Chapter

Sustained Drug Release from Biopolymer-Based Hydrogels and Hydrogel Coatings

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Abstract

Biopolymer based hydrogels are three-dimensional physically or chemically crosslinked polymeric networks based on natural polymers, with an intrinsic hydrophilic character due to their functional groups. They display high water content, softness, flexibility, permeability, and biocompatibility and possess a very high affinity for biological fluids. These properties resemble those of many soft living tissues, which opens up many opportunities in the biomedical field. In this regard, hydrogels provide fine systems for drug delivery and sustained release of drugs. Moreover, biopolymer based hydrogels can be applied as coatings on medical implants in order to enhance the biocompatibility of the implants and to prevent medical conditions. In this chapter we review the latest achievements concerning the use of biopolymeric physical and chemically crosslinked hydrogels as well as hydrogel coatings as sustained drug release platforms.

Keywords: sustained release, drug delivery, biopolymers, hydrogels, hydrogel coating

1. Introduction

Gels can be defined as three-dimensional cross-linked polymeric networks which swollen in contact with a liquid. When the polymers forming the gel contain mainly hydrophilic functional groups, the liquid that causes the swelling is water, and the gel is called hydrogel [1]. Biopolymers are often used for the synthesis of hydrogels as the natural composition of the polymer leads to extremely high biocompatibility and potential applications in the biomedical field [2].

Hydrogels can be classified as physical hydrogels when the properties of the gel depend on chain entanglements and other interactions, mainly hydrogen bonds or hydrophobic interactions [3]. In this case, properties are highly dependent on chain molecular weight as well as concentration, as mobility of the chains modifies the structure of the hydrogel and therefore its physical properties. Water temperature, salt content, and pH can also affect the mobility of the chains and interactions and must be controlled [4].

Chemically crosslinked hydrogels present a much more stable structure than physical hydrogels. In chemical hydrogels, the polymeric chains are covalently bonded

using one or more crosslinking agents, using a chemical process [5]. In general, crosslinked hydrogels are less biocompatible than physical hydrogels, but this is compensated by other advantages: cross-linked hydrogels are insoluble, more stable, and rheological properties such as elasticity or viscosity, their pore size, and their degradation rate can be more optimized than with physical hydrogels.

Hydrogels can present different physical forms: from macrogels to micro and nanogels, which are particulate systems with similar chemical structure but different macroscopic size; implantable gels, with strong physical properties, or injectable gels, more fluids or composed of nano-microparticles which can pass through a needle; hydrogel coatings, where hydrogel nano or microlayer is immobilized on a surface; thermoresponsive or pH-responsive gels, where a trigger modulates the sol–gel properties, can be easily injected in a liquid form before gelation in physiological conditions [6].

Physical properties of physically and chemically crosslinked hydrogels, are similar to several soft biological tissues, and therefore they can be used as substitutes or supplements when the biological function of these soft tissues is compromised. Such hydrogels have been widely used as medical devices for different applications: in traumatology, as substitute or supplement of synovial fluid in osteoarthritis; in ophthalmology, as a substitute of aqueous humor during in cataract surgery; in esthetics and reconstructive surgery, as dermal fillers for rid correction and lipoatrophy for patients with VIH; in wound healing, as wound dressings to promote regeneration and healing of wounds [7].

The biomedical use of the hydrogels can be expanded by the employ of the hydrogels as a sustained release system. Concerning this the controlled release of pharmaceutical ingredients leads to important advantages as a control of the biodisponibility, dose control, local delivery and less side effects [8]. This chapter aims to cover a general overview concerning the sustained drug release from hydrogels and hydrogel coatings. In that regard, *Section 1 Introduction* presents the topic and outlines the content of the chapter; *Section 2 Mechanism of drug release form hydrogels*, reviews the most significant theories on drug release mechanism; *Section 3 Drug release from physical hydrogels* summarizes the recent advances on the area; *Section 4 Drug release from chemically cross-linked hydrogels* revises the latest works on sustained release from chitosan, hyaluronic acid and other biopolymers; *Section 5 Drug release from hydrogel-based bioactive coatings* introduces the most relevant concepts on drug release form coatings; finally *Section 6 Conclusion* synopsizes the content of this chapter.

2. Mechanism of drug release form hydrogels

The release of drugs from hydrogels can be achieved by different mechanisms such as swelling/deswelling, diffusion, and chemical mechanism. As previously mentioned, hydrogels are three-dimensional crosslinked polymeric networks that swelled in the presence of water. The crosslink can be physical (hydrophobic interactions, electrostatic interactions and hydrogen bonding) or chemical (covalent bonding) and is responsible of the network structure of the hydrogel. Such networks display open spaces, the size of which is referred to as the mesh size of the hydrogel [9]. Importantly, the mesh size of the hydrogels is one of the main parameters that affect how drugs diffuse through the hydrogel network, being dependent on polymer and crosslinker concentrations, as well as external stimuli. The gelation of hydrogels

by polymerization means leads to network irregularities and polymer polydispersity upon formation, and as a result, the mesh size is usually heterogeneous. A number of approaches exist to determine the mesh size [9].

When the mesh is larger than the drug ($r_{mesh}/r_{drug} > 1$), the drug release process is dominated by diffusion. Small drug molecules migrate freely through the network, and diffusion is largely independent of the mesh size. The diffusivity, D, in this situation depends on the radius of the drug molecule (r_{drug}) and the viscosity of the solution (η) via the Stokes–Einstein equation Eq. (1) [10]:

$$D = \frac{RT}{6\pi\eta r_{drug}} \quad (1)$$

where R is the gas constant and T is the absolute temperature.

