Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

The application of nano-hydrogels and hydrogels in wound dressings

Masoumeh Ghorbani[1], Fatemeh Ghorbani[2], Sepehr Kahrizi[3], Hossein Naderi-Manesh[4], Danial Kahrizi[5*]

[1] Nanobiotechnology Department, Faculty of Innovative Science and Technology, Razi University, Kermanshah, Iran
[2] Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran
[3] School of Medicine, Islamic Azad University, Qeshm Branch, Qeshm, Iran
[4] Department of Nanobiotechnology, Faculty of Biological Sciences, Tarbiat Modares University, Tehran 14115-154, Iran
[5] Agricultural Biotechnology Department, Faculty of Agriculture, Tarbiat Modares University, Tehran, Iran

ARTICLE INFO

Review

Article history:
Received: June 28, 2023
Accepted: November 09, 2023
Published: November 15, 2023

Keywords:

Hydrogel, nanohydrogel, wound healing, wound dressing

ABSTRACT

Wounds and the healing process are one of the main concerns of medical science today. A wound is any loss of integrity, or rupture of the layers of skin (epidermis, dermis, and hypodermis) or subcutaneous tissue caused by physical factors (surgical incision, trauma, pressure, and gunshot wounds) or chemical factors (acid burns). It is observed that soft tissue, muscle, or bone is involved in occurrences of wounds. Lesions and fractures of the skin surface necessitate medical attention, wherein dressings expedite the healing process by establishing a physical barrier between the wound and the external environment, thereby preventing further injury or infection. Hydrogel dressings create a moist environment that facilitates common healing steps, such as granulation hyperplasia, epidermal repair, and removal of excess dead tissue. The limited adhesion of the hydrogel and the hydrated wound bed allows for easy removal of the dressing without secondary damage, thereby significantly reducing the discomfort and risk of infection during dressing changes. These modern, wet dressings foster a moist healing environment by absorbing excess inflammatory secretions and allowing proper passage of steam and air, which expedites the healing process. In this analysis, the utilization of hydrogels as wound dressings is briefly presented.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.11.19

Introduction

The skin is the largest organ of the human body that protects it from the external environment (1). Wounds occur when the natural structure and function of the skin are damaged (2). In this process, peripheral blood mononuclear cells, resident skin cells, extracellular matrix, cytokines, chemokines, growth factors, and regulatory molecules participate in the wound healing process (3). Chronic ulcers are generally caused by decubitus ulcers, leg ulcers, and burns. Wound healing is a dynamic and complex process of tissue regeneration and growth progression in four different stages (a) coagulation and homeostasis (immediately after injury). (b) The inflammatory stage (shortly after tissue damage) during which swelling occurs. (c) the reproductive period, in which new tissues and blood vessels are formed, and (d) the stage of puberty, in which new tissues are regenerated (4-7). On the other hand, chronic wounds do not progress in the normal stages of healing and cannot be repaired in a timely and regular manner (7). Today's "gold standard" treatments mainly include full-thickness skin grafts, as well as skin flaps, skin extension techniques, and skin replacements (8-10). However, the serious problems associated with the above methods are usually the lack of donor site and hypertrophic or colloidal scars, which eventually lead to severe functional and psychosocial problems (11, 12). In recent decades, various bioengineering and synthetic alternatives have been developed that are generally located within the damage and provide barrier function along with protection against microorganisms, reduction of wound pain, and promotion of wound healing by tissue regeneration (13-15). These skin grafts represent a heterogeneous group of wound dressings that can be placed on the wound site to temporarily or permanently replace skin functions, depending on the characteristics of the product (16). Dermal substitutes can be categorized into two primary classifications, namely biological and artificial substitutes. The former exhibits a more preserved extracellular matrix architecture, while the latter can be artificially synthesized upon requirement (17). Recently, hydrogels have been considered one of the promising materials for wound dressing (18). Hydrogels are extensively employed in wound healing due to their resemblance to the native extracellular matrix (ECM) and their capacity to generate a moist environment (19). This review article discusses the types of hydrogels and nanohydrogels, their properties, and their application in wound healing.

Skin structure and function

The skin comprises three layers, the epidermis, the dermis, and the hypodermis, all of which are different in anatomy and function. The structure of the skin is composed of a complex network that acts as the body's primary barrier against pathogens, ultraviolet rays, chemicals, and mecha-

* Corresponding author. Email: dkahrizi@modares.ac.ir

nical damage (20). It is also involved in immunological monitoring, sensory perception, control of imperceptible fluid loss, and general homeostasis. The skin is also very compatible with different thicknesses and specialized functions in other body parts (21, 22).

