conjugations (Nair et al., 2014). The most popular type of Michael-addition reaction in the field of hydrogel synthesis is the addition of thiols to maleimides. The adduct possesses certain dynamic properties such as the capability of thiol exchanges. Due to the high temperatures of >60° C, this effect is not applicable to hydrogels in biological systems (Zhang et al., 2018).

Attention has to be paid when proteins are to be delivered from the hydrogels, as exposed cysteine residues are possible reaction partners for the Michael acceptor (Nair et al., 2014). Degradation of hydrogels formed via the thiol Michael-addition is possible via two direct routes. Firstly, the glutathione mediated retro thiol Michael-addition reaction can be used to degrade the gels. Kharkar et al. (2015) used this approach in conjunction with two other mechanisms to achieve a highly tunable degradation profile. Secondly, the gels can be degraded using a radical mechanism. Radicals formed by photoinitiators such as Lithium Phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) lead to an irreversible cleavage (Hebner et al., 2024).

2.2.3. Inverse electron-demand Diels–Alder reaction

The inverse electron-demand Diels–Alder reaction is a [4+2] Cycloaddition between an electron-rich dienophile and an electron-poor diene (Carboni and Lindsey, 1959). Two common combinations of reaction partners are tetrazine with either norbornene or transcyclooctene. Gel formation happens on the order of seconds (Ziegler et al., 2021b). Though the reaction kinetics can be adjusted by modifying either the tetrazine or by choosing trans-cyclooctene (TCO), which reacts faster, or norbornene, which reacts slower (Karver et al., 2011).

The iEDDA reaction fits all of Sharpless' criteria for "click" reactions (Kolb et al., 2001) and also shows excellent bio-orthogonality (Madl and Heilshorn, 2018). For in-vivo degradation of the formed gels, secondary mechanisms need to be introduced as the adduct is not biodegradable (Ziegler et al., 2022). Strategies include attaching the reaction partners via hydrolyzable groups or using a degradable polymer backbone.

The nitrogen byproduct of the iEDDA reaction often cannot be dissolved by the reaction medium, leading to microbubbles inside the hydrogel. This can lead to expedited release kinetics (Gulfam et al., 2022).

2.2.4. Thiol-ene photoclick reaction

The thiol-ene photoclick is a radically mediated cross-linking reaction. It is robust against the presence of oxygen and propagates via a radical step-growth mechanism (Cramer et al., 2003). Due to its robustness, visible light, as well as UV-photoinitiation can be used to cross-link the polymers. Initiation with thermal radical initiators is also possible, though less popular. Eosin-Y is a popular choice for photoinitiation, due to its low cost, biocompatibility and visible light initiation (Shih and Lin, 2013). The photoclick reaction leads to rapid gelation on the order of 30 s. The formed gels possess good structural stability. Nevertheless, the formed thio-ethers are not biodegradable. Thus measures have to be taken, to introduce another way of degradability. This can be achieved via the modulation of the cross-linking moiety. Several strategies, from enzymatically cleavable linkers to photosensitive ones, have been applied (Fairbanks et al., 2009; Ki et al., 2013). For applications that require in-situ gelation, the thiol-ene photoclick reaction possesses two disadvantages. Firstly, for light initiation the penetration depth into tissue, depending on the wavelength, is rather low (Finlayson et al., 2022). This can be improved by using visible light photoinitiators, as longer wavelengths can reach deeper tissues. Secondly, due to the abundance of thiols in human tissue in the form of cysteine, the reaction is not completely bioorthogonal. Depending on the application this can be circumvented by initiating the gelation ex-situ and then introducing the gels into the body, for example as a granular hydrogel (Sletten and Bertozzi, 2009; Ooi et al., 2018).

2.3. Dynamic-covalent cross-linking

Dynamic-Covalent encompass a wide range of motifs (Fig. 4). They are characterized by their ability to break and reform. Whether they behave more like physical or covalent bonds can be gauged from their equilibrium constants. To get a more comprehensive picture of dynamic-covalent bonds and the macroscopic networks they form, one also has to consider their respective forward and backward reaction rate constants as well as the relaxation time (Marco-Dufort et al., 2020). The latter scales with the backwards reaction-rate constant (Rubinstein and Semenov, 1998). All of these parameters can be modified through modification of the involved functional groups or environmental parameters such as pH, making dynamic-covalent chemistry highly tunable and an attractive choice for imparting stimuli-responsive properties on hydrogels (Yesilyurt et al., 2016; Zhang et al., 2021a; Marco-Dufort et al., 2020).

2.3.1. Diels–Alder reaction

The Diels–Alder (DA) reaction is a [4 + 2] cycloaddition between an electron poor dienophile and an electron rich diene. Due to its high specificity and rapid kinetics, it can be considered a "click" reaction (Kolb et al., 2001). Several combinations of reaction partners are possible (Cadamuro et al., 2021), while the combination of furan and maleimide is the most popular.

The majority of dynamic-covalent or physically cross-linked hydrogels undergo degradation through a one-step reaction, resulting from the equilibrium between linked and unlinked cross-links, which enables surface erosion. In contrast, the retro-Diels–Alder (rDA) reaction exhibits a low rate at body temperature, and cannot be solely responsible for the observed degradation behavior. A second step is necessary to explain the degradation process. Following the bond cleavage via the rDA reaction, the maleimide educt undergoes hydrolysis, thereby preventing the reformation of the DA bond. The rate of this second process is dependent on the pH of the environment (Kirchhof et al., 2015). In contrast to other dynamic covalent cross-linking reactions, classic Diels–Alder gels do not readily self-heal at body temperature (Bertsch et al., 2023). However, this limitation can be overcome through modification of the reaction partners (Wei et al., 2013).

