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REVIEW

Progress in Pluronic F127 Derivatives for Application in Wound Healing and Repair

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Abstract: Pluronic F127 hydrogel biomaterial has garnered considerable attention in wound healing and repair due to its remarkable properties including temperature sensitivity, injectability, biodegradability, and maintain a moist wound environment. This comprehensive review provides an in-depth exploration of the recent advancements in Pluronic F127-derived hydrogels, such as F127-CHO, F127-NH_2, and F127-DA, focusing on their applications in the treatment of various types of wounds, ranging from burns and acute wounds to infected wounds, diabetic wounds, cutaneous tumor wounds, and uterine scars. Furthermore, the review meticulously examines the intricate interaction mechanisms employed by these hydrogels within the wound microenvironment. By elucidating the underlying mechanisms, discussing the strengths and weaknesses of Pluronic F127, analyzing the current state of wound healing development, and expanding on the trend of targeting mitochondria and cells with F127 as a nanomaterial. The review enhances our understanding of the therapeutic effects of these hydrogels aims to foster the development of effective and safe wound-healing modalities. The valuable insights provided this review have the potential to inspire novel ideas for clinical treatment and facilitate the advancement of innovative wound management approaches.

Keywords: Pluronic F127, F127-CHO, F127-NH_2, F127-DA, wound healing and repair

Introduction

Every year, hundreds of millions of people experience wounds of different etiologies.[1–4] Once a wound is formed, it is difficult to heal if the person is afflicted by an underlying disease such as diabetes, and can easily lead to other complications. Some wounds may not heal for months or years, which not only has a serious impact on patients' health, but also increases their financial burden. Therefore, the development of biomaterials that promote wound healing has received increasing research attention. Hydrogels are excellent materials for treating wounds.They have a network structure similar to that of extracellular matrices, can absorb wound exudate, and can provide a wet environment to the wound.[5] These systems are also able to deliver drugs[6] and cells to promote tissue repair.[7] Researchers have developed various functional hydrogels have been developed according to the requirements of different tissues.[8,9]

Pluronic F127 (F127) is an FDA-approved hydrogel[10] with the composition polyoxyethylene-polyoxypropylene-polyoxyethylene (PEO-PPO-PEO), where PEO is hydrophilic and PPO is lipophilic. When this copolymer is heated to physiological temperature (ie, ~37 °C), the hydrophobic PPO block dehydrates and crosslinks with the hydrophilic PEO block to form spherical microgels. These microgels then crosslink with one another to form porous three-dimensional reticular hydrogels, which revert to the solution phase at 4 °C[11–14] (Scheme 1). As previously reported, Pluronic F127 is temperature-sensitive,[15] injectable,[16] biodegradable,[17] non-toxic,[10] and biocompatible.[18] This article reviews the research

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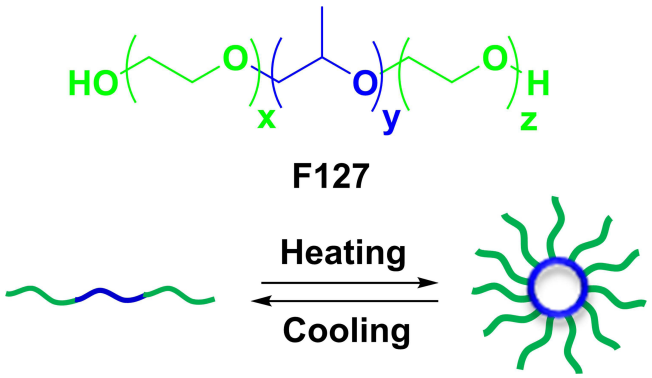


Scheme 1 Changes in the morphology of F127 at different temperatures. Adapted from Klouda L, Mikos AG, 68(1), Thermoresponsive hydrogels in biomedical applications. European Journal of Pharmaceutics and Biopharmaceutics, 34–45, Copyright (2008), with permission from Elsevier.[19]

and applications of F127 and its derivatives in wound dressing, acute and chronic wound closure, seamless wound closure, deep wound closure, wound infection healing, and wound repair.

Wound healing is a dynamic and complex tissue repair and regeneration process consisting of a hemostatic, inflammatory, proliferative, and remodeling phase. In the hemostatic phase, the body activates the clotting system after an injury, activating platelets and releasing growth factors, which in turn begins the healing process. In the inflammatory phase, neutrophils reach the wound site to kill local bacteria within minutes after injury while releasing pro-inflammatory factors; in the later stages of injury, macrophages emerge to engulf bacteria, dead neutrophils, and damaged tissues to play a reparative role and release transforming growth factors, cytokines, and chemokines to inhibit further inflammation. In the proliferative phase, macrophages, fibroblasts, endothelial cells, and keratinocytes work together to cause the body to produce new tissue and blood vessels within 1–2 days after injury, completing the re-epithelialization of the wound and the formation of granulation tissue. In the final proliferation stage, the wound edges slowly shrink and come closer together. In the remodeling phase, tissue begins to remodel with the formation of a mature scar during the proliferative phase. During this phase, the body simultaneously produces and breaks down collagen, maintaining a balance between the need for tensile strength and the remodeling of new tissue to form new skin or scar tissue with functionality.[20,21] Wounds are classified as acute and chronic based on the rate of healing.[22] In this review, acute wounds[23,24] and chronic wounds(diabetic wounds)[25,26] are discussed. Acute wounds generally require hemostasis and infection prevention, while diabetic wounds have a high glycemic microenvironment with persistent and enhanced periods of inflammation (hypoxia), and prolonged open wounds, resulting in extreme susceptibility to infection, which in turn also delays healing.[27,28] Burns are one of the most common types of wounds and can be classified into four categories according to the depth of the wound: Wounding only affecting the superficial epidermis (the germ layer is alive), wounds affecting the epidermal germ layer and dermal papillae, wounds affecting the deep dermis, and wounds affecting the entire skin layer.[29] This review covers superficial epidermal burns,[30,31] deep burns,[32] and deep partial-thickness burn.[33]

The F127 hydrogel was first synthesized and applied to treat burns by Schmolka in 1972.[30] Later, F127 was combined with bactericidal agents (eg, silver nitrate and silver lactate) for the treatment of thermal burns.[31] It was also found that the addition of silver nanoparticles (AgNPs) led to complete inhibition of the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The gel formulation exhibited an anti-biofilm activity and > 95% survival of human fibroblasts. The commercially available 1% silver sulfadiazine cream was highly cytotoxic to human fibroblasts, with 18% fibroblast survival after 4 h of application, suggesting that the gel may be an alternative to 1% silver sulfadiazine cream for wound treatment.[34] F127 gel stimulates the expression of the vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1), which promote healing.[35]

F127 hydrogels usually have poor mechanical strength, adhesion and self-healing ability. These issues can be addressed by the formation of various derivatives, such as aldehyde-terminated Pluronic F127 (F127-CHO), alkoxyamine-terminated Pluronic F127 (F127-NH_2), and Pluronic F127 diacrylate (F127-DA) (Figure 1).

