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Published in:
Expert Opinion on Biological Therapy

Link to article, DOI:
10.1080/14712598.2022.2008353

Publication date:
2022

Document Version
Peer reviewed version

Citation (APA):
Ghandforoushan, P., Golafshan, N., Babu Kadumudi, F., Castilho, M., Dolatshahi-Pirouz, A., & Orive, G. (2022). Injectable and adhesive hydrogels for dealing with wounds. *Expert Opinion on Biological Therapy*, *22*(4), 519-533 . https://doi.org/10.1080/14712598.2022.2008353

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Journal:	*Expert Opinion On Biological Therapy*
Manuscript ID	EOBT-2021-ST-0057.R1
Manuscript Type:	Review
Keywords:	Injectable gels, adhesive gels, wound healing, self-repair

Injectable and Adhesive Hydrogels for Dealing with Wounds

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Abstract

Introduction: The development of wound dressing materials that combine healing properties, ability to self-repair the material damages, skin-friendly adhesive nature, and competent mechanical properties have surpassing functional importance in healthcare. Due to their specificity, hydrogels have been recognized as a new gateway in biological materials to treat dysfunctional tissues. The design and creation of injectable hydrogel-based scaffolds have extensively progressed in recent years to improve their therapeutic efficacy and to pave the way for their easy minimally invasive administration. Hence, injectable hydrogel biomaterials have been prepared to eventually translate into minimally invasive therapy and pose a lasting effect on regenerative medicine.

Areas Covered: This review highlights the recent development of adhesive and injectable hydrogels that have applications in wound healing and wound dressing. Such hydrogel materials are not only expected to improve therapeutic outcomes but also to facilitate the easy surgical process in both wound healing and dressing.

Expert Opinion: Wound healing seems to be an appealing approach for treating countless life-threatening disorders. With the average increase of life expectancy in human societies, an increase in demand for injectable skin replacements and drug delivery carriers for chronic wound healing is expected.

Keywords: adhesive, biomaterials, injectable hydrogel, medical applications, tissue engineering, wound healing

Article highlights:

- The globally debilitating ailment that affects millions of people is related to chronic wounds.
- Traditional dressings have been progressively replaced by multifunctional bioactive ones, which are based on biopolymers such as hydrogels, and are loaded by therapeutic agents for specific wound healing purposes.
- Hydrogels are excellent materials that can be engineered to be adhesive and injectable.

- The antibacterial capability, injectability, and enhanced tissue adhesion are the more attractive features of the hydrogels in adhesive fields.

1. Introduction

During surgery, closure of damaged tissues is a crucial step in rehabilitating the structure and function of the tissue. According to the MedMarket Diligence study, almost 114 million surgical and procedural injuries happen globally each year, and by 2018, the global wound closure market is anticipated to achieve $14 billion [1]. Chronic wounds are a health crisis that has adverse impacts on patients and adds enormous costs to healthcare systems and communities [2]. Chronic wounds are characterized by delayed healing, impaired extracellular matrix (ECM) function, and uncontrolled inflammation, which can weaken the immune system's protective act and lead to infection by bacteria [3]. Specifically, the activation of fibrogen at the woundsite, and it's transformation to fibrin can create an optimal environment for bacterias and lead to unwanted inflammatory responses [4,5]. According to recently published reports, in the United States, more than 6 million people suffer from chronic wounds and their mortality rate exceeds that of cancer. Even the best of hands, just two-thirds recover, and even with optimistic figures, the cost to the US healthcare system reaches $25 billion [6].

In essence, any skin lesion has the potential to become chronic, and therefore, chronic wounds are classified based on their underlying cause [7]. Amongst these, full-thickness wounds are the hardest to heal, especially under low-hydration conditions. Accordingly, the making of wound dressings is required, which can serve as temporary replacements for the skin to accelerate the closure of wounds, promote tissue growth, and minimize scar formation. These wound dressings are used not only for the skin repair due to burns or treatment of chronic leg ulcers, *e.g.* due to diabetes but can also be applied in the field of skin protection against contamination and water loss. Additional features, such as wound oxygenation, delivery of growth factors, balancing wound hydration, prevention and treatment of infection using antimicrobial agents, and absorption of fluids and exudates have added recently when considering wound dressings [8].

Full-thickness chronic wounds are often hard to heal completely. Besides, more time is needed for effective wound repair under low-hydration conditions. Accordingly, the making of wound dressings is required, which can serve as temporary replacements for the skin to accelerate the closure of wounds, promote tissue growth, and minimize scar formation. Biomaterials having the ability to form *in situ* gels have conceived as injectable matrices for controlled drug delivery or tissue engineering injectable scaffolds. This kind of biomaterial is categorized as gelation based adhesives [9]. Hydrogels, which are capable of holding significant amounts of water (up to 90% of their volume) and show excellent biocompatibility, have been considered potential candidates for novel wound dressing products manufactured in the latest years [10]. They ideally provide a three-dimensional porous network, which allow oxygen permeability, absorbance of the exudates, and provides a moist environment to facilitate wound healing without promoting adverse secondary damage [11]. Furthermore, hydrogel should ideally isolate the cloning of internal bacteria and allow the exchanges of gases that hinder anaerobic bacteria proliferation [12,13]. Hydrogels have also received significant attention for several soft tissue applications as they can be used as adhesives for bonding tissues or seal leaks [14]. Moreover, the injectable bioadhesive hydrogels deliver secure and efficient sealants for wound site, which avoid infections and improve wound healing procedures. However, concerning their potential to attach to the tissues hydrogels can serve as sealing, hemostatic and non-invasive dressing of the wound. Besides this, it is possible to incorporate biological agents, such as, antibiotics in the bioadhesive injectable hydrogel systems to have sustained release and support the healing process [15]. Here we provide an overview of wound healing by adhesive and injectable hydrogels, and we address wound healing details as long as better focus on injectable hydrogel application in this area.

1.1 Structure and function of the skin

The skin is an extremely structured organ having different features that serve as a major external defense system of our inner body structures. It acts as a natural barrier to protect the body from external environmental conditions and microorganisms, as well to keep the body homeostasis equilibrium and to guarantee that vital tasks can be performed by the body [16]. Human skin consists of a multilayered structure often categorized as epidermis, dermis, and hypodermis [17]. Each layer has distinctive features that are vital to its physiology. The epidermis, the outermost layer, contacts the environment directly and controls the release of water from the body. This layer also plays a protective role against UV radiation and pathogens. On the other side the dermis, consists of thick composite connective tissue of structural proteins and proteoglycans, and is located below the epidermis layer and exposed to the blood flow. The overall mechanical strength of the skin structure contributes to the dermis layer and provides an effective route to absorb drugs systemically. Besides these functions, dermis layer host many higher-order structures such as sebaceous and sweat glands, hair follicles, and arrector pili muscles, which together help to maintain essential cellular nutrition, by oxygen exchange and nerve signaling and ensures thermoregulation [18,19]. Finally, the hypodermis is the deepest layer (thickness of 10-20 μm) of the skin that ensures isolation and shock-adsorption. It is rich in collagen and fat, act as a reservoir of energy and connects the skin with the underlying muscles and bones [20].

Stratum corneum (SC) layer is the primary obstacle to therapeutic dermis transport. In fact, only low-molecular-mass biological agents (< 500 Da) can penetrate the skin naturally, which considerably restricts the transdermal delivery of drug molecules and genes [21]. Different methodologies have been explored to overcome this protective barrier in order to physically and/or chemically improve the permeability of the SC layer for effective drug and gene delivery [22,23]. A Schematic illustration of the skin structure is shown in Figure1a.

Skin injury is one of human history's most widespread physical lesions [24]. Figure 1b illustrates a typical dermal wound repair process that comprises four dynamic stages. 1) Hemostasis, the initial quick response to the wound, in which the blood clot is detected at the wound site.

2) Inflammatory stage begins immediately after the injury lasts from 24 h to 4-6 days. In this period, the injured blood vessels leak transudate, causing localized swelling. Inflammation both regulates bleeding and stops the infection. This stage comprises the emitting of immune cells (macrophages) to the wound area.

3) Proliferation stage in which new granulation tissue is formed and begins to grow on the wound zone by building new collagen and extracellular matrix (ECM).

4) Remodeling stage in which the composition of the matrix changes, and type III collagen is substituted with type I that causes an expansion in the new tissue tensile strength.