Skin wounds

Wounds are attributable to a diverse range of causative agents, comprising surgical interventions, traumas, extraneous factors (including but not limited to compression, thermal burns, and lacerations), or pathological states such as diabetes or vascular disorders. These injuries are categorized as either acute or chronic wounds, contingent upon the underlying etiology and resultant implications (23). Skin wound healing demonstrates a unique cellular mechanism of action that is unique and involves the interaction of several cells, growth factors, and cytokines (24). The process of regeneration is characterized by a series of sequential steps that are subject to regulation by gene expression through autocrine or paracrine mechanisms. The cessation of active operations is accomplished using gene deactivation as the regeneration process progresses (25). In the initial few minutes following an injury, blood platelets adhere to one other and the wound site. Platelets become amorphous when they come into contact with collagen, resulting in activation and accumulation. Furthermore, thrombin is synthesized, which initiates the coagulation cascade (26, 27).

Types of wounds

Wounds are typically categorized as either acute or chronic (28). Acute wounds, which include traumatic and surgical wounds, progress through the standard stages of wound healing, resulting in an anticipated and systematic tissue repair sequence (29). Conversely, chronic ulcers are characterized by an irregular healing process and can be primarily classified as vascular ulcers (including venous and arterial ulcers), diabetic ulcers, and pressure ulcers (30). The fundamental physical indications of chronic wounds, such as discharge, persistent infection, and necrosis, contribute to the complexity of wound management and care (31). Although these different unhealed wounds may have other causes, they all have common wound characteristics, such as elevated protease levels, increased inflammatory cytokines, stable oxygen species (ROS), the presence of aging fibroblasts, long-term infection, and cells inefficient and inadequate (32).

Wound Dressings

Dry wounds were used to treat wounds until the mid-1970s. Dry (traditional) dressings, which are more common in Third World countries, do not have many of the characteristics of an ideal dressing. These dressings adhere to the wound bed, causing pain and tissue damage again when the dressing is removed. Dry dressings cannot create and maintain a moist environment that is very effective in speeding up the wound healing process. The use of these dressings is limited to conditions where the wound is dry and clean or used only as a secondary dressing. In 1969, Winter concluded in his clinical observations that in most wounds exposed to the open air, a scab forms around the wound that covers the wound and prevents the production of epidermal cells. Delays wound healing (33). Recent studies have shown that wound healing occurs faster in humid environments than in dry environments (34). It has also minimized the time it takes for the wound to heal. Wet dressings (modern), by creating additional inflammatory secretions and proper passage of steam and air, make a moist healing environment for the wound, which increases the speed of healing (35).

Regardless of the severity of the wound, it is essential to take care of it according to the recommendations of the wound care professional. The difference between using a bandage and dressing should be considered. Dressings are designed to be applied to the wound while bandages hold the dressings in place (36). In the event of a wound is sealed with a dressing, it is subjected to a consistent exposure of proteinases, chemotactic agents, supplements, and growth factors that are devastated in the proximity of the wound. Consequently, during the latter half of the twentieth century, the development of occlusive dressings was initiated to safeguard and establish a damp environment for wounds. These dressings have been observed to expedite epithelialization, and collagen synthesis, and promote angiogenesis by inducing hypoxia in the wound bed and lowering the pH of the wound bed, which in turn curbs wound infection (37).

Hydrogel

Polymers are considered one of the most essential sources for the production of wound dressings. Depending on the characteristics and needs of wounds, various types of biological and synthetic polymer dressings have been developed (38). The use of synthetic polymers such as polyurethane, polyester, and polylactic acid is less considered due to limitations such as low moisture absorption, inability to separate them from new tissue, and slow wound healing (39). In contrast, polymers of natural origin such as alginate, chitosan, collagen, hyaluronic acid, and cellulose, which are highly biodegradable and biodegradable due to their high compatibility and biodegradability, are particularly valuable in some cases. Alginate has moist wound-healing properties (40-44). Hydrogels are hydrophilic polymers with a three-dimensional lattice structure that swell rapidly in water, become semi-solid, retain large amounts of water, and are slightly degraded in the laboratory for some time. In general, the water content of the hydrogel matrix is more than 90%, which provides good conditions for maintaining a humid environment (37, 45, 46). In contrast to other biomaterial varieties, hydrogels possess several advantages, including heightened biocompatibility, biodegradability, appropriate mechanical strength, and a porous structure, among others (47). Owing to the hydrogels' characteristics, such as their high water content, soft and rubbery consistency, and low surface tension with water or biological fluids, these materials are anticipated to be viable substitutes for natural tissues (48).

Types of hydrogels

Hydrogels can be classified as natural, synthetic, or a combination of both. Hydrogels obtained from natural polymers are classified as natural polymer hydrogels (49). Natural and synthetic derivative polymers can be converted to hydrogels, from polymers formed by physical entanglement to polymers stabilized by covalent crosslinking. Hydrogels may be further adapted to integrating chemically and biologically active identifying moieties, such as molecules that respond to stimuli and growth factors that enhance their function (50-52). Natural hydrogels, such as collagen, silk fibroin, hyaluronic acid, chitosan, alginate, and tissue-derived hydrogels, possess unique properties, including biocompatibility, biodegradability, low cytotoxicity, the potential to transform hydrogels into injectable gels, and physiological environment similarity. Nevertheless, natural hydrogels exhibit certain limitations, such as weak mechanical properties and inconsistency across batches, which render them difficult to control. Consequently, natural hydrogels are frequently combined with synthetic hydrogels to create composite polymers and remain a subject of extensive experimentation (53, 54). Hydrogels are typically founded on the attributes of side groups (ionic or nonionic), structural facets (homo or copolymer), physical constitution (crystalline, amorphous, supermolecular), and receptiveness to a plethora of extrinsic stimuli, including temperature and PH. These gels can be categorized accordingly (55).