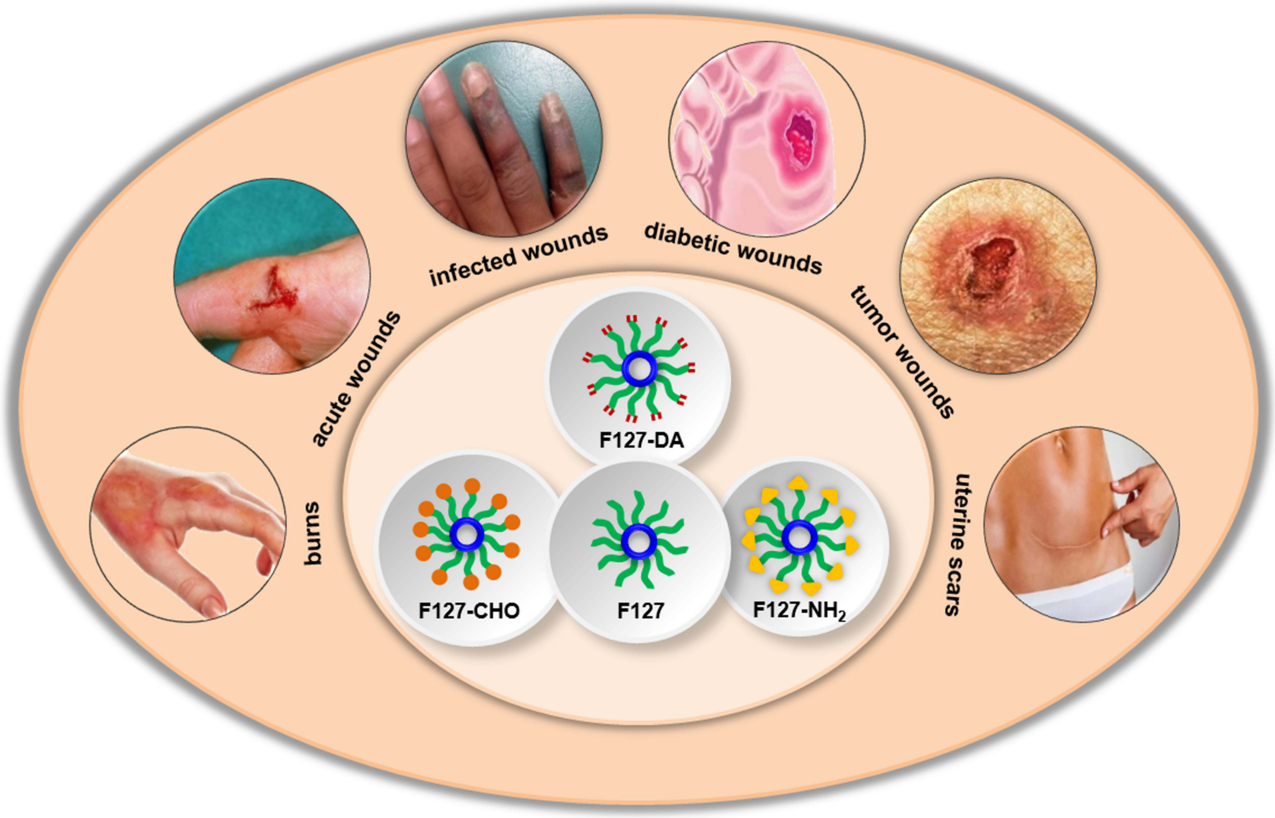


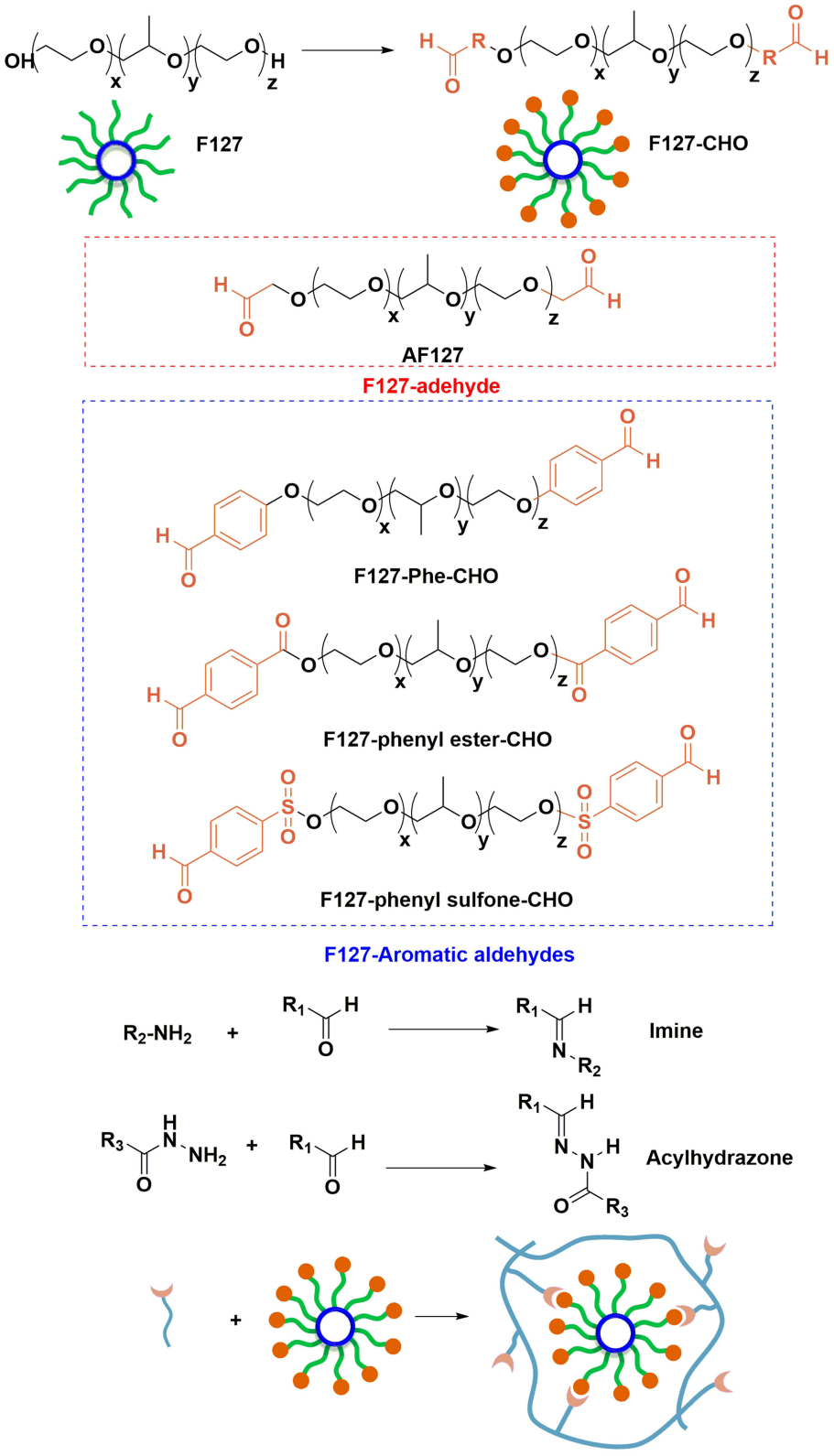
Figure 1 F127 derivatives for wound healing and repair.

Aldehyde-Terminated Pluronic F127 Hydrogels

In 2011, the Mei group obtained the filtrate F127-CHO by dissolving F127 in dry dichloromethane and adding Dess-Martin periodinane, stirring overnight at room temperature, followed by cold ether treatment of the product and filtering of the precipitate (Scheme 2).[36] Subsequently, the investigators performed similar reactions using acetaldehyde, 4-hydroxybenzaldehyde, 4-carboxybenzaldehyde and methanesulfonyl chloride/4-hydroxybenzaldehyde to introduce hydrophilic aldehyde groups into the structure to obtain F127-aldehyde (AF127)[37] and F127-aromatic aldehyde hydrogels (F127-Phe-CHO,[33,38] F127-phenyl ester-CHO,[39] and F127-phenyl sulfone-CHO)[25] (Scheme 2).

The investigators found that the aldehyde-terminated F127 hydrogels exhibited enhanced mechanical strengths and superior self-healing and tissue adhesion properties compared to the original F127 hydrogels. Their successful application in wound repair and regeneration was attributed to two main mechanisms: Firstly, the formation of a C=N bond can promote tissue healing and repair. More specifically, the aldehyde-terminated F127 reacts readily with an amine group[25] to form an imine or with a hydrazide[40] to form an acylhydrazone (Scheme 2). Imines and acylhydrazones exhibit greater mechanical strength in hydrogels, while imine structures tend to be more potent in wound healing than acylhydrazide-containing structures, and acylhydrazones exhibit good self-healing ability in slightly acidic environments (ie, pH 4.0–6.0).[41,42]

Second, F127-CHO self-assembles in water into nano-cavities whose inner cavities can be used to load additional substances that promote wound healing and tissue repair. More specifically, the aldehyde-containing F127 hydrogel contains a spherical cavity owing to the interaction between the aldehyde group, hydrophilic PEO, and the lipophilic PPO. This cavity can be used to load substances such as curcumin,[23] 7.8-dihydroxy flavones,[43] bromelain/EGF,[32] insulin,[25] and ceria-based nanocomposites,[44] among others.



Scheme 2 Synthesis of F127-CHO from F127, structures of F127-aldehyde and F127-aromatic aldehydes, and F127-CHO, which reacts with amine-modified or hydrazide-modified polymers to form imines or acylhydrazones respectively.

Formation of Hydrogels with Hydrazide-Based Polymers at the Aldehyde End of Pluronic F127

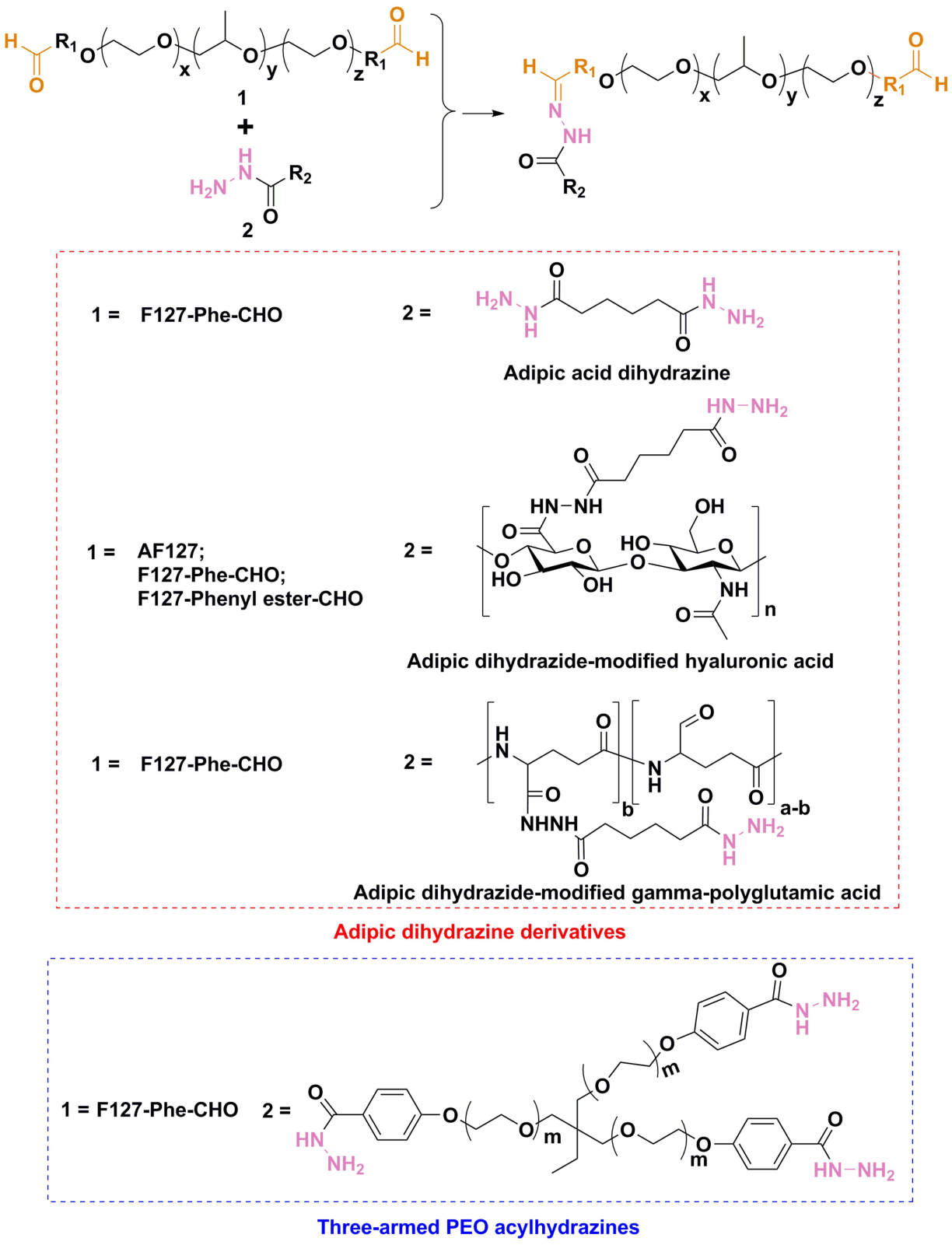
As mentioned above, aldehyde-terminated F127 hydrogels react with hydrazide groups to form acylhydrazones, which can be used for sports wounds, wound infections, deep burns, and uterine scars. Currently, the known aldehyde-terminated F127 hydrogels include AF127,[40] F127-Phe-CHO,[33] and F127-phenyl ester-CHO.[45] In addition, aromatic acylhydrazones are more stable than aliphatic acylhydrazones due to conjugation effect,[46] thereby accounting for the fact that the F127-aromatic aldehydes are mechanically stronger than F127-aldehydes. Their corresponding hydrazide-based polymers can be divided into two main categories: adipic dihydrazide derivatives (adipic dihydrazide,[47] adipic dihydrazide-modified hyaluronic acid,[39] adipic dihydrazide-modified γ-polyglutamic acid)[38] and the three-armed PEO hydrazides[48] (Scheme 3).