Although, skin has great regenerative capacity to regenerate, this regenerative capacity is not observed in the event of full thickness wounds or chronic disease. This represents an increasing burden to the global health sector, which is estimated to grow up tremendously in the years to come [25]. When harm is immense and the second or third-degree burns penetrate the subdermal layers, the majority of the skin tissue organization is typically lost and regenerative signals are either absent or deregulated resulting in extremely fibrotic scar tissue formation [26]. In addition, long recovery periods are needed for effective wound repair under low hydration circumstances.

Accordingly, the development of new wound materials is imperative. Such materials can operate as temporary skin replacements to accelerate the closure of the wound, stimulate tissue development, and importantly decrease scar formation. In the early phase of wound healing, frequently used dry wound dressings such as gauzes and bandages are crucial; however, these dry dressings cannot provide a humid healing environment and stick readily to the wound, which induces wound damage when removed [27]. As an alternative, traditional cures (such as gauze and cotton wool dressing) have now been replaced by advanced treatments, including wound dressing with biological agents, such as growth factors and medicines [28]. Moreover, the unstable junction between traditional dressing materials and wound place, is usually attributed to the weakening of their accessibility and dependability [29]. Figure 1c demonstrates schematic representation of the various traditional and modern biomedical systems for wound healing purposes.

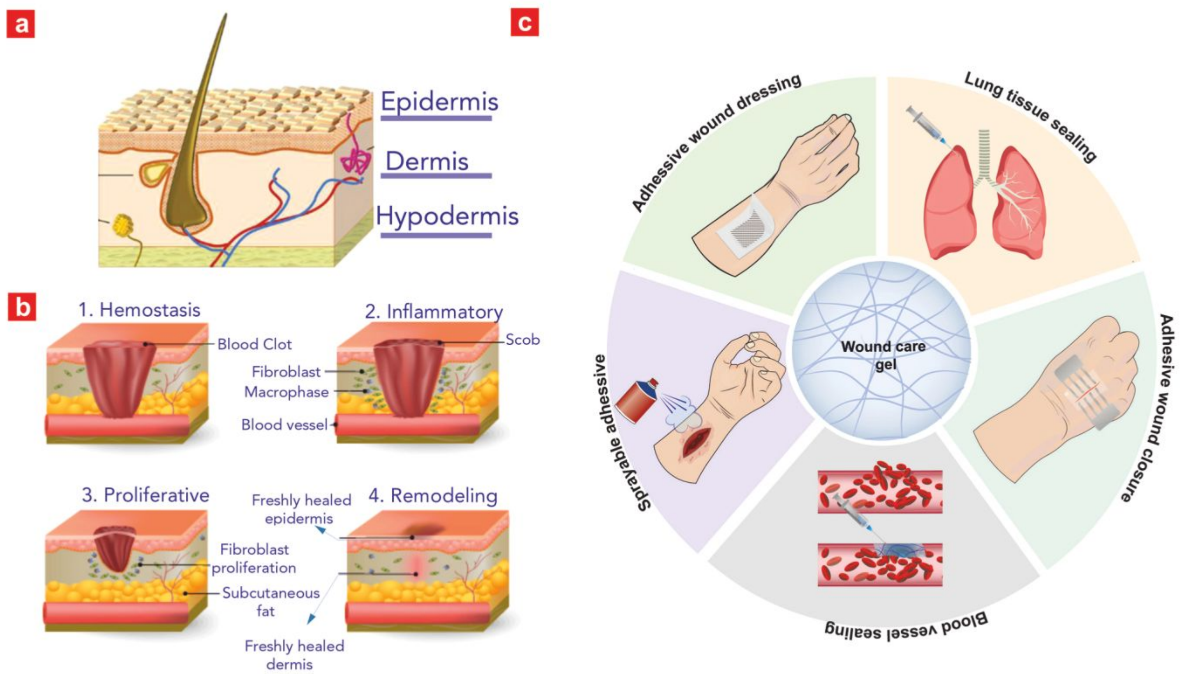

Figure 1. a) Skin layers structure, Reproduced with permission from [30], b) Wound healing stages, Reproduced with permission from [31], c) Various wound dressing approaches.

2. Bio-adhesive systems in wound healing

For many years, suturing has been considered the adequate option for wound closure and bleeding control, mostly due of its high mechanical properties and low dehiscence. However, drawbacks associated with suturing such as, high infection rate, discomfort in handling, further tissue trauma, and concern about probable transmission of blood-borne illness via needles have led to developing new strategies [32]. These included the use of multiple hemostasis agents, clips, staples, tapes, and tissue adhesives to assist in the quicker and more efficient control of bleeding from limited wound closure [33]. Although promising, these strategies were still not effective in ensuring adequate fitting to the wound and instant sealing. As an alternative, injectable bioadhesive sealants have been recently introduced. Tissue adhesives and sealants are can substitute sutures and staples for improved closure, minimized blood loss, swifter execution, and easier and less painful operation. In this regard, a variety of biomaterials has been explored. The primary challenge in developing an appropriate sealant or bioadhesive biomaterial is to attain adequate tissue adhesion strength in a moist environment without compromising the tissue function, while ensuring biodegradability. Besides, a highly elastic surgical sealant/adhesive is needed to adapt to the dynamic motion of native tissues [1].

The biomaterials applied as adhesives materials can be into three groups: Natural-based, which include; 1) polysaccharides such as chitin [34] and chitosan [15], dextran [35], chondroitin sulfate [36], and hyaluronic acid [37], 2) protein-based , such as, fibrin sealant [38], gelatin [39], collagen [40], and albumin, and 3) synthetic-based , which include polyethylene glycol, polyurethane [41], and polyester [42]. Important to keep in mind, that owing to the variability of living tissue properties in the human body, the selection of the bioadhesive biomaterial class and respective features should be carefully engineered and optimized for the target tissue. To this end, understanding the relationships between the adhesive biomaterials and that specific tissue through *in vitro* testing is crucial. In addition to the requirement of providing physically adhesion, future injectable bioadhesives will actively promote tissue regeneration [43]. Most of the hydrogels frequently show ineffective adhesive features on the wound area in contrast to conventional wound closure dressings, and therefore they are not proper for clinical use. Adhesive hydrogels can absorb a substantial volume of exudates and reduce their re-penetration into the wound. They provide a moist healing environment for the wound site, there is no need to be removed. In emergency bleeding cases, high adhesion hydrogels can quickly seal the wound site and stop bleeding [44]. They can additionally reduce healing time, simplify surgeries, and promote the quality of patient care [45]. Nevertheless, adhesive hydrogels do have some drawbacks like weak mechanical properties, limited adhesion, and inflammation. The most prominent advantage of injectable hydrogels is especially for chronic wound healing since they considerably reduce the necessity for invasive surgery. They possess satisfying fluidity and flexibility. Consequently, they can reach and fill deep and irregular wound sites. They can form an in situ gel. However, injectable hydrogels encounter numerous disadvantages such as weak mechanical features, formation of blood clots during or following the injection process, or even unstable performance. All these limitations have hugely restricted the utilization of injectable hydrogels [46]. Taken together, despite the growth of several bioadhesive systems on the market, cost-effective surgical sealants or tissue adhesives with high mechanical characteristics and tissue adhesion resistance are still needed.

3. Injectable materials

Designing injectable, efficient, and cost-effective tissue adhesive biomaterials is an unmet clinical demand for the minimally invasive sealing of injured tissues, especially while sutures or staples are not desirable [47]. Injectable biomaterials have been assessed for application in tissue engineering domain for their impressive features, such as the comfort of handling, rendering better integration of the native tissue through filling irregular defects, and holding controllable chemical and physical attributes, thereby accelerating the repair process [48,49]. These distinct features of injectable biomaterials can overwhelm the limitations of cell adhesion, cell seeding, and delivery of therapeutic factors as they can be merged with the material solution before in situ injections [50]. Injectable biomaterials expedite a minimally invasive procedure compared to traditional open operations, which can decrease the expense, and speed up the recovery time for the sufferers [51]. For hard tissues, such as bone and dental, calcium phosphate cement (CPCs) has been admitted as a promising injectable material due to their capacity to harden in situ also their chemical similarity to the bone. Nevertheless, CPC injectable materials suffer some drawbacks like brittleness [52]. Poly (lactic acid)-based biomaterials and collagen are proper injectable biomaterials candidates for dental tissue engineering [53]. The main drawbacks lying with injectable materials are their manipulation and handling to be placed into the target sites.