Applications of hydrogels

The adaptability of the hydrogel system has led to its wide range of applications in various fields, including biomedicine (48). For example, when a hydrogel is formed with suitable stiffness and bioactive parts, it modulates the behavior of embedded cells (56, 57). Many hydrogels can increase the shelf life of drugs due to their adhesive and bioadhesive properties, which makes them suitable candidates for drug carriers (58). Since the properties of hydrogels can be manipulated by a variety of chemical methods, their logical design and engineering have led to the introduction of new methods for the delivery of small molecules (59, 60), proteins (61, 62), and cells (63). As tissue engineering scaffolds to guide cell destiny/lineage (64), stem cell expansion (65-68) and tissue regeneration have been (69, 70).

Nanohydrogels

Depending on the method used to synthesize the hydrogels and the type of molecules, used, and the connections between the molecules, the hydrogels can be divided into two groups: macro hydrogels and nanohydrogels. If the hydrogel is formed based on intermolecular bonds, it will have macroscopic dimensions; if the hydrogel is formed based on intramolecular bonds, nanohydrogels will be formed. Nanohydrogels are nanoparticles whose properties are a combination of the properties of hydrogels and nanoparticles. Such nanoparticles have unique properties due to their size. These include high availability surface, physical and chemical resistance, remarkable durability, high load capacity, biocompatibility, and flexibility. In recent years the development of intelligent particles has been considered. Depending on the type of molecules that make them up and their properties, nanohydrogels can be used in various fields of drug delivery and release, treatment of diseases such as diabetes, brain tumors, infectious diseases, tissue engineering and repair, and gene therapy. Such nanoparticles can also be used in various industries, including textiles, cosmetics, and agriculture (71-73).

An overview of nano-hydrogel synthesis methods

The methods of synthesis of nanohydrogels are very diverse. In a general classification, these methods can be divided into two categories: chemical and physical. Chemical methods are methods in which nanohydrogels are formed based on intramolecular bonds, which are usually of the covalent type. The basis of physical methods is also intermolecular bonds of the physical type, such as hydrogen bonds and electrostatic forces. In addition to the general classification, physical and chemical methods also have different classifications. One of the chemical methods for the synthesis of nanohydrogels is the use of the nano-microemulsion polymerization method. Using this method, the size of the synthesized nanohydrogels can be well controlled. In this method, polymerization of nanohydrogels is performed inside the nano microemulsion cores of oil in the aqueous medium, and reverse polymerization, and encapsulation is performed within the nano microemulsion cores of water in an oil medium. Other chemical methods for the synthesis of nanohydrogels include top-down lithographic methods and liposome-based nanoparticles. In the division of physical methods, we come across various methods, including the synthesis of self-accumulated nanohydrogels by dual-friendly polymers and the synthesis of self-accumulated nanohydrogels by convergent polymers (74-76).

Advantages and limitations of nanohydrogels

To work with nanohydrogels, it is necessary to be well acquainted with the advantages of this type of nanoparticles and their limitations to have the best choice for their use in therapeutic applications, because sometimes we may encounter their side effects during the treatment process. One of the significant advantages of nanohydrogels is their high biocompatibility and biodegradability. Such particles can encapsulate hydrophilic and hydrophobic drugs. The polymer networks in nanohydrogels control their loading and prevent their untimely release. The inflatability of nanohydrogels can be controlled by factors such as temperature, pH, ionic strength, monomer concentration, and surface charge density. In addition to these advantages, it is necessary to point out some significant limitations. Nanohydrogels have certain limitations and capacities in the amount of drug-loaded. In addition, sometimes monomers, and surface activators that are used in the structure of nanohydrogels are possible Can cause side effects. And removing them from the environment faces challenges (77-79).

Application of nano hydrogel in wound healing

Burn is one of the most complex injuries, and its treatment is challenging. Various factors such as physical, chemical, and even radiation can cause it. In addition to different treatment methods such as surgery for damaged tissue, care of burn wounds is an essential part of treatment. The use of silver nanohydrogels due to their antibacterial properties and resistance to therapeutic drugs can heal wounds and They are effective in preventing infection. In fact, silver nanohydrogels prevent infection of wounds by inactivating the thiol groups in bacteria and can increase the effectiveness of treatment. They are also used for purposes related to tissue engineering. Using nanohydrogels and combining them with specific cells or proteins, an extracellular matrix can be prepared to repair damaged tissues (80-82).