Adipic Dihydrazide Derivatives

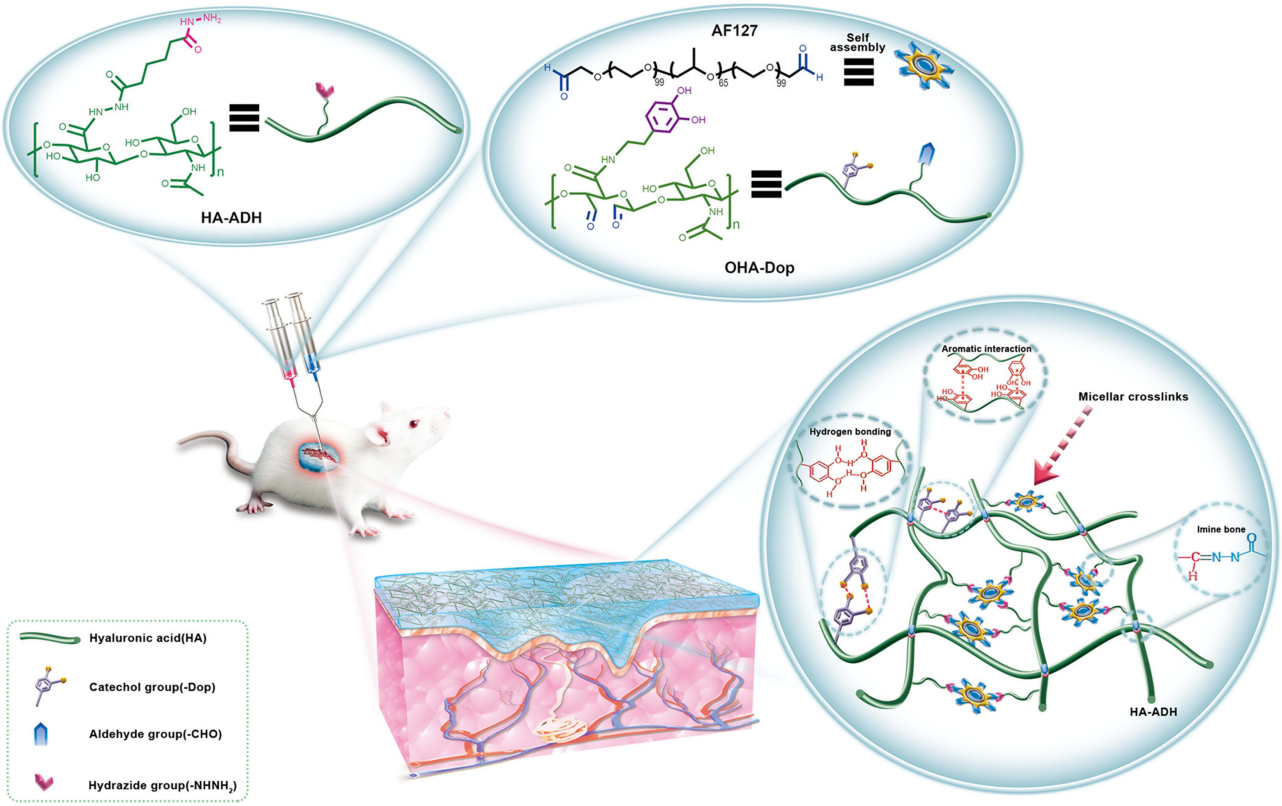
Adipic dihydrazide is commonly employed as a cross-linking agent for form aldehyde-containing compounds. Yang et al synthesized injectable, self-healing, thermosensitive hydrogels of dynamically cross-linked acylhydrazones based on F127-Phe-CHO using adipic dihydrazide.[47] Subsequently, Chen et al reported the use of adipic dihydrazide modified hyaluronic acid (HAAD) instead of adipic dihydrazide, and dissolved lyophilized HAAD with F127-Phe-CHO in PBS to form an injectable thermosensitive hydrogel. The mechanical strength of this hydrogel (modulus of elasticity G′between 1000.0 ~ 10,000.0 Pa) is similar to that of the natural skin tissue, with an elongation at break of 2400.0% and a transient recovery rate of 85.2% after 3 compressions, in addition to good biocompatibility, tissue adhesion, and fluid absorption properties, which effectively promoted the repair of deep burn wounds.[33] Based on the above hydrogel, Gu et al replaced F127-Phe-CHO with acetaldehyde-terminated F127 (AF127) (Scheme 4), and formed hydrogels by micelles of AF127, HAAD, and dopamine-functionalized oxidized hyaluronic acid (OHA-Dop) dissolved in PBS. Owing to the unconjugated nature of the resultant aliphatic hydrazide, this hydrogel exhibitedless-favorable mechanical properties.[40] The hydrogel is supplemented with OHA-Dop was then examined as dopamine readily forms π-π stacking interactions and hydrogen bonds with the amine, imidazole, and thiol groups on biological substrates, thereby leading to strong adhesion.[37] The hydrogel exhibited an adhesion force of 31 kPa. AF127 micelles, dynamically cross-linked and immobilized on HA-ADH hydrogel network by C=N bonding, showed much higher mechanical strength, rapid self-healing, and enhanced shear thinning behavior compared to single network HA-ADH hydrogels. Compared to commercial Mepitel, this hydrogel has excellent wound healing properties (greater wound shrinkage, more collagen deposition, less scarring, simultaneous production of skin appendages, granulation tissue, and blood vessels) and is a new approach to wound healing.[40]

Zhou et al resuspended *Lactobacillus rhamnosus* in HA-ADH solution and dissolved F127-phenyl ester-CHO and fucoidan in PBS solution, after which the two solutions were mixed to prepare different ratios of hydrogels (Scheme 5). Among them, *Lactobacillus rhamnosus* antagonizes *Candida albicans*, inhibiting infection by *Pseudomonas aeruginosa*, promoting the healing of skin wounds, and reducing scar formation. Compared with F127-Phe-CHO, F127-phenyl ester-CHO contains a greater number of ester groups, leading to the formation of additional hydrogen bonds and a relatively enhanced mechanical strength. The hydrogel has comparable antibacterial and healing rates compared to commercially available Prontosan gels, but is superior to Prontosan gels in terms of collagen deposition. In conclusion, the hydrogel is a potential alternative for the treatment of superbug-based infections and wounds.[39] In another study, Deng loaded umbilical cord mesenchymal stem cells (UCMSCs) and asiaticoside microspheres (AMs) onto F127-phenyl ester-CHO and AHA hydrogels for uterine scar repair.[45] It was found that asiaticoside inhibits scar proliferation and promotes the healing of initially inflamed wounds. The UCMSCs repaired the damaged endometrial epithelial cells. Angiogenesis experiments pointed to an increase in this hydrogel's vascular connections and vascular length (184.3±9.8 and 1.24±0.04, respectively). The system slowed the release of AMs for up to 7 days, reduced endometrial fibrosis, promoted endometrial cell proliferation, facilitated glandular regeneration, and restored the uterus in rats, thus demonstrating its potential clinical application in uterine scar repair.[45]

Cai et al formed two-dimensional PDA nanosheets loaded with NO donor N,N′-disubstituted-butyl-N,N′-dinitroso -1,4-phenylenediamine (BNN6) to form PDA- BNN6 using DNA as a template, in the presence of tris(hydroxymethyl) aminomethane. The hydrazine group of γ-PGA-ADH with the aldehyde group of F127-Phe-CHO loaded PDA- BNN6, the



Scheme 3 Reaction ofF127-CHO with hydrazine-based polymers to form Schiff bases.