Various injectable systems have previously been reported to serve soft tissue regeneration demands. Most commercial injectable systems are hyaluronic acid-based gels, notably to improve skin contouring and depressions for esthetical cases [54]. The progression of new strategies in the development of injectable scaffolds focuses on biological responses by emphasizing the promotion of biological interactions of injectable biomaterials with tissues/cells, adhesiveness, and mouldability [53].

Due to the distinctions of features of living tissues, the characteristics of each adhesive or sealant material should be thoroughly superintended and optimized for each intent. For this goal, it is imperative to perceive the interactions between the prepared adhesive biomaterials and that target tissue by offering in vivo inquiries.

Wounds are frequently unmanageable with old wound dressings, and a biodegradable wound dressing possessing bioactive features is required. For this purpose, utilizing injectable hydrogels as active bioadhesive materials can be a promising strategy for wound healing applications.

4. Hydrogels for wound dressing

Among numerous biomaterials designed for regenerative medicine applications, owing to their unique properties such as high amount of water holding capacity (up to 99.5 %), similarity to biological tissues, non-adhesive feature, biocompatibility, and malleability, hydrogels have gained growing attention as an ideal dressing candidate [55-58]. Besides, in aqueous solutions, hydrogels reversibly confer the property of swelling and de-swelling, henceforward, their use in a variety of areas like regenerative medicine, drug delivery, and wound dressing appealed immense attention. The use of hydrogels to mimic stem cell microenvironments to control stem cell differentiation and tissue regeneration has been an immense success to date [59]. To this end, several hydrogels have been designed for both in vitro and in vivo research to represent a basic knowledge of cell-material interactions and their roles in tissue regeneration guidance [60-62].

Most artificial, tough hydrogels are not adhesive. Alternative efforts, particular designs, have been targeted using effective biomimetic maneuverings [63]. Bio-adhesive hydrogels originating from either synthetic or natural materials could be applied for soft tissue recovery. Tissue adhesive hydrogel performs a crucial function in the wound healing process by managing bleeding and limiting the gas or fluid leakage [29]. By creating the desired features for bioadhesive hydrogels, they can be employed in biomedicine. Accordingly, this practicality has inspired the origin of numerous bioadhesive hydrogels with unique qualities [64]. Bioadhesive hydrogels have been fabricated for wound infection prevention [65], cosmetic applications [66], ocular applications [65], drug delivery [67,68], and wound hemostasis [69]. The most commonly used bio-adhesive hydrogels are chitosan [70], fibrin, cyanoacrylates, glutaraldehyde-based adhesives [71], Poloxamer, Xyloglucan, Alginate, Hydroxypropyl methylcellulose (HPMC) and Poly(acrylic acid) [72]. Two more utilized polymeric compounds with mucoadhesive properties are polycarbophil and sodium alginate, which can adhere to the mucosal barrier and have the epithelial properties, as well as the mechanical and rheological properties demanded. These hydrogel systems could employ in the injectable form due to their thermo-sensitivity features [73].

The main advantage of in situ gelling mucoadhesive formulations is the ability to administer them as a liquid form, allowing them to be used even by injection conveniently [74]. Upon reaching their target, the formed gel with distinctive mucoadhesive features can increase resistance to flow and long residence time [75]. An extended residence period of delivery devices on mucosal membranes can enhance their local or systemic therapeutic effectiveness in many instances. Polymers play a crucial role in providing such a prolonged residence time. On the one side, biological agents like drugs can be readily integrated into three-dimensional polymeric networks and simultaneously, controlled release of drugs can be accomplished by using polymer-drug interactions such as hydrogen bonds or ionic interactions [72]. Appropriate polymers are necessitated to provide both adequate in situ gelling characteristics and high mucoadhesion. Gelation may be triggered by a physical or chemical cross-linking of polymers caused by environmental changes such as pH or temperature changes or increased electrolyte concentrations or covalent bond formation [76,77]. Figure 2. demonstrates various injectable hydrogels in wound healing.

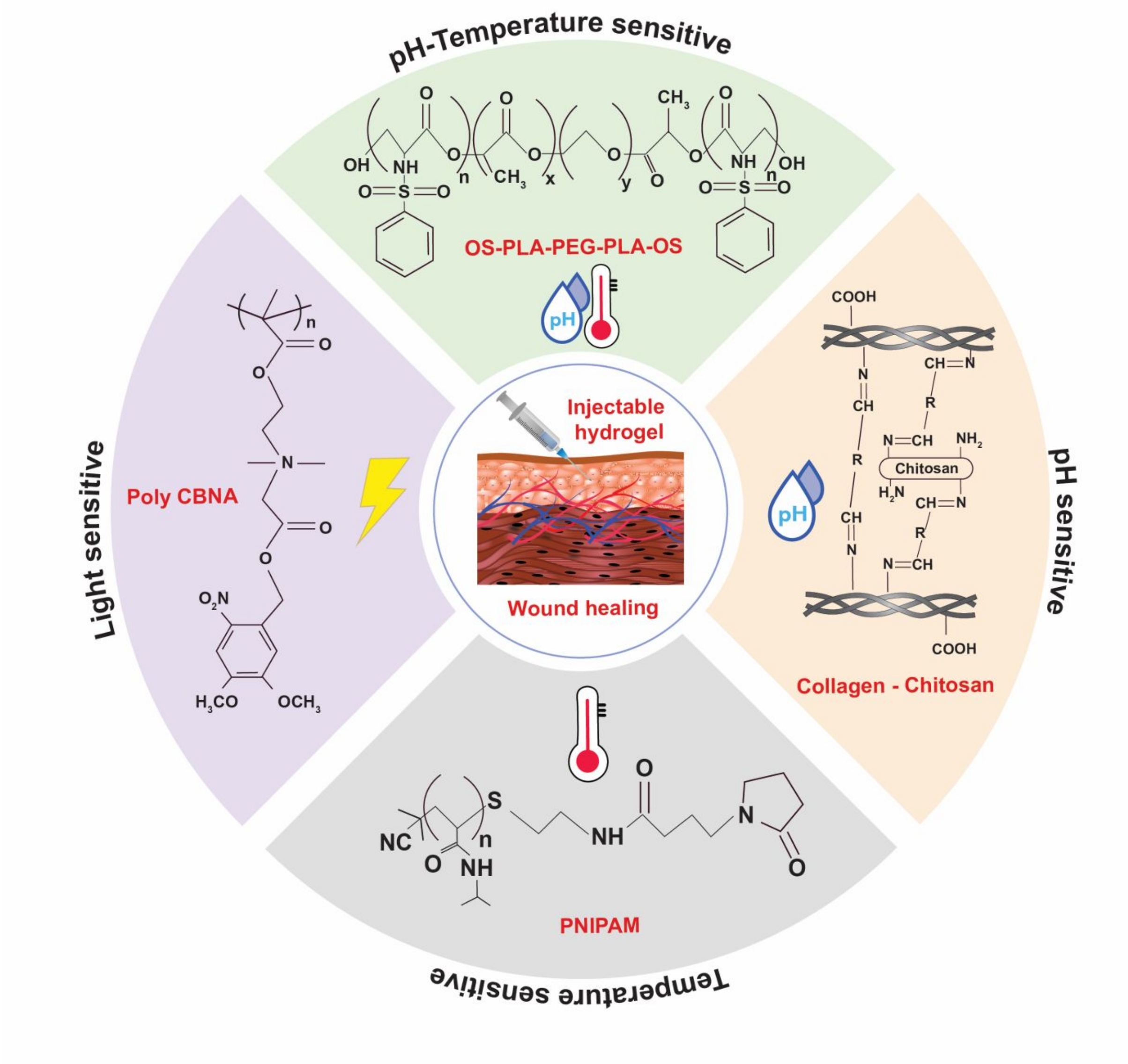

Figure 2. Injectable hydrogels in wound healing.

4.1. Temperature-responsive hydrogels

The biomaterials are considered hydrogels “temperature-responsive" or "thermo-sensitive" with the characteristics of different hydrophobic groups, such as methyl, ethyl, propyl, etc. The exposure to the environmental temperature changes results in changes in the overall mechanical properties of such hydrogels especially in the form of swelling or exhibiting sol-gel transition behavior. Of course, the transition temperature of the sol-gel occurs at the specific temperature range. Thermally sensitive hydrogels apply temperature to modulate their gelation behavior so that the transition from liquid to hydrogel depends exclusively on temperature [78]. Temperature-sensitive hydrogels are generally based on polymers with lower critical solution temperature (LCST), i.e. when the temperature increases, the gels collapse [79]. Temperature-sensitive hydrogels owing to the sol-to-gel transition could be a desirable choice for wound healing.