Application of hydrogels in wound healing

Hydrogel dressings produce a moist wound environment, facilitating normal healing phases, including granulation hyperplasia, epidermal restoration, and dead tissue clearance. The hydrogel's reduced adherence to the hydrated wound bed allows the dressing to be removed without causing additional injury, considerably lowering pain and the risk of infection associated with dressing changes (83, 84). A hydrogel patch can be used to treat burn wounds in any mix of the following ways: (a) it can stop germs from growing in the wound, (b) it can deliver drugs that speed up the healing process, and (c) it can keep the wound moist, which reduces pain (85). In a humid environment, the high water content of hydrogels (70-90%) promotes granulation and epithelial tissues. The hydrogels' soft elasticity allows for simple application and removal following wound healing without causing any harm. Hydrogels, which have a soothing and cooling effect, lower the temperature of skin wounds. Hydrogels treat chronic dry, necrotic, pressure ulcer, and burn wounds (86). Hydrogel dressings are appropriate for all four phases of wound healing except infected wounds and extensive drainage. Non-irritating hydrogel dressings are metabolite permeable and non-reactive with biological tissue. Many studies have shown that hydrogel dressings may help cure persistent foot ulcers. The issue with hydrogel dressings is that exudate buildup encourages bacterial soaking and proliferation, resulting in a foul odor in the wounds. Furthermore, the poor mechanical strength of hydrogels makes them difficult to deal with (7). Hydrogel wound dressings and creams may aid in wound healing and positively impact the end outcome. Intelligent wound hydrogels allow for real-time monitoring and the transfer of bioactive compounds (87). Non-adhesion, moisture retention, gas permeability, secretion absorption, biocompatibility, and patient comfort make hydrogels appropriate for healing deep wounds. Furthermore, they contain an extracellular matrix structure comparable to skin tissue, enable cell migration, and may promote partial tissue regeneration. Hydrogels' intrinsic qualities may be enhanced by including active chemicals like antibiotics, nanoparticles, stem cells, and growth hormones, which is a major benefit. Hydrogels that change shape in response to stimuli might be used to deliver controlled medications or track healing progress (88, 89). The dressing must be non-toxic and non-allergenic to reach the wound surface to not cause an immune response at the wound site. It is also important not to damage the wound after removal. It must be resistant to bacteria, allow the exchange of gas and water vapor, and be economical on a large scale. Therefore, one of the most widely used hydrogels is wound healing (1).

Application of hydrogel in wound medicine

Due to the unique properties of hydrogels, such as non-toxicity, high water content, high oxygen permeability, improved biocompatibility, ease of loading and releasing drugs, structural diversity, and no immune response at the wound site (90, 91), antibiotic-containing hydrogels are used in several wound healing conditions. Stem cells can be sent to a wound spot with the help of hydrogels. They are an excellent option for transportation cars because they make stem cells at the cut site live longer. This quality comes from the fact that certain hydrogels can help cells join and stimulate stem cell activity by keeping regular groups together. The initial growth of stem cells within hydrogels in vitro enhances these features, as seen by displaced cells at the wound site for more than 11 days following transplantation (92-96). In addition to transporting bioactive substances, hydrogels can also transport heparin, hyaluronic acid, and ibuprofen. Hydrogels must have excellent immunity, antibacterial resistance, loading capacity, and simple drug release. It must be able to keep its characteristics for an extended period since certain wounds must be treated for an extended period (97-100).

Discussion and conclusion

The usefulness of hydrogels as biomaterials stems from their elastic physical qualities, ability to contain tiny molecules and macromolecular medicines, ability to retain water, flexibility, and regulated biodegradability. Hydrogels may be made with a variety of characteristics. They may be made from biostable, bioabsorbable, and biodegradable polymer matrices with mechanical parts and swelling levels appropriate for the purpose. Because of their distinguishing characteristics, they have a potential future in drug delivery systems, applied biomedicine, and tissue engineering in wound healing.

