INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN: 2320-2831

IJPAR |Vol.10 | Issue 2 | Apr - Jun -2021

Journal Home page: www.ijpar.com

Review Study Open Access

Review on hydrogels – its topical application for wound healing action

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ABSTRACT

In the area of wound healing, the need for treating broad and deep untreatable wounds is growing with each day. Wide, deformed, deep, or massive wounds are unable to repair by our cell system or tissue repair mechanism, resulting in dysfunction and deformity. Furthermore, the dressings or medications often used relieve pain result in slow healing, scarring, and sometimes even death. As a result, hydrogel is used to repair and seal the loss component as a 3D polymeric matrix with a broad range of properties for soft, sensitive to hard and tough tissue or organ. There are several sophisticated, smart, and intelligent hydrogels that are made up of natural and synthetic polymers and are developed for proper encapsulation and regulated release of drugs or biomolecules under key biological circumstances. As a result, the hydrogel is being used amongst the most effective matrices for tissue regeneration and drug testing. In this article, we address the polymer used to make hydrogels, as well as methods for evaluating hydrogel wound dressings to help direct the development of new hydrogels.

Keywords: Hydrogel, Wound healing, Polymers, Evaluation

INTRODUCTION

Hydrogels are essentially three-dimensional network structures made of various natural and synthetic polymers. They have the capacity to absorb and transport a sufficient amount of water owing to their porous nature[1]. Hydrogels comprise polymeric matrices which swell in water but just don't dissolve[2]. Hydrogels can contain up to 99 percent water. Hydrogels are usually dried and can absorb water in the following ways:

- Primary Bound Water: Primary bound water is formed when a dried hydrogel engrosses water through association with hydrophilic groups.
- Secondary Bound water: When more water is consumed by the hydrogels following primary bound water, it requires additional hydrophilic group interaction and is referred to as secondary bound water.
- Total Bound Water: Total bound water was its mixture of primary and secondary bound water.
- Free Water: Once all of the other classes are waterlogged, more water absorption is referred to as free water, which occupies all or most of the spaces[3].

Because of their high moisture content, porosity, and smooth texture, hydrogels stimulate natural living tissue more than almost any other form of synthetic biomaterial. Hydrogels could be chemically stable or disintegrate and degrade over time[4].

The hydrophilic functional group attached to the polymeric backbone gives hydrogels their ability to hold water. High moisture penetration allows only few small molecules, such as oxygen, metabolites, and nutrients, to move through the hydrogel structure. Hydrogels' ability to retain water makes them ideal candidates for use in controlled dosage forms.

Benefits for the treatment of diseases requiring selective drug delivery can be obtained by adequate design and

experimental procedures. Because of their high drug affinity and stability, hydrogels are extremely important. Different stimuli for inducing release of the drug from hydrogel networks include light, temperature, magnetic field, electrical signals, PH, and ionic strength. They can be given in a variety of ways, including orally, nasally, ocularly, subcutaneously, and transdermally.

Hydrogels are now being used extensively as wound dressings. Because of its distinct and significant properties such as cooling effect, cushioning effect and clarity, hydrogel is a good candidate for topical application. The high water content of hydrogels contributes significantly to skin elasticity as well as moisturization[6].

There are various types of hydrogels that have been developed and tested for bio-medical applications as wound healing materials[7]. Because of their high water holding capacity, biocompatibility, compressive modulus, strong elasticity, close structure to biological tissue, non-adhesion with soft tissue, and controllable biodegradability, they have the ability to repair damaged tissue and regenerate[8]. It was confirmed that the hydrogel's water uptake ability solved the problem of ablation and puffiness of healing wounds, as well as providing a moist environment all around wounds for improved vascularisation[9]

Hydrogels are quickly applied and convenient materials to adapt for wound healing, with a pain-relieving effect on the wounded tissue. Because of their high moisture content, hydrogels reduce wound temperature and soothe the injured region[10]. Hydrogel, in particular, is useful in the treatment of dry wounds. Hydrogels are appropriate for all stages of wound healing, including inflammation, cell proliferation, maturation, and homeostasis. They are non-reactive, non-irritant to biological tissue, and metabolite permeable[11]. The different types of hydrogel dressing are most suitable for wound treatments that are applied to a specific wound. These defining characteristics of hydrogels prevent their rapid entry into the dressing industry, where hydrogels are available as saturated gauze, gels, or sheets[12].

