ISSN NO. 2320–7418 DOI: 10.22270/jmpas.V10I5.1569

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

Recent advances in polymeric hydrogel scaffolds for skin tissue engineering and regenerative medicine

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ABSTRACT

Lack of self-healing capability in skin tissue defects caused by various traumatic conditions often leads to a challenging situation for clinical practitioners. Although various procedures are offered in clinics, some of which effectively restores the skin tissue to some patients, none of them result in an adequate tissue repair that can withstand mechanical stresses under natural weight-bearing conditions. The ability of hydrogels to form 3D networks, which can be fine-tuned using biocompatibility and biodegradability factors, has sparked much interest in these hydrophilic polymers. A systematic overview of emerging hydrogel-based therapies for skin tissue repair is presented in the current study to address the unsolved issue of skin tissue defects and test whether such therapeutic approaches may enhance the healing process where skin tissue has been damaged.

Keywords: Skin, Wound healing, Hydrogel, scaffold, polymers

Received - 26-07-2021, Reviewed - 20/08/2021, Revised/ Accepted- 17/10/2021

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INTRODUCTION

Lack of self-healing capability in skin tissue defects caused by various traumatic conditions often leads to a challenging situation for clinical practitioners. [1, 2] Although various procedures are offered in clinics, some of which effectively restores the skin tissue to some patients, none of them result in an adequate tissue repair that can withstand mechanical stresses under natural weight-bearing conditions (As shown in Table 1).[3,4]

Strategies that utilize synthetic and natural polymers adapted for skin tissue repair may be beneficial in enhancing tissue regeneration at the skin defect sites.[5,6] In addition to being biocompatible and biodegradable, these polymers must provide an adapted mechanical environment, provide nutrient transport, and support cell growth and differentiation.[7,8] Such system types include natural and synthetic scaffolds and hydrogels with specific physical and mechanical properties and advantages and limitations.[9]

The ability of hydrogels to form 3D networks, which can be fine-tuned using biocompatibility and biodegradability factors, has sparked much interest in these hydrophilic polymers.[10] In addition, hydrogels can be used to promote the controlled delivery of peptides, proteins, cells, and drug moieties.[11,12] A systematic overview of emerging hydrogel-based therapies for skin tissue repair is presented in the current study to address unsolved issue of skin tissue defects and test whether such therapeutic approaches may enhance the healing process where skin tissue has been damaged.

Current Treatment Strategies for Skin tissue Regeneration

A. Non-Surgical Approaches

Bandages

The bandage is a fabricated product used to support a medical device such as a dressing or splint or a separate device supporting or restricting movement. In order to stop the blood leakage, bandages act as the first line of defence for any open wounds. The bandage is used in conjunction with a dressing to hold the dressing in place. However, the bandage alone is not an ideal approach for deep skin tissue defects since the bandages can cause pain and mechanical trauma during their removal in case of these defects.[13,14]

B. Drug based approach

- **Antimicrobials**

Povidone Iodine

Due to their favourable efficacy and tolerability, Anti-microbial agents like Iodopovidone, also called povidone-iodine, continue to be popular antiseptic that's used to disinfect skin prior and after surgery even after their decades of usage.[15,16] However, besides its excellent penetrability, anti-inflammatory, cytocompatibility characteristics, povidone-iodine has not been observed to worsen wound healing during clinical use.[17,18]

Moreover, the large area of treated surfaces may experience chronically elevated blood total iodine after receiving 10% povidone-iodine for a long time or even resulting in milder symptoms of thyroid dysfunction.[19]

Silver Sulfadiazine (SSD)

Several silver-based agents have been used for burns, chronic skin ulcers, and a few other medical conditions due to their superior bactericidal efficiency and less likelihood of triggering drug resistance.[20,21] Among the top creams for burn wound infection, silver sulfadiazine cream (SSD) is recognized as the gold standard to treat and prevent infection, highlighting its prophylactic and therapeutic efficacy to limit the spread of bacteria that can impede wound recovery.[22] SSD is cytotoxic to fibroblasts and keratinocytes in vitro, as well as impairing wound healing in vivo.[23]

Table 1. Represents the advantages and disadvantages of the different wound healing products available in market.