When the mesh size is close to the drug size ($r_{mesh}/r_{drug} \approx 1$), the effect of steric hindrance on drug diffusion becomes relevant. Finally, for an extremely small mesh size and/or very large drug molecules ($r_{mesh}/r_{drug} < 1$), strong steric hindrance immobilizes the drugs and it remains physically entrapped inside the network, unless the network degrades or the mesh size expands in response for example, to external stimuli.

Several methods accompanied by mathematical model development have been created in parallel to hydrogel technology, in order to predict drug release from the network. The drug release fitting models (i.e. the zero order equation; the first order equation; the Higuchi's equation; the Korsmeyer-Peppas' equation; the Hixon-Crowell's equation, the Weibull equation, among others) are the most abundant, however, they are not predictive but simple mathematical fitting equations. In the last years, mechanistic and statistical models are growing quite fast. Mechanistic models combining the mass transport with the system mechanics developed with a "fully coupled" approach considers the influence of the mass transport on the mechanics as well as the opposite, which makes this approach the only candidate to produce reliable first-principle models.

Statistical models, are receiving a lot of attention due to the consensus of the regulatory authority and the possibility to predict the hydrogels behavior, in the analyzed design space, regardless the complicate phenomenology, with quick and inexpensive experimental designs [11]. Recently, Wu and Brazel developed a method for the simulation of water uptake profile and drug release from homogeneous hydrogels. This model successfully predicted the initial burst release observed experimentally [12]. Sheth et al. developed a mathematical and computational model using time snapshots of diffusivity and hydrogel geometry data measured experimentally as inputs to predict release profiles of two model proteins of varying molecular weights from degradable hydrogels [13].

3. Drug release from physical hydrogels

Physical hydrogels are those formed by reversible and dynamic crosslinks grounded on noncovalent interactions. In this regard the network of physical hydrogels is reversibly held together by molecular entanglements, resulting from a dynamic competition between pro-assembly forces (for example, hydrophobic interactions, attractive electrostatic forces and hydrogen bonding) and anti-assembly forces (for example, solvation and electrostatic repulsion [3]. These interactions that occur in

this type of hydrogels are usually weak. However, they are numerous and contribute to the presence of complex behaviors.

Polyampholytes may also be used to construct physical hydrogels, with randomly dispersed cationic and anionic groups. The randomness leads to a wide distribution of strengths: The strong bonds serve as structural crosslinks, imparting elasticity, whereas the weak bonds reversibly break and re-form, dissipating energy. Consequently, physical hydrogels have reversible liquid to solid transition, also called sol–gel transition, in response to different changes in environmental conditions such as temperature, ionic strength, pH, or others [14]. Since the interactions depend significantly on external stimuli, they allow hydrogels to be highly versatile concerning the environment, unlike covalently bonded materials [15].

Physical hydrogels can be engineered to undergo spontaneous biodegradation under physiological conditions, which constitutes another way of controlling the release of active molecules [16]. Degradation is typically mediated by hydrolysis [17, 18] or enzyme activity [19]. The erosion or loss of polymer mass through degradation, can take place simultaneously in the bulk or on the surface of the hydrogel. For a variety of hydrogels, the bulk and surface erosion can be tuned to obtain desirable release kinetics ranging from weeks to months. Bulk erosion occurs because of the permeability to water or degrading enzymes when the rate of diffusion of these agents is rapid compared to the rate of bond degradation. Surface erosion, in contrast, results when the rate of bond breakage is more rapid than the rate of enzyme or water diffusion from the exterior into the bulk of the gel [13].

Representatives of reversible physical hydrogels are the shear-thinning hydrogels which flow like low-viscosity fluids under shear stress during injection, but quickly recover their initial stiffness after removal of shear stress in the body [3]. Alginate hydrogels are shear-thinning, formed via electrostatic interactions between alginate and multivalent cations (for example, calcium and zinc). They can be readily injected via a needle after gelation in a syringe and have been used to achieve sustained local delivery of bioactive vascular endothelial growth factor (VEGF) in ischemic murine hindlimbs for 15 days [20, 21].

3.1 Peptide based physical hydrogels

Another example of physical hydrogels forming materials are the self-assembling peptide systems, where amino acid-based chains undergo the sol–gel transition without the need of any chemical crosslinking agent. This property makes them useful materials to safely in situ encapsulate living cells or sensitive drugs, among others. In addition, this peptide-driven self-assembly into physical hydrogels is highly specific, sourced mainly by the biorecognition of peptide segments scattered among the macromolecular chains. They form dynamic well-defined, hierarchically organized 3D structures with reversibility of the assembly and disassembly processes [22]. Another example are elastin-like polypeptides cross-linked via electrostatic interactions between their cationic lysine residues and anionic organophosphorus cross-linkers [23]. Non-covalent interactions between heparin and heparin-binding peptides and proteins can also be used to form hydrogels for growth factor delivery [24, 25].

Peptide self-assembly can also be achieved by taking advantage of interactions between metal cations and amino acid residues of the peptides. This was demonstrated with gelation of a β-sheet-rich fibrillar hydrogel with zinc ions [26].