2.3.2. Schiff base

The Schiff base cross-linking or broader, imine-based cross-linking, like the Diels–Alder reaction can be counted under the dissociative dynamic cross-linking reactions (Jourdain et al., 2020). The imine bond is formed via a condensation reaction between an amine and an aldehyde. These two functional groups can either be introduced using two polymers modified with the respective moiety (Kim et al., 2020) or by using a cross-linker. Glutaraldehyde is the most popular cross-linker providing two aldehyde functional groups that can cross-link amine modified polymer backbones (Feyissa et al., 2023).

Imine bonds show greater stability at neutral pH than at lower pH-values (Xu et al., 2019). This effect can be used to create stimuli responsive gels. Qu et al. (2017) developed a hydrogel relying on this increased instability to deliver doxorubicin to a hepatocellular carcinoma. Due to the decreased pH in the tumor microenvironment, the drug was released there more quickly.

If instead of amines, hydrazides are used, hydrazone bonds are created. Compared to imines, they show higher thermodynamic stability (Conant and Bartlett, 1932; Belowich and Stoddart, 2012). Through the introduction of electron withdrawing groups, dynamic behavior can be enhanced (Sun et al., 2019a). Hydrazone cross-linked hydrogels also exhibit shear-thinning behavior (Wang and Burdick, 2017). Replacing amines with hydroxylamines, leads to the formation of oxime bonds which have a higher equilibrium constant than amines or hydrazones. By mixing linkers with different functionalizations, the stiffness of hydrogels can be finely tuned (Morgan et al., 2022).

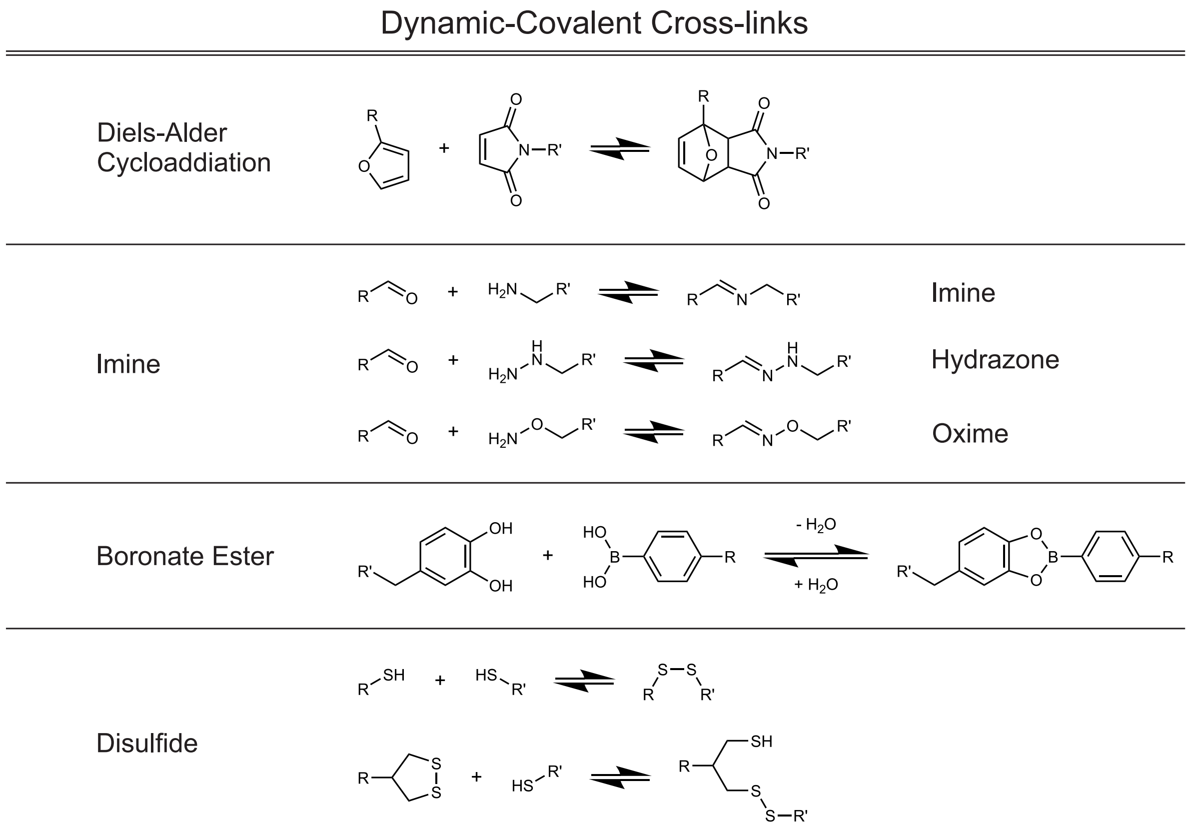

Fig. 4. Overview of the dynamic-covalent cross-linking mechanisms discussed in this review.

2.3.3. Boronic acid

Boronic acid cross-linking is based on the formation of esters between boronic acid and diols. PVA is a popular material for modification with boronic acid, as each monomer contains a hydroxy-group, providing ample opportunities for cross-linking (Ji et al., 2023; Nunes et al., 2016). Affinity to diols decreases in the order *cis*-1,2-diol > 1,3-diol ≫ *trans*-1,2-diol (Nakagawa and Yukishige, 2012). To form the esters, the pH has to be greater or equal to the pK_a of the boronic acid. Lower pK_a values can be achieved via introduction of substituents such as fluorine or formyl to the boronic acid (Yesilyurt et al., 2016). This gives boronic acid based hydrogels a native pH-sensitivity (He et al., 2011). Another smart property is the responsiveness to glucose. Due to competitive binding with the diol moiety of glucose, the mesh size of the hydrogel is increased. This cue was used by Yesilyurt et al. (2016) to release IgG from the hydrogel.

The glucose response of the hydrogels seems to be concentration dependent. Some groups observed deswelling when incubating formed gels in glucose solutions (Tierney et al., 2009; Horgan et al., 2006).