HYDROGEL CLASSIFICATION

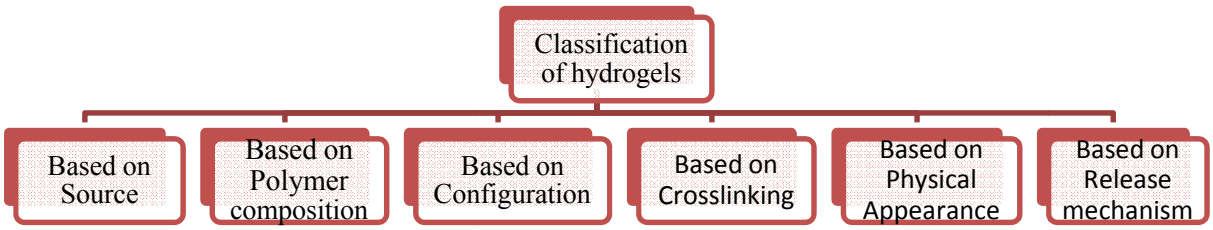

Figure 1

RELEASE MECHANISM

a) DIFFUSION CONTROLLED

The most popular method of drug release from hydrogels is diffusion-controlled release. In this form of drug release, Fick's diffusion theory is applied to kinetic modelling. Drug diffusion from porous hydrogels with pore sizes greater than drug molecule specifications can be related to hydrogel porosity and tortuosity. Hydrogels with diffusion-controlled release may serve as reservoirs or a matrix. Since drug molecules in reservoir drug delivery systems are embedded and enclosed by polymeric hydrogels, drug release often follows Fickian diffusion's first rule.

b) SWELLING CONTROLLED

When the rate of drug diffusion exceeds the rate of hydrogel swelling, swelling-controlled release of the drug can appear. For strictly swelling mediated drug release, the kinetic model of release could be mostly suited to a zero-order model. Hydrogels may go through a swelling-induced transitional stage (at glass transition temperature or Tg) from glassy to rubbery, resulting in quicker drug diffusion and release from polymeric chains. In swelling-controlled delivery systems, the greater the rate of hydrogel swelling, the greater the rate of drug release, and that rate and ability of hydrogel moisture absorption, and also the thickness of polymeric gels, are significant considerations in swelling-controlled delivery systems.

c) CHEMICALLY CONTROLLED

The mechanism by which a reaction takes place within the hydrogel matrix is explained by chemically-controlled drug release mechanism. Enzymatic or hydrolytic cleavage of its polymeric matrix is liable for drug release in such reactions. Release of drug in chemically-controlled delivery systems could occur via cleavage of polymeric chains via bulk or surface erosion, and the entrapped or tethered drug would be released from hydrogels as a result of such mechanisms[13-17].

ADVANTAGES

- Because of their high water content, their flexibility is quite identical to that of natural tissue.
- The environmentally responsive hydrogels can detect changes in temperature, pH or metabolite concentration and release the load with response to the change.
- They are injectable, biocompatible, and biodegradable.
- Microbial cell entrapment inside hydrogel beads has the benefit of being low toxicity.
- Hydrogels have better transport features and allow for the controlled release of growth factors and other nutrients[18].

DISADVANTAGES

- They are expensive and have poor mechanical strength

- They are non-adherent and may require secondary dressing. They may induce a discomfort similar to that caused by maggot movement.
- They can be difficult to manage.
- It may be difficult to load with drugs/nutrients.
- Contact lens hydrogels induce lens deposition, hypoxia, dehydration, and red eye symptoms.

POLYMERS

Polymers are present everywhere naturally or synthetically.
Classification:

1. Natural polymers
2. Synthetic
3. Semi – synthetic

Table - 1

Polymer	Applications
Chitosan	Used in biomedical applications for drug administration as well as wound healing. Chitosan scaffolds are also being developed[19].
Hyaluronic acid	It is used in the preparation of hydrogels and has the benefit of delayed drug release and a longer time of action [[20]].
Carrageenan	It has an advantage of controlled drug release and tissue engineering applications[21].
Alginic acid	Used as co – transplantation on rat spinal injury[22].
Collagen	It has the potential to regulate drug release from hydrogels as well as stimulate cell development[23].
Gelatin	The dressing, which is dependent on sodium alginate and gelatin, was created by cross-linking sodium chloride and glutaraldehyde[24].
Polyethylene glycol	Capable of forming controlled gelation as a result of a proto initiator or by combining with cross linkers used in the enzyme immobilization[25].
Polyvinyl pyrrolidone	Biomedical applications[25].
Polyvinyl alcohol	PVA-based hydrogels are used in the replacement of damaged cartilage and in orthopedic applications[26].
Polycaprolactone	Used in drug delivery and tissue engineering.
Carboxymethyl cellulose	Hydrogels based on CMC are being used as scaffolds in a sustained release system.
Hydroxyethyl cellulose	As HEC is cross-linked with CMC, it has stronger swelling properties which form novelty hydrogels[27].
Hydroxyethyl cellulose	Used in tissue engineering applications[28].
Ethyl cellulose	Used as coating for sustained release