3.2 Chitosan based physical hydrogels

Additional interesting example of physical hydrogels for drug release applications are pectin-chitosan hydrogels, which showed to be thermo-reversible and capable of prolonging the release of three different model hydrophobic drugs: mesalamin, curcumin and progesterone. In vitro drug-release studies revealed that lower percentage of pectin in the hydrogel led to slower release rates owing to smaller mesh size arising from stronger interactions between the polyelectrolytes. Also, the release was slower when the total polymer concentration was higher. Finally, a slower release in PBS solution compared to HCl solution was attributed to the fact that at pH 7.4, both polymers are charged, with strong electrostatic forces and consequently, smaller mesh size. At the molecular scale, the polymer chains can possess abundant binding sites for the drugs. DSC and FTIR analysis exhibited some interactions between the drugs and both chitosan and pectin that can contribute to the prolonged release of the drugs [27]. Another in situ-gelling hydrogel was formed with a polyelectrolyte complex, which showed a sustained release of insulin and avidin proteins [28].

4. Drug release from chemically cross-linked hydrogels

Crosslinking of biopolymers provide a stable and non-soluble biomaterial which preserves the properties of the original biopolymer and displays a longer durability. Consequently, the half-life time of the hydrogels is increased when performing its biological application [5].

Usually, biopolymer crosslinking can be accomplished in two ways: by direct addition of a cross-linking agent followed by formation of a the three-dimensional (3D) network, or by chemical modification of the biopolymer chains with functional groups suitable for crosslinking with a compatible cross-linker. The first approach takes advance of the functional groups already present in the biopolymer, typically amine (NH_2), hydroxyl (-OH), carboxylic acid (-COOH), amide (-CONH-, -$CONH_2$), thiol (-SH) or sulfate (-SO_3H) groups [29]. Examples of cross-linkers are dialdehyde derivatives, NH_2-PEG-NH_2 molecules, COOH-PEG-COOH derivatives, diglycidyl ether compounds, vinyl sulfone groups, etc. These agents cross-link through Michael-type addition, thiol exchange/disulfide cross-linking or Schiff-base processes among others [30]. In some case the addition of coupling agents such as carbodiimides derivatives, N-hydroxysuccinimide (NHS) or N-hydroxybenzo triazole (HOBt), is required for the cross-linking. In the second approach new active functionalities are created in the biopolymer [31, 32] which are appropriate for a broad range of cross-linking processes such as azide–alkyne cycloadditions, Diels–Alder reactions, ultraviolet (UV) photoinitiated crosslinking, (meth)acrylation reactions [5, 32]. Examples of cross-linkers are oxanorbornadiene, cyclooctyne, maleimide, trans-cyclooctene, norbornene, PEG-di(meth)acrylates among others.

The crosslinking of biopolymers produces hydrogels with elastic and deformable structures and great topochemical accessibility which is able to accommodate different kind of active molecules, such as drugs, for sustained release (**Figure 1**).

4.1 Chitosan based chemically crosslinked hydrogels

Chitosan (CHI) is a linear polysaccharide formed by arbitrarily allocated β-(1 → 4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine

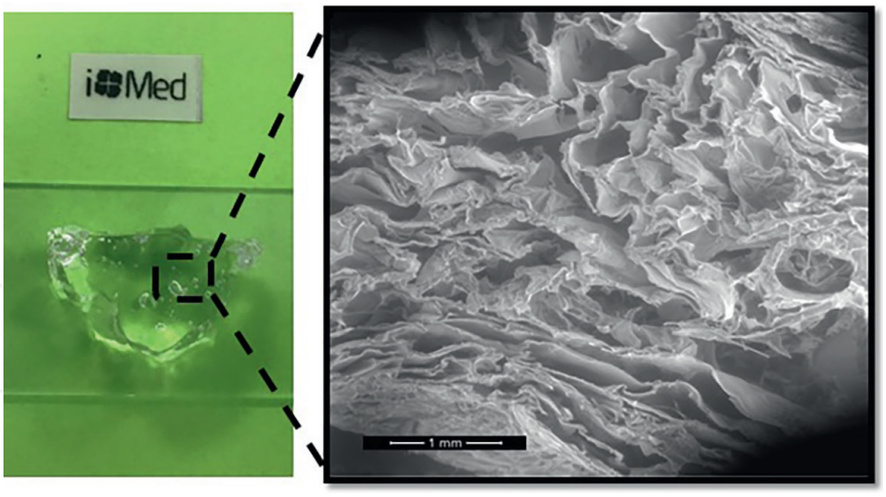

Figure 1.
Left: Image of a hydrogel based on crosslinked hyaluronic acid. Right: Scanning electron microscopy (SEM) picture of the hydrogel. Figure produced by the authors.

(acetylated unit). Chitosan is one of the most versatile biopolymers due to its unique properties: biodegradability, biocompatibility, non-toxicity, antioxidant, anti-inflammatory, antifungal, and antibacterial "contact killing" [33]. Therefore the applicability of this polysaccharide extends to a wide range of various biomedical areas, such as cosmetics, drug delivery, and tissue engineering, among others [34].