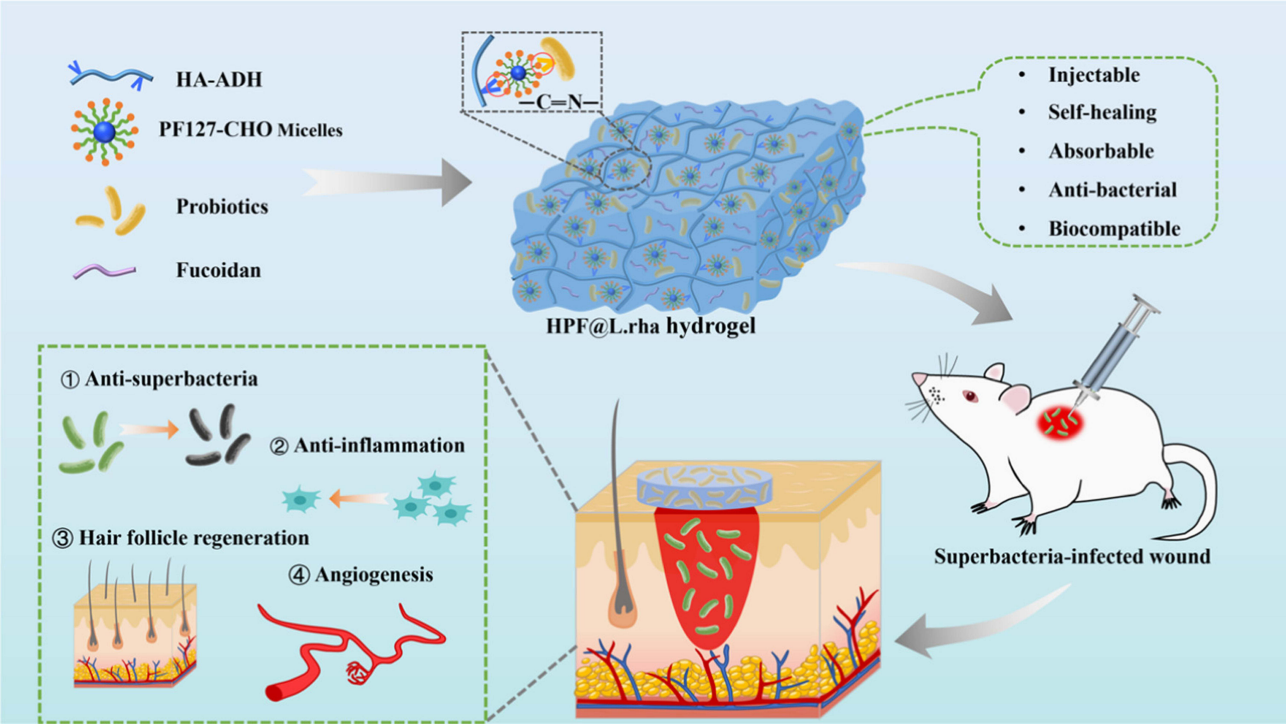


Scheme 4 Injectable, self-healing and strongly-adhesive hydrogel dressings in wound healing. Adapted with permission from Injectable Adhesive Self-Healing Multicross-Linked Double-Network Hydrogel Facilitates Full-Thickness Skin Wound Healing, *ACS Appl. Mater.* Inter. 2020;12(52):57782–57797. Copyright (2020) American Chemical Society.[40]

hydrogel was obtained in less than 55s by the Schiff base reaction and the micellar action of F127-Phe-CHO[38] (Scheme 6). NO is of particular interest because of its close association with wound healing, including the control of skin blood flow, skin defense and tissue repair systems.[15] In addition, PDA NSs have recently been reported as a new material for use in photothermal therapy (PTT). The photothermal conversion performance of PDA NS in this system (56.1%) was better under 808 nm NIR, while NO was released on demand. In the antibacterial experiments, the hydrogel achieved 98.9% and 99.7% bactericidal efficiency against *E. coli* and *S. aureus* in vitro. The storage modulus (G′) and loss modulus (G″) of the hydrogel at 37 °C are higher than those at 25 °C, indicating that F127-CHO not only enhances the mechanical properties, but also promotes the formation of the hydrogel with the increase of temperature. In summary, the combination of photothermal effect and NO gas was synergistically antibacterial, thereby providing a new approach for the preparation of wound dressings for infected skin.[38] Hydrogels synthesized from F127-CHO and adipic dihydrazide derivatives are one of the key materials for use in wound repair and skin regeneration.

Three-Armed PEO Acylhydrazides

Chen et al reported a dynamically cross-linked acylhydrazone composed of three-armed PEO acylhydrazine and F127-Phe-CHO. The three arm PEO acyl hydrazide contains three hydrazide groups, which increases the probability of forming acylhydrazone with F127-Phe-CHO. The acylhydrazone bond is a reversible chemical bond under acidic and neutral conditions, and the bond has self-healing properties, good mechanical properties and adaptability. In addition, F127-Phe-CHO forms self-assembled micelles and Schiff bases, which have dual effects and give the hydrogels excellent in mechanical properties, including tensile properties (stretching to 117 times the initial length), high toughness (tensile toughness of 14.1 MJ m^{-3}), and good self-healing ability (self-healing strength within 24 h is 85% of the initial strength).[48] The hydrogel has the potential to be used as a sports wound dressing.



Scheme 5 Preparation of an injectable, self-healing HPF@L.rha hydrogel via Schiff base for superbug-infected wounds. Reprinted with permission from Injectable and Self-Healing Probiotics-Loaded Hydrogel for Promoting Superbacteria-Infected Wound Healing, ACS Appl. Mater. Inter. 2022;14(18):20538–20550. Copyright (2022) American Chemical Society.[39]

Formation of Hydrogels with Amine-Modified Compounds at the Aldehyde-Capped End of Pluronic F127

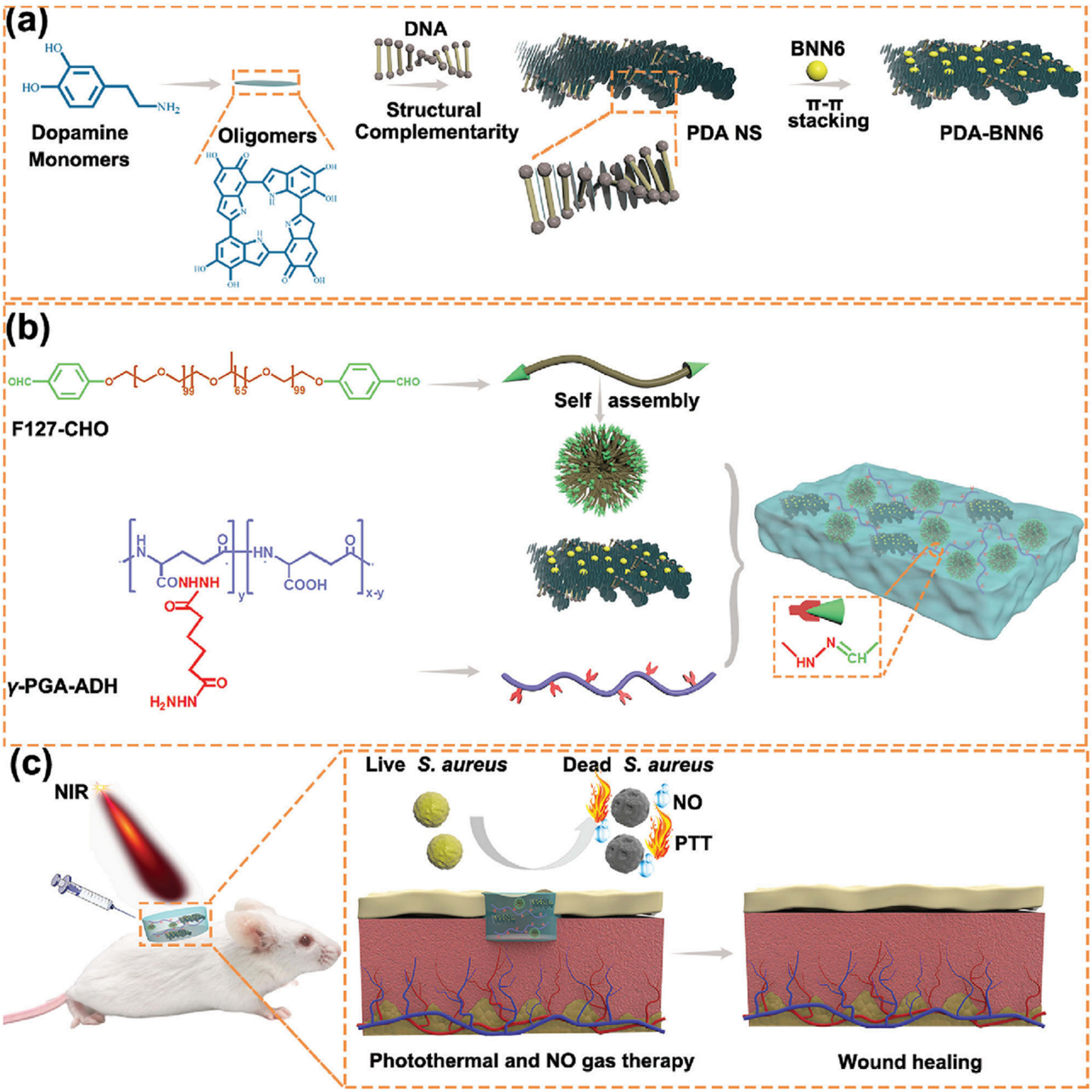
The aldehyde-terminated F127 can form hydrogels with amines via Schiff bases and is commonly used for full-thickness skin wounds, joint wounds, diabetic wounds, burn wounds and skin tumors. The most commonly used amines for this purpose can be divided into three categories: quaternized chitosan (QCS),[23] ε-polylysine derivatives (ε-polylysine-coated MnO_2 NSs[25] and polyvinyl alcohol modified with sulfhydryl and amine groups),[32] and polyethylenimine-coated cerium oxide nanorods[44] (Scheme 7).