METHODS OF PREPARATION

Physical cross-linking, chemical cross-linking, grafting polymerisation, and radiation cross-linking are some of the preparation techniques used. These modifications may enhance the mechanical properties and visco elasticity for applications in pharmaceutical and biotechnology fields[29].
The following are the general methods for producing physical and chemical gels:
1. Physical cross linking
Physical or reversible gels have gained popularity due to their ease of processing and the benefit of not requiring cross-linking agents. These agents have an effect on the integrity of the substances to be entrapped (e.g., cells, proteins, etc.) as well as the need to remove them prior to application.
a) Heating/Cooling of a polymer solution
The gel is formed as a result of helix formation, helice association, and the formation of junction zones. Carrageenan exists as a random coil conformation in hot solution above the melting transition temperature. When it cools, it turns into rigid helical rods. In the presence of salt (K+, Na+, etc.), double helices further aggregate to form stable gels owing to screening of repulsion of sulphonic group (SO–3). Polyethylene oxide-polypropylene oxide and polyethylene glycol-polylactic acid hydrogel are two examples[30].
b) Complex coacervation
By combining a polyanion and a polycation, complex coacervate gels could be produced. This method's underlying theory is that polymers containing opposite charges stay together and form soluble and insoluble complexes based on the concentration and pH of the respective solutions. Coacervating polyanionic xanthan with polycationic chitosan is one such example. Proteins that are positively charged below their isoelectric point are more likely to interact with anionic hydrocolloids and form polyion complex hydrogels[31].
c) Interaction of ions
The inclusion of di- or trivalent counterions will cross-link ionic polymers. This approach is based on the concept of gelling a polyelectrolyte solution (for example, Na+ alginate-) with a multivalent ion to opposite charges (for example, Ca2+ + 2Cl-). Chitosan-polylysine, chitosan-glycerol phosphate salt, and chitosan-dextran hydrogels may be other examples[32].
2. Chemical cross-linking
Chemical cross-linking requires the grafting of monomers onto the polymer backbone with the use of a cross-linking agent to connect two polymer chains. Natural and synthetic polymers can be cross-linked by interacting their functional groups (such as OH, COOH, and NH2) with cross-linkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). To create the cross-linked hydrogel, cross-linkers such as glutaraldehyde, epichlorohydrin, and others

have been commonly used. One example is a hydrogel made by cross-linking corn starch and polyvinyl alcohol with glutaraldehyde as a cross-linker. Hydrogels can be made from cellulose in NaOH/urea aqueous solutions through using epichlorohydrin as a cross-linker and heating and freezing techniques[33].

3. Irradiation-induced polymerization

Ionizing high power radiation, such as gamma rays and electron beams, is being used as a precursor in the preparation of unsaturated compound hydrogels[34].

TOPICAL APPLICATION FOR WOUND HEALING:

Topical drug delivery is among the simplest administration routes, and it is used to eliminate side effects and localize large quantities of drug at the target location. Hydrogels are considered ideal vehicles for topical drug delivery due to the relatively low toxicity and long-term drug release. Furthermore, hydrogels have the advantages of biocompatibility, smoothness and water - holding capacity, which can imitate natural tissue properties and, due to their swelling and hydrating capacity, can prevent discomfort to enclosed tissues. Another significant benefit of hydrogels is their ability to shield drugs from adverse environmental conditions[35].

A wound is any type of damage or breakage of skin caused by a medical, physiological disease, or trauma[36].

When an injured or wounded tissue is restored toward its previous or natural anatomical form, structure, and function within an acceptable time span, it is considered completely healed. Wounds can be classified into the following categories based on the defected skin component and the number of skin layers

- Superficial wounds: Epidermis is affected.
- Partial thickness wounds include the epidermal as well as deeper dermal layers.
- Full thickness wounds contain deeper tissues including subcutaneous layers.

Wounds are also classified as:

a. Acute wounds

b. Chronic wounds

c. Complicated wounds

Wound healing process

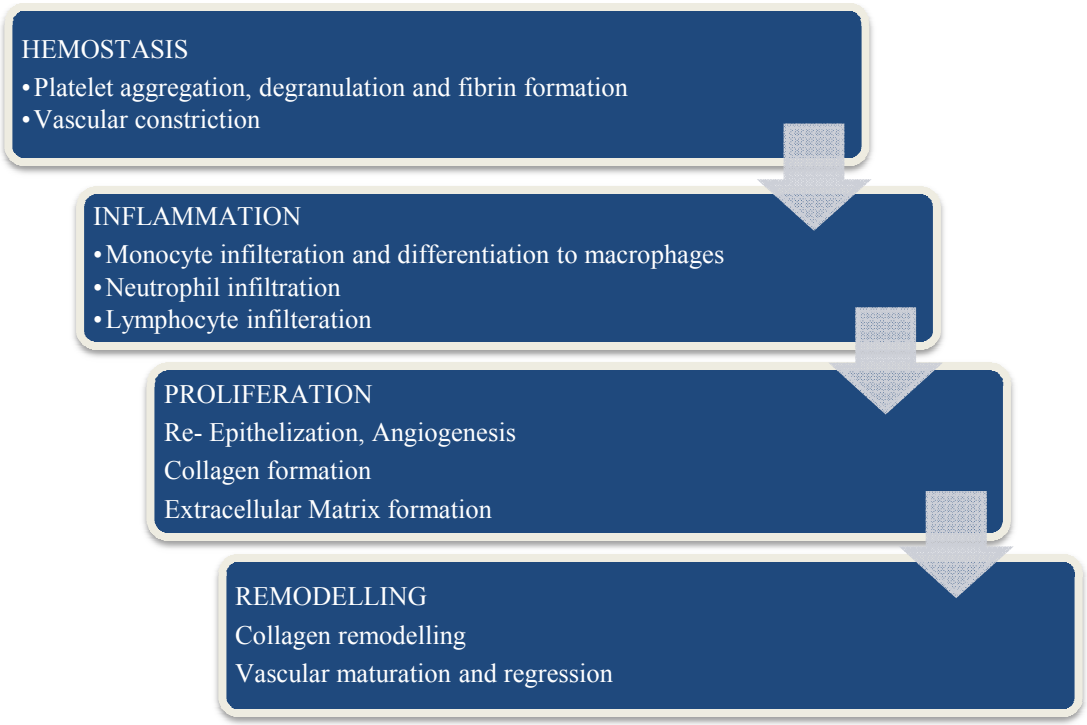

Figure 2

Wound healing is a sequential process that consists of four overarching, defined, and automated phases. Each phase must be regulated in an efficient and accurate manner. Any disruption or continuation in these processes may cause the wound to take longer to heal, and there is a risk of this wound being chronic[37].

Wound dressings are mostly polymers in the form of gauzes, gels, hydrogels, hydrocolloids, and so on. Hydrogels have been the most viable technique in wound healing of these. Hydrogels are ideal wound dressings because they can provide a humid environment in the wound site, aid in the elimination of wound exudates, avoid infection, and provide an environment conducive to tissue regeneration[38]. A wound is an injury that occurs in body tissues, either inside or outside, primarily in the skin, as a result of fracture, cut, or other damage. Normal tissue structure and function can be disrupted as a result of the wound[39].

Acute and chronic wounds are the two forms of wounds. Acute wounds heal fully in a shorter period of time, while chronic wounds take longer to heal. Haemostasis, inflammation, replication, and remodelling are all part of the wound healing process[40]. Wound infection, wound depth, foreign body contact, stress, strain, age, diseases, and other factors all have an effect on the wound healing process.

Scarring developed during normal healing as a result of the deposition of collagen fibres, and it will remain for a long time. Scarless healing happens with the aid of wound dressings[41].

Anti-bacterial and anti-inflammatory hydrogels have a positive effect in wound dressing applications[42]. A wound healing multipurpose and pH-responsive hybrid hydrogel composed of carboxylated agarose and tannic acid that is ionically cross linked with zinc salts. Tannic acid's anti-microbial, anti-inflammatory, and anti-oxidant properties, coupled with the pH-responsive property of carboxylated cellulose, resulted in improved strength properties and anti-bacterial activity[43]. Dextran is another polysaccharide that is used in the production of hydrogel. It improves wound healing in vivo by assisting in situ gelation and controlled release of immobilized growth factor through chitosan microparticles[44].

With its haemostatic properties, chitosan is an outstanding wound healing material. A physically cross-linked chitosan hydrogel has the ability to regenerate the skin of third - degree burns in the dorsal region of a pig[45]. A disulphide bond cross-linking of thiolated polyethylene glycol and silver nitrate was used to create an injectable hydrogel. This hydrogel contains desferrioxamine, an angiogenic drug that has the potential to heal diabetic wounds due to its angiogenic activity. A broad variety of hydrogel-related wound care products are commercially available to help prevent wound-related diseases and scarring[46].

The various forms of hydrogel wound dressing available on the market include amorphous gel, hydrogel pads, hydrogel film, and hydrogel impregnated gauze[47]. This hydrogel promotes wound healing by autolytic debridement and moisture distribution to the wound region. The moist atmosphere promotes wound granulation and epithelisation[48]. The key benefits are that it reduces wound pain and is simple to use. It is used in conjunction with secondary film dressing to cover hydrogel[49].