In this regard a covalently crosslinked chitosan hydrogel was produced Diels Alder reaction of furan and maleimide functionalized CHI. The resulting biopolymer held the typical pH sensitivity and antibacterial properties of non-functionalized CHI. The drug delivery capabilities of this system were evaluated with model drug antibiotic chloramphenicol (ClPh). Drug release experiment did not show an initial burst, which indicated that the ClPh was successfully encapsulated, whereas it displayed a sustained delivery of the drug with a complete release of the total amount of drug loaded (2.61 ± 0.036 mg ClPh/g hydrogel) after 4 hours [35].

CHI was also crosslinked with genipin (GP) to obtain biocompatible, antibacterial and anti-inflammatory hydrogels with wound healing properties. Sustained release of acetylsalicylic acid (ASA), cefuroxime (CFX), tetracycline (TCN) and amoxicillin (AMX) from the hydrogels displayed a Pharmacologic Half Life t1/2 values of 88 h, 62 h, 135 h, and 240 h for ASA, CFX, TCN and AMX respectively. These antibiotic releases generated antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* that reached almost 100% bacterial reduction and an antibacterial efficacy R > 2. The synergistic anti-inflammatory activity was confirmed by the reduction in the amount of pro-inflammatory cytokines when ASA was mixed with CFX (5.39 ± 0.81 ng·mL^{-1} TNF-α), TCN (4.70 ± 0.21 ng·mL^{-1} TNF-α and 49.06 ± 9.64 ng·mL^{-1} IL-8), and AMX (2.28 ± 0.36 ng·mL^{-1} TNF-α, 14.84 ± 5.57 ng·mL^{-1} IL-8, and total IL-6 removal) [36].

Moreover, dialdehyde-β-cyclodextrin (DA-β-CD) crosslinked carboxymethyl chitosan (CMCS) hydrogels were prepared from carboxymethyl chitosan (CMCS) and periodate oxidized β-CD. Phenolphthalein (PhP), a formerly used laxative agent, [16] was selected as a model molecule to investigate the drug loading and sustained release capabilities of such hydrogels. PhP release results show that increasing crosslinking rate between DA-β-CD and CMCS delays the drug liberation process. On the other hand, DA-β-CD/CMCS system displays faster releases, with a 50% release in 2 h

and about 90% within 12 h, compared to CMCS crosslinked with glyoxal dialdehyde which only releases 19% of PhP after 24 h [37].

CHI based hydrogels (N-succinyl chitosan-g-Poly(acrylamide-co-acrylic acid) were synthesized by free radical mediated cross-linking of N-succinyl chitosan, acrylamide and acrylic acid [38]. Drug delivery capabilities of the system were tested by encapsulation of theophylline, a phosphodiesterase inhibiting drug used for the treatment of respiratory diseases. The drug release experiments showed a pH dependent behavior. In this regard, at pH 1.2 the theophylline released rate was found to be between 14 and 24% whereas at pH 7.4 the release of the drug reached 67–93%. CHI itself has been used as a cross-linking agent for poly(acrylic acid). The resulting hydrogels display pH sensitive properties that have been exploited to control the release of antibiotic amoxicillin and anti-inflammatory drug meloxicam. Concerning this, the release rates of these molecules rise with increasing pH due to the disruption of hydrogen bonds between the hydrogel components and the drugs. As a result 30%, ~60% and ~80% of amoxicillin is released after 800 min at pH 1.2, 6.8 and 7.4, respectively. The corresponding release data for meloxicam are ~20%, ~70% and ~90% at pH 1.2, 6.8 and 7.4, respectively [39].

4.2 Hyaluronic acid based chemically cross-linked hydrogels

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan constituted by repeating disaccharide β-1,4-D-glucuronic acid–β-1,3 N-acetyl-D-glucosamine units that form hydrogels in aqueous solutions. This naturally occurring polysaccharide is found in connective tissues, skin, and synovial joint fluids of the human body. HA displays bio-functionality, biocompatibility, and physicochemical properties, such as viscoelasticity and high-water retention. As a result hyaluronic acid is used for the treatment of dry eye disease, dermatological conditions as well as a as a viscosupplement for the treatment of osteoarthritis [5].

Biocompatible antibacterial hydrogels of HA were synthetized by crosslinking HA solution with divinyl sulfone (DVS) followed by loading with antibiotic molecules. This way cefuroxime (CFX), tetracycline (TCN) and amoxicillin (AMX) loaded hydrogels displayed in vitro antibacterial activity against S. aureus. The antibacterial properties of the hydrogels were synergically enhanced by merging antibiotics with anti-inflammatory agent acetyl salicylic acid (ASA). Consequently it was observed an increase in the log10 reduction value (R) from 3.2, in the absence of ASA, to R 5.55 when TCN or CFX were combined with ASA [40].

Hyaluronic acid was crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and loaded with quetiapine (QTP), an antipsychotic drug, and quercetin (QCT), a hyaluronidase (HAase) inhibitor that decreases the biodegradation of HA. Subcutaneous injection in rats of the system showed that the cHA hydrogel with QCT exhibited a lower maximum QTP concentration (Cmax. 782.6 ± 174.4 ng/mL) and longer half-life (t1/2 23.5 ± 2.7 h) and mean residence time values (MRT 30.9 ± 3.9 h) compared to the hydrogel without QCT (Cmax. 1827.6 ± 481.3 ng/mL, t1/2 13.4 ± 4.9 h, MRT 14.3 ± 4.8 h). These results demonstrated that HAase containing HA hydrogels are suitable systems for sustained drug delivery applications [41].