Quaternized Chitosan

The parent ring structure of QCS contains many amines and hence can form dynamic imines upon reaction with aldehydes.[49] In addition, QCS is more soluble than chitosan under physiological conditions, and has been demonstrated to possess antifungal[50] and antioxidant properties.[51] Through the combination of QCS and curcumin-loaded F127-Phe-CHO, Guo et al formed an antimicrobial hydrogel system with self-healing properties and good mechanical properties. The content of F127-Phe-CHO allows controlled release of curcumin. The physical cross-linking of F127-Phe-CHO micelles and the dynamic Schiff base interaction with QCS make the hydrogel self-healing. The weight of the hydrogel can reach 100 g when the adhesive force is tested with fresh pig skin, which may be due to the close contact between the aldehyde group of the hydrogel and the amino group on the surface of the tissue to form a Schiff base. This hydrogel system accelerated wound healing, increased the thickness of granulation tissue, and promoted the distribution of collagen and VEGF can be used as a joint wound dressing.[23]

ε-PL Derivatives

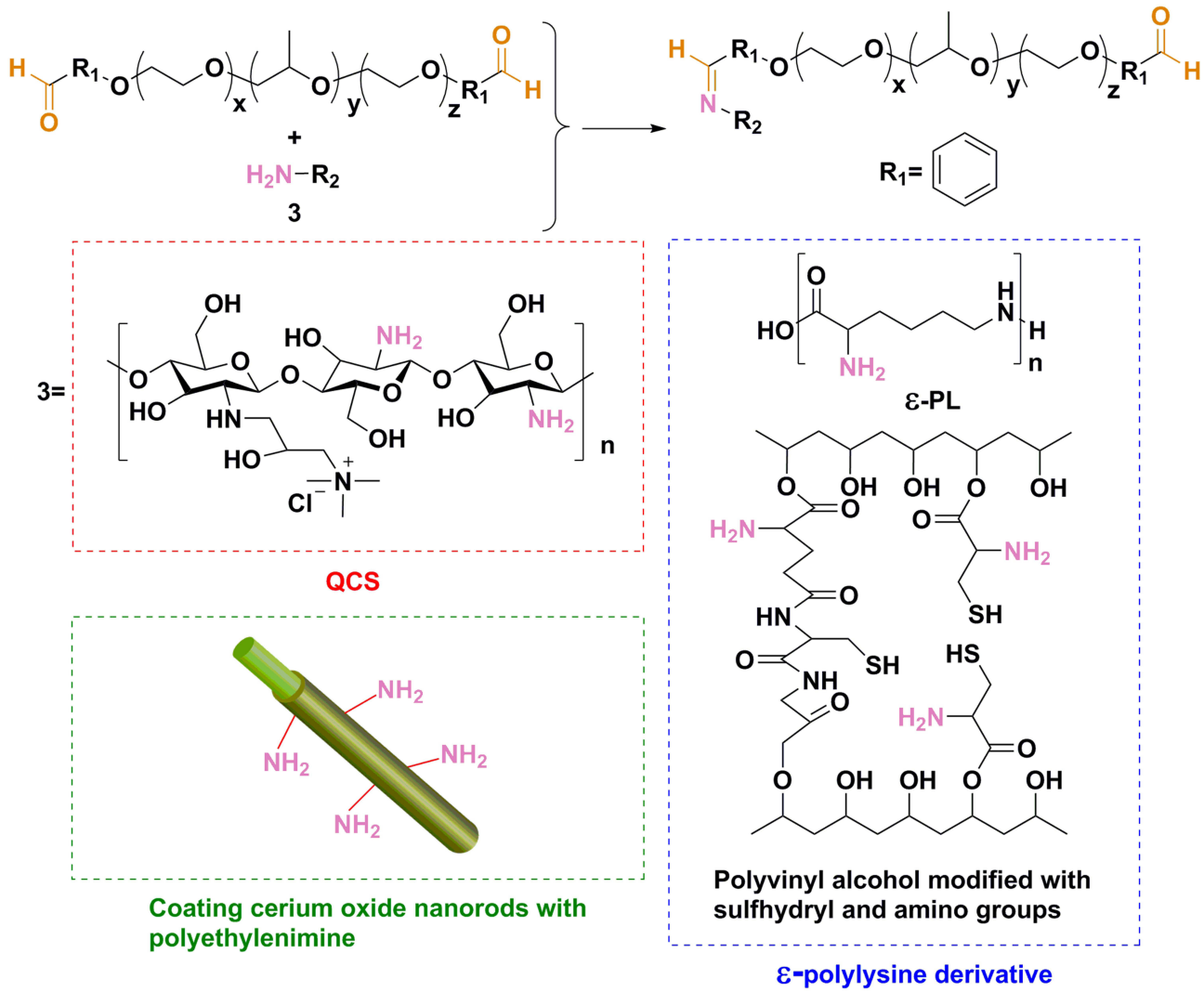
ε-Polylysine (ε-PL) is known to exhibit antimicrobial properties.[52] Zhang et al prepared hydrogels from ε-PL-coated manganese dioxide NSs (EM) and insulin-loaded F127-phenyl sulfone-CHO micelles. Note that the MnO_2 NSs catalyze the decomposition of endogenous H_2O_2 into O_2 to reduce the oxidative stress in cells. Thus, through the synergistic



Scheme 6 (**a**) Preparation of PDA-BNN6 nanosheets. (**b**) Raw materials and preparation of hydrogels. (**c**) Application of hydrogels in wound infection sites. Used with permission of [Royal Society of Chemistry], from [Polydopamine Nanosheets Doped Injectable Hydrogel with Nitric Oxide Release and Photothermal Effects for Bacterial Ablation and Wound Healing. Liu G, Wang L, He Yet al 10, 23, 2021]; permission conveyed through Copyright Clearance Center, Inc.[38]

combination of the positively charged ε-PL and MnO_2 NSs, the resulting hydrogel exhibited extraordinary antibacterial properties (The authors used a diabetic trauma model with MRSA infection to test the antibacterial effect and wound healing ability of the hydrogel and observed that it was the most effective bactericide on day 3 with approximately 100% bactericidal effect on day 14) against multidrug-resistant (MDR) bacteria. In addition, it was demonstrated that this hydrogel is pH and redox responsive, and that it can control the release of insulin, thereby regulating blood glucose levels and accelerating the healing (wound healing rate on day 7 was 78.2%) of diabetic wounds infected by MDR bacteria. This hydrogel therefore provides a new strategy for wound healing in diabetic patients.[25]

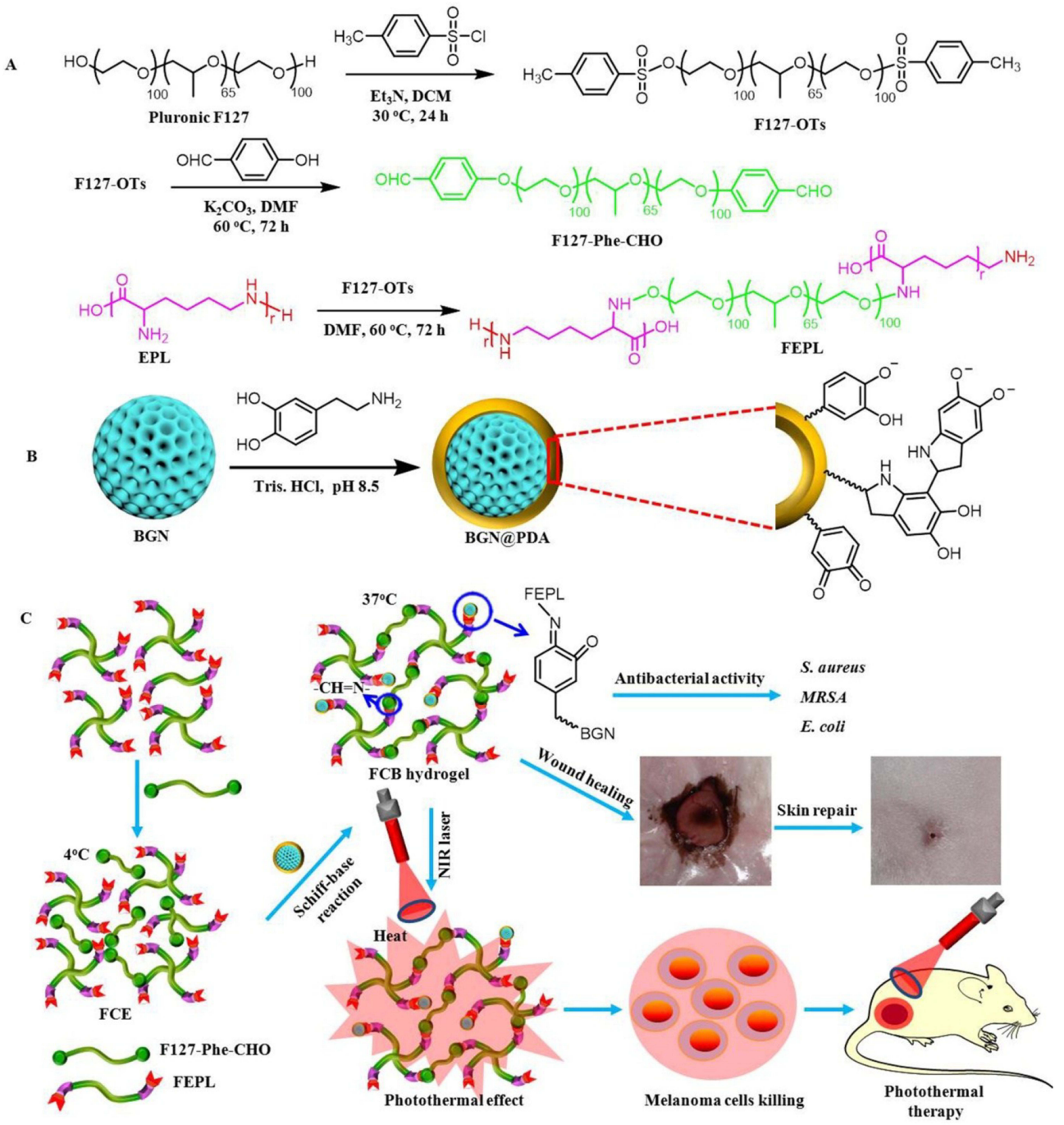
Yang et al employed ε-PL for Schiff base formation with F127-Phe-CHO, wherein F127-Phe-CHO was cross-linked with ε-PL and sulfhydryl-modified polyvinyl alcohol (PVA-SH/ε-PL). It was loaded with bromelain and the epidermal



Scheme 7 Reaction of F127-CHO with various amino-modified compounds to form Schiff bases.

growth factor stepwise to obtain hydrogels for wound cleansing and healing.[32] In this system, pineapple proteins were commonly employed in burn debridement[53] as the sulfhydryl groups in PVA-SH prevent their oxidation. By using the swelling test to evaluate its liquid absorption performance and moisturizing property, the hydrogel had the largest swelling ratio at 50 min. It then gradually decreased, with the liquid absorption performance up to 59.62%, moisturizing rate up to 88%, and biodegradation rate over 40% after 72 h. These results indicate that the hydrogel has good liquid absorption, biodegradation, and moisturizing rate. This hydrogel is therefore a potentially injectable wound dressing for the treatment of deep burn wounds.[32]