Wu et al. (2019) used boronic acid as both a dynamic covalent and a true covalent cross-linking partner. This was achieved by introducing two different reaction partners into the polymer backbone. To create covalent cross-links the partner was nopoldiol. For the dynamic interactions 2-gluconamidoethyl methacrylamide was used. This led to highly tunable networks from which doxorubicin could be released.

2.3.4. Disulfides

One of the earliest examples in which disulfides are utilized for polymer cross-linking, is in rubber vulcanization (Craig, 1957). In proteins disulfides play an integral role in creating the tertiary structure (Wedemeyer et al., 2000).

Disulfides are created through the oxidation of two thiols (Shu et al., 2002). Oxidation is possible via oxygen present in the air and tissues, or via dedicated oxidation agents such as hydrogen peroxide and sodium periodate (Sakloetsakun et al., 2009). The oxidation of thiols is a comparatively slow process, making in-situ gelation difficult. By instead relying on a thiol-disulfide exchange reaction, rates that are up to 20 times faster can be achieved (Zhang et al., 2023a).

Conversely reducing environments lead to the degradation of disulfide cross-linked hydrogels. This makes disulfides natively stimuli responsive (Meng et al., 2009). An important reducing agent inside the body is glutathione. It leads to the degradation of disulfide cross-linked hydrogels via thiol-disulfide exchange. Elevated glutathione levels have been observed in some tumor microenvironments (Gamcsik et al., 2012). Through the incorporation of shielded disulfides into the gel strain-stiffening behavior can be created within the gels. After reduction to thiols and application of strain, the thiols can form new disulfide bonds between polymer chains, leading to a higher stiffness (Tran et al., 2017).

Cross-linking hydrogels via diselenide bonds is also possible. Like disulfides they are formed via oxidation and cleaved via reduction. Due to their lower bond energies, they are more susceptible to cleavage (Gong et al., 2017). Due to this homolytic bond dissociation by visible light, irradiation can be used to initiate self-healing in the hydrogel (Ji et al., 2015).

3. Introducing the second cross-link

Even though it does come with added synthetic complexity, introducing a second cross-linking mechanism is often worthwhile. Due to the high number of possible cross-link combinations, strategies for their introduction vary widely. The approaches can be grouped in several different ways. One approach is to group them by the relative position of the cross-links to each other. Most often the two mechanisms are used in parallel. However, in some cases they can also be used in series (Fig. 1c). Jiang et al. (2022) used this approach to create hydrogels that were readily injectable, due to the guest-host component and pH-responsive due to the acylhydrazone linkage.

Alternatively dual cross-linked hydrogels can be grouped by the method of introduction of the two cross-linking mechanisms. Several different approaches are possible. Either polymers which themselves are able to cross-link are used or unfunctionalized polymers are modified with two different endgroups to enable dual cross-linking. The first approach is synthetically simpler, as only one additional modification has to be introduced. Possible combinations are limited by the cross-linking mechanisms provided by the unmodified polymers. Examples for this first approach are alginates and PVA. Alginates can be physically cross-linked with metal-ions from calcium to zinc (Malektaj et al., 2023) due to their carboxy-groups. To introduce a second cross-linking mechanism, they can be further modified via EDC-NHS chemistry. Kim et al. (2021) outlined strategies for the modification of gelatin with norbornene and hydroxyphenylacetic acid and carbohydrazide respectively to create gels with on-demand stiffening abilities (Fig. 5). PVA forms crystalline regions after freeze-thawing cycles. Chen et al. (2022) combined this property with glutaraldehyde as a covalent cross-linker to form dual cross-linked hydrogels. First, glutaraldehyde was added to the precursor solution. In a second step, the gels were freeze-thawed. This approach has the disadvantage that the gels prepared in this manner can only be prepared ex-vivo and need to be implanted in a further step. Dual cross-link approaches often bear the difficulty of controlling the ratio of cross-links, as this has a large influence on material properties.

Using unfunctionalized polymers like polyethylene glycol (PEG) provides the highest degree of control over the resulting cross-linking mechanisms. This comes at the price of higher synthetic complexity as two distinct cross-linking mechanisms need to be introduced. Tan et al. (2018) mitigated this, by using a single moiety for the physical as well as the covalent cross-link. They combined 4armPEG modified with dibenzocyclooctyl (DBCO) with 4armPEG modified with azide. These two partners can take part in a strain promoted azide alkine cycloaddition (Agard et al., 2004), producing a non-hydrolyzable cross-link. The hydrophobic DBCO residues, when not involved in the strain-promoted alkyne-azide cycloaddition (SPAAC) cross-linking, associate due to hydrophobic interactions. This provides the gels with a second, non-covalent, cross-link. Varying the ratio of covalent to non-covalent cross-links is particularly easy with this approach, as only the ratio of DBCO- to azide-PEG has to be varied. More complex approaches introduce all functional groups needed for two cross-linking mechanisms.

Methods for characterizing the dual cross-linked hydrogels are largely identical to single-cross-linked gels. Thus, already established methods for the characterization of hydrogels can be used. They can be characterized based on their performance in mechanical or chemical measurements. Mechanical testing can include measurements under tension or compression and rheological measurements to determine, for example, the self-healing capacity (Oyen, 2014; Gu et al., 2017). Chemical characterization includes a broad range of methods, from measuring degradation kinetics (Rodell et al., 2015b) and surface morphology (Norman et al., 2021) to release rates (Tiwari and Badiger, 2016). Depending on the intended application the most suitable procedures have to be chosen.

4. Applications of dual cross-linking

During the development of hydrogels several problems can arise, from insufficient mechanical strength to overly fast release kinetics. Dual cross-linking provides a versatile tool to address these shortcomings. From guest-host interactions, which enable material-drug interactions to slow down release, to Schiff base ligations which enable stimuli response. Table 1 shows several combinations of cross-linking mechanism and polymer backbone that have already been utilized for drug delivery.