Name of the materials	Advantages	Disadvantages	Commercial available Products	Reference
Bandages	Stops the blood leakage, and also act as the first line of defense for any open wounds.	Can cause pain and mechanical trauma during their removal.	Xeroform™.	(13,14)
Anti-microbial agents	Excellent penetrability, anti-inflammatory, and cytocompatibility characteristics (Eg. Povidone Iodine). Demonstrates superior bactericidal efficiency. (Eg. SSD).	Even results in milder symptoms of thyroid dysfunction (Eg. Povidone Iodine). Cytotoxic to fibroblasts and keratinocytes (Eg. SSD).	Betadine, Clinidine, Silvadene, Thermazene.	(15-23)
NSAIDS	Plays a significant role in down regulation of pain and inflammation (Eg. Diclofenac sodium and Ibuprofen).	Small-scale systemic short-term administration of diclofenac could minimize the fibroblast activity (Eg. Diclofenac Sodium)	Voltaren® Gel, Ibugel, Ibuleve,	(24-30)
Autografts	Autografts plays a significant role in fixing large skin defects.	Revascularization was also problematic in wounds caused by burns or physical stress.	ReCell® grafts	(31-33)
Allografts	Change of wound dressings is less frequent.	Chance of acute tissue rejection is quite high.	TheraSkin®, AlloDerm®.	(34, 35)
Hydrogel	Demonstrates ideal cytocompatibility, biocompatibility, biodegradability, biomimetic and moisture retention characteristics.	It is difficult to shape hydrogels in predesigned geometries.	Intrasite™, Nu-gel™, Aquaform™	(36-60)

C. NSAIDS

Diclofenac Sodium

A non-steroidal anti-inflammatory drug (NSAID), diclofenac inhibits cyclooxygenases, providing relief from inflammation and pain associated with prostaglandins. However, it remains controversial whether systemic diclofenac, although becoming increasingly common, can be harmful.[24,25] Numerous experimental and clinical studies have suggested it can delay tissue healing, cause lack luster intestinal anastomoses, and impede other surgical procedures. Previously, studies using rats demonstrated that small-scale systemic short-term administration of diclofenac could minimize the fibroblast activity; however, the decreased activity did not affect healing significantly. [26]

Ibuprofen

NSAIDs, such as Ibuprofen, are well-known for their anti-inflammatory, antipyretic, and pain-relieving properties. It acts via inhibition of the two forms of cyclooxygenase (COX-1 and COX-2) responsible for prostaglandin production.[27,28] Ibuprofen must be repeated frequently to maintain an optimal plasma concentration as it has a short half-life, rapid biotransformation, and metabolism.[29] Multiplying ibuprofen doses can hinder compliance and decrease clinical effectiveness.[30]

Surgical Approaches

Autografts

Techniques of auto grafting play a significant role in fixing large skin defects; it involves the transplantation of skin from one side of the body to the site of tissue defects by using the stretching technique.[31] The traditional autograft procedure has some limitations, despite its importance for treating large and severe skin wounds. A skin graft may cause secondary wounds on the patient's skin, which are significant when larger lesions are involved. As discussed above, autologous skin grafting causes secondary wounds in the case of the transplanted skin; further, the revascularization was also problematic in wounds caused by burns or physical stress. [32, 33]

Allografts

Human skin (allografts) is used in certain circumstances to overcome the disadvantages of autologous transplantation. It is difficult to completely exclude the possibility of communicable disease transmission in these approaches, but it is minimal when allografts are made with carefully characterized cells line and under good manufacturing practice (GMP) conditions. Hematological examinations usually reveal signs of acute tissue rejection after allografts have been in place for a mean of 14.5 days, but exceptions have been reported. [34, 35]

Hydrogel scaffold for skin tissue regeneration

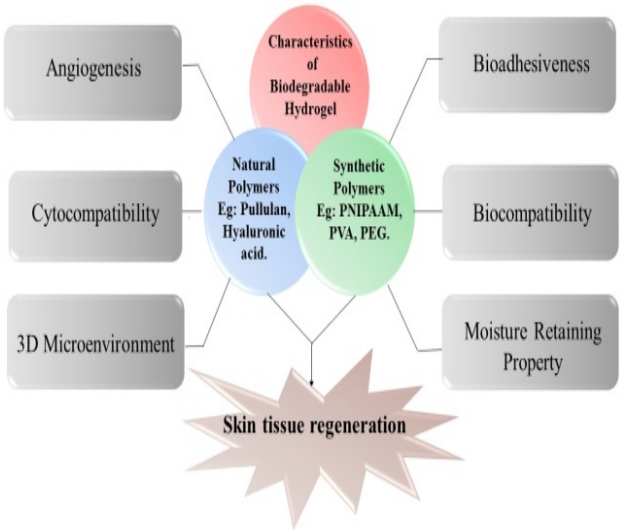
Various pharmaceutical and biomedical applications (e.g., delivery of therapeutic agents and tissue engineering) have been developed using hydrogels, which are three-dimensional crosslinked hydrophilic polymers with a similar structure to the extracellular matrix (ECM). Due to their remarkable properties like porous properties, ease of fabrication, ability to store vast quantities of water or biological fluids, mimic tissue characteristics, biocompatibility, and the ability to store therapeutic nanoparticles and biomolecules within their networks.[36] Recent technologies have shown that hydrogels with injectable characteristics can be easily administered