References

1. Tavakoli S, Klar AS. Advanced hydrogels as wound dressings. Biomolecules. 2020;10(8):1169.
2. Ibrahim NI, Wong SK, Mohamed IN, Mohamed N, Chin K-Y, Ima-Nirwana S, et al. Wound healing properties of selected natural products. Int J Environ Res Public Health. 2018;15(11):2360.
3. Cañedo-Dorantes L, Cañedo-Ayala M. Skin acute wound healing: a comprehensive review. International Int J Inflam. 2019.
4. Dowsett C, Newton H. Wound bed preparation: TIME in practice. WOUNDS UK. 2005;1(3):58.
5. Vanwijck R. Surgical biology of wound healing. Bull Mem Acad R Med Belg. 2001;156(3-4):175-184.
6. Hunt TK, Hopf H, Hussain Z. Physiology of wound healing. Adv Skin Wound Care. 2000;13:6.
7. Selvaraj D, Viswanadha VP, Elango S. Wound dressings—A review. BioMedicine. 2015;5:22.
8. Schiestl C, Stiefel D, Meuli M. Giant naevus, giant excision, eleg (i) ant closure? Reconstructive surgery with Integra Artificial Skin® to treat giant congenital melanocytic naevi in children. J Plast Reconstr Aesthet Surg. 2010;63(4):610-615.
9. Schiestl C, Neuhaus K, Biedermann T, Böttcher-Haberzeth S, Reichmann E, Meuli M. Novel treatment for massive lower extremity avulsion injuries in children: slow, but effective with good cosmesis. Eur J Pediatr Surg. 2011;21(02):106-110.
10. Böttcher-Haberzeth S, Kapoor S, Meuli M, Neuhaus K, Biedermann T, Reichmann E, et al. Osmotic expanders in children: no filling–no control–no problem? Eur J Pediatr Surg. 2011;21(03):163-167.
11. Barbour JR, Schweppe M, Seung-Jun O. Lower-extremity burn

reconstruction in the child. J Craniofac Surg. 2008;19(4):976-988.