4.1. Cell delivery

Cells are an especially demanding payload for delivery from hydrogels. Great care has to be taken to mimic the properties of extracellular matrix to increase the habitability for cells. A first measure to increase the habitability for cells, is the choice of polymer. Natural polymers like hyalurone, collagen or gelatin are able to be recognized by cells and facilitate material-cell interactions (Tibbitt and Anseth, 2009). Synthetic polymers can be modified with peptides such as arginylglycylaspartic acid (RGD) to increase their attractiveness to cells (Zhu, 2010). Another important factor for successful cellular therapy are the viscoelastic properties of the hydrogel. For this purpose dual cross-link hydrogels allow the modulation of the viscoelasticity independent of the initial elastic modulus by tweaking the ratio and types of cross-linkers (Chaudhuri et al., 2020). The viscoelastic properties of a hydrogel can also influence cell differentiation. These gels were formulated by combining ionic cross-linking of alginate with iEDDA cross-linking or thiol-ene photoclick and guest-host cross-linking (Vining et al., 2022). Furthermore, depending on the cross-linking chemistries used, cell infiltration into the hydrogel is also possible (Wang et al., 2023).

Feng et al. (2019) delivered mesenchymal stem cells in combination with icaritin for treating an animal model of steroid-associated osteonecrosis of the hip. The hydrogel consisted of gelatin and oligomerized acryloyl β-cyclodextrin (Ac-β-CD). The covalent cross-links were formed via multiple-substituted Ac-β-CD and were responsible for the long-term shape stability. Physical cross-links resulted from the interaction of aromatic residues of gelatin and the cavity of the β-cyclodextrin. They were able to show that the resulting gels were self-healing, shear-thinning, injectable and allowed for cell infiltration. These traits are largely mediated via the physical cross-linking reaction. Moreover, due to excess Ac-β-CD, the small hydrophobic molecule icaritin was able to be incorporated and released over a time span of up to 2 weeks. Through the combination of these two mechanisms, they were able to speed up bone regeneration.

Zheng et al. (2022) reported good survival of bone marrow derived stem cells (BMSCs) in hydrogels composed of maleimide modified hyaluronic acid and thiol modified gelatin. Cross-linking was achieved via Michael-addition and complexation of Fe^{3+} ions by the carboxyl groups of the hyaluronic acid. The cells survived for at least one week and were able to retain their original morphology. Furthermore they were able to show an increase in myocardial wall-thickness and reduced infarct size. They postulate an effect of exosomes released by the BMSCs.

4.2. Increased mechanical strength

Mechanical strength of hydrogels is of paramount importance for tissue engineering, as well as drug delivery, as the gels are placed in highly dynamic environments that challenge them with a broad range of stresses (Fuchs et al., 2020). These have to be carefully considered as mechanical deformation can have a large impact on the release behavior of hydrogels (Urciuolo et al., 2008; Caccavo et al., 2020). These specifics have not been investigated for many hydrogel types. Increasing the mechanical strength of hydrogels is in essence a problem of energy dissipation (Zhao et al., 2022). In single network covalent hydrogels energy is dissipated via the breaking of covalent bonds, be it the polymer backbone or the introduced cross-linkers. To toughen hydrogels, favorable breaking mechanisms have to be introduced. Biological tissues like bone or collagen gain their exceptional strength and toughness from sacrificial bonds (Rennekamp et al., 2023; Fantner

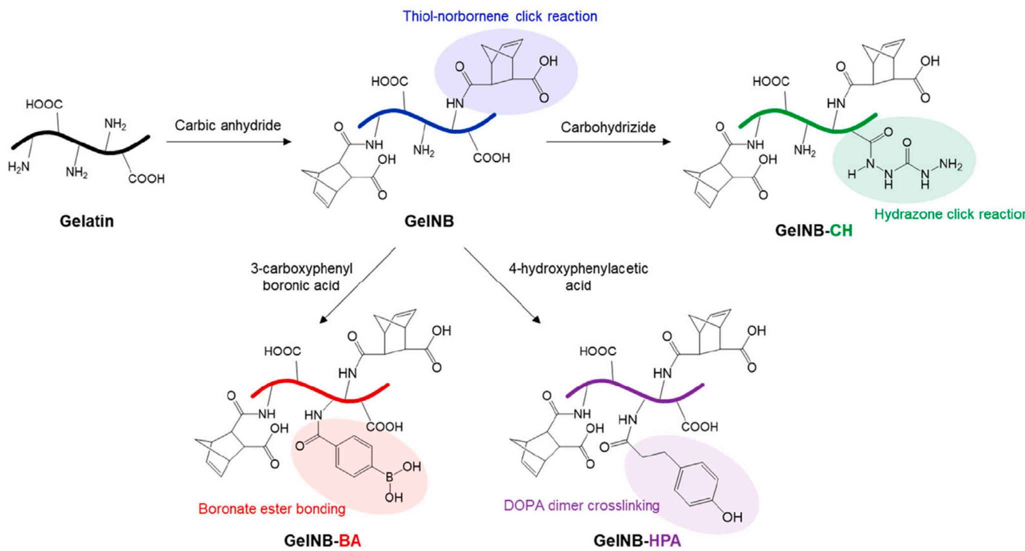

Fig. 5. Strategies for the dual modification of gelatin. The introduced moieties can in a second step be used to cross-link the gelatin. Covalent cross-linking is enabled by norbornene, dynamic-covalent cross-linking by carbohydrazide and boronic acid, lastly non-covalent cross-linking is enabled by the catechol moiety. Reprinted with permission from Kim et al. (2021). Copyright 2025 American Chemical Society.

Table 1
Overview of dual cross-linked hydrogels that have been investigated for the delivery of drugs.