via minimally invasive procedures, thus helping to reduce bleeding and promote the healing of wounds.[37] Further, the hydrogel scaffolds can fill irregularly shaped wounds and provide a significant reduction in pain and scarring when applied to deep bleeding wounds. In addition to these features, the ideal hydrogel scaffolds should ensure that it is also antimicrobial, biodegradable, cytocompatible, and biocompatible without releasing toxic substances since it will directly contact psychological fluids (Fig.1) (Table 2). [38]

Selective Polymeric hydrogel scaffolds for skin tissue engineering and regenerative medicine

Poly (N-isopropyl acrylamide) (PNIPAM)

Figure 1: represents the characteristics of the polymeric hydrogel scaffolds



Temperature-responsive reversible sol-to-gel phase transition can be used to control both skin adhesion as well as detachment of wound dressings. A thermosensitive polymer, poly (N-isopropyl acrylamide) (pNIPAM), has a lower critical solution temperature (LCST) of about 32 °C, which can be adjusted by modifying its copolymer components. Apart from its thermosensitivity, PNIPAM also has other properties that are of benefit to biomedical applications, including its tunable structure and low toxicity. Further, Angiogenesis and anti-inflammation are essential for fastening the wound healing activity in case of skin tissue defects. Lin et al. developed an innovative SA/bFGF@pNIPAM/DS@ p (NIPAM-co-AA) composite hydrogel dressing that delivers diclofenac sodium (DS) and basic fibroblast growth factor (bFGF) stepwise during the inflammation phase and regeneration phase. In addition to its mechanical properties, this SA/bFGF@ pNIPAM/DS@ p (NIPAM-co-AA) hydrogel showed a high fluid uptake capacity and an excellent water vapor transmission rate, as well as minimal cytotoxicity. However, from the in-vitro studies, it was identified that these hydrogels exhibit two different rates of release (i.e., DS exhibits 92% of sustained-release during the first three days, whereas bFGF exhibit 80% of controlled release on later eight days.). Further, the composite hydrogels (SA/bFGF@pNIPAM/DS@ p (NIPAM-co-AA)) improved wound healing in vivo in rats when applied as a wound dressing, reducing wound inflammation and facilitating angiogenesis. Therefore, SA/bFGF@pNIPAM/DS@p (NIPAM-co-AA) hydrogel proved to be a potentially effective dressing for skin tissue defects. [39]

Due to its temperature sensitivity, poly (N-isopropyl acrylamide) (PNIPAM) has received much attention, especially in the world of biomedicine. PNIPAM's critical transition temperature is close to the human body's temperature, made it an ideal polymer for drug loading. For example, Dong et al. fabricated a superoxide dismutase (SOD) loaded poly (N-isopropyl-acrylamide)/poly (γ-glutamic acid) hydrogel for wound repair. The thermo sensitive hydrogels could absorb more water and withheld their moisture better while releasing SOD sustainably and exhibiting good biocompatibility. SOD-loaded hydrogel has shown a favorable effect on wound healing activity by fastening the reepithelization and tissue reconstruction in diabetic rats. Using thermo-sensitive hydrogels as a design platform provides new ideas for hydrogels that possess environmental sensitivity; further, the SOD-loaded hydrogels hold good promise for wound healing. [40]

The loss of skin integrity resulting from injury, illness, or burning calls for new therapeutical options. Recently, skin tissue engineering concepts were identified to solve these defects because of their ideal biodegradable and flexible nature. Oroojalian et al. developed biodegradable and flexible PNIPAAm-PCL-PCL-PNIPAAm polymeric hydrogels for fastening the skin tissue regeneration process. Moreover, in the Penta block copolymer hydrogel, HNFF-PI8 cells were attached and became viable without apparent toxicity. Its ability to provide attachment and growth surfaces for fibroblast cells were not affected by the external modification. As part of routine wound healing, fibroblasts produce collagen, an essential ECM component. As a result of collagen type I and III mRNA expression up regulation, exposure to copolymer also increases the number of cells in the ECM. Further, it was shown that PNIPAAm-PCL-PCL-PNIPAAm stimulated the proliferation of fibroblasts. Furthermore, the Penta block copolymer is an injectable carrier for sustained drug delivery systems, skin tissue engineering, and wound healing applications. [41]