A thiol functionalized hyaluronic acid HA-SH was used, together with DMSO, for the fabrication of HA-SS-HA hydrogels. This system was loaded with antitumoral drugs such as doxorubicin (DOX), zinc phthalocyanine (ZnPc), and indocyanine green ICG, for implant post peritumoral administration. In vivo experiments validated that drug loaded hydrogel implant possessed satisfactory biocompatibility and

succeeded in long term sustained release of drugs. As a result the system to ensured high tumor aggregation efficiency and adequate tumor suppression [42]. Hyaluronic acid (HA) functionalized with thiol and hydrazide moieties has been combined with oxidized sodium alginate (ALG)to produced cross-linked hydrogels (HA/ALG). These materials display tunable physicochemical properties and drug release behavior as a function of the HA/ALG precursor concentration. In this regard for HA2/ALG2 (2% w/v), HA3/ALG3 (3% w/v) and HA4/ALG4 (4% w/v) the yield stress of hydrogels were 1724, 4349 and 5306 Pa, and the degradation percentage were about 64%, 51%, and 42% after 35 days incubation, respectively. Thus, in vitro cumulative release of Bovine serum albumin (BSA) for HA2/ALG2, HA3/ALG3 and HA4/ALG4 were 79%, 72%, and 69% respectively for a 20 day release assay [43].

Near-infrared (NIR) light-triggered and reactive oxygen species (ROS)-degradable hyaluronic acid hydrogels (HPTG) were synthesized through the formation of dynamic covalent acylhydrazone bonds. Such system was loaded with photosensitizer protophorphyrin IX (PpIX) and anticancer drug doxorubicin (DOX), to obtain a with light-tunable on-demand drug release for chemo-photodynamic therapy. In this regard NIR light irradiation generated ROS that induced the required degradation of hydrogel and subsequent on-demand DOX release for cascaded chemotherapy. In vivo imaging-guided antitumor study using 4 T1 tumor- mouse model demonstrated that the treatment of DOX-loaded HPTG with laser irradiation nearly accomplished the suppression of tumor growth without noticeable regrowth [44].

Tyramine functionalized HA solutions were combined silk fibroin (SF) to produce a series of HA/SF hydrogels for application in cartilage tissue engineering an and drug delivery. These hydrogels were loaded with Vanillic acid (VA) or Epimedin C (Epi C), both with anti-catabolic, anti-inflammatory and anabolic effects on human cartilage cells. Hydrogels with HA20/SF80 polymeric ratios displayed the longest and the most sustained release profile with 70.1% release of VA after 60 days of release assay and 54% release of Epi C after 7 days of release. Such behavior makes HA20/SF80 hydrogels a prospective material for the treatment of osteoarthritic joint conditions [45].

Polyethylene glycol (PEG)-HA was modified also with a small biologically active molecule, as dopamine, to fabricate a HD-PEG polymer. This polymer was crosslinked with α -cyclodextrin (α-CD) to afford a polypseudorotaxane supramolecular complex HD-PEG/α-CD. The system was loaded with poly(lactic-co-glycolic acid) (PLGA)/donepezil microspheres (PDM) in order to evaluate the drug delivery capabilities of the system. The released amounts of donepezil, a drug used for the treatment of mental conditions, reaches 39.9% and 56.7%, after 7 and 14 days respectively. These results demonstrate that the HD-PEG/α-CD/PDM system could be used for the subcutaneous injection of long acting donepezil [46]. Similarly, poly(L-lactide-co-glycolide) (PLGA) – dexamethasone (DEX) nanoparticles PLGADEX were combined with crosslinked HA for drug release applications. In this case the chemical crosslinking occurred doubly, by mixing amino-hyaluronic acid and aldehyde-hyaluronic acid in the presence of genipin as a cross-linker agent. Drug delivery experiments showed full DEX release after 2 months for a HPLGADEX hydrogel [47].

Oxidized hyaluronic acid (OHA) was combined with carboxymethyl chitosan (CMC) via Schiff base reaction to fabricate a hydrogel (OHA-CMC) with antibacterial and hemostatic activities. The drug delivery potential of the system was exploited by encapsulating PLGA-PEG nanoparticles of curcumin (CNP) and epidermal growth factor (EGF) that afforded a OHA-CMC/CNP/EGF hydrogel. This system displayed outstanding anti-inflammatory, antioxidant and cell migration-promoting effects *in vitro* and improved wound healing *in vivo* with optimal granulation tissue

formation, re-epithelialization, and skin appendage regeneration. The cumulative release percentage of CNP reached 55.3% on day 1, 75.5% on day 3 and ~ 90% after 6 days of release experiment. EGF displayed a 28.6% of release on day 1, 51.3% on day 2 and 88.1% in 9 days. These results demonstrate the potential of the hydrogel for the treatment of diabetic wound healing [48].

Finally, HA has been used as well as a biopolymer for the fabrication of a 3D printable dual-network hydrogel with drug delivery capabilities. For that acrylamide-modified HA was synthesized and subsequently mixed with folic acid and Fe3+ to form a physical crosslinking network. Afterwards acrylamide residues were polymerized by ultraviolet radiation affording a material suitable for wound dressing with high elasticity and fatigue resistance. The drug delivery properties were investigated using acetylsalicylic acid (ASA) as a drug model and resulted in a pH responsive hydrogels with the sustained release of ASA over 300 hours [49].