First cross-linking mechanism	Second cross-linking mechanism	Polymer backbone	Substance release	Ref.
Schiff base	Hydrogen bonding	pAAm[a]	EGF[b]	Chen et al. (2018)
Acrylate	Hydrogen bonding	Gelatin	DFO-Lip[c], PTX-Lip[d], BSA-Lip[e]	Cheng et al. (2018)
Acrylate	Guest-Host	Gelatin/oligomerized Ac-CD	Icaritin/MSCs	Feng et al. (2019)
Schiff base	Ionic interaction	Alginate/Chitosan	Amoxicillin	Feyisa et al. (2023)
Schiff base	Ionic interaction	Alginate/Chitosan	Metronidazole	Feyissa et al. (2023)
IEDDA	Ionic interaction	Alginate/Oligosaccharide	Ketoprofen	Hoang et al. (2022)
Acylhydrazone	Guest-host	Cellulose	Doxorubicin	Jiang et al. (2022)
Acrylate	π-stacking, Hydrogen bonding	NPMAA[f]	Ibuprofen	Li et al. (2010)
Silan	Ionic interaction	Carboxymethyl Chitosan	AgNP[g] 60 to 120 nm	Mo et al. (2022)
Schiff base	Metal coordination	Alginate/Gelatin	Doxorubicin	Shen et al. (2023)
Genipin	Ionic interaction	Chitosan/Gelatin	Timolol maleate	Song et al. (2018)
Acrylate	Boronate ester	PEG[h]/Hyaluronic acid	Tannic acid	Sun et al. (2019b)
Amide	Disulfide	PAA[i]	AgNP[g]	Tiwari and Badiger (2016)
Polyurethane	Guest-host	Polyether	Curcurmine	Torchio et al. (2024)
Acrylate	Guest-host	Hyaluronic acid	DPCA[j]	Wang et al. (2024b)
Sugar benzoxaborolate	Nopoldiol benzoxaborolate	PEG[h]	Doxorubicin	Wu et al. (2019)
Diels–Alder	Hydrophobic interaction	PEG	Latex particles 4 µm	Yan et al. (2023)
Dynamic covalent Schiff base	Ionic interaction	Chitosan/Alginate	Rhodamine	Yu et al. (2023)
Thiol-ene photoclick	Guest-host	PEG	Ellagic acid	Zhang et al. (2023b)
Thiol-Michael	Hydrogen bonding	Hyaluronic acid	P-aTIGIT&PDA@IL-15[k]	Zhao et al. (2024)
Michael addition	Ionic interaction	Hyaluronic acid/Gelatin	BMSCs[l]	Zheng et al. (2022)

[a] Poly-acrylamide.
[b] Epidermal growth factor.
[c] Deferoxamine loaded liposome.
[d] Paclitaxel loaded liposome.
[e] Bovine serum albumin loaded liposome.
[f] Poly(nitrophenyl methacrylate-*co*-methacrylic acid).
[g] Silver nanoparticles.
[h] Polyethylene glycol.
[i] Poly(acrylic acid).
[j] 1,4-dihydrophenonthrolin-4-one-3-carboxylic acid.
[k] Platelet-conjugated anti-TIGIT antibody & polydopamine encapsulated IL-15.
[l] Bone mesenchymal stem cells.

et al., 2005). These are bonds that break before others in the network. This leads to the dissipation of energy, protecting the remaining bonds (Li and Gong, 2024). Sacrificial bonds can be covalent as well as non-covalent. The latter have the ability to reform after the applied force is released or during the application of the force. This leads to a certain degree of plasticity in hydrogels, formed via a dual cross-linking approach. Some covalent cross-links also possess the ability to reform after breaking (Watabe et al., 2022).

An important factor in the mechanical behavior of the dual cross-linked gels is the relaxation time of the transient cross-links (Zhao et al., 2022). Ducrot et al. (2014) investigated sacrificial bonds via the introduction of chemiluminescent cross-linkers. These cross-linkers emitted light upon breaking, enabling real-time visualization of bonds breaking.

Previously, the concept of sacrificial bonds has been applied in dual-network hydrogels. These consist of two distinct polymer species which

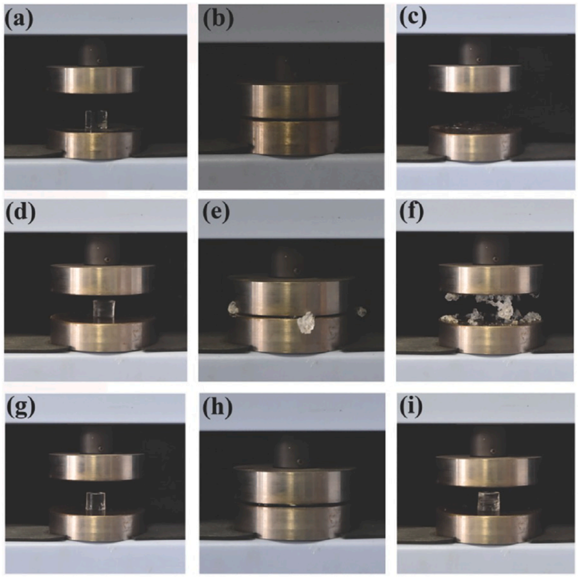

Fig. 6. Compression photographs of (a–c) physical, (d–f) chemical and (g–i) dual cross-linked hydrogels to a compression strain of 90%. While both the physical and covalent cross-linked gels are permanently deformed the dual cross-linked gel can recover its initial shape. Physical cross-linking was realized via the introduction of cationic micelles, covalent cross-linking via acrylate cross-linking. For the dual cross-linked gels both mechanisms were used in tandem. Courtesy of Gu et al. (2017).

are cross-linked using two different mechanisms (Xu et al., 2021). Similar effects in regards to their mechanical properties were observed.

By adding sacrificial cross-linking mechanisms to covalently cross-linked gels, higher mechanical stability can be achieved. For dual cross-linked hydrogels their mechanical strength exceeds the properties of each mechanism on its own (Fig. 6) (Gu et al., 2017). This opens up new applications, especially in the field of tissue engineering where materials are exposed to highly stressful, dynamic environments. Some of these physical cross-linking mechanisms can also act as mediators of material-tissue interaction. Dopamine modified polymers are one example. Han et al. (2022) used this effect to create hydrogel-based wound dressings that show good adhesion to skin and other materials. The catchols also act as the second cross-linking mechanism in tandem with acrylate cross-linking, due to the hydrogen bonds between them.