Hydrogel with near-infrared (NIR) responses are stimuli-responsive gels in which the radiation intensity, duration of light exposure, and irradiation site can be precisely controlled. Depending on the stimulus, hydrogels can undergo phase or volume changes as well as show specific functions. Han et al., in their research, engineered a poly (N-isopropyl acrylamide) (PNIPAM) hydrogel interconnected network to contain polydopamine nanoparticles

(PDA-NPs) because of its ideal NIR response, self-healing ability, and cell/tissue adhesion characteristics. Moreover, the hydrogel containing PDA-NPs/PNIPAM displayed phase transitions and volume changes after encapsulating the PDA-NPs. In this way, the hydrogel can create pulsatile drug release while also acting as a therapeutic actuator, triggered by NIR, and promoting wound healing with NIR. Because of the reactive catechol groups on PDA-NPs, the hydrogel successfully immobilized growth factor/protein on hydrogel surfaces after being coated with PDA-NPs. Further, the PDA-NPs coating on the hydrogel and the immobilized growth factor showed a synergistic effect on wound healing in an in vivo full-skin defect experiment. Finally, due to its ideal cellular affinity, the PDA-coated hydrogel also demonstrated success in wound dressings, indicating that this hydrogel can aid in skin tissue repair. (42)

Since they can form a highly moist environment, hydrogels are investigated as potential wound treatment biomaterials since they facilitate cellular migration and tissue regeneration. Additionally, they can serve as a vehicle for the delivery of local drugs, and they can stimulate immune cells to speed up wound healing. Andrgie et al. developed an ibuprofen-loaded heparin/ Poly (N-isopropyl acrylamide) hydrogel and investigated its potential in cutaneous wound healing. In addition, the embedment of Ibuprofen in hydrogel during the healing process resulted in the reduction of inflammation and pain. In vitro studies showed that the hydrogel release of Ibuprofen significantly inhibited lipopolysaccharide-induced inflammation in RAW 264.7 macrophages by suppressing NO, PGE2, and TNF-α production. Further, the in vivo studies revealed that Ibuprofen-loaded hydrogel promoted rapid wound healing compared to the phosphate-buffered saline treatment group because of its excellent anti-inflammatory and tissue regeneration potential. Finally, the Injectable Hep-PNIPAM hydrogel combined with Ibuprofen improved wound healing and is a promising candidate for skin tissue regeneration studies. (43)

Hyaluronic Acid

Hyaluronic acid was selected because it is both biocompatible and does not contain any toxic chemicals, a critical factor for the extracellular matrix (ECM). Adaptable, biomimetic, and reversible, supramolecular hydrogels can control a wide range of structural properties. For clinical applications, it is crucial to design supramolecular hydrogels that mimic the damaged organ structures and functions. However, the ideal wound healing process using supramolecular polysaccharide hydrogels to modulate epidermal growth factor (EGF) delivery remains challenging. Zhao et al. using azobenzene and β-cyclodextrin groups conjugated to hyaluronic acid chains, developed photo-responsive supramolecular polysaccharide hydrogels for fastening the wound healing process. The cross-link density of a supramolecular hydrogel featuring dynamic spatial network cross-linking was achieved using the photo isomerization characteristics of azobenzene under different wavelengths. An in vivo study of wound healing through a full-thickness skin defect model found that granulation tissue formation, growth factors, and angiogenesis were improved in fluorescein is thiocyanate isomer I (FITC) labeled EGF loaded hydrogel treatment group. In this regard, the proposed FITC labeled EGF-loaded hyaluronic acid - β-cyclodextrin hydrogels may prove helpful in future clinical wound healing applications. (44)