Yun et al. explored a thermogel as a synthetic scaffold for in-vivo skin tissue engineering. Their applied temperature-sensitive hydrogel was poly-(ethylene glycol)-b-poly-($_{\text{L}}$-alanine) (PEG-$_{\text{L}}$-PA) loaded by fibroblasts. They noted significant progress in wound healing and regeneration process of dermal tissue [80]. In another example, Lee et al. fabricated a temperature-sensitive injectable hydrogel tissue adhesive with hyaluronic acid/pluronic composition. The in-situ synthesized hydrogels displayed outstanding tissue-adhesiveness with enhanced gel stability in vivo condition and are possibly helpful for the delivery of drugs and cells [81].

As far as mucoadhesive characteristics are concerned, polymers should be able to penetrate deep into the mucus layer to boost the region of potential adhesive interactions and provide anchors for the stable delivery system and relatively more firm mucus near the epithelium [82]. In situ gelling polymers can flow deep into rough surface structures and become anchored and stabilized by a sharp increase in viscosity. The higher the polymer adhesion properties of the in situ gel polymers to the mucus layer, the better the bonding of the system can be assured.

The structures with positive physiological pH charges are the reasonable options for bio-adhesive because this property improved on-site retention time. One of the chief purposes of producing intelligent polymers is to promote the adhesion of bio-adhesive materials to epithelial surfaces. In clinical applications, therefore, hydrophobically modified bioadhesive polyelectrolyte hydrogels are introduced [83].

Regarding the proper bio-adhesive properties, in situ gelling hydrogel systems can utilize in the place of standard suppositories and act as both drug carriers and tissue adhesives. Also, the injectable hydrogels become noteworthy in tissue engineering as formulations could be easily injected as a liquid form (such as drops or spray) uniformly distributes over the mucosa, and subsequently form a hydrogel at the target site providing a non-toxic biocompatible flexible scaffold for cells delivery [84].

In principle, the tensile module of hydrogel dressings must be similar to the underlying and neighboring tissue modules, as this similarity can guarantee their integrity and hydrogel adhesives attaching to the skin can protect the safety of the wound until it is cured [29].

Balakrishnan et al. have reported an in situ gelling adhesive hydrogels based on chitosan and dextran, which has adhesion strength in the range 200–400 gf/cm^2 that is nearly 4–5 times higher than of fibrin glue. As a hemostat, the adhesive could seal bleeding and the tissue reaction at 14 days in the rabbit liver injury model, which is comparable with commercially available BioGlue. This injectable biocompatible adhesive can also function as a vehicle for drugs and therapeutic peptide and protein delivery with high efficacy [85].

According to the recent study conducted by Guyot et al.[86], blending sodium bicarbonate and catechol-chitosan produced thermosensitive and bioadhesive hydrogels. The fabricated injectable hydrogels demonstrated shear-thinning performance along with a high modulus with time, increasing overall bioadhesive properties. The hydrogels displayed quick gelation at 37 °C.

In a recent study conducted by May et al. [87], a series of thermoresponsive hydrogels were developed. The synthesized injectable hydrogels were composed of poly (polyethylene glycol) methacrylate [Poly (PEGMA)] copolymers, possessing bio-adhesion features. They exhibited effective performance for intra-articular delivery of triamcinolone acetonide. Usually, following intra-articular injection, the drug solutions tend to leave the joint cavity to the systemic circulation due to the leaky nature of the joint membrane. This bioadhesive hydrogel could circumvent this occurring through adhesion to the joint cavity and release the triamcinolone acetonide in the target site. Furthermore, the in vivo investigations of this research confirmed the prevalence of intra-articular injection of prepared injectable hydrogels for relieving the inflammation of adjuvant-induced arthritis in rat models.

4.2. pH-responsive hydrogels

Hydrogels with high transparency are the ideal choice for skin tissue engineering. The injured skin's physiological environment is slightly acidic. Accordingly, pH-responsive injectable hydrogel dressing that could smartly release encapsulated biological agents could meet the real needs. Indeed Injectable hydrogels are a wise choice as a strategy to save on the consumption of dermal substances.

Le et al. have reported an injectable adhesive hydrogel based on poly ethylene glycol-poly (sulfamethazine ester urethane) with both temperature and pH-responsive features for skin wound healing. This in situ forming hydrogel serves a depot for DNA-bearing polyplexes, which could be great therapy for skin and other biomedical domains. Eventually, at alkaline pH and room temperature (pH 8.5, 23 °C), the free-flowing PEG-PSMEU copolymer sols were transformed into a stable gel in physiological condition (pH 7.4, 37 °C) [88].

Similarly, Zhao et al., were designed the glucose and pH-responsive injectable hydrogels for diabetic wound healing. The hydrogel composed of phenylboronic-modified chitosan, poly (vinyl alcohol), and benzaldehyde-capped poly-(ethylene glycol), could release incorporated insulin and L929 cells at pH=7.4. Overall, their proposed injectable hydrogels demonstrate increased neovascularization and deposition of collagen along with improved wound healing that recommended these bioactive dressings as a delivery mechanism for wound-healing applications [89].

In a recent study published by He et al., they successfully designed adhesive pH-responsive hydrogels for the wound healing process (Figure 3) [90]. These injectable self-healing hydrogels holding the homeostatic properties could accelerate coagulation, resulting in gastric bleeding and wound healing following endoscopic treatment. The hydrogels were composed of 6-aminocaproic acid (AA) and AA-g-N-hydroxysuccinimide (AA-NHS), which AA-NHS as a micro-cross-linker displayed improved adhesive strength. Furthermore, their potential as endoscopic sprayable bioadhesive materials was evaluated to prove if they could efficiently stop hemorrhage and improve the wound healing through a swine gastric hemorrhage/wound model. The schematic illustration of their study is displayed in Figure 3a. The result of the strain amplitude sweep in Figure 3b revealed that the intersection point between G' and G'' was 1900%, which implies that AA/AA-NHS10 can endure a large external mechanical while keeping their integrity below the critical point (1900%). The strain amplitude sweep analysis revealed that the healing strength of the prepared hydrogel was reproducible and reversible throughout the cyclic experiments.

They conducted a macroscopic self-healing analysis to confirm the healing behavior of the prepared hydrogels (Figure 3c). Based on their observations, healing appeared in hydrogels immediately following the bezel was removed. Following 5 min healing, the obtained hydrogels kept their integrity, without showing any tears in the interface of the weld line. Consequently, the healed hydrogels can sustain substantial deformations after 10 min of healing, verified the most high-grade self-healing performance of the AA/AA-NHS10 hydrogels. They employed the hydrogels to the substrates of the porcine stomach to evaluate the adhesive strength of the AA/AA-NHS hydrogels. They employed the hydrogels to the porcine stomach substrates to evaluate the adhesive strength of the AA/AA-NHS hydrogels and observed the lowest adhesive strength in the AA/AA-NHS0 (2.19 kPa) and AA/AA-NHS5 (2.32 kPa) hydrogels. With increasing the concentration of AA-NHS, the adhesive strength of the hydrogel displayed a growing tendency, and they noticed the greatest adhesive strength in the AA/AA-NHS10 (6.63 kPa) and AA/AA-NHS15 (7.96 kPa) hydrogels (Figure 3d).

One of the requirements of hydrogels employed in adhesive hemostatic purposes is suitable hemocompatibility. The hemolytic activity results demonstrated notable hemolytic activity, which is desirable for biomedical purposes (Figure 3e). According to the results, the AA/AA-NHS10 hydrogel demonstrated an instantaneous hemostatic role by stopping bleeding in seconds by gelation on the bleeding center (Figure 3f). For in vivo assays, they employed a swine gastric wound model. They resected the gastric mucosal layer, and utilizing a spray tube, they sprayed hydrogel into the gastric wound region. They observed that all swine survived. The gastric wound surface was sealed following 14 days in the AA/AA-NHS hydrogel-treated swine compared with the control swine and the PPI-treated. Within 28 days in the hydrogel-treated group, the resected mucosal layer was cured completely without exhibiting any systemic inflammation or physical impairment symptoms (Figure 3g).