An especially challenging environment for the sustained delivery of drugs is the myocardium. Due to the repeated contraction of the heart, the hydrogel is subjected to high stress. It is imperative that the hydrogel does not react to this with dose dumping. In this environment dual cross-linked hydrogels, that show a high stability after many loading and unloading cycles, can be applied. Zheng et al. (2022) formulated a hydrogel via the combination of Michael-addition cross-linking and iron-complexation by carboxyl groups. Maleimide was used in the Michael-addition as well as for immobilization of the therapeutic payload consisting of a matrix-metalloprotease cleavable sequence conjugated to the KLTWQELYQLKYKGI (KLT) peptide sequence which promotes angiogenesis. They were able to show that in-vivo the hydrogel could release its cargo in a sustained fashion over a period of eight days without burst release after injection and lasted for 28 days before degradation.

4.3. *Self-healing*

Self-healing and self-recovery are two mechanisms that increase the longevity of biomaterials. They are realized through the introduction of re-configurable bonds, either physical or dynamic-covalent. Not all physical and dynamic covalent cross-linking mechanisms are suitable for self-healing materials. When physical cross-linking is combined with dynamic covalent cross-linking, full recovery of the mechanical properties can be achieved. During the process two distinct time regimes become evident. First, the physical bonds reform. Over a longer time the dynamic covalent bonds are reformed. This is exemplified by the combination of Diels–Alder cross-linking with hydrogen bonds. The Diels–Alder reaction can be seen as covalent at room temperature and as dynamic-covalent after heating to 90 °C. When a gel is cut and put back together at room temperature, only the hydrogen bonds reform, leading to incomplete recovery of mechanical strength. If the second healing step is initiated via heating, the Diels–Alder bonds reform and nearly full recovery is reached (Zhang et al., 2015).

For dual cross-linked hydrogels it is important to consider, that compared to single-cross-link gels, interdiffusion of polymer chains after mending, is significantly reduced or completely absent. When a covalent cross-linking mechanism is combined with a dynamic or physical mechanism, interdiffusion is fully stopped. For combinations of dynamic covalent and physical mechanisms, it depends on the bond energies of the respective mechanisms. This lack of interdiffusion can also negatively influence the strength of the mended hydrogel. Hai et al. (2022) showed, that with increasing covalent cross-link content, the self-healing ability as well as the polymer diffusivity declined.

Self-healing is closely connected to the injectability of hydrogels. When non-covalent interactions are responsible for the self-healing behavior, they often form thixotropic hydrogels. For example in the case of guest-host interaction between adamantane and cyclodextrin (Rodell et al., 2013).

Wang et al. (2019b) produced a dual cross-linked hydrogel by using gelatin methacrylate (GelMA) and modifying cyclodextrin with two 2-isocyanatoethyl acrylate residues. These in tandem produced the covalently cross-linked hydrogel network. In addition, adamantane with a polyethylene glycol spacer and an acrylate residue was also added to the GelMA backbone, enabling guest-host inclusion complexes with the cyclodextrin. Through the combination of these two cross-linking mechanisms, mechanically stable hydrogels with good self-healing properties could be created. After cutting a cast hydrogel in half and bringing the two halves in contact for one hour, the self-healing efficiency, measured via tensile testing, reached up to 80% for high polymer content gels (Fig. 7).

4.4. *Modification of release*

The release mechanism from hydrogels can broadly be categorized as erosive or diffusive (Li and Mooney, 2016). Solutes that are significantly smaller than the mesh size of the hydrogel and do not interact with the matrix are able to freely diffuse inside the hydrogel. When the hydrodynamic diameter of the solute approaches the mesh size, frictional drag slows down the diffusion of the solutes (Amsden, 1998) until they become immobile. In this case release occurs primarily via erosion. This is especially the case for nanoparticles, proteins and other macromolecules (Segovia et al., 2015; Ozekp et al., 2001).

Dual cross-link hydrogels offer several methods to fine tune this release behavior. These can be broadly classified into active and passive mechanisms. Active mechanisms trigger the release in response to a stimulus. This can be an internal stimulus, such as raised pH or the presence of reductive oxygen species, or an external stimulus, such as light or ultrasound. Passive modulation occurs due to material-drug interactions, for example formation of inclusion complexes with cyclodextrin or pi-pi interactions. These interactions are highly dependent on the molecule which has to be delivered.

4.4.1. *Active*

Active control of release from hydrogels is an often desired trait for hydrogels, making them smart biomaterials (Mazidi et al., 2022; Bordbar-Khiabani and Gasik, 2022). Some cross-linking chemistries are especially suited to these approaches. Examples include Schiff base cross-links, which are cleaved in response to lower pH-values, as is the