For wounds to close and heal properly, with the best functional and cosmetic outcomes, wounds must be treated early and effectively. Moreover, the utilization of human amniotic membrane was proved to be safe and effective for wound care and management. Despite this, amniotic membrane wound healing products have not been widely utilized because thin sheets of membrane and living cellular zed tissue are difficult to handle and place. Murphy et al. developed a novel amnion membrane-derived product that is processed into a cell-free solution and at the same time maintains the presence of high levels of cell-derived growth factors and cytokines. Hyaluronic acid (HA) and solubilized amnion membrane (SAM) hydrogel (HA-SAM) are convenient to produce, store, and apply to wounds. Further, from the in vivo studies, it was identified that Hyaluronic acid (HA) - solubilized amnion membrane (SAM) hydrogel significantly enhanced the angiogenesis and reepithelization process in skin tissue defects and thus fastened the wound healing activity. Finally, the hydrogel delivery system for SAM in this study provides many of the advantages associated with fresh, cryopreserved, or dehydrated tissue and overcomes many limitations associated with moist, fresh, or cryopreserved tissues. (45)

Due to the pro-regenerative structural and functional properties of skin, the most challenging aspect of designing wound dressings is to mimic the tissue microenvironment. Using thiol-modified poly (γ-glutamic acid) (γ-PGA-SH) and oxidized hyaluronic acid (HA-CHO), Yang et al. designed a type of bionic extracellular matrix (ECM) hydrogel. Hydrogels formed from the rapid addition of thiols and aldehydes in γ-PGA-SH and HA-CHO contained a dynamic covalent network capable of adaptability and self-healing, providing immediate wound coverage used for a long time. Additionally, these hydrogels exhibited typical viscoelastic properties similar to natural ECM, exhibited degradation properties in vitro and in vivo, and free radical scavenging abilities. Moreover, by altering polymer content, hydrogels can be tailored for specific properties such as gelation, rheological behaviour, mechanical strength, and degradation. Moreover, the ECM-inspired hydrogels significantly improved wound healing in vivo than commercial dressing (TegadermTM) by promoting angiogenesis and collagen deposition.

Finally, as a wound dressing, multifunctional hydrogel significantly demonstrated a wide range of potential in biomedical applications.(46) There is no effective therapy available for improving the clinical outcome of skin wounds caused by trauma, inflammation, surgery, or burns. Zhou et al. presented an injectable copper sulfide nanoparticle-loaded hyaluronic acid (CuS/HA) hydrogel that promotes wound healing by stimulating angiogenesis. Aside from being injectable into the wound, the hydrogel also shows good photothermal properties; after 10 minutes of near-infrared light irradiation, the temperature of the prepared hydrogel increased to 50°C from room temperature. Further, the cell culture technique, in vivo studies, and immunohistochemical staining techniques identified that CuS/HA hydrogel treatment groups showed significant reepithelization, angiogenesis, and minimal cytotoxic characteristics compared to other treatment groups. It is feasible to conclude that the CuS/HA hydrogel preparation can upregulate VEGF expression, promote angiogenesis, and therefore may be used to treat skin wounds to increase collagen deposition and promote wound healing. (47)

A wound is a significant health concern related to skin damage from different types of injuries. Also, patients with diabetes are likely to experience wounds that heal very slowly. Mittal et al. fabricated a polymeric hybrid hydrogel with dimethyl amine ethyl acrylate and hyaluronic acid (pDMAEMA-HA), incorporated with a Didymocarpus pedicellatus herbal extract for fastening the wound healing process in case of the topical wounds of diabetic patients. Therefore, the ratio of pDPi-DMAEMA-HA hybrid hydrogel has been suggested for use as novel polymeric material for wound management in light of its excellent impregnation ability, great flexibility, and more remarkable water absorption ability. Wound healing evaluations revealed that the pDPi-DMAEMA-HA hybrid hydrogel group resulted in a significant level of reepithelization than marketed formulations and polymerized hybrid hydrogels. Histo pathologic examinations indicated that hyaluronic acid plays a vital role in various stages of wound repair in pDPi-DMAEMA-HA hybrid hydrogel and polymeric hybrid hydrogel-treated groups, compared with the standard group. Finally, it is hoped that these hybrid formulations will treat various types of wounds such as burns, skin irritations, fractures, accidental wounds, and diabetic wounds. (48)

Pullulan

A linear structure is formed by the interconnection of malt triose units through α-1, 4 & α- 1, 6 glycosidic bonds. In spite of its higher cost, pullulan retains many advantages such as cytocompatibility, hydrophilicity, and biodegradability. Moreover, this pullulan inter connection pattern provides exceptional film-forming capabilities, bio adhesiveness, and mechanical strength in case of pullulan based hydrogel.