4.3 Other chemically cross-linked biopolymers

Lignin is a sustainable biopolymer derived from lignol precursors that has been historically related to the paper industry. Hydrogels of hardwood lignin (TCA) have been synthesized through crosslinking with poly(ethylene) glycol diglycidyl ether (PEGDGE) and loaded with paracetamol for drug release applications. Here, decreasing amounts of crosslinker diminishes the interaction paracetamol - hydrogel network and, as a result, the release of paracetamol increases. In this regard, hydrogels produced with a lignin:PEGDGE 1:1 ratio displayed up to 30% of paracetamol release after 120 h assay. The release data follow a pseudo-Fickian behavior of diffusion when fitted to the Korsmeyer-Peppas model [50]. Furthermore, lignin polymers have been mixed with cellulose to generate drug delivery systems. Mechanical and sustained release performances of these gels are tailored by varying the ratio of the precursors: cellulose, hardwood lignin (TCA), and epichlorohydrin (ECH) cross-linker. TCA containing hydrogels display the best release rate (>90%) for drug model paracetamol comparing to the pure cellulose hydrogels (~40%) after 7 hours of release experiment. This behavior is attributed to the lower affinity of paracetamol for lignin compared to cellulose [51].

Cellulose itself have been used for the fabrication of hydrogels with drug release properties. In this regard, carboxymethyl cellulose (CMC) functionalized with β-cyclodextrin and nucleic acids have been crosslinked by using of arylazopyrazoles (AAPs) and loaded with anti-cancer molecule Doxorubicin (DOX). The resulting hydrogel behaves as a functional matrix for the UV light mediated ON/OFF release DOX. Irradiation of the matrix provokes the photoisomerization of the trans-AAP to cis-AAP residues and the generation of the low-stiffness hydrogel that releases DOX. Therefore, the liberation of the DOX could be changed between ON and OFF states by oscillating the photoisomerization of the hydrogel by employing UV/Vis irradiation [52].

Xanthan is a heteropolysaccharide produced by fermentation from the bacteria *Xanthomonas campestris* with applications as thickening agent in food industry as well as pharmaceutical aid and release retarding polymer in drug delivery systems [53]. Hydrogels form this biopolymer have been produced by crosslinking oxidized xanthan, with a PEG hydrazine derivative through pH-responsive hydrazone linkages. The drug delivery properties of the hydrogel were assessed by performing release studies of the antitumoral drug Doxorubicin (DOX), at pH 5.5 (tumoral) and 7.4 (physiological). At pH 5.5 the cumulative release of DOX from 3, 4, and 5% hydrogels was 81.06, 61.98, and 41.67% respectively whereas the release at pH 7.4 was 47.43, 37.01, and 35.34% after 30 days of assay. Moreover DOX-loaded hydrogels possessed cytotoxicity against

A549 cells after exposure to DOX containing released media [54]. Curdlan is another example of polysaccharide produced by fermentation and with applications in the food industry. Phosphorylated curdlan (PC) was crosslinked with,4-butanediol diglycidyl ether (BDDE) and loaded with tetracycline (TCN) to fabricate hydrogels with drug delivery applications. Drug release profiles at equilibrium release (3.5 h), pH 6.8, 37°C reached 87% for hydrogels produced exclusively from phosphorylated curdlan (PC), whereas release from curdlan hydrogels achieved 48% of release [55].

Casein is a proline-rich, open-structured protein found in raw milk. It displays high hydrophilicity, good biocompatibility and a lack of toxicity that makes of it a potential candidate for hydrogel development. Casein can be chemically cross-linked with enzymes such as microbial transglutaminase (MTG). This feature was utilized to produced crosslinked casein -γ-polyglutamic acid (PGA) hydrogels in 1/5 and 1/9 ratio. Drug release experiments showed that both composition displayed similar release rate values for aspirin (~ 100% after 10 h), while 1/9 hydrogels possessed a higher release rate for vitamin B12, ~100% after nearly 12 h versus ~20% for 1/5 casein/γ-PGA hydrogels [56].

5. Drug release from hydrogel-based bioactive coatings

Historically, the development of medical implants has been a great concern for biomedical community. Besides, their need has risen dramatically due to the increased number of surgical procedures that are predicted to be even higher in 2030 [57]. Thus, improving the performance of implantable biomaterials has become a high-priority trend, which is reflected in the large number of research realized to successfully meet the upward demand [58].

Implantable medical devices (e. g. coronary stents, cardiac pacemakers, prostheses, insulin pumps) are classified in four main groups: ceramics [59], polymers [60], composites [61], and metals [62]. Among them, metallic biomaterials as titanium and its alloys are of outmost interest thanks to their inert chemical and biological behavior *in vivo* [63]. Even so, their bioactivity can be improved creating coatings by surface modification techniques and thereby, add other beneficial properties [64].

The use of these bioactive coatings entails the development of an improved version of bioactive materials that modulates biological systems response by the establishment of interactions with adjacent tissues and bones [65]. Nevertheless, these coatings require the most suitable physicochemical, mechanical, and biological functionality for a successful implantation and integration so as not to produce any counterproductive disorder in humans [66]. Therefore, it is imperative to develop functional bioactive coatings onto the surface of biomaterials (**Figure 2**, produced by the authors) that combine biocompatibility [67], antibacterial [68], anti-inflammatory [69], self-healing [70], wound healing [71], bone tissue engineering [72], and osseointegration [73] properties.