12. Berman B, Viera MH, Amini S, Huo R, Jones IS. Prevention and management of hypertrophic scars and keloids after burns in children. J Craniofac Surg. 2008;19(4):989-1006.
13. Alonso L, Fuchs E. Stem cells of the skin epithelium. Proc Natl Acad Sci U S A. 2003;100(suppl 1):11830-11835.
14. Clark R. a F., Ghosh, K., & Tonnesen, MG. Tissue engineering for cutaneous wounds J Invest Dermatol. 2007;127(5):1018-1029.
15. Komal V, Atul C, Shweta T, Saurabh D, Rajnish S, Shreekumar P. Advances in Skin Regeneration Using Tissue Engineering. Int J Mol Sci. 2017;18(4): 789.
16. Augustine R, Kalarikkal N, Thomas S. Advancement of wound care from grafts to bioengineered smart skin substitutes. Prog Biomater. 2014; 3: 103–113..
17. Halim AS, Khoo TL, Yussof SJM. Biologic and synthetic skin substitutes: an overview. Indian J Plast Surg. 2010;43(S 01):S23-S8.
18. Zhao X, Sun X, Yildirimer L, Lang Q, Lin ZYW, Zheng R, et al. Cell infiltrative hydrogel fibrous scaffolds for accelerated wound healing. Acta Biomater. 2017;49:66-77.
19. Asadi N, Pazoki-Toroudi H, Del Bakhshayesh AR, Akbarzadeh A, Davaran S, Annabi N. Multifunctional hydrogels for wound healing: Special focus on biomacromolecular based hydrogels. Int J Biol Macromol. 2021;170:728-750.
20. Island T. StatPearls Publishing; 2020 Jan. PMID.
21. Maranduca MA, Branisteanu D, Serban DN, Branisteanu DC, Stoleriu G, Manolache N, et al. Synthesis and physiological implications of melanic pigments. Oncol Lett. 2019;17(5):4183-4187.
22. Someya T, Amagai M. Toward a new generation of smart skins. Nat Biotechnol. 2019;37(4):382-388.
23. Karimi K, Odhav A, Kollipara R, Fike J, Stanford C, Hall JC. Acute cutaneous necrosis: A guide to early diagnosis and treatment. J Cutan Med Surg. 2017;21(5):425-437.
24. Tottoli EM, Dorati R, Genta I, Chiesa E, Pisani S, Conti B. Skin wound healing process and new emerging technologies for skin wound care and regeneration. Pharmaceutics. 2020;12(8):735.
25. Erickson JR, Echeverri K. Learning from regeneration research organisms: The circuitous road to scar free wound healing. Dev Biol. 2018;433(2):144-154.
26. Yun S-H, Sim E-H, Goh R-Y, Park J-I, Han J-Y. Platelet activation: the mechanisms and potential biomarkers. Biomed Res Intl, 2016.
27. Rasche H. Haemostasis and thrombosis: an overview. Eur Heart J Suppl. 2001;3(suppl_Q):Q3-Q7.
28. Vickers NJ. Animal communication: when i'm calling you, will you answer too? C Curr Biol. 2017;27(14):R713-R5.
29. Lindholm C, Searle R. Wound management for the 21st century: combining effectiveness and efficiency. Int Wound J. 2016;13:5-15.
30. Mustoe T. Understanding chronic wounds: a unifying hypothesis on their pathogenesis and implications for therapy. Am J Surg. 2004;187(5):S65-S70.
31. Widgerow AD, King K, Tocco-Tussardi I, Banyard DA, Chiang R, Awad A, et al. The burn wound exudate—An under-utilized resource. Burns. 2015;41(1):11-17.
32. Uccioli L, Izzo V, Meloni M, Vainieri E, Ruotolo V, Giurato L. Non-healing foot ulcers in diabetic patients: general and local interfering conditions and management options with advanced wound dressings. J Wound Care. 2015;24(Sup4b):35-42.
33. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. Nature. 1962;193(4812):293-294.
34. Boateng J, Catanzano O. Advanced therapeutic dressings for effective wound healing—a review. J Pharm Sci. 2015;104(11):3653-3680.
35. Delmar K, Bianco-Peled H. Composite chitosan hydrogels for extended release of hydrophobic drugs. Carbohydr Polym. 2016;136:570-580.
36. Daunton C. Kothari S. Smith L, Steele D. A history of materials and practices for wound management. Wound Pract Res J Austr Wound Manag Assoc. 2012; 20(4):174-176.
37. Li H, Yang J, Hu X, Liang J, Fan Y, Zhang X. Superabsorbent polysaccharide hydrogels based on pullulan derivate as antibacterial release wound dressing. Wound Pract. Res A. 2011;98(1):31-39.
38. Broussard KC, Powers JG. Wound dressings: selecting the most appropriate type. Am J Clin Dermatol. 2013;14(6) : 449-459.
39. Mogoşanu GD, Grumezescu AM. Natural and synthetic polymers for wounds and burns dressing. Int J Pharm. 2014;463(2):127-136.
40. Ren K, He C, Xiao C, Li G, Chen X. Injectable glycopolypeptide hydrogels as biomimetic scaffolds for cartilage tissue engineering. Biomaterials. 2015;51:238-249.
41. Gong Y, Wang C, Lai RC, Su K, Zhang F, Wang D-a. An improved injectable polysaccharide hydrogel: modified gellan gum for long-term cartilage regeneration in vitro. J Mater Chem. 2009;19(14):1968-1977.
42. Bidarra SJ, Barrias CC, Granja PL. Injectable alginate hydrogels for cell delivery in tissue engineering. Acta Biomater. 2014;10(4):1646-1662.
43. Akmal M, Singh A, Anand A, Kesani A, Aslam N, Goodship A, et al. The effects of hyaluronic acid on articular chondrocytes. J Bone Joint Surg Br. 2005;87(8):1143-1149.
44. Liu M, Zeng X, Ma C, Yi H, Ali Z, Mou X, et al. Injectable hydrogels for cartilage and bone tissue engineering. Bone Res. 2017;5(1):1-20.
45. Caló E, Khutoryanskiy VV. Biomedical applications of hydrogels: A review of patents and commercial products. Eur. Polym. J. 2015;65:252-267.
46. Tyeb S, Kumar N, Kumar A, Verma V. Flexible agar-sericin hydrogel film dressing for chronic wounds. Carbohydr Polym. 2018;200:572-582.
47. Chai Q, Jiao Y, Yu X. Gels, 2017; 3 (1): 6.
48. Bajpai AK, Shukla SK, Bhanu S, Kankane S. Responsive polymers in controlled drug delivery. Prog. Polym. Sci. 2008;3911):1088-1011.
49. Bashir S, Hina M, Iqbal J, Rajpar A, Mujtaba M, Alghamdi N, et al. Fundamental concepts of hydrogels: Synthesis, properties, and their applications. Polymers (Basel). 2020;12(11):2702.
50. Burdick JA, Murphy WL. Moving from static to dynamic complexity in hydrogel design. Nat Commun. 2012;3(1):1-8.
51. Nichol JW, Koshy ST, Bae H, Hwang CM, Yamanlar S, Khademhosseini A. Cell-laden microengineered gelatin methacrylate hydrogels. Biomaterials. 2010;31(21):5536-5544.
52. Hoffman A. Hydrogel biomedical articles. Adv Drug Deliv Rev. 2002;54(90):3-12.
53. Catoira MC, Fusaro L, Di Francesco D, Ramella M, Boccafoschi F. Overview of natural hydrogels for regenerative medicine applications. J Mater Sci Mater Med. 2019;10(30):10-11.
54. Jabbari E, Leijten J, Xu Q, Khademhosseini A. The matrix reloaded: the evolution of regenerative hydrogels. Mater. today. 2016;19(4):190-196.
55. Jacob S, Nair AB, Shah J, Sreeharsha N, Gupta S, Shinu P. Emerging role of hydrogels in drug delivery systems, tissue engineering and wound management. Pharmaceutics. 2021;13(3):357.
56. Engler A, Sen S. Sweeney hl, Discher DE. Matrix elasticity directs stem cell lineage specification cell. 2006;126:677-689.
57. Huebsch N, Arany P, Mao A, Shvartsman D. O. a. Ali, S. a. Bencherif, J. Rivera-Feliciano and DJ Mooney. Nat Mater.