Even though many commercial dressings are available today, there are currently no ideal products that can effectively deal with large wounds with high exudate or pressure sores like diabetic foot ulcers. Therefore, the development of wound dressings that are designed explicitly for chronic wounds is pressing. Park et al. developed an Ulmus davidiana var. japonica (UD) root bark powder loaded pullulan hydrogel film and evaluated for its tissue regeneration potential in case of cutaneous wounds. The UD root bark powders, on the other hand, provide distinct gelling properties and an excellent gel swelling capability, which are attributed primarily to the mucilage composition. (49)

Moreover, the unique properties of UD root bark powder make it ideal for hydrogel films. Indeed, the study results confirmed that the UD-loaded pullulan hydrogel films possessed a markedly higher water absorption than commercial wet dressings and, when tested in a mice wound model, showed superior wound healing effects (faster wound closure and dermal regeneration) to control groups. Furthermore, UD hydrogel films' differential adhesiveness, which depends on dry or wet conditions, renders them superior to other wound dressings in wound healing. Finally, UD root bark powders proved to be helpful as a material for hydrogel wound dressings, and UD hydrogel films could be used therapeutically for wound healing.

Burn patients and those with chronic wounds benefit greatly from skin substitutes that reduce their morbidity and mortality. Present-day skin substitutes, however, have some drawbacks, including high costs and insufficient skin regeneration. Therefore, a new skin substitute is required. Nicholas et al. created an inexpensive hydrogel-PG-1 for "pullulan-gelatin first-generation hydrogel" by combining two polymers, pullulan with antioxidant properties and gelatin with high water absorption properties. Moreover, embedment of both fibroblasts and keratinocytes into the Pullulan-Gelatin hydrogel resulted in bilayered skin substitute with ideal cytocompatibility, cellular proliferation, and differentiation characteristics. Further, a mouse model developed a significantly thicker neo-dermis after two distinct layers consisting of cells, increasing the proliferation of skin cells after 14 days. Finally, the pullulan-gelatin-based hydrogel demonstrated a significant reduction of macrophage infiltration and support of muscle growth, suggesting that it is suitable for treating burns and chronic skin wounds where skin inflammation is high. (50)

Every year billions of dollars were spent for the treatment of scarring caused by wounds or trauma. Moreover, the fibrotic responses and scar formation upon wound repair may be facilitated by activating focal adhesion kinases (FAKs). The FAK has proven challenging to translate into clinical practice because of the lack of effective drug delivery systems for large wounds. As a solution to

this problem, Ma et al. developed a pullulan collagen-based hydrogel that can deliver FAK to mice with burns and excisional wounds. Moreover, using pullulan collagen hydrogels, FAK controlled delivery accelerated wound healing and enhanced collagen synthesis and myofibroblasts activation. Finally, the FAK loaded hydrogel serves as an ideal candidate for treating and managing any large wounds. (51)

A limited number of cell-based wound healing therapies exist due to inadequate delivery systems that lack protective mechanisms against the acute inflammatory response. Based on the polymer pullulan known for its potent antioxidant properties, Wong et al. developed a biomimetic hydrogel system using the Mesenchymal stem cells (MSCs) loaded pullulan hydrogel to enhance the skin tissue regeneration process. With increased oxidative stress, seeded MSCs onto pullulan hydrogels demonstrated enhanced viability and improved antioxidant property compared to controls. The in vivo studies identified that the hydrogel scaffolds made from pullulan enhanced MSC engraftment significantly compared to local injections. Finally, the pullulan-based hydrogel proved to be an ideal vehicle for mesenchymal stem cells because of its excellent biomimetic and biocompatible characteristics. Hence due to this reason, pullulan-based hydrogel might show promise in skin regeneration methods based on progenitor cells. (52)

Polyvinyl alcohol (PVA)

Due to its ideal biodegradable, hydrophilic, biocompatible and mechanical characteristics, polyvinyl alcohol is considered a various skin tissue regeneration studies. However, a wound dressing is essential to the healing of cutaneous wounds. Shamloo et al. developed honey-loaded Chitosan/PVA/Gelatin hydrogel and later evaluated them for their anti-microbial and wound healing efficacy in case of skin tissue defects. An investigation of the mechanical, viscoelastic, antibacterial, and physical properties, degradation, cellular proliferation, and biocompatibility characteristics of the hydrogels demonstrated the ideal functional capabilities of the developed hydrogels. In vivo evaluations were conducted to determine the tissue regeneration potential of honey-loaded Chitosan/PVA/Gelatin hydrogel for optimal wound healing. However, it was also identified that a higher concentration of honey within hydrogel enhanced the biocompatibility and anti-microbial potency of the Chitosan/PVA/Gelatin hydrogel. Although honey weakens the hydrogel's mechanical properties and speeds up the degradation process, the samples still possessed sufficient tensile strength and viscoelastic properties to heal the wound. Finally, from the in vivo results, it was observed that the honey-loaded hydrogel resulted in a well-structured epidermis layer that contains mature collagen in case of skin tissue defects. (53)