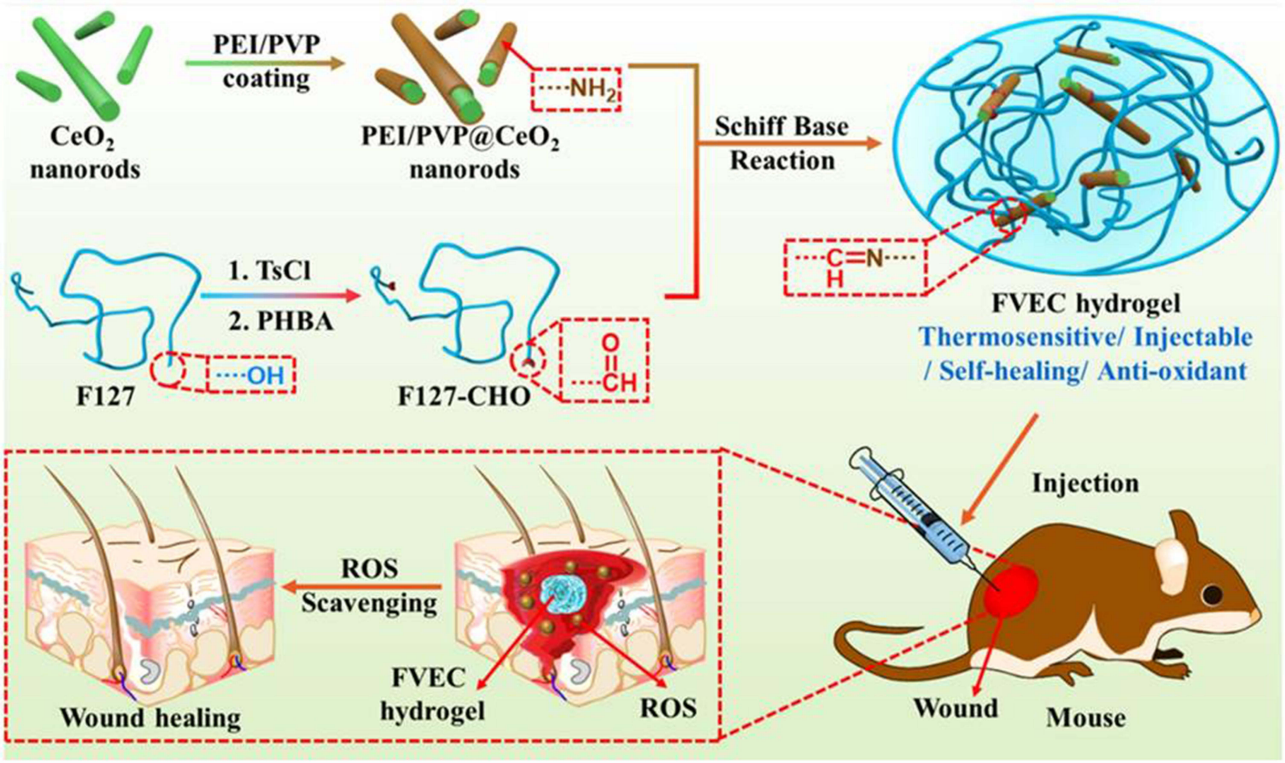
Later, Lei et al generated F127-OTs by the room temperature reaction of F127 with pyridine and toluenesulfonyl chloride (TsCl), later added 4-hydroxybenzaldehyde to obtain F127-Phe-CHO. ε-PL can also react with F127-OTs to obtain FEPL, and F127-Phe-CHO forms FCE with FEPL, which is loaded with monodisperse polydopamine functionalized biological by Schiff base activated glass nanoparticles (BGN@PDA) to kill melanoma, antibacterial, and heal wounds under the action of NIR Laser and heat. Among them, BGN@PDA can stimulate skin repair under photothermal conditions. The hydrogel effectively kills tumor cells (>90%) and inhibits tumor growth (94% inhibition at day 18) in a subcutaneous skin tumor model. Higher wound healing rates with this hydrogel compared to commercial 3M dressings. This nanocomposite hydrogel promotes wound healing in skin tumors via PTT[54] (Scheme 8).



Scheme 8 (**A**) Chemical synthesis process of hydrogel; (**B**) Schematic diagram of BNG@PDA; (**C**) Application of hydrogel in tumor wound healing. Reprinted with permission from Injectable Self-Healing Antibacterial Bioactive Polypeptide-Based Hybrid Nanosystems for Efficiently Treating Multidrug Resistant Infection, Skin-Tumor Therapy, and Enhancing Wound Healing. *Adv. Funct. Mater.* 2019;29(22):1806883. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[54]

Polyethyleneimine-Coated Cerium Oxide Nanorods

Common hydrogel dressings are prone to bioflocculation, which leads to bacterial infection and generates large amounts of reactive oxygen species (ROS) that hinder wound repair and skin regeneration.[55] To address this issue, Lei et al designed a novel nanocomposite hydrogel material. Firstly, PEI/PVP@ CeO_2 nanorods were obtained by adding polyethyleneimine (PEI) and polyvinylpyridone (PVP) to CeO_2 aqueous solution after the reaction. Next, F127 was reacted with TsCl to form F127-TsCl, followed by the addition of 4-hydroxybenzaldehyde to obtain F127-CHO. Finally, PEI/PVP@ CeO_2 was linked with F127-CHO using Schiff base to form nanocomposite hydrogels (FVEC hydrogels)[44] (Scheme 9). Cerium oxide adheres

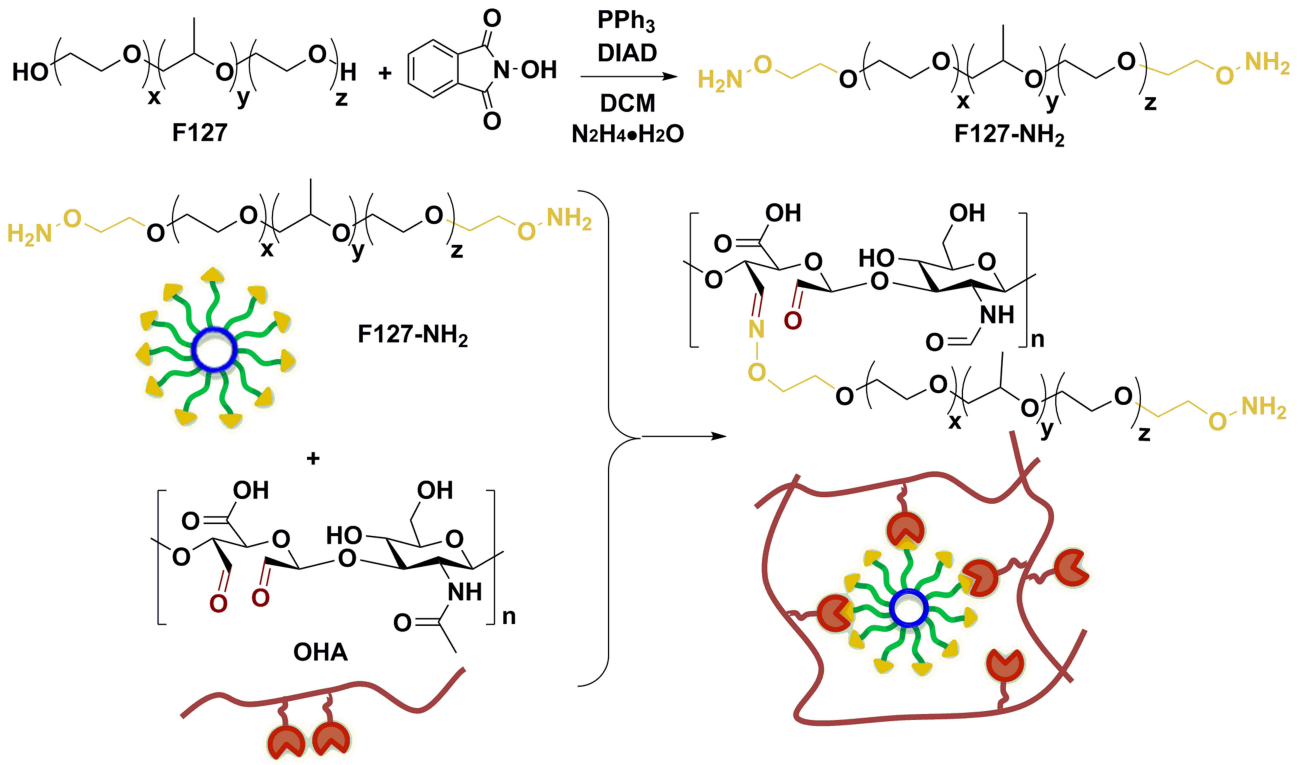


Scheme 9 Schematic diagram of hydrogel formation by polyethyleneimine-coated CeO_2 nanorods and F127-Phe-CHO for skin wound repair. Reprinted from Gong X, Luo M, Wang M, et al. Injectable self-healing ceria-based nanocomposite hydrogel with ROS-scavenging activity for skin wound repair, *Regen. Biomater.* 2022;9(1):rbab074. This is an open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.[44]

strongly to tissues and exhibits a high ROS scavenging activity, thereby protecting cells from oxidative stress.[56] A rat model evaluated skin wound healing, and FVEC hydrogel completely closed the wound in mice on day 14, and the wound was covered by new smooth skin, which was superior to the existing treatment 3M Tegaderm film healing efficiency. The healing effect was further evaluated by histological examination (H&E staining), which concluded that hair follicles and adipocytes could be generated at day 14. By implanting the hydrogel subcutaneously on the back of mice and subsequently examining the mice histologically, it was found that the hydrogel degraded significantly at 3 days and was essentially completely degraded after 7 days due to hydrolysis of Schiff base in the in vivo environment. This amphiphilic F127 micelles being broken down in vivo. Combined with the thermal sensitivity, injectability, biocompatibility, and biodegradability of F127-CHO hydrogels. This provided a new strategy for the healing and regeneration of full-thickness skin wounds (wounds that extend from the epidermis and dermis to subcutaneous tissue, along with fascia and muscle injuries).[44]

Alkoxyamine-Terminated Pluronic F127 Hydrogels

Some researchers synthesized Schiff bases by another method (F127-NH_2 and OHA), where F127-NH_2 was synthesized as follows. The synthesis of F127-NH_2 is as follows: PPh_3 and N-hydroxyphthalimide were added to F127 dissolved in tetrahydrofuran, and DIAD was added in drops at 0°C. The reaction was carried out at room temperature for 24 h. Pluronic F127 bis-phthalimide derivatives were precipitated by quenching in petroleum ether, crystallized and purified, then dissolved in dichloromethane. After that, hydrazine monohydrate was added in drops at room temperature for 12 h. The filtrate was obtained by removing the precipitate as F127-NH_2 (Scheme 10). At 37°C, the G′ value of F127-NH_2 /OHA hydrogel was approximately 3000pa, the G″ value was approximately 500 pa, and the bond strength of pigskin was 4.6 kPa, much higher than F127 hydrogel. In vitro studies also demonstrated its biocompatibility and its anti-adhesive effect on fibroblasts. Furthermore, its ability to adhere to tissues was moderate, and due to its self-fixation ability, this hydrogel was suitable for use as a physical barrier to prevent post operative adhesions.[57]



Scheme 10 Synthesis of F127-NH_2 from F127, where F127 reacts with OHA to form an oxime hydrogel.