COMMERCIALLY AVAILABLE HYDROGELS

Table - 2

Product name	Company name	Hydrogel composition	Application
ActivHeal®	Advanced Medical Solutions Ltd.	It is a primary wound dressing that is composed of 85 percent water.	Leg ulcers, pressure ulcers, Diabetes-related foot ulcers, wounds in the cavity
DermaSyn®	DermaRite industries	It's a primary wound dressing that's high in vitamin E.	Partial and full thickness wounds, either acute or chronic
NU-GEL™	Systagenix	Sodium alginate is used to efficiently debride necrotic tissue as well as fibrinous slough.	Chronic wounds, diabetic foot ulcers, venous leg ulcers, and bedsores
INTRASITE Gel	Smith and Nephew	Carboxymethyl cellulose and propylene glycol are the main components.	Diabetic foot ulcers, pressure sores Incisions made during surgery, Ulcers of the vena cava
Derma Gauze™	DermaRite industries	Gauze dressing impregnated with hydrogel. Derma Gauze contains an ingredient called acrylate polymer.	Partial and full thickness wounds, either acute or chronic
Suprasorb® G	Lohmann & Rauscher Global	With a water content of 70%, this hydrogel film is composed of acrylic polymers, polyethylene, and phenoxyethanol.	Dry wounds, lower leg ulcers, pressure sores, first and second-degree burns, and scalds

EVALUATION

a) pH

The pH of hydrogels is determined using a digital pH meter. Before using a pH meter, it should be calibrated.

b) Scanning Electron Microscopy.

SEM may be used to determine the structure, surface topography, and other properties of a sample, such as electrical conductivity. SEM magnification can be adjusted over a six-order-of-magnitude scale, from around 10 to 500,000 times[50].

c) Fourier's Infrared Transform Spectroscopy

It is a beneficial technique to determine a substance's chemical structure. It is based on the idea that the key elements of a material, namely chemical bonds, can be excited and absorb infrared light at normal chemical bond frequencies[51 - 52].

d) Measurement of swelling[53]

The dry hydrogel is submerged in deionized water for 48 hours at room temperature on a roller mixer. Upon swelling, the hydrogel is filtered through a stainless steel net with a mesh size of 30 meshes (681 m). The swelling is measured in the following manner.

WS-Wd/Wd = Swelling

Where

Ws - The swollen weight of the hydrogel

Ws - the weight of hydrogel in dry state.

e) X-ray diffraction

Diffraction analysis is used to determine whether a material is crystalline or amorphous. It is used to determine whether the polymers maintain their crystalline structure or are deformed during the pressurization process. Diffraction analysis is a common method for characterizing the morphology of hydrogels.

f) *In-vitro* drug release study

Since hydrogels are swollen polymeric networks with drug molecules occupying the interior, release studies are conducted to understand the mechanism of release over

time. The criteria are matched with the regular plot to determine the equivalence of the drug solutions[54].

g) Rheology

The viscosity of hydrogels is measured using a Cone plate style viscometer at a constant temperature of 4°C. This viscometer is very specific for determining viscosity. The viscosity is calculated by a simple equation involving the angle of repose and height and length.

h) Spread ability study

The apparatus was constructed from a wooden block with a scale and two glass slides, each with a pan fixed on a pulley. Surplus formulation was sandwiched between two glass slides, and a 100 gm weight was put on the upper glass slide for 5 minutes to compare the formulation's thickness. Weight can be applied, and the time it takes to separate the two slides was used to calculate spread ability.

$S = (m \times l) / t$

Where S is spreadabilty,

M is weight tied on upper slide,

L is length of glass slide

T is time taken in seconds.

i) Studies on skin irritancy

Rabbits are used in skin irritancy experiments. The preparation was applied to two rabbits, and the affected area was bandaged or gauzed. The formulation was withdrawn after 24 hours, and the region was examined for signs of edema and erythema.

Average irritation scores = (erythema reaction scores + edema reaction scores) / time interval [55].

j) Network Pore Size

A variety of technologies, including electron microscopy and mercury porosimetry, are used to determine pore size.

CONCLUSION

Wound healing is a complex biological process related to growth and tissue regeneration in which different cells and endogenous factors are involved. The stages of wound healing vary but are specifically described as haemostasis, inflammation, proliferation, and maturation. People are researching together to create advanced wound dressings in order to minimize the risk of wound infection and speed up wound healing. Because of its excellent biocompatibility, high moisture retention, and activation of immune cells to improve wound healing, hydrogel is an optimal dressing material. Practitioners have broadened the complexity of its application by investigating new chemical and physical cross-linking methods such like click chemistry, enzymatic reactions, crystallization, amphiphilic block copolymers, and so forth. Furthermore, they work to improve hydrogel specifications in order to broaden the spectrum of applications for hydrogels. It is anticipate that future hydrogel studies will focus on lower costs and greater precision. Future studies will concentrate on the impact on chronic wounds. Designers will accomplish this by discovering more bioactive hydrogel materials. Alternatively, concentrate on the function of natural polymer structural modification; after all, structural limitations remain one of the major challenges of future study. Many factors influence hydrogel production; the conditions differ greatly depending on the cross-linking materials. Furthermore, optimizing the production process in terms of polymer stability, process ability, and solubility may be a major barrier to study. Different researchers might be able to solve problems mentioned above in the near future.