Hydrogels, among novel formulations aimed at healing damaged skin, provide the wound with a moist environment. Loutfipour et al. using chitosan, PVA, and propylene glycol plasticizer, oxytetracycline hydrogels were prepared by Freeze-Thaw (F-T) cycles. Moreover, hydrogels showed lower permeability, possibly as a consequence of the dermal barrier. This barrier allowed the hydrogel film to absorb less water and the matrix site to swell less at release time. Further, the physiological and physicochemical properties of the biological membrane and the chemical properties of the drug were controlling factors in transdermal patch penetration and release. Further, from the results, it was identified that the F-T technique is a suitable method for preparing hydrogel patches that can effectively treat and heal skin ulcers in general. (54)

According to Li et al., freeze-thaw and phase separation methods successfully produced a PVA/CMC/PEG bi-layer hydrogel and demonstrated that it could be used as a wound dressing. A longitudinal section of the bi-layer hydrogel showed a gradual increase in pore size from the upper to the lower layer, and both layers were bonded tightly together. Bilayer hydrogels containing PVA/CMC/PEG showed good tensile properties, adequate water vapour transmission rate, good antibacterial activity, biocompatibility, and minimal adhesion to wounds. Further from the in vivo studies, bi-layer hydrogel promoted wound healing extensively when applied to full-thickness skin defects. Overall, all the results showed that PVA/CMC/PEG hydrogel had the exceptional potential for wound dressings. (55)

Uppuluri et al proposed a 7, 8- Dihydroxy flavone loaded PVA/Agar Hydrogels as a promising approach for regenerating skin tissue which had multiple advantages over the existing treatments. Moreover, the characterization studies demonstrated about the ideal hemocompatibility and invitro drug release potential of this hydrogel scaffold. Further, the histological staining's carried out on the hydrogel scaffold provided significant evidence for its potential in reepithelialisation and revascularization. Finally, from these findings it was identified that 7, 8- Dihydroxy flavone loaded PVA/Agar Hydrogels acts as a promising candidate for fastening the tissue regeneration process in case of skin tissue defects.(56)

Polyethylene glycol (PEG)

Polyethylene glycol played a significant role in wound healing concepts, because of its ideal biocompatible, viscoelastic and moisture retention characteristics. As part of an effort to discover a formulation that would accelerate wound healing, Sh Ahmed et al. conducted an in vivo analysis in rabbits to assess the wound healing potential of asiaticoside loaded hydrogel. It was demonstrated that the hydrogel formulation induced no irritation on the rabbit skin and that the wounds healed faster than those without treatment (i.e., 15% faster than the commercial cream and more than 40% faster than the wounds washed without treatment). The skin showed signs of healing

in all wounds, with thick epithelial and keratinized layers and moderate amounts of granulation tissue, fibroblasts, and collagen forming, but no fibrinoid necrosis was apparent. Finally, the asiaticoside rich PVA/ PEG hydrogel proved to be an ideal candidate for wound healing because of its excellent reepithelization and revascularization potential. (57)

It is challenging to deliver genetic materials into cells or tissues of interest since they are susceptible to nucleases degradation, do not penetrate cell membranes, and have a short half-life in vivo, severely limiting their use in therapeutics. Le et al. fabricated a pH- and temperature-sensitive in situ-forming injectable hydrogel depot that could deliver DNA-bearing polyplexes for multiple purposes in biomedicine. Under physiological conditions, polymer sols flowed into gels at low temperatures. Two months after applying the hydrogels to SD rats, the PEG-PSMEU copolymer hydrogel was discovered to be bioresorbable. Due to this fact, this smart hydrogel is expected to deliver DNA, among other therapeutic genetic materials, continuously. Hydrogels based on PEG-PSMEU copolymers showed excellent adhesion to a wide range of hydrophilic, hydrophobic, and metal substrates, making them an ideal biomedical material suited to several biomedical applications. By applying PEG-PSMEU copolymer adhesive hydrogels loaded with polyp Lex, wounds were sealed, wound exudates were absorbed, and wound tissues were regenerated. As a result, PEG-PSMEU copolymer has potential in many biomedical applications due to its pH- and temperature-adjust ability. Hydrogels can also be used for other biomedical purposes, including controlled delivery, tissue adhesive, and engineering, simply by mixing therapeutic agents with PEG-PSMEU copolymer hydrogels. (58)