2010;9:518-526.
58. Nezhad-Mokhtari P, Ghorbani M, Roshangar L, Rad JS. A review on the construction of hydrogel scaffolds by various chemically techniques for tissue engineering. Eur. Polym. 2019;117:64-76.
59. Liechty WB, Scheuerle RL, Vela Ramirez JE, Peppas NA. Uptake and function of membrane-destabilizing cationic nanogels for intracellular drug delivery. Bioeng Transl Med. 2019;4(1):17-29.
60. Clegg JR, Irani AS, Ander EW, Ludolph CM, Venkataraman AK, Zhong JX, et al. Synthetic networks with tunable responsiveness, biodegradation, and molecular recognition for precision medicine applications. Sci Adv. 2019;5(9):eaax7946.
61. Gawade PM, Shadish JA, Badeau BA, DeForest CA. Boolean Biomaterials: Logic-Based Delivery of Site-Specifically Modified Proteins from Environmentally Responsive Hydrogel Biomaterials (Adv. Mater. 33/2019). Adv Mater. 2019;31(33):1970237.
62. Shadish JA, Strange AC, DeForest CA. Genetically encoded photocleavable linkers for patterned protein release from biomaterials. J Am Chem Soc. 2019;141(39):15619-15625.
63. Drury JL, Mooney DJ. Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials. 2003;24(24):4337-4351.
64. Engler AJ, Sen S, Sweeney HL, Discher DE. Matrix elasticity directs stem cell lineage specification. Cell. 2006;126(4):677-689.
65. Rao VV, Vu MK, Ma H, Killaars AR, Anseth KS. Rescuing mesenchymal stem cell regenerative properties on hydrogel substrates post serial expansion. Bioeng Transl Med. 2019;4(1):51-60.
66. Mahadik BP, Bharadwaj NA, Ewoldt RH, Harley BA. Regulating dynamic signaling between hematopoietic stem cells and niche cells via a hydrogel matrix. Biomaterials. 2017;125:54-64.
67. Nguyen EH, Daly WT, Le NNT, Farnoodian M, Belair DG, Schwartz MP, et al. Versatile synthetic alternatives to Matrigel for vascular toxicity screening and stem cell expansion. Nat Biomed Eng. 2017;1(7):1-14.
68. Wang X, Maruotti J, Majumdar S, Roman J, Mao HQ, Zack DJ, et al. Collagen vitrigels with low-fibril density enhance human embryonic stem cell-derived retinal pigment epithelial cell maturation. J Tissue Eng Regen Med. 2018;12(3):821-829.
69. Yue K, Liu Y, Byambaa B, Singh V, Liu W, Li X, et al. Visible light crosslinkable human hair keratin hydrogels. Bioeng Transl Med. 2018;3(1):37-48.
70. Almeida H, Domingues RM, Mithieux SM, Pires RA, Gonçalves AI, Gomez-Florit M, et al. Tropoelastin-coated tendon biomimetic scaffolds promote stem cell tenogenic commitment and deposition of elastin-rich matrix. ACS Appl Mater Interfaces. 2019;11(22):19830-19840.
71. Guerrero-Ramírez L, Nuno-Donlucas S, Cesteros L, Katime I. Smart copolymeric nanohydrogels: Synthesis, characterization and properties. Mater Chem Phys. 2008;112(3):1088-1092.
72. Yuan F, Ma M, Lu L, Pan Z, Zhou W, Cai J, et al. Preparation and properties of polyvinyl alcohol (PVA) and hydroxylapatite (HA) hydrogels for cartilage tissue engineering. Cell Mol Biol. 2017;63(5):32-35.
73. Del Prado-Audelo ML, Gómez-Zaldivar FJ, Pérez-Díaz M, Sánchez-Sánchez R, González-Torres M, González-Del Carmen M, et al. Radiation-induced graft polymerization of elastin onto polyvinylpyrrolidone as a possible wound dressing. Cell Mol Biol. 2021;67(1):64-72.
74. Godoy-Alvarez FK, González-Torres M, Giraldo-Gomez DM, Sánchez-Sánchez R, Pérez-Díaz MA, González-Del Carmen M, et al. Synthesis by gamma irradiation of hyaluronic acid-polyvinyl alcohol hydrogel for biomedical applications. Cell Mol Biol. 2021;67(1):58-63.
75. Sasaki Y, Akiyoshi K. Nanogel engineering for new nanobiomaterials: from chaperoning engineering to biomedical applications. Chem Rec. 2010;10(6):366-376.
76. Cortes H, Caballero-Florán IH, Mendoza-Muñoz N, Escutia-Guadarrama L, Figueroa-González G, Reyes-Hernández OD, et al. Xanthan gum in drug release. Cell Mol Biol. 2020;66(4):199-207.
77. Sharma AK, Garg T, Goyal AK, Rath G. Role of microemuslsions in advanced drug delivery. Artificial Cells, Artif Cells Nanomed Biotechnol. 2016;44(4):1177-1185.
78. Cortes H, Caballero-Florán IH, Mendoza-Muñoz N, Córdova-Villanueva EN, Escutia-Guadarrama L, Figueroa-González G, et al. Hyaluronic acid in wound dressings. Cell Mol Biol. 2020;66(4):191-198.
79. Chen RR, Mooney DJ. Polymeric growth factor delivery strategies for tissue engineering. Pharm Res. 2003;20(8):1103-1112.
80. Leyva-Gómez G, González-Torres M, Alcalá-Alcalá S, Bernal-Chávez SA, Morales-Morfin JC, González-Del Carmen M, et al. Development of films from natural sources for infections during wound healing. Cell Mol Biol. 2021;67(1):96-100.
81. Liang Z, Jing-long T, Chun-ren W, Yan-mei C, Zhe D, Zhong-liang L, et al. Release characteristics of nano-silver gel versus nano-silver hydrogel in simulated body fluid. CJTER. 2011;15(8):1417.
82. Xi P, Li Y, Ge X, Liu D, Miao M. Effect of nano-silver hydrogel coating film on deep partial thickness scald model of rabbit. Saudi J Biol Sci. 2018;25(4):797-800.
83. Xiang J, Shen L, Hong Y. Status and future scope of hydrogels in wound healing: Synthesis, materials and evaluation. Eur. Polym. J. 2020;130:109609.
84. Madaghiele M, Demitri C, Sannino A, Ambrosio L. Polymeric hydrogels for burn wound care: Advanced skin wound dressings and regenerative templates. Burns Trauma. 2014;2(4):2321-3868.143616.
85. Mandal A, Clegg JR, Anselmo AC, Mitragotri S. Hydrogels in the clinic. Bioeng Transl Med. 2020;5(2):e10158.
86. Morgan D. What should a dressings formulary include? HOSPITAL PHARMACIST-LONDON-. 2002;9(9):261-266.
87. Stan D, Tanase C, Avram M, Apetrei R, Mincu NB, Mateescu AL, et al. Wound healing applications of creams and “smart” hydrogels. Exp Dermatol. 2021;30(9):1218-1232.
88. Francesko A, Petkova P, Tzanov T. Hydrogel dressings for advanced wound management. Curr Med Chem. 2018;25(41):5782-5797.
89. Caló E, Ballamy L, Khutoryanskiy VV. Hydrogels in wound management. Hydrogels: Design, synthesis and application in drug delivery and regenerative medicine. 2018;128.
90. Zhang X, Soontornworajit B, Zhang Z, Chen N, Wang Y. Enhanced loading and controlled release of antibiotics using nucleic acids as an antibiotic-binding effector in hydrogels. Biomacromolecules. 2012;13(7):2202-2210.
91. Singh D, Singh MR. Development of antibiotic and debriding enzyme-loaded PLGA microspheres entrapped in PVA-gelatin hydrogel for complete wound management. Artif. Cells Nanomed. Biotechnol. 2012;40(5):345-353.
92. Kim YH, Tabata Y. Recruitment of mesenchymal stem cells and macrophages by dual release of stromal cell-derived factor-1 and a macrophage recruitment agent enhances wound closure. J Biomed Mater Res A. 2016;104(4):942-956.
93. Natesan S, Zamora DO, Wrice NL, Baer DG, Christy RJ. Bilayer hydrogel with autologous stem cells derived from debrided human burn skin for improved skin regeneration. J Burn Care Res. 2013;34(1):18-30.
94. Kosaraju R, Rennert RC, Maan ZN, Duscher D, Barrera J, Whittam AJ, et al. Adipose-derived stem cell-seeded hydrogels increase endogenous progenitor cell recruitment and neovascularization in wounds. Tissue Eng Part A. 2016;22(3-4):295-305.
95. Kaisang L, Siyu W, Lijun F, Daoyan P, Xian CJ, Jie S. Adipose-