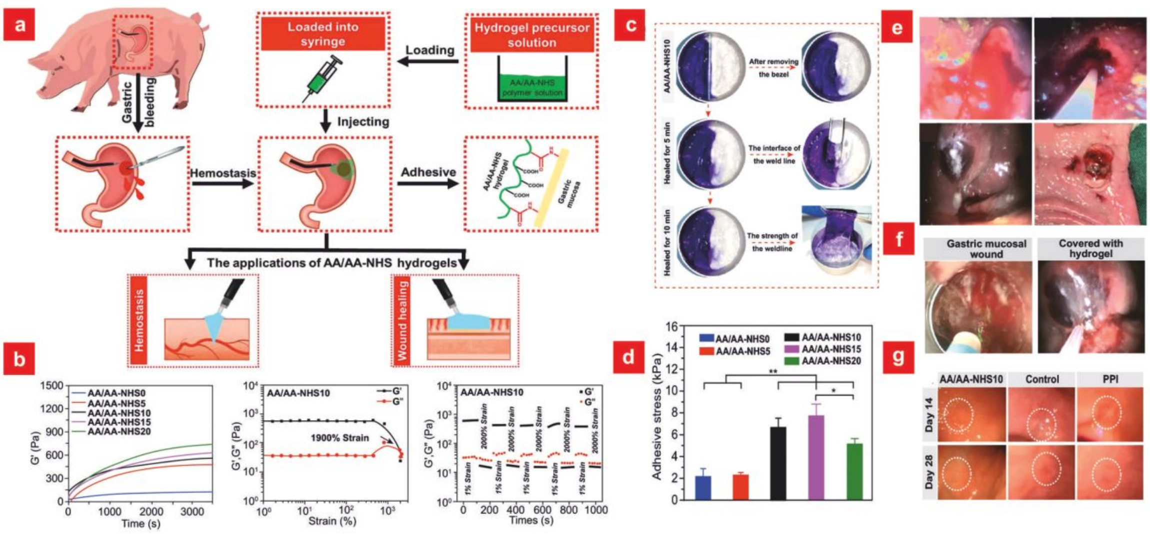

Figure 3. a) The schematic illustration of AA/AA-NHS hydrogels applications for wound healing and hemostasis. b) Rheological properties and behavior related to AA/AA-NHS hydrogels. c) The self-healing analysis of the AA/AA-NHS10 hydrogel. d) The adhesive strength of the AA/AA-NHS hydrogels on the porcine stomach substrates. e) Bleeding model of Swine gastric. f) The wound healing function of the synthesized AA/AA-NHS10 hydrogel in the swine gastric ESD model. g) The healing state of the gastric wound on AA/AA-NHS10 hydrogel during 28 days. Reproduced with permission from the reference [90].

5. General requirements as wound dressing biomaterials

The synthesis and evaluation of bioadhesive that can demonstrate intrinsic antibacterial, mechanical, and biological features while also being used as a general filler of dead space for wound closure to prevent the growth of bacteria and infections are great of importance [91]. Along with these thoughts, and because of the unique properties of the structure of the skin, joint analyzes on wound dressings include antibacterial tests, hydrogel degradation studies, swelling and moisture retention analysis, rheological and morphological analysis, adhesion tests should be carried out on biomaterials used for dressing skin ulcers. Moreover, efficient hemostatic performance with good mechanical properties and biocompatibility, which is more useful for real requirements.

An ideal injectable bandage should solidify and accelerate the natural cascade of clotting following injection into the wound area. Furthermore, after having achieved hemostasis, the injectable bandage should trigger a wound-healing reaction. In this regard, Lokhande et al. have synthesized a mechanically reinforced hydrogel for wound healing purposes (Figure 4a). The injectable nanocomposite consists of κCA and nano silicate hydrogels have excellent ability to accelerate coagulation by two-fold as well as providing wound healing therapeutics at the same time. The integration of nano silicates in κCA hydrogels enhances the nanocomposite's physiological stability, hemostatic, and wound healing potential [92].

They investigated the effect of nano silicates on platelet adhesion and blood clotting (Figure 4b). They noticed reducing blood clotting time to < 6 times, Because of the highly anionic nature attributed to κCA (1%). As they reported, increasing the nano silicates could reduce the clotting time to < 3 mins, reduced the clotting time to <3 mins, indicating the potential of nano silicates to improve clotting. Their study showed the potential utility of κCA for hemostasis for the first time (Figure 4c). In chronic and acute wounds, Because of the proteolytic microenvironment, excessive blood loss resulting in VEGF decrease. To this end, they employed vascular endothelial growth factor (VEGF) for accelerated wound healing. They encapsulated VEGF inside κCA-nano silicate hydrogels to study the potential impression of VEGF release on the wound healing process. The employed scratch assay to assess the bioactivity of released VEGF (Figure 4d). They observed that external delivery of VEGF led to accelerated wound closure via cellular migration into the wound zone and enhanced cell proliferation (Figure 4e). Additionally, they investigated the effect of nano-silicates adding up to κCA. They observed enhanced adhesion of platelets and RBCs while the hydrogels were subjected to plasma poor blood or blood. These results signify that the hydrogel's surface performs a significant function in platelet activation also clotting (Figure 4f).

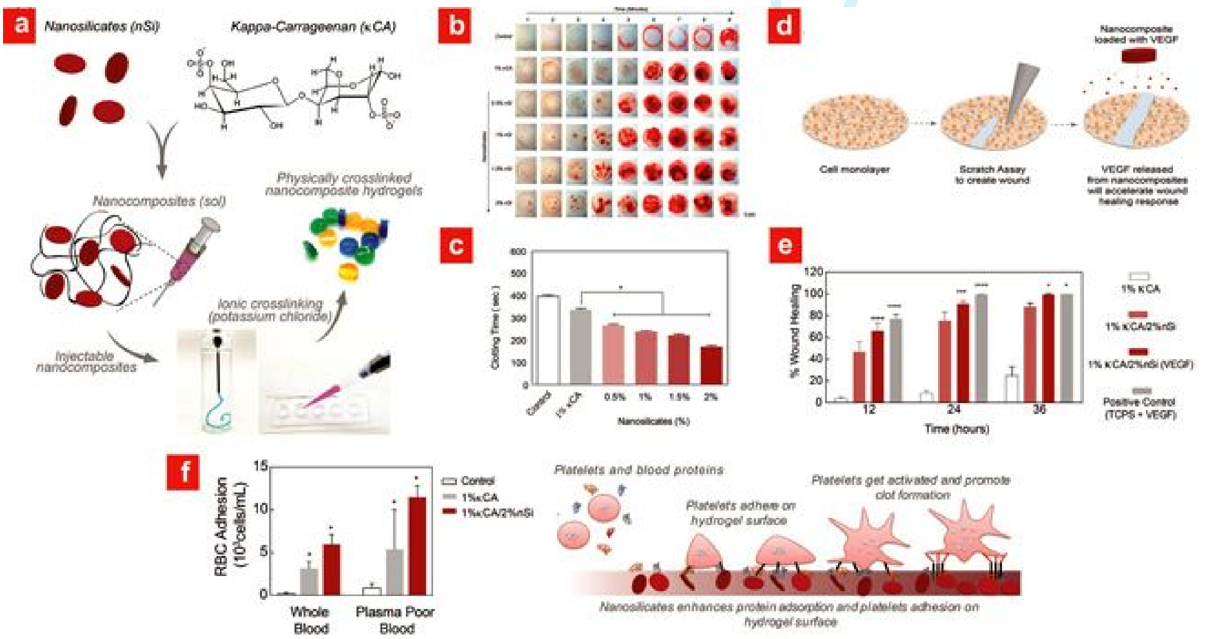

Figure 4. a) Schematic construction figure of injectable nanocomposite hydrogels via mixing nano silicates (Si) and kappa-carrageenan (κCA). KCl solution was used for crosslinking the hydrogel. b) Nano silicates could accelerate blood clotting to achieve hemostasis. The control groups displayed clotting around 9 mins, while κCA groups clot formation occurred in 6 mins. c) They observed a notable decrease in clotting time with the addition of nano silicates (more than 2-fold). d) Schematic illustration of the scratch assay to examine the wound healing potential of the nanocomposite hydrogels. e) Following 36 h, they noticed entirely wound closure in the 1% κCA, 1%/ 2% nano silicate/VEGF group. The groups which showed sustained release of VEGF displayed the most rapid wound closure. They concluded that sustained release of VEGF from nanocomposites facilitates cell migration and therefore accelerates wound healing. f) They employed flow cytometry to determine accelerated clotting on the nanocomposite hydrogel. They related this clotting to the enhanced adhesion of platelets and red blood cells (RBC). Adapted with permission from reference [92].