REFERENCES

1. Mohan YM, Premkumar T, Lee K, Geckeler KE. Fabrication of silver nanoparticles in hydrogel networks. Macromol Rapid Commun. 2006 Aug 23; 27(16):1346-54. doi: 10.1002/marc.200600297.
2. Akala EO, Kopečková P, Kopeček J. Novel pH-sensitive hydrogels with adjustable swelling kinetics. Biomaterials. 1998 Jun 1; 19(11-12):1037-47. doi: 10.1016/s0142-9612(98)00023-4, PMID 9692802.
3. Ullah K, Sohail M, Murtaza G, Khan SA. Natural and synthetic materials based cmch/PVA hydrogels for oxaliplatin delivery: fabrication, characterization, in-vitro and in-vivo safety profiling. Int J Biol Macromol. 2019 Feb 1; 122:538-48. doi: 10.1016/j.ijbiomac.2018.10.203, PMID 30389527.
4. Peppas NA, Bures P, Leobandung WS, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000 Jul 3; 50(1):27-46. doi: 10.1016/s0939-6411(00)00090-4, PMID 10840191.
5. Yang C, Xu L, Zhou Y, Zhang X, Huang X, Wang M, Han Y, Zhai M, Wei S, Li J. A green fabrication approach of gelatin/CM-chitosan hybrid hydrogel for wound healing. Carbohydr Polym. 2010; 82(4):1297-305. doi: 10.1016/j.carbpol.2010.07.013.
6. Shen YI, Song HG, Papa A, Burke J, Volk SW, Gerecht S. Acellular hydrogels for regenerative burn wound healing: translation from a porcine model. J Invest Dermatol. 2015; 135(10):2519-29. doi: 10.1038/jid.2015.182, PMID 26358387.
7. Gupta A, Kowalczuk M, Heaselgrave W, Britland ST, Martin C, Radecka I. The production and application of hydrogels for wound management: a review. Eur Polym J. 2019; 111:134-51. doi: 10.1016/j.eurpolymj.2018.12.019.
8. Tamirisa PA, Hess DW. Water and moisture uptake by plasma polymerized thermo responsive hydrogel films. Macromolecules. 2006; 39(20):7092-7. doi: 10.1021/ma060944u.
9. Coburn J, Gibson M, Bandalini PA, Laird C, Mao HQ, Moroni L, Seliktar D, and Elisseeff J. Biomimetics of the extracellular matrix: an integrated three-dimensional fiber-hydrogel composite for cartilage tissue engineering. Smart Struct Syst. 2011; 7(3):213-22. doi: 10.12989/sss.2011.7.3.213, PMID 22287978.
10. Honiger J, Balladur P, Mariani P, Calmus Y, Vaubourdolle M, Delelo R, Capeau J, Nordlinger B. Permeability and biocompatibility of a new hydrogel used for encapsulation of hepatocytes. Biomaterials. 1995; 16(10):753-9. doi: 10.1016/0142-9612(95)99637-2, PMID 7492705.
11. Klouda L, Mikos AG. Thermo responsive hydrogels in biomedical applications. Eur J Pharm Biopharm. 2008; 68(1):34-45. doi: 10.1016/j.ejpb.2007.02.025, PMID 17881200.
12. Jeong B, Kim SW, Bae YH. Thermo sensitive sol-gel reversible hydrogels. Adv Drug Deliv Rev. 2002; 54(1):37-51. doi: 10.1016/s0169-409x (01)00242-3. PMID 11755705.