derived stem cells seeded in Pluronic F-127 hydrogel promotes diabetic wound healing. J Surg Res. 2017;217,63-74.

96. Cheng N-C, Lin W-J, Ling T-Y, Young T-H. Sustained release of adipose-derived stem cells by thermosensitive chitosan/gelatin hydrogel for therapeutic angiogenesis. Acta Biomatera. 2017;51:258-267.

97. Shamloo A, Sarmadi M, Aghababaie Z, Vossoughi M. Accelerated full-thickness wound healing via sustained bFGF delivery based on a PVA/chitosan/gelatin hydrogel incorporating PCL microspheres. Int J Pharm. 2018;537(1-2):278-289.

98. Wu J, Zhu J, He C, Xiao Z, Ye J, Li Y, et al. Comparative study of heparin-poloxamer hydrogel modified bFGF and aFGF for in vivo wound healing efficiency. ACS Appl Mater Interfaces. 2016;8(29):18710-18721.

99. Goh M, Hwang Y, Tae G. Epidermal growth factor loaded heparin-based hydrogel sheet for skin wound healing. Carbohydr Polym. 2016;147:251-260.

100. Babavalian H, Tebyanian H, Latifi A, Shokrgozar M, Bonakdar S, Shakeri F. The effect of synthetic alginate sulfate hydrogels with recombinant PDGF-BB on Wound healing. Bratisl Lek Listy. 2018;119(6):391-396.