Pluronic F127 Diacrylate Hydrogels

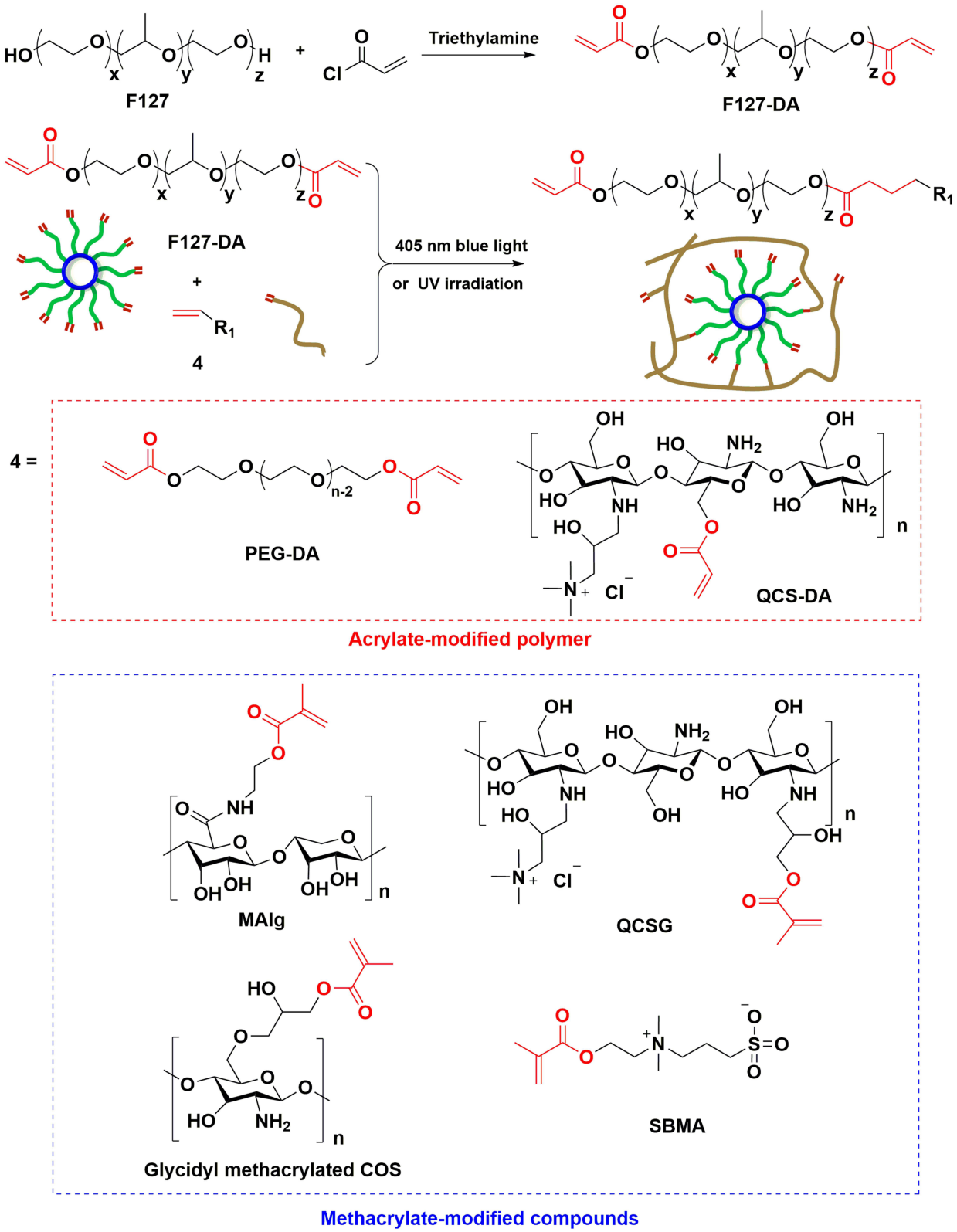
F127-DA hydrogels were first synthesized by Tirelli et al in 2002. The synthesis method is as follows: Under nitrogen atmosphere, F127 dissolved in toluene was extracted by reflux through a Soxhlet extractor. The extract was cooled slowly in a flask placed in an ice bath. After that, triethylamine, dichloromethane, and acryloyl chloride were added sequentially in the flask with a dropping funnel. Dichloromethane was added continuously and diluted, stirred for 12h, filtered, and precipitated to obtain a viscous oil F127-DA (Scheme 11). The F127-DA hydrogel self-assembled under aqueous conditions to form polymeric micelles with a vinyl-bearing surface for the solubilization and loading of hydrophobic drugs.[58] F127-DA hydrogels are generally used in combination with compounds that possess alkenes, since these can be subjected to photopolymerization.[59] Photocurable alkene radical polymerization can be carried out under UV or 405 nm light irradiation to form hydrogels with good biocompatibility, temperature sensitivity, and strong mechanical properties (high strength and toughness).[60,61] In such systems, the alkenes-containing compounds can be divided into two categories: acrylate-modified polymers(poly(ethylene glycol)diacrylate (PEG-DA) and quaternized chitosan diacrylate (QCSDA)), and methacrylate-modified compounds (glycidyl methacrylate functionalized quaternized chitosan (QCSG), glycidyl methacrylate COS, sulfobetaine methacrylate (SBMA), and modified sodium alginate (MAlg)), as presented in Scheme 11.

Formation of Hydrogels with F127-DA and Acrylate-Based Polymers

Acrylate-based polymers are common light-curing hydrogel materials that have been widely studied in the fields of four-dimensional (4D) printing[62] and spinal cord regeneration.[63] The following subsections summarize the use of F127-DA with acrylate-based polymers (PEG-DA or QCSDA) photocuring for sutureless wound closure.

PEG-DA

PEG-DA is a common hydrogel that is known to gel rapidly using a photoinitiator. It possesses a high water content and a good elasticity, and therefore, has been widely used as a new scaffold in tissue engineering[64] and regenerative medicine.[65] Wang et al investigated the application of a hydrogel patch synthesized from PEG-DA, QCS and tannic



Scheme 1 Synthesis of F127-DA from F127 by the reaction of F127-DA with alkenes.

acid (TA) for sutureless wound closure.[66] The first application of TA was in 1928, when Davidson et al employed it to treat burns.[67] Owing to the presence of multiple hydroxyl groups in its structure, TA can be used as a substitute for the hydrogel binder dopamine, and readily forms hydrogen bonds to improve the adhesion of the hydrogel. Meng et al used the non-swellable and highly mechanical F127-DA and PEG-DA as raw materials to form hydrogel patches in the presence of a photoinitiator under 395 nm irradiation, and demonstrated the potential of these patches to close and repair wounds without the requirement for sutures.[61] Based on the above literature, Wang et al used PEG-DA, F127-DA, MAlg, and TA as raw materials to form new insoluble hydrogels using UV light, in which TA formed hydrogen bonds with PEG-DA, F127-DA, and MAlg, both PEG-DA and MAlg can be photocured with a double bond of F127-DA to improve the mechanical strength. Measurements from tensile and compressive tests revealed that the hydrogel containing 20% F127-DA had 7.7 times higher tensile stress, 3.7 times higher compressive stress, and an increase in Young's modulus from 0.5 ± 0.1 kPa to 2.1 ± 0.2 kPa than the hydrogel without F127-DA. The bond strength of hydrogels with TA added was 102 times higher (0.41 | 0.05 kPa) than that without TA added. This hydrogel patch could be degraded and absorbed in vivo. The high fracture strength of sealed incisions compared to commercial adhesive pad seals makes them more suitable for wireless wound healing.[68] In summary, the hydrogel synthesized by F127-DA and PEG-DA can generally be used for wireless suture wound closure.

QCSDA

The quaternary ammonium salt of chitosan has been demonstrated to possess antifungal and antioxidant properties. Therefore, to enhance the reactivity of QCS, the introduction of acrylate to a chitosan quaternary ammonium salt via a double bond linkage was examined. Pei et al used F127-DA, QCSDA, silk fibroin (SF), and TA to form hydrogels, wherein SF exhibited hemostatic function. Rheological and tensile tests tested the mechanical properties of the hydrogels. The tensile strain was 767% at 2% SF content, which showed good elastic properties. TA formed hydrogen bonds with other components, which increased the tensile stress and decreased the elongation; in contrast, the hydrogel with SF content of 2% soaked in TA for 16 h had the most maximum tensile stress (76.22 kPa) and good elongation (629%). In conclusion, the hydrogel had good mechanical properties. The adhesion of the hydrogel to pigskin was quantitatively determined by the bending and shearing method, and its adhesive strength was 11.41×0.99 and could adhere to metal, plastic, glass, and wet tissue paper. In addition, the described hydrogel exhibited low dilatability, toughness, antibacterial, antioxidant, and hemostatic functions, while also promoting tissue regeneration.[24] This hydrogel holds promise for clinical wound healing.

