Mini Review

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Hydrogel as a prospective substance for wound healing and sealing

Abstract

In the field of wound healing, the demand for treatment of large size and deep incurable wounds has been increasing day by day. Large, deformed, deep or full-thickness wounds cannot heal themselves by our cell system or tissue repair mechanism and results in infection and deformity. As well as the dressing or drugs used for the treatment of wounds results in poor healing, scar tissue and even death of an individual. Therefore, hydrogel as a 3D polymeric matrix having a wide range of properties for soft, sensible to hard and tough tissue or organ is used to heal and seal the loss part. There are lots of advanced, smart and intelligent hydrogel consist of natural and synthetic polymers designed for proper encapsulation and controlled release of drugs or biomolecules under specific physiological conditions. Thus, the hydrogel is used as one of the potent matrices for the regeneration of tissue and drug testing.

Keywords: biomaterials, hydrogel, polymer, wounds, sealing, synthetic

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Introduction

Wound – distortion or damage of tissue either internally or externally that may result in the form of burn, cut, incisions, punctured etc. Some of wounds such superficial wound can be healed by themselves, although others like large or deep wounds need proper medication and treatment for faster healing and to prevent infection.[1] Non-healing, infectious or non-curable type of wounds results death of an individual. Currently for the wound care and cure different type of ointment, drug and wound dressing materials like gauze, collagen membrane etc., has been used at clinical level.[2] Although these treatments having healing properties but they have demerits like immunogenic response, chances of graft rejection, high cost of treatment, poor healing rate, limits their applicability. Clinically, for the large, full thickness and deformed wounds treatments wound coverage and healing are major problems faced by the researcher. Cotton gauze, bio-synthetic grafts replacement during dressing causes removal of healed tissue layer and formation of scar at wound site.[3,4] It was reported that allografts like amniotic membrane, acellular tissue have natural healing properties and negligible immunogenic response without graft rejection.[5,6] Autogenic graft and acellular allogenic grafts shows scar less better healing without inflammation, but the shortage of donor tissue and use only for the superficial wound limits their applicability.[7] Thus, to overcome this problem Hydrogel has been used as healing and sealing material to fill the loss tissue part and replaced the damaged tissue/cells with new one.[8]

A hydrogel is consists of 3 dimensional insoluble and hydrophilic polymer form semi-solid, jelly like cross linked polymeric structure posses properties ranging from soft, weak to hard and tough.[9] There are different kinds of hydrogel fabricated and evaluated for the bio-medical application as a wound healing material.[10,11] They have capacity to heal damage tissue and regeneration because of high water absorption capacity, biocompatibility, compressive modulus, good elasticity, similar structure to biological tissue and non-adhesion with soft tissue and controllable biodegradability.[9] It was reported that to the water uptake capacity of hydrogel overcome the problem of debridement and dryness of healing wounds as well as provide humid environment around the wounds for better vascularization.[12] Other than it, the properties like pore size, shape and surface volume ratio, water content, strength and swelling activities are measure parameters to design novel hydrogels.[8] Therefore, researcher focused on the biomaterials used for hydrogel having controlled degradation rate with proper cell interaction i.e., surface chemistry, tensional forces and 3D space.[13] In tissue engineering and cell culture system, hydrogel act as scaffold or ECM (Extracellular Matrix) having cell adhesion sites, differentiation and proliferation property with controlled release of growth factors or signaling factors for the regeneration of bio-functional tissue.[14] A part from benefit for the wound healing, hydrogels are easily applicable and comfortable materials to change with pain alleviating effect for the wounded tissue. The temperature of wound is decreased by hydrogel due to their high water content soothing the wounded area.[15] Particularly hydrogel is important in the treatment of dry wounds. Hydrogel are suitable for all the stage of healing process that is inflammation, cell proliferation, maturation and homeostasis of a wide range of wounds. They are non-reactive and non-irritant with biological tissue and permeable to metabolites. The variety of hydrogel dressing is most effective for wound treatments applying to a particular wound. These dominant features of