Taken together, they concluded that the hydrogels displays adequate compression and stretching properties, great tissue adhesiveness and modulus similar to human soft tissue and hence offer an applicable option as a wound dressing for joints in compared to traditional bandages [93]. This prominent feature of the hydrogels could provide patient comfort and convenience [94,95].

5.1 Injectable hydrogels with antibacterial features

Another noticeable viewpoint of hydrogels functioning as a substitute for the skin is their resistance against microbial infection. Surprisingly, some hydrogels having inherent antibacterial properties. Therefore, wound dressings should have desirable antibacterial operations against bacterial infection to safeguard injuries [96,97]. In comparison to dressings with antibacterial agents, wound dressings with intrinsic antibacterial ability can possess enduring antibacterial impacts while reducing cell damage [98]. For example, chitosan (CS) has commonly used in hydrogel wound products due to its intrinsic antibacterial characteristics and other characteristics, including pain relief and hemostasis [99]. To this end, Chen et al. have developed an injectable chitosan-based hydrogel with antibacterial property. This self-healing adhesive hydrogel had antibacterial properties and resulted in shortened healing of the wound in an *in-vivo* model [100]. In another study, Qu et al. have designed a multi-functional injectable hydrogel with acceptable antibacterial and antioxidant capability for skin tissue engineering. Oxidized hyaluronic acid- phenyl/amino-capped aniline tetramer/N-carboxyethyl chitosan (OHA-AT/CEC) hydrogel with excellent biodegradability and elevated CD31 expression promoted vessel regeneration and decreased the production of TNF-α proinflammatory factor around the wound bed [101]. Zhao et al. synthesized a series of injectable and self-healing bioactive hydrogels with antibacterial activity for wound dressings. Their results showed that in a full-thickness skin defect model, they considerably improved the wound healing process. This wound dressing having an excellent ability for blood clotting can enhance the in vivo wound healing process. The conductive quaternized chitosan-g-polyaniline (QCSP) hydrogel containing TGF-β, VEGF, and EGF incorporated in the system could promote ECM synthesis, hemostasis, and collagen deposition in the acute wound [102].

Surgical site infections are the most prevalent kind of infection occurring in nosocomial environments for hospitalized patients [103]. Due to bacterial infection, the wound healing process can be slowed due to wound infection; therefore, an anticipated hydrogel should hold the inherent antibacterial activity in order to accelerate wound healing by reducing the complications in the wound site [104]. Therefore, the development of bioadhesives that can integrate well with tissue and as well as killing bacteria could reduce the incidence of surgical site infections considerably.

As a proof-of-concept, Du and colleagues developed an injectable hydrogel with multifunctional properties for wound healing purposes composed of chitosan and dextran. These hydrophobically modified hydrogels tested on rat skin, and demonstrated antibacterial activity against *S. aureus and P. aeruginosa* for healing hemorrhagic and infected wound [105].

Ma et al. reported the antibacterial properties of the injectable composite hydrogel made of hydroxypropyl chitin/tannic acid/ferric ion (HPCH/ TA/Fe) for infected wound healing. Here, the cross linker TA present in the hydrogel act as an antibacterial factor that can efficiently destroy E. coli and S. aureus long-lasting cells. This pH and temperature-sensitive hydrogel exhibited great broad-spectrum antibacterial activity for up to 7 days and accelerate the wound healing process [106].

Wang and colleagues have fabricated an in situ forming hydrogel for wound infection prevention. This injectable bioadhesive hydrogel based on epsilon-poly-L-lysine (EPL) prepared by enzymatic cross-linking, possess inherent antibacterial property (against both Gram-positive and Gram-negative bacteria) to prevent the wound infection. The adhesiveness of the hydrogel ranged from 10 kPa to 35 kPa, which is greater than fibrin glue adhesives [107].

Hoque et al. have developed an injectable biocompatible hydrogel comprised of an antibacterial polymer, N- (2-hydroxypropyl)-3-trimethylammonium chitosan chlorides (HTCC) for wound healing. This bioadhesive hydrogel could be employed as an efficient sealant due to non-invasive wound filling features [108]. Qu et al. have invented a type of multifunctional injectable conductive hydrogel for skin wound healing. Aniline tetramer hydrogel (AT) has significantly accelerated the rate of wound healing in the depth of the defected skin. Hydrogel exhibited an effective antibacterial property by encapsulating antibiotic amoxicillin and ultimately reduced the production of the pro-inflammatory factor TNF-α around the wound bed [109].

5.2 Injectable hydrogels with desirable elastomeric features

The elastomeric behavior of the hydrogel is the critical parameter for the treatment of wound dressing biomaterials and providing the appropriate mechanical properties [110]. The elastic property can be tuned by using altering the density, chain length or molecular weight of the polymers and changing the cross-linking degree or the water amount of the hydrogels. A novel synthetic hydrogel was produced in a study by Resmi et al. Hydrogel components include gelatin methacrylate (GelMA) and2-hydroxypropyl methacrylate (HPMA). This biomaterial incorporating silver nanoparticles (SNP) with antimicrobial properties that protect poly (ethylene glycol) (PEG) has been proposed for use in the temporary replaceable skin dressing. The incorporation of SNP did not have a significant impact on the hydrogel 's swelling properties [111].

5.3 Injectable hydrogels as bioactive delivery systems

Bioadhesive hydrogels consolidate the attributes of bio-adhesion as well as the large swelling capacity of hydrogels. Bioadhesive hydrogel in the form of films, tablets, and nanoparticles has been extensively employed for delivering active pharmaceutical ingredients via buccal, transdermal, gastrointestinal, parenteral, vaginal, and rectal routes of administration [112]. The injectable hydrogels could be utilized as a flexible scaffold for imparting mechanical stability on the surrounding environment for tissue growth promotion as well as a biological molecules depot to deliver drugs to the site of skin ulcers; they can adhere to wounds and even can fill the defect ulcer sites [113,114].

Indeed, the released biomolecules could be an essential factor in the wound healing process [115,116]. Growth factors such as transforming growth factor β (TGF-β) family [117] and human epidermal growth factor (hEGF) [118] could be encapsulated in injectable hydrogels and promote the wound healing process. Table 1 summarizes common bio-adhesive hydrogels applied in tissue engineering fields.

Table 1. Various bio-adhesive hydrogel systems in tissue engineering.

Hydrogel	**Application**	**Ref.**
PEO–PPO–PEO[1] polyether and PAA(Pluronic-PAA[2])	Mucoadhesive (topical and oesophageal) system as oral and topical drug delivery vehicle	[119]
(PNIPAAm-g-CS[2])	*In-vitro* thermogelling injectable bio-adhesive hydrogel used in the intervertebral disk tissue engineering	[120]
Methacrylated alginate/8-arm PEG hydrogels	Biocompatible, biodegradable and bio-adhesive with tunable mechanical property used in skin tissue engineering	[121]
PEG-GEL-Silicates	*In-vitro* research of nanocomposite hydrogel with cell adherence properties for silicate complicated tissue structures improved mechanical stiffness and differentiation variables, while the quantity of Gel contributes to cell adherence	[122]
PEG diacrylate (PEGDA) hydrogel	Exhibiting cell-adhesive behavior with biological function and anisotropic mechanical property used as heart valve tissue engineering	[123]
Alginate-collagen	Nanoparticle adhesives could enhance the adhesion of the hydrogel blocks for 3D tissues engineering applications	[124]
Polydopamine-based hydrogel (PDA–pGO–PAM)[3]	Self-healable and self-adhesive tough hydrogel for cell stimulation used as implanted electrode in rabbit for *in-vivo* signal records	[125]
Chitosan-based hydrogel (QCS/PF)[4]	TNF-α and VEGF encapsulated in antibacterial adhesive injectable hydrogels promote the wound self-healing process for *in-vivo* joint skin healing	[104]
HGM[5]supramolecular gelatin hydrogel	Long-term *in-vivo* bio-adhesive, injectable hydrogel for tissue regeneration having mechanically resilient	[126]
Polydextran aldehyde-N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride	Dual function injectable hydrogel loaded with vancomycin capable of delivering the antibiotic to the target site	[127]

1. poly(propylene oxide)–poly(ethylene oxide)–poly(propylene oxide)
2. poly(acrylic acid) (PAA)
3. chondroitin sulfate
4. quaternized chitosan (QCS) and benzaldehyde-terminated Pluronic®F127 (PF127-CHO)
5. host-guest supramolecular macromer

Various injectable hydrogel systems used in skin tissue engineering listed in table 2.