Formation of Hydrogels Between F127-DA and Methacrylate-Based Polymers

Methacrylate-based polymers are commonly employed in contact lenses[69] and 3D printing,[70] and have recently been examined for the preparation of hydrogels for tissue repair. As summarized in the following subsections, F127-DA has been QCSG, combined with glycidyl methacrylated(COS) and SBMA to provide a range of new hydrogels for acute wounds, postoperative wounds, and diabetic wounds.

QCSG

QCSG can exert hemostatic effects through electrostatic adsorption of positively charged quaternary ammonium functional groups. Carbon nanotubes (CNTs) are conductive and responsive to NIR stimuli responsive ability and can improve the gel's mechanical properties. Guo et al used CNT, QCSG and F127-DA as the substrate formula to form injectable antimicrobial conductive cryogels loaded with ibuprofen for wound dressing. The cryogel showed better hemostasis in a mouse tail amputation model and a liver injury model (CNT content of 4 mg/mL in the cryogel system showed better hemostasis than gauze and gelatin hemostatic sponges). The cryogel has excellent healing capabilities (high wound shrinkage, low inflammatory cells, and high angiogenesis) compared to Tegaderm™ film. In addition has strong mechanical strength, electrical conductivity, rapid blood-triggered shape recovery, sustained drug stability, hemocompatibility, slow release cytocompatibility and high blood uptake capacity, providing a potential new approach to the clinical application of F127.[71]

Glycidylmethacrylated COS

Yoo et al reported the preparation of a hydrogel by mixing photoluminescent glycidyl methacrylated COS and F127-DA loaded with recombinant human epidermal growth factor (rhEGF) for wound care in diabetic ulcers. This hydrogel acts as a thermoresponsive hydrogel hat serves as a wound adhesive. It was found that the incorporation of COS and rhEGGs significantly enhanced epidermal differentiation during wound healing. The release rate of rhEGF was dependent on the degradation rate of the hydrogel. This hydrogel could facilitate wound healing and promote keratinized cell differentiation in epidermal tissue, which is beneficial for diabetic wound care.[26] Later, the authors replaced rhEGF with the basic fibroblast growth factor and heparin, and proposed that the resulting hydrogel could be used as a protein delivery systems and a tissue engineering scaffold.[72]

SBMA

SBMA is a promising amphiphilic material that has recently been used in antifouling and wound healing regeneration owing to its highly hydrophilic nature.[73,74] Ashraf et al found that *N,N′*-methylene bis(acrylamide)(MBAAm) can be used as a cross-linking agent for SBMA.[75] Based on this, Fu et al used MBAAm and F127-DA as cross-linking agents for SBMA to generate mechanically reactive hydrogel dressings for acute wounds. The hydrogel's ultimate tensile strength, tensile strain and compressive stress were 112 kPa, 1420% and 1.41 MPa, respectively. The bonding strength of the hydrogel to pig skin was evaluated by the lap-shear method, and the adhesion force of the hydrogel to the pig skin tissue was 5.97 kPa. The drug release can be controlled under the application of mechanical force. In terms of protein adsorption, there was a 35% reduction over commercial chitinous dressings and an 8% reduction over commercial UrgoTul Ag dressings. In terms of adhesion of Staphylococcus aureus to the dressing, it was reduced by ~ 2.33 orders of magnitude compared to commercial UrgoClean. In conclusion, this hydrogel dressing can be used as an alternative to acute sports wound dressings.[76]

Conclusions

This review summarizes recent work on Pluronic F127 hydrogels and their derivatives (F127-CHO, F127-NH_2 and F127-DA) for wound healing and repair. The F127 molecule contains hydrophobic (PPO) and hydrophilic (PEO) segments, and this hydrophobic property allows it to self-assemble into nanomicelles in water, commonly used for the solubilization and loading of hydrophobic drugs. In addition, F127 is thermosensitive, non-toxic, injectable, biocompatible, biodegradable. It is used as a drug carrier, wound dressing, surfactant, and 3D printing ink preparation. F127 was reacted with Dess-Martin periodinane, to obtain F127-CHO, which readily reacts with amine or hydrazine to form dynamic C=N bonds, enhancing mechanical properties, self-healing properties, and tissue adhesion properties. This hydrogel is mainly used for burns, bacterial/superbacterial infections, diabetic wounds, and uterine scars. F127 is obtained by reacting with PPh3, DIAD, and $N_2H_2{\cdot}H_2O$ to obtain F127-NH_2, which reacts with the aldehyde group of OHA to form a hydrogel with high modulus, stability, and self-fixation ability for preventing postoperative adhesions. The molecular chain of F127 The introduction of propylene groups forms F127-DA, which has light-curing ability, excellent mechanical properties, and exhibits high strength and toughness in diabetic wound care and severe wounds. When PEG-DA or TA is present in the system, it can be used for sutureless wound closure. In summary, F127 derivatives have important applications in wound repair and regeneration (Table 1).

In general, F127 is usually readily cleared and degraded in vivo, thus limiting the distribution and therapeutic effect of F127 in vivo, in addition to having moderate mechanical strength, adhesion and self-healing ability. F127-CHO and F127-NH_2 can form Schiff bases to improve these partial properties, but Schiff bases are dynamic and not mechanically strong enough to be used in high strength mechanics such as bones, teeth and 3D printing. F127-DA is irreversible once chemical bonds are formed with double bonded light curing, at which point it has excellent mechanical strength and toughness, but at the same time will lose self-healing properties. In addition, F127 and its derivatives are generally not used alone and need to be added to other materials to improve performance. These limits its application in biomedical fields.

Table 1 Summary of the Application of F127 Derivatives in Wound Healing

Pluronic F127 Modification Strategy	Advantages	Wound Types	
F127-CHO	Self-assembly; Thermosensitivity; Injectability; Biodegradable; Load substances; High mechanical strength; Superior self-healing; Excellent tissue adhesion properties	Burn wound	Burn wound healing; Deep burn wound; Full-thickness skin wound healing
		Other wound healing	Bacterial ablation and wound healing; Super bacteria-infected wound healing; Healing of diabetic wounds; Uterine scars; Skin wound repair
F127-NH_2	Self-assembly; Thermosensitivity; Injectability; Biodegradable; Load substances; Higher modulus and stability; Adhesion to tissues was Moderate; Self-fixation ability	Prevent Post Operative Adhesions	
F127-DA	Self-assembly; Thermosensitivity; Injectability; Load substances; Strong tissue adhesion and mechanical strength; Non-swellable; Sutureless wound closure when PEG-DA or TA are present in the system	Wound Healing; Diabetic Wound; Acute Wounds; Sutureless Wound Closure	

Future Perspective

In order to enhance the mechanical strength, media adhesion and self-healing ability of F127 hydrogel during wound healing and repair, and to solve the problem of rapid removal and degradation in vivo, these problems can be solved in the future by chemical modification of F127 (position, number, type, and spatial site resistance, etc.), physical modification of cavity-loaded substances (temperature sensitizers, photosensitizers, pH responders, electrosensitizers, and enzymes, etc.), binding to other molecules (ligands, enzymes, drugs and proteins, cell membranes and mitochondria, etc.), and binding to nanomaterials (nanoparticles, nanowires, polymeric nanoparticles and nanofibers, etc.).

For wound healing, there is still a lot of room for development of F127 derivatives. For example, for wound dressings, there is a need to improve healing efficiency and time. For wireless suture adhesives, there is a need for a perioperative period that can be prepared successfully and address issues such as hemostasis, proper adhesion, and copolymer-induced inflammation. For anti-adhesive agents in the abdomen, heart, and tendons, issues such as low tissue adhesion, rapid degradation, and poor in vivo retention need to be addressed. In addition, a process for monitoring wound healing needs to be developed to establish a guideline for each stage of the wound to determine what treatment is needed when and how to treat it. After obtaining dynamic data on the wound, the structure and function of the hydrogel will be further designed to enable personalized treatment.

In recent years, mitochondria have attracted increasing attention in wound healing, and mitochondrial involvement in wound repair and regeneration is mainly focused on ROS levels,[77,78] mitochondrial respiration,[79] mitochondrial fracture,[80] mitochondrial metabolism,[81] and mitochondrial transfer,[82] etc. Nanomaterials targeting cell-loaded drugs are one of the hot spots of research in recent years.[83] Among the nanomaterials (mesoporous polydopamine nanoparticles,[84] Au nanocage)[85] and

mitochondria for diabetic wound healing have also been reported. In the future, it is possible to target cells near the wound (fibroblasts,[27] neutrophils,[86] and macrophages,[87] etc.) or mitochondria for wound repair by F127 nanoscaffolds for wound repair. This can be achieved by several methods: 1. Mitochondrial removal by modified F127, which causes apoptosis in the vicinity of the wound for wound healing but leads to both mitochondrial dysfunction and delayed wound healing. 2. F127 responds accordingly to target cells by adjusting ROS levels, mitochondrial respiration, mitochondrial breakage, mitochondrial metabolism and mitochondrial translocation to achieve wound healing. 3. F127 loaded with drugs and ligands, targeting wound cells to further localize to mitochondria, releasing drugs and thus healing the wound. 3. F127 is loaded with drug, stimulus response agent (photosensitizer, acoustic sensitizer, photothermal imaging contrast agent, photothermal transducer and pH responsive material), and mitochondria target the stimulus response agent, and in response to the stimulus response, the drug is released to the target cells where the mitochondria are located to achieve wound healing.

As researchers continue to practice and accumulate knowledge, materials including F127 derivatives, which are believed to be increasingly available, will be widely used in the near future, not only for wound healing and scar repair, but also for bone repair,[88] periodontitis,[89] otitis externa,[90] conjunctivitis,[91] analgesia,[92] and HIV infection[93] to further improve the quality of life of patients.

Databases

We used the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com/wos/alldb/basic-search) databases in this review, with "F127" and "wound" as keywords and any year, the last five years were chosen as far as possible, and ultimately novelty and relevance as the principle to determine whether to introduce articles.

Author Contributions

Shanshan Li, Cheng Yang, and Junqiang Li contributed equally to this review. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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