Such features can be incorporated onto the surface of biomaterials by the use of biopolymer-based coatings, mostly based on hyaluronic acid and chitosan [74]. Moreover, these coatings acquire hydrogel-like three dimensional microstructure after crosslinking for bioactive agents delivery applications (**Figure 3**, produced by the authors). In such manner, bioactive properties that already possess biomaterials can be upgraded or even provide novel outstanding properties [75]. Specifically, hydrogel coatings take advantage of hydrogels peculiar ability of releasing in a controlled space–time manner to the therapeutic target the entrapped bioactive agents (drugs, proteins, peptides, growth factors, inorganic or polymeric nanoparticles, and nucleic acids) through their polymeric network [76].

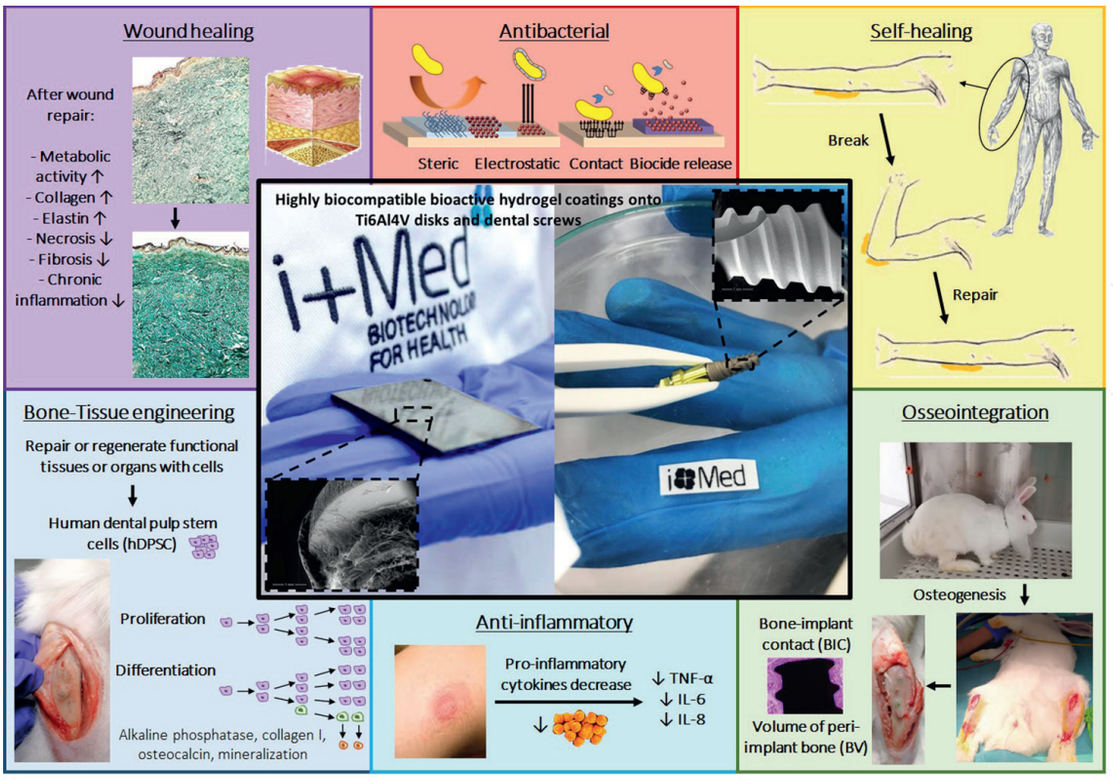

Figure 2.
Bioactive properties of functional hydrogel coatings for biomaterials successful implantation. Figure produced by the authors.

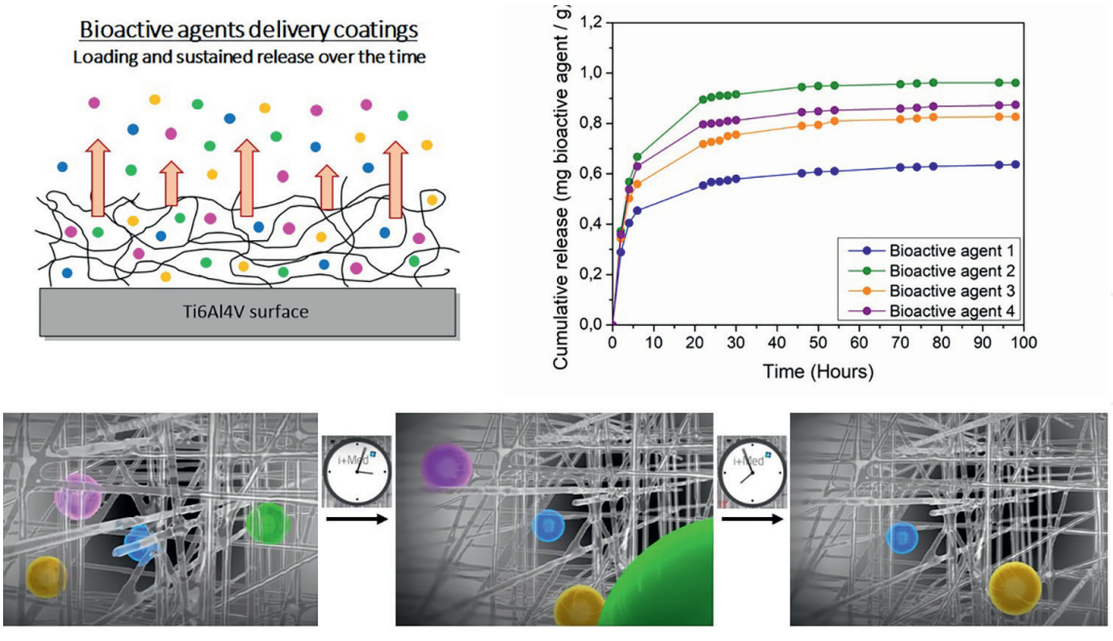

Figure 3.
Bioactive agents loading and controlled release ability from hydrogel-based coatings. Figure produced by the authors.