Table 2. Various injectable Hydrogel systems and their applications as wound dressing tissue engineering.

Hydrogel	Responsive behavior	Specific properties	Application	Ref.
(NIPAM) (CBAA-1-C2)[1] (NIPAM)	Thermoresponsive	Enhancement of cell attachment to mammalian cells during tissue regeneration	Antimicrobial feature for wound dressing application, in-situ gelation property and also controlled antimicrobial drug release beside long-term biocompatibility	[128]
Arginine-NIPAAm[2] hybrid hydrogel	Thermoresponsive	-	*In-vitro* and *in-vivo* study with antimicrobial property	[129]
PNIPAAm-co-Acrylamid (AAm)	Thermosensitive	Adhesion and dividing of the cells on surface was observed	Hydrogel loaded with Bromelain showed controlled release fashion of delivery for topical and wound healing	[130]
Citric acid (CA)-PEG-Dopamine (iCMBA)	Thermosensitive	Completely degradable, stronger wet tissue adhesion strength.	Innovative biomaterial for tissue adhesive as suture-less wound closure with hemostasis and high wet strength features.	[110]
Collagen-chitosan	Thermosensitive pH- responsive	Self-healing, strain-sensitive, with hemostatic ability.	Sensitive epidermal sensor adhere on wet wound surface to promote wound healing	[131]
Poly (γ-glutamic acid)-silica hybrid	pH-responsive	High mechanical strength, cytocompatible, conductive	Drug delivery system for promoting wound healing.	[132]
P(MPC-co-FBEMA)-ASNP [2]	Thermosensitive pH-responsive	Self-healing, tunable mechanical	Localized drug delivery vehicle for wound healing	[133]

[1]CBAA: Ziwtterionic form of NIPAM: poly (N-1-(ethoxycarbonylmethyl)-N- (3-acryloylamino-propyl)-N, N-dimethyl ammonium salicylate)]

[1]PAA: poly acrylic acid

[2]N-isopropylacrylamide

[3]PVA: Polyvinyl alcohol

2-methacryloy-loxyethyl phosphorylcholin- -formylbenzoicacid- 2-hydroxyethyl methacrylatesilica nanoparticles

6. Injectable hydrogels as smart wound dressing systems

Smart wound dressings with accelerated wound healing features have attracted a great deal of curiosity in recent decades [134]. The fourth generation of biomaterials is called " Intelligent Biomaterials or Smart Biomaterials " which indicate materials that show significant conformation changes in response to external stimuli in biological systems such as enzymes [135], glucose [136,137], reactive oxygen species (ROS) [138], pH [139], magnetic or electrical field [140], and UV radiation [141]. Indeed, biomaterials of the fourth generation capable of monitoring extracellular and intracellular electrical processes are essential to understand intracellular and intercellular signaling as well as how cells communicate across large systems [142]. These smart hydrogels play a crucial role in many biotechnological applications due to their excellent unique properties. Some of them are classified as “multi-responsive" materials that can respond to two or more environmental stimuli. In this situation, the reaction is triggered if both stimuli are present or occur simultaneously [143].

Smart wound dressings based on a hydrogel that combine the traditional favorable properties of hydrogels as skincare materials with sensing functions of relevant biological parameters for remote wound healing monitoring are progressing. Based on the above considerations, Zhao et al. successfully developed methacrylate gelatine (GelMA) that encapsulates both antimicrobial and fluorescent vesicles. In vitro and in vivo experiments both designated that their suggested wound dressing was efficient in preventing pathogenic bacteria and rendering a colorimetric/fluorometric response. Besides, the system successfully assisted in wound healing by embedding vesicles into the hydrogel. The proposed nanocomposite wound dressing offers a methodology for the sensing of wound conditions that could be widely applicable beyond burning [144].

Rasool et al. have successfully prepared chitosan-PVP stimuli-responsive blend hydrogels for wound healing applications. The addition PVP in to the hydrogel structure, the thermal stability of the hydrogels were improved than the pristine chitosan and PVP. It has also been demonstrated their potential in drug delivery systems for wound healing and wound dressing [145].

Hu et al. developed an injectable pH- and reactive oxygen species (ROS)-responsive hydrogel with self-repairing and remodeling capacity to achieve release of drugs in the inflammation site. This inflammation-responsive smart hydrogel composed of alginate-hyaluronic acid and preloaded micelles by naproxen and amikacin showed excellent anti-inflammatory activity as well as antibacterial activity. The drug release studies showed that inflammation-responsive amikacin and naproxen released with high potency (over 80% at 24 h) from the hydrogel. These smart injectable hydrogels are promising candidate in wound care and opens the door for further functionalization of stimuli-responsive hydrogels [146]. In another study by Ajovalasit and the colleagues, xyloglucan-based hydrogel developed for wound dressing applications. The gelling property of Xyloglucan is high. Glycerol was added to provide flexibility for hydrogel and PVA to increase the swelling property and porosity of hydrogels. This non-cytotoxic composite film has the ability to integrate a sensor into its structure which can be used in animal model studies to monitor the wound healing process [147].

6. Conclusion

Chronic wound healing is a principal healthcare concern, imposes a huge burden on patients and the healthcare system. In the vulnerable groups, such as the elderly and diabetics, current treatment strategies remain marginally successful and frequently ineffective to closure the chronic wounds. Numerous clinical experiments are examining the safety and effectiveness of injectable and adhesive therapies for the treatment of burns and aberrant wounds. The field of hydrogel design has emerged as a promising therapy modality, with the potential to render adhesiveness and filling features. Some of the successes in this area demonstrate the potential of the injectable hydrogels with existing clinical applications to address deficiencies such as short half-lives or dysfunctional deliveries in multiple injections and complement each other. Hence, injectable hydrogel biomaterials have been prepared to eventually translate into minimally invasive therapy and pose a lasting effect on regenerative medicine. Overall, hydrogel design optimization will depend strongly on fundamental science developments and our capacity to synthetically replicate the complex dynamics of biological systems.

7. Expert opinion

In the field of regenerative medicine, the necessity to recognize and harness the effects of natural biomaterials in conjunction with active compounds plays a crucial role. It is important to standardize the problems posed by the multiple factors influencing tissue recovery and reconstruction and hold the recognized standards to increase the quality of effectiveness in the wound healing process. Advancements in materials science have now rendered researchers multiple methods where hydrogel formation can happen in situ through standard needles upon delivery. This matter offers an effective and convenient way for delivering therapeutics and living cells minimally invasively, filling complex tissue defects, and consequently triggering the regeneration of damaged body parts. Once achieving their missions, they can be engineered to be degradable and eventually removed from the body.

Wound healing seems to be an appealing approach for treating countless life-threatening disorders. With the average growth of life expectancy in human societies, especially among the elderly population, we expect to see an increase in demand for injectable skin replacements and drug delivery carriers for chronic wound healing. Hence, injectable hydrogel biomaterials have been prepared to eventually translate into minimally invasive therapy and pose a lasting effect on regenerative medicine. We hypothesize that this new course will be accompanied by the usage of injectable hydrogels and adhesives with significant clinical advances in wound healing treatments.

Currently, due to high fabricating costs and long-drawn regulatory approval times, clinical availability is restricted for all sections of society. While numerous injectable hydrogels for drug delivery and wound repair have been established, researchers' capability to synthetically handling the complexities of the native ECM abides unrefined so far. More all-embracing insight into wound healing processes and the advancement of modern injectable processing methods would result in the construction of new scaffolds with enhanced efficiency in the coming years.

Tissue engineering and regenerative medicine are emerging as the future trends of medicine for the treatment of acute and chronic diseases. Due to their specificity, hydrogels have been recognized as a new gateway in biological materials to treat dysfunctional tissues. The design and creation of injectable hydrogel-based scaffolds have extensively progressed in recent years to improve their therapeutic efficacy and also to pave the way for their easy minimally-invasive administration. Advances in our perception around regenerative biomaterials and their definite position in the formation of new tissues can open up new frontiers in regenerative medicine and empower scientists to fabricate tissues and organs in the laboratory. We hypothesize that this new course will be accompanied by the usage of injectable hydrogels and adhesives with significant clinical advances in wound healing treatments.

Funding

G Orive wishes to thank the Spanish Ministry of Economy, Industry, and Competitiveness (SAF2016-76150-R and BFU2017-82421-P) and technical assistance from the ICTS NANBIOSIS (Drug Formulation Unit, U10) at the University of the Basque Country. We also appreciate the support from the Basque Country Government (Grupos Consolidados, No ref:

IT907-16). We also appreciate the support from the Basque Country Government (Grupos Consolidados, No ref: IT907-16).