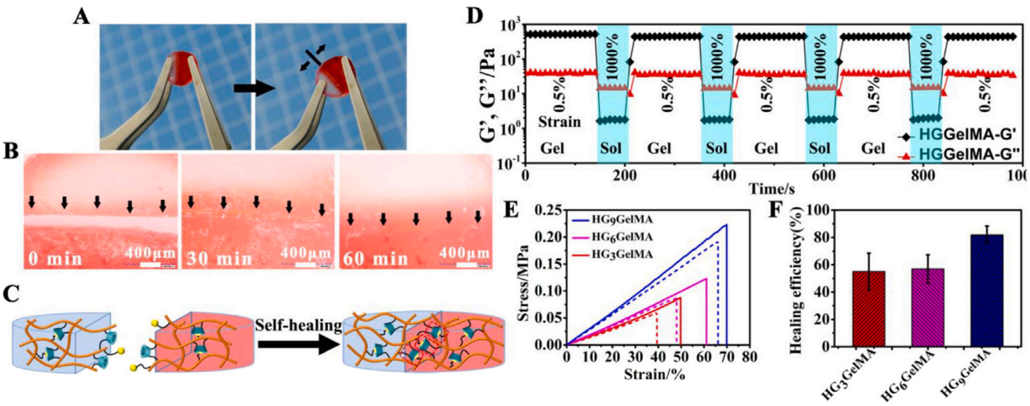

Fig. 7. Self-healing properties of an acrylate and guest-host cross-linked hydrogel (HGGelMA). (a) Photographs showing self healing of dual cross-linked hydrogel. (b) Three-dimensional rotational microscopic images showing the change of the incision during the self-healing of the hydrogel. The arrows indicate the position of the original incision. (c) Illustration of the possible mechanism for the self-healing of HGGelMA. (d) Measurements of the continuous step strain (0.5% strain → 1000% strain → 0.5% strain) at 37 °C showing the rapid self-healing of HGGelMA. (e) Stress–strain plots of HGGelMAs in different concentrations. Solid and dashed lines represent original and self-healed hydrogels respectively. Host-guest interaction partner content was varied from 3 to 9%. (f) The self-healing efficiency of hydrogels with different concentrations based on rapture energy (n = 3). Courtesy of Wang et al. (2019a).

case in cancerous tissue (Zhang et al., 2017; Xu et al., 2019). Boronic acid esters can be transesterified in the presence of glucose, leading to a decrease in cross-linking density. This effect can be utilized in the treatment of high blood sugar concentrations (Matsumoto et al., 2012; Tierney et al., 2009). Redox sensitivity plays an important role in cancer therapy, where the tumor environment provides a reductive surrounding (Ilangovan et al., 2002). This can be utilized for targeted release of chemotherapeutics by introducing disulfide cross-linkers (Vu et al., 2022).

Liubimtsev et al. (2023) created photoresponsive hydrogels by combining guest-host inclusion complexes with acrylate cross-linking. α-cyclodextrin was used as the host molecule, azobenzene as the guest. The guest molecule could be switched from a *trans*- to a *cis*-conformation via irradiation with 324 nm reversibly breaking the complex. This led to a swelling of the hydrogel. After subsequent irradiation with 426 nm light the azobenzene switched back into the *trans*-conformation, allowing the guest-host complex to reform and deswell the hydrogel. This may be a promising approach to release incorporated drugs at "the push of a button".

Wang et al. (2024a) created a hydrogel for the treatment of myocardial infarction. It was cross-linked via the photoinitiated acrylate cross-linking and the guest host interaction between carboxylated calixarene and 1,4-dihydrophenonthrolin-4-one-3-carboxylic acid (DPCA). DPCA also acted as the therapeutic cargo to stabilize the expression of hypoxia-inducible factor 1α. Stimuli response was realized by attaching the DPCA via a disulfide bond to the hyaluronic acid backbone. Disulfides scavenge excess reactive oxygen species after myocardial infarction and release DPCA in response. Through this combination of physical and covalent cross-linking, injectable hydrogels with stimuli response and sustained release were realized.

4.4.2. Passive

Double cross-linking enables fine tuning of hydrogel release characteristics, while maintaining excellent mechanical stability. The sustained delivery of small molecules from hydrogels is notoriously difficult. Due to the size difference between the molecule and the mesh size of the hydrogel, diffusion is nearly unhindered. This leads to a rapid release of solutes from the hydrogel (Mealy et al., 2015). Strategies such as the incorporation of the molecules into nanoparticles have been proposed. Nevertheless, this poses new challenges for example too slow release and added system complexity. Guest-host hydrogels which are able to complex the small molecule are one option to achieve sustained release. However, this comes at the expense of mechanical stability and fast erosion. By combining the ability of host molecules to complex the solutes with covalent cross-linking, sustained release over long time periods can be realized. Wang et al. (2018) developed a hydrogel for the concurrent delivery of hydrophobic and hydrophilic solutes on two different timescales. They achieved this via covalent cross-linking of lysine residue, introduced into the sequence of elastin like protein (ELP). Afterwards, the gels were physically cross-linked via the temperature induced coacervation of ELP. This shows an interesting application of dual cross-linking for introducing microscale inhomogeneities into hydrogels. The structure of these inhomogeneities could be controlled via changes in pH, stochiometry and reaction time.

Jiang et al. (2022) used the guest-host interaction between beta-cyclodextrin and adamantane and covalent cross-linking via acylhydrazone bonds to create a hydrogel, which could release doxorubicin in a sustained way. This effect relies on the formation of an inclusion complex between doxorubicin and cyclodextrin. The hydrogels showed high mechanical stability as well as self-healing behavior. Due to the acylhydrazone linker, the hydrogel was also able to release doxorubicin in response to lowered pH.

Sun et al. (2019b) formulated ultrasound responsive hydrogels. By combining acrylate cross-linking for mechanical stability and boronic ester linkages for the modulated release, they were able to deliver tannic acid in response to application of ultrasound to the gel. The gel showed a low basal release, which significantly increased after application of ultrasound.

The introduction of catechol groups can fulfill several functions. They mediate tissue adhesion of the hydrogel, which is an often desired trait for tissue engineering applications (Zhang et al., 2020), and they can also interact with each other to form hydrogen bonds. These act as physical cross-links in a hydrogel. Chen et al. (2018) used both of these effects to formulate tough, adhesive hydrogels for wound healing, which could also release epidermal growth factor (EGF). They postulate that EGF was immobilized through aryl-aryl interactions, Michael-type addition reactions or other non-covalent mechanisms. This allowed for a long term release of EGF to facilitate wound healing. Shen et al. (2023) combined three cross-linking mechanisms, namely imine-bonds, boronate esters and calcium complexation in a single gel based on gelatin and alginate. Through the combination of these three mechanisms, the gel could respond to peroxide via an increased release and to a more acidic pH via a reduction of release.