By modifying cellulose derivatives with citric acid (CA) and PEG, Capanema et al. develop eco-friendly and biocompatible wound dressings and skin substitutes. Results showed that superabsorbent hydrogels (SAP) could vary degrees of swelling, from 100% to 5000%, according to the degree of substitution of CMC, the length of cross-linking with CA, and the addition of PEG. MTT, an in vitro test, indicated that these hydrogels showed no sign of cytotoxicity (HEK297T). In order to achieve SAP hydrogels with tunable properties through cross-linking, these matrices had to absorb large volumes of water without causing permanent degradation. It makes them exciting as promising superabsorbent hydrogels with a key role as skin replacements for chronic wounds. In particular, they are seen as the next generation of wound healing agents. (59)

Biomaterial implants need an immune response to function properly, especially when it comes to vascularization, transplantation, and survival. In contrast to direct delivery of influential growth factors, immuno-regenerative approaches can recruit the innate immune cells that help coordinate healing, resulting in long-lasting therapeutic effects. The material's physical properties can be engineered to optimize the recruitment of pro-regenerative leukocyte subsets that mature into corresponding wound-healing macrophages to fabricate immune-smart materials. Ogle et al. demonstrate that SDF-1α or FTY720 delivered in vivo separately stimulate Ly-6Clow monocyte recruitment and that co-delivery promotes maturation and recruitment of pro-regenerative CD206 + macrophages to regulate micro vascular network remodelling in vivo. This study demonstrates that by combining dual affinity biomaterials utilizing distinct signalling modules, it is possible to design biomaterials with the ability to control specific therapeutic immunity cell types. The aHep-N-PEG-DA platform also offers a flexible tool for utilizing the expanding knowledge of local bioactive lipid signalling in biomaterial-induced inflammation and evaluating how such signalling works in concert with proteins.(60)

Table 2. Depicts the application of various polymers in skin tissue engineering concept.

Name of the Polymer	Application	Reference
Poly (N-isopropyl acrylamide)	PNIAPAAM hydrogel is soft, has a large amount of water, and is suitable for the encapsulation of growth factors, nanoparticles and drug molecules which require soft viscoelastic behaviour to avoid organ injury, and a high solvent swelling for compatibility with living systems.	(39-43)
Hyaluronic acid	Adaptable, biomimetic, and reversible, characteristics of the hyaluronic polymer based hydrogels fastened the skin tissue regeneration process.	(44-48)
Pullulan	Pullulan has many benefits of a natural polysaccharide, in addition to its ideal swelling and antioxidant characteristics, its unique chemical structure also makes pullulan capable of forming strong, resilient hydrogels for effective tissue regeneration at the site of tissue defects.	(49-52)
PVA	Because of their ideal biocompatibility, and mechanical characteristics, poly (vinyl alcohol) (PVA) hydrogels played a significant role in skin tissue engineering concepts.	(53-56)
PEG	Due to its ideal hydrophilicity, biocompatibility and minimal cytotoxic characteristics PEG based hydrogels plays a significant role in fastening the wound healing process in case of skin tissue defects.	(57-60)

CONCLUSION

Recent advances have improved our general knowledge regarding the feasibility of using biodegradable hydrogels in skin tissue research. Nevertheless, more focus needs to be done on the studies that demonstrate these systems' potential as convenient, adaptable, and safe treatments for skin tissue defects. Furthermore, taking the first step in clinical trials where application of wide range of optimized hydrogels to patients is vital for future translational approaches that can provide in-vivo systems capable of improving skin tissue repair in a short time frame.

FUNDING INFORMATION

The authors didn't receive any kind of funding for the publication of this work.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ACKNOWLEDGMENT

The authors are thankful to Vels Institute of Science, Technology & Advanced Studies (VISTAS), Chennai, for the facilities extended.

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How to cite this article

Varuna Naga Venkata Arjun Uppuluri, Shanmugarajan T.S., Sai Krishna. Bhimavarapu, Lokesh E, 2021. “Recent advances in polymeric hydrogel scaffolds for skin tissue engineering and regenerative medicine: A comprehensive review”. Jour. of Med. P’ceutical & Allied. Sci. V 10 - I 5, 1569, P- 3698-3706. doi: 10.22270/ jmpas.V10I5.1569