13. Lin CC, Metters AT. Hydrogels in controlled release formulations: network design and mathematical modeling. Adv Drug Deliv Rev. 2006 Nov 30; 58(12-13):1379-408. doi: 10.1016/j.addr.2006.09.004, PMID 17081649.
14. Amsden B. Solute diffusion within hydrogels. Mechanisms and models. Macromolecules. 1998 Nov 17; 31(23):8382-95. doi: 10.1021/ma980765f.
15. Peppas NA, Bures P, Leobandung WS, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000 Jul 3; 50(1):27-46. doi: 10.1016/s0939-6411(00)00090-4, PMID 10840191.
16. Lin CC, Anseth KS. PEG hydrogels for the controlled release of biomolecules in regenerative medicine. Pharm Res. 2009 Mar; 26(3):631-43. doi: 10.1007/s11095-008-9801-2, PMID 19089601.
17. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2001; 48(2-3):139-57. doi: 10.1016/s0169-409x (01)00112-0. PMID 11369079.
18. Ravaine V, Ancla C, Catargi B. Chemically controlled closed-loop insulin delivery. J Control Release. 2008 Nov 24; 132(1):2-11. doi: 10.1016/j.jconrel.2008.08.009, PMID 18782593.
19. Thakur G, Rousseau D. Hydrogels: characterization, drug delivery, and tissue engineering applications. Encyclopedia of biomedical polymers and polymeric biomaterials. New York: Taylor & Francis; 2016. p. 3853-78.
20. Dutta PK, Dutta J, Tripathi VS. Chitin and chitosan: chemistry, properties and applications.
21. Bulpitt P, Aeschlimann D. New strategy for chemical modification of hyaluronic acid: preparation of functionalized derivatives and their use in the formation of novel biocompatible hydrogels. J Biomed Mater Res. 1999 Nov; 47(2):152-69. doi: 10.1002/ (sici) 1097-4636(199911)47:2<152: aid-jbm5>3.0.co; 2-i, PMID 10449626.
22. Santo VE, Frias AM, Carida M, Cancedda R, Gomes ME, Mano JF, Reis RL. Carrageenan-based hydrogels for the controlled delivery of PDGF-BB in bone tissue engineering applications. Biomacromolecules. 2009 Jun 8; 10(6):1392-401. doi: 10.1021/bm8014973, PMID 19385660.
23. Rao JK, Ramesh DV, Rao KP. Implantable controlled delivery systems for proteins based on collagen—pHEMA hydrogels. Biomaterials. 1994 Apr 1; 15(5):383-9. doi: 10.1016/0142-9612(94)90251-8, PMID 8061130.
24. Saarai A, Kasparkova V, Sedlacek T, Sáha P. On the development and characterization of cross linked sodium alginate/gelatine hydrogels. J Mech Behav Biomed Mater. 2013 Feb 1; 18:152-66. doi: 10.1016/j.jmbbm.2012.11.010, PMID 23274732.
25. Almany L, Seliktar D. Biosynthetic hydrogel scaffolds made from fibrinogen and polyethylene glycol for 3D cell cultures. Biomaterials. 2005 May 1; 26(15):2467-77. doi: 10.1016/j.biomaterials.2004.06.047, PMID 15585249.
26. Baker MI, Walsh SP, Schwartz Z, Boyan BD. A review of polyvinyl alcohol and its uses in cartilage and orthopedic applications. J Biomed Mater Res B Appl Biomater. 2012 Jul; 100(5):1451-7. doi: 10.1002/jbm.b.32694, PMID 22514196.
27. Sannino A, Demitri C, Madaghiele M. Biodegradable cellulose-based hydrogels: design and applications. Materials. 2009 Jun; 2(2):353-73. doi: 10.3390/ma2020353.
28. Thirumala S, Gimble JM, Devireddy RV. Methylcellulose based thermally reversible hydrogel system for tissue engineering applications. Cells. 2013 Sep; 2(3):460-75. doi: 10.3390/cells2030460, PMID 24709793.
29. Singh A, Sharma PK, Garg VK, Garg G. Hydrogels: a review. Int J Pharm Sci Rev Res. 2010; 4(2):97-105.
30. Funami T, Hiroe M, Noda S, and Asai I, Ikeda S, Nishinari K. Influence of molecular structure imaged with atomic force microscopy on the rheological behavior of carrageenan aqueous systems in the presence or absence of cations. Food Hydrocoll. 2007 Jun 1; 21(4):617-29. doi: 10.1016/j.foodhyd.2006.07.013.
31. Magnin D, Lefebvre J, Chornet E, Dumitriu S. Physicochemical and structural characterization of a polyionic matrix of interest in biotechnology, in the pharmaceutical and biomedical fields. Carbohydr Polym. 2004 Mar 15; 55(4):437-53. doi: 10.1016/j.carbpol.2003.11.013.
32. Gulrez SK, Al-Assaf S, Phillips GO. Hydrogels: methods of preparation, characterization and applications. Prog Mol Environ Bioeng Anal Model Technol Appl. 2011 Aug 1:117-50.
33. Chang C, Zhang L, Zhou J, Zhang L, Kennedy JF. Structure and properties of hydrogels prepared from cellulose in NaOH/urea aqueous solutions. Carbohydr Polym. 2010 Aug 2; 82(1):122-7. doi: 10.1016/j.carbpol.2010.04.033.
34. Chen J, Li D, Koshikawa H, Asano M, Maekawa Y. Crosslinking and grafting of polyetheretherketone film by radiation techniques for application in fuel cells. J Membr Sci. 2010 Oct 15; 362(1-2):488-94. doi: 10.1016/j.memsci.2010.07.012.
35. Morsi NM, Abdelbary GA, Ahmed MA. Silver sulfadiazine based cubosome hydrogels for topical treatment of burns: development and in vitro/in vivo characterization. Eur J Pharm Biopharm. 2014 Feb; 86(2):178-89. doi: 10.1016/j.ejpb.2013.04.018, PMID 23688805.
36. Caló VV. Khutoryanskiy. Biomedical applications of hydrogels: a review of patents and commercial Products. 2015; 65:252-67.
37. Gupta P, Vermani K, Garg S. Hydrogels: from controlled release to pH-responsive drug delivery. Drug Discov Today. 2002 May 15; 7(10):569-79. doi: 10.1016/s1359-6446(02)02255-9, PMID 12047857.
38. Tavakoli S, Mokhtari H, Kharaziha M, Kermanpur A, Talebi A, Moshtaghian J. A multifunctional nanocomposite spray dressing of kappa-carrageenan-polydopamine modified ZnO/L-glutamic acid for diabetic wounds. Mater Sci Eng C Mater Biol Appl. 2020 Jun 1; 111:110837. doi: 10.1016/j.msec.2020.110837.
39. Jones A, Vaughan D. Hydrogel dressings in the management of a variety of wound types: a review. J Orthop Nurs. 2005 Dec 1; 9:S1-S11. doi: 10.1016/S1361-3111(05)80001-9.
40. Gupta B, Agarwal R, Alam MS. Hydrogels for wound healing applications. In: Biomedical hydrogels. Wood head Publishing; 2011 Jan 1. p. 184-227.
41. Basu P, Narendra Kumar U, Manjubala I. Wound healing materials – a perspective for skin tissue engineering. Curr Sci. 2017; 112(12):2392-404. doi: 10.18520/cs/v112/i12/2392-2404.
42. Whitney JD. Overview: acute and chronic wounds. Nurs Clin North Am. 2005 Jun 1; 40(2):191-205, v. doi: 10.1016/j.cnur.2004.09.002, PMID 15924889.