4.5. Improved injectability

Injectability is an often desired trait in hydrogels. Many hydrogels aim to deliver drugs for chronic diseases, leveraging their sustained release behavior. While long release times are possible, reapplication of the hydrogels will still be necessary. For gels that have to be implanted, this comes with increased patient discomfort and higher cost (Rizzo and Kehr, 2021). This makes subcutaneous injection a more desirable application pathway, even though it poses several problems for single cross-link systems. For cross-linking reactions with fast gelation kinetics, such as the iEDDA reaction, handling of the gel precursors is difficult, as it has to be injected within seconds after mixing. Cross-linking mechanisms with slow gelation kinetics face the problem, that after subcutaneous injection they quickly lose their shape leading to a rapid release of their cargo which is often not desired (Jons et al., 2022).

Thixotropy is an advantageous trait for hydrogels which carry drugs and are meant to be injected. High viscosity of the gel is desirable before and immediately after injection, to limit diffusion out of the gel causing burst release of the therapeutic cargo. When larger cargo, such as nanoparticles or proteins, are incorporated, high viscosity prevents aggregation and sedimentation. During the injection, low viscosity is important to make the injection possible. These thixotropic properties are generally created via physical cross-links. After injection purely physically cross-linked gels often suffer from low mechanical stability. Covalent cross-links can be used to mitigate this problem. When choosing a covalent cross-linking chemistry it should be slow enough that no significant number of cross-links are formed during the injection, as these could cause interferences.

Rodell et al. (2016) used this shear-thinning behavior to great effect. They combined the guest-host interaction between adamantane and cyclodextrin with a Michael-addition between thiol and methacrylate. Hyaluronic acid was used as the polymer backbone, whereas the guest-host interaction cross-links the gel almost instantaneous the Michael-addition is a slow process showing gel times of >45min (Rodell et al., 2015a). This allowed them to inject and locate the gel using physical cross-linking with subsequent strengthening of the gels to compressive moduli <40kPa.

Liu and Yao (2015) used this approach by combining the shear thinning properties of xanthan gum, which arise due to hydrogen bonding between chains (Patel et al., 2020), with covalent cross-linking of previously attached dopamine residues.

Diels–Alder reactions often show slow gelation kinetics. To mitigate this problem, Gregoritza et al. (2016, 2017) added hydrophobic spacer chains between the PEG backbone and the furan and maleimide groups. This led to thermogelation at physiological temperatures due to decreased solubility of the incorporated hydrophobic spacer chains. In addition the reaction partner for the Diels–Alder reaction were brought into closer proximity leading to a twice as fast gelation.

4.5.1. Microporous annealed particle scaffolds

A novel way to increase the injectability of hydrogels is via the formulation as microporous annealed particle scaffolds (MAP). These scaffolds consist of pre-manufactured hydrogel microparticles, which then interact through a secondary cross-linking mechanism to form bulk materials (Griffin et al., 2015).

Microparticles can be produced via several methods, the most popular being batch-emulsification and microfluidics. Batch emulsification has lower material requirements than the microfluidic process. This comes at the expense of control over the particle properties. Microfluidic methods produce particles with narrower size distribution (Liu and García, 2016). Complex geometries such as Janus-particles (Liu et al., 2022a) and core–shell geometries (Yu et al., 2019) can also be realized using the microfluidic process.

These particles are then combined to create the MAP scaffold. This is realized through secondary interactions, usually physical cross-linking. The functional groups that interact through these mechanisms can be incorporated in one of two ways.

In the first approach, intraparticle cross-linking, both functional groups for the annealing step are present in the same polymer. This makes each microparticle a dual cross-linked network hydrogel. When the hydrogel microparticles are then combined to form the MAP scaffold, the functional groups that are exposed on the surface of different particles can interact with each other to create cross-links between the different particles. This is called intraparticle cross-linking.

The second approach is interparticle cross-linking. Here two different species of hydrogel are produced. Each is modified with a different reaction partner. Upon mixing the exposed functional groups can interact and cross-link the scaffold (Widener et al., 2021). Functional groups that lie in the core of the hydrogel microparticle are unable to find interaction partners. This leads to an abundance of dangling chains inside the gel, reducing the mesh size and leading to network imperfections (Radi et al., 2013). An advantage of interparticle cross-linking is the possibility to use a covalent cross-linking mechanism for the secondary cross-linking (Caldwell et al., 2017).

Formation of microgels and ex-vivo gelation provide several benefits. They enable the application of non-bioorthogonal cross-linking reactions for injection such as thiol-ene and thiol-maleimide cross-linking. These normally come with the risk of cross reaction with cysteine in the body.

5. Conclusion

This review has given a broad overview of dual cross-link hydrogels and their applications in drug delivery and tissue engineering. In recent years there has been an increasing interest in these promising biomaterials. This has mostly come from the perspective of tissue engineering and additive manufacturing such as 3D-printing. Though these are promising applications, the potential of these materials for drug delivery should not be disregarded. We showed how many problems, that are faced by single cross-link hydrogels, can be addressed by the dual cross-link approach. These improvements come at the cost of increased synthetic complexity. Furthermore, tightly controlling the ratios of included cross-linkers remains challenging.

While we have shown many combinations of cross-linking mechanisms in this review, there is a clear lack of comparative studies. This, together with the sparse theoretical models for these materials, makes the rational design of new dual cross-link hydrogels challenging. Nevertheless, the benefits to be gained from a dual cross-link hydrogel outweigh the costs. The benefits range from increased injectability over higher mechanical strength to better control of release kinetics. These improvements in turn enable the use of hydrogels in new, more challenging, environments. Especially highly dynamic ones such as the myocardium which demand dynamic, yet strong materials.

CRediT authorship contribution statement

Carsten Damm: Writing – review & editing, Writing – original draft, Visualization. **Achim Goepferich:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Achim Goepferich reports financial support was provided by Federal Ministry of Education and Research Bonn Office. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

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

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