Declaration of Interests

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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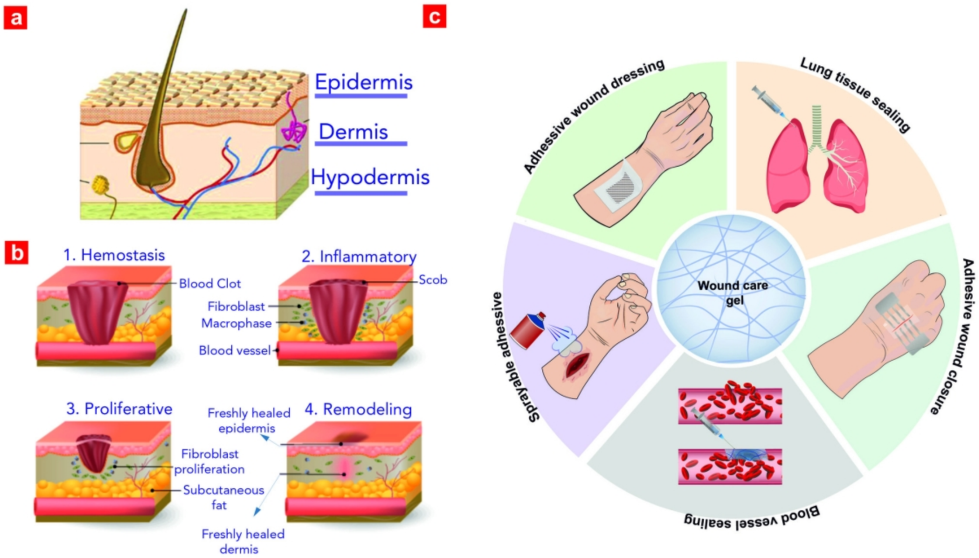

Figure 1

174x102mm (300 x 300 DPI)

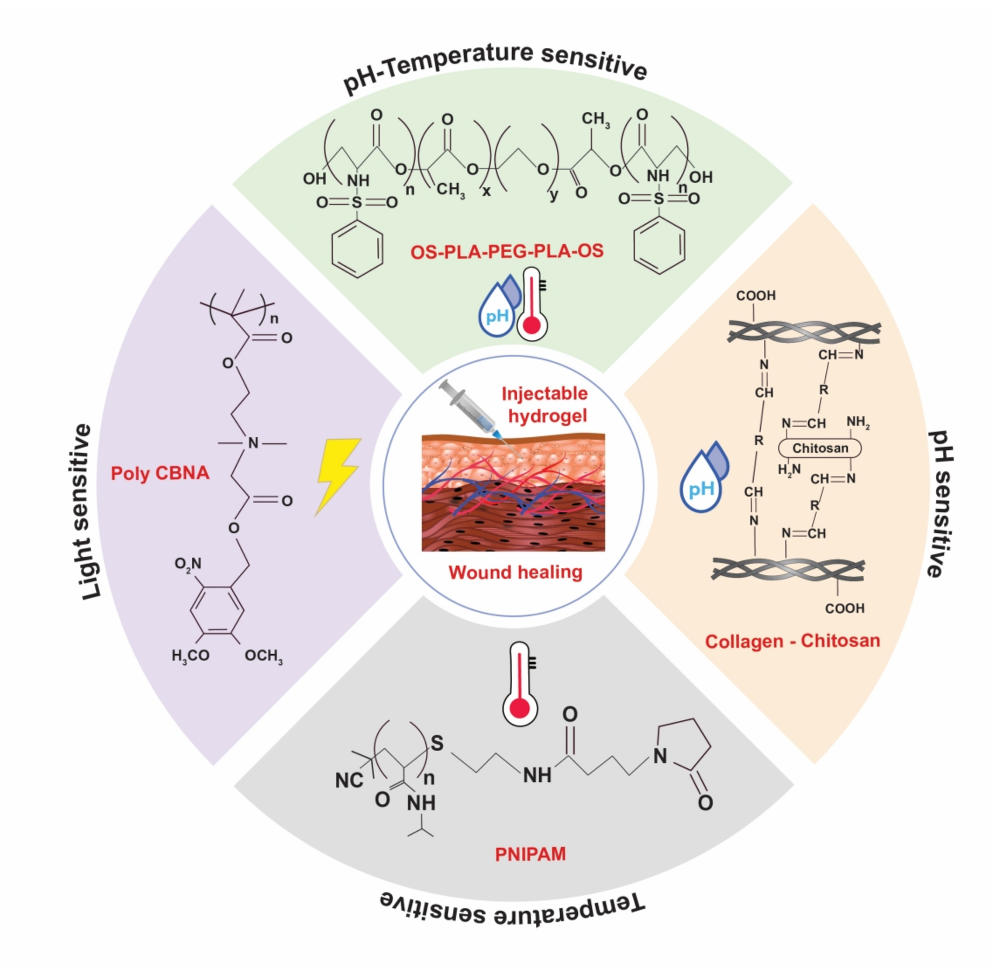

Figure 2

940x913mm (72 x 72 DPI)

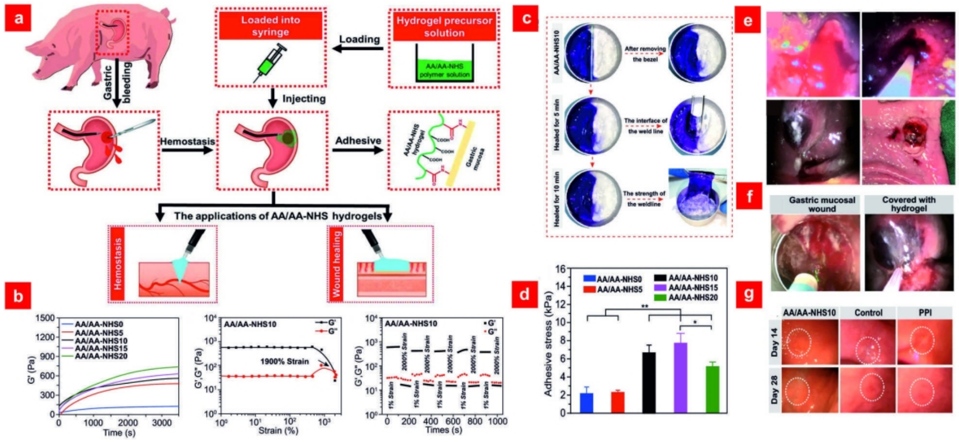

Figure 3

174x84mm (300 x 300 DPI)

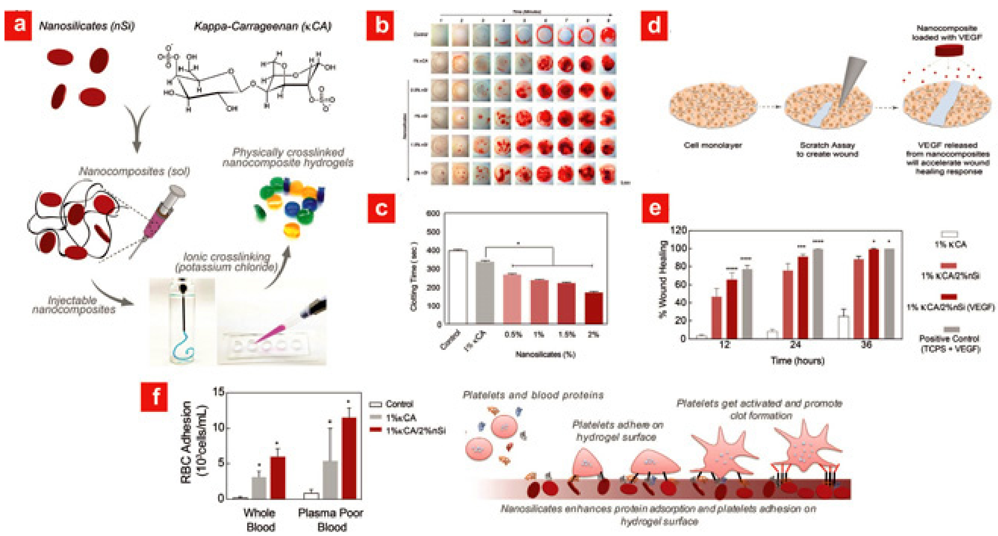

Figure 4

174x92mm (96 x 96 DPI)