43. Liu H, Wang C, Li C, Qin Y, Wang Z, Yang F, Li Z, Wang J. A functional chitosan-based hydrogel as a wound dressing and drug delivery system in the treatment of wound healing. RSC Adv. 2018;8(14):7533-49. doi: 10.1039/C7RA13510F.
44. Ninan N, Forget A, Shastri VP, Voelcker NH, Blencowe A. Antibacterial and anti-inflammatory pH-responsive tannic acid-carboxylated agarose composite hydrogels for wound healing. ACS Appl Mater Interfaces. 2016; 8(42):28511-21. doi: 10.1021/acsami.6b10491, PMID 27704757.
45. Ribeiro MP, Morgado PI, Miguel SP, Coutinho P, Correia IJ. Dextran-based hydrogel containing chitosan micro particles loaded with growth factors to be used in wound healing. Mater Sci Eng C Mater Biol Appl. 2013; 33(5):2958-66. doi: 10.1016/j.msec.2013.03.025. PMID 23623119.
46. Ahmed S, Ikram S. Chitosan based scaffolds and their applications in wound healing. Achievements in the Life Sciences. 2016; 10(1):27-37. doi: 10.1016/j.als.2016.04.001.
47. Chen H, Cheng R, Zhao X, Zhang Y, Tam A, Yan Y, Shen H, Zhang YS, Qi J, Feng Y, Liu L, Pan G, Cui W, Deng L. An injectable self-healing coordinative hydrogel with antibacterial and angiogenic properties for diabetic skin wound repair. NPG Asia Mater. 2019; 11(1):3. doi: 10.1038/s41427-018-0103-9.
48. Boucard N, Viton C, Agay D, Mari E, Roger T, Chancerelle Y, Domard A. The use of physical hydrogels of chitosan for skin regeneration following third-degree burns. Biomaterials. 2007; 28(24):3478-88. doi: 10.1016/j.biomaterials.2007.04.021, PMID 17482258.
49. Tahsildar AG, Shinkar DM, Saudagar RB. Hydrogel-a novel technique for preparation of topical gel. World J Pharm Sci. 2013; 2(6):4520-41.
50. Mansur HS, Oréfice RL, Mansur AAP. Characterization of poly (vinyl alcohol)/poly (ethylene glycol) hydrogels and PVA-derived hybrids by small-angle X-ray scattering and FTIR spectroscopy. Polymer. 2004 Sep 29; 45(21):7193-202. doi: 10.1016/j.polymer.2004.08.036.
51. Torres R, Usall J, Teixidó N, Abadias M, Viñas I. Liquid formulation of the biocontrol agent Candida sake by modifying water activity or adding protectants. J Appl Microbiol. 2003 Feb; 94(2):330-9. doi: 10.1046/j.1365-2672.2003.01843.x, PMID 12534826.
52. Qavi S, Pourmahdian S, Eslami H. Acrylamide hydrogels preparation via free radical crosslinking copolymerization: kinetic study and morphological investigation. J Macromol Sci A. 2014 Oct 3; 51(10):842-8. doi: 10.1080/10601325.2014.937132.
53. Sri B, Ashok V, Arkendu C. As a review on hydrogels as drug delivery in the pharmaceutical field. *Int J Pharm Chem Sci.* 2012; 1(2):642-1.
54. Amin S, Rajabnezhad S, Kohli K. Hydrogels as potential drug delivery systems. Sci Res Essays. 2009 Nov 30; 4(11):1175-83.
55. Morkhande VK, Pentewar R, Gapat SV, Sayyad SR, Amol BD, Sachin B, Sandip K. A review on hydrogel. Indo Am J Pharm Res. 2016; 6(3):4678-88.