Bioactive agents controlled delivery reduces side effects in patients undergoing implant procedures. In addition, highly stable (from hours to months) hydrogel coatings with great loading ability provide a not sudden, uniform, and prolonged

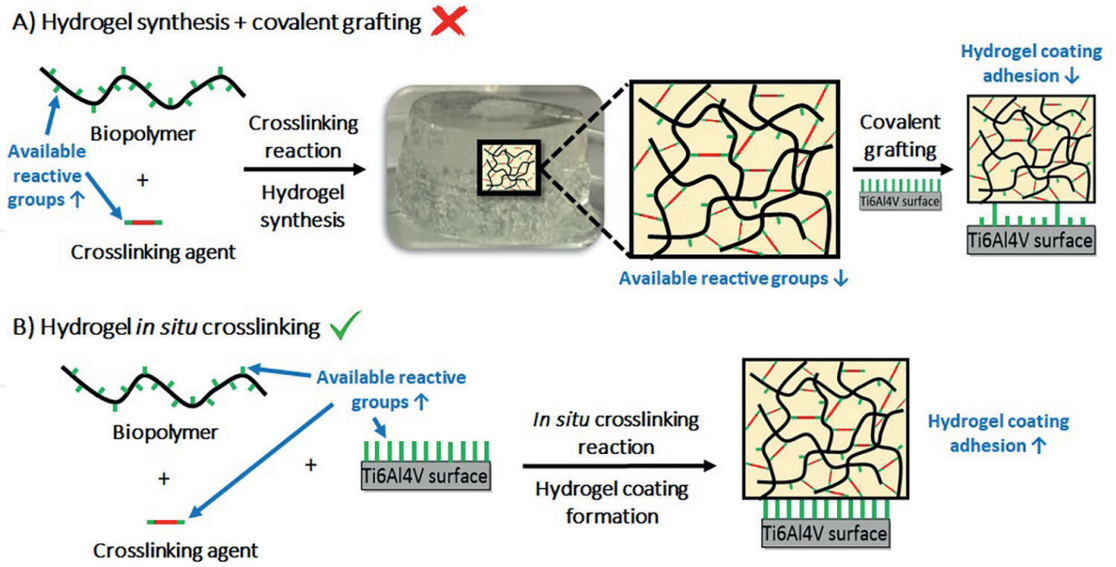

Figure 4.
A) Conventional and B) in situ crosslinking strategies to form hydrogel coating onto the surface of biomaterials. Figure produced by the authors.

release of specific low- to high-doses [77]. This way, therapeutic effect of bioactive substances is extended, and the over-excessed concentration peaks of conventional methods are diminished. These features endow hydrogel coatings with privileged pharmacokinetic profiles, which can be modulated for personalized therapies [78]. Further, hydrogel coatings do not need to modulate specific linkages to release bioactive agents since their release mechanisms are mainly governed by simple diffusion, swelling, and degradation processes [79].

Nowadays, researchers are focusing their attention is the hinder of hydrogel coatings attachment to surfaces, which occurs due to hydrogels excessively huge swelling and macroscale thickness. One promising alternative approach to create highly adhesive hydrogel coatings with strong and resistant hydrogel-surface attachment is the *in situ* hydrogel crosslinking onto the surface of biomaterials (**Figure 4B**, produced by the authors) [80]. This way, hydrogel crosslinking and hydrogel coating formation occurs almost at the same time, and thereby, all the active groups available in the structure of biopolymers react equitably with crosslinking agent and surface. Conversely, the conventional strategy of first synthesizing hydrogel followed by covalent grafting to the surface (**Figure 4A**, produced by the authors) limits hydrogel-surface adhesion since hydrogel formation consumed almost entirely reactive functional groups and therefore, few of them remain available for the subsequent linkage formation the surface. Additionally, although this method requires purification steps to eliminate toxic unreacted monomers, crosslinkers and initiators, common dialysis processes are used to easily remove these harmful molecules from coatings before their biomedical real-life application [1].

6. Conclusions

The number of works related to the development of novel biopolymer-based hydrogel systems, mainly those synthesized with hyaluronic acid and chitosan,

that promote the sustained release of bioactive agents increases year by year. In the current chapter we have summarized the recent accomplishments of biopolymer based physical and chemically crosslinked hydrogels, as well as hydrogel coatings for drug delivery and sustained release applications. The future perspectives in this field involve the development of hydrogel based medicines with specific temporal and spatial controlled release of drugs. Such medicines afford dose control, local delivery and reduced side effects that increase the efficacy and security of the treatment and the adherence of the patient to it. This strategy will lower pharmaceutical costs and improve the quality of life of the patient and the society overall.

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Conflict of interest

All the authors are employees of the company i+Med S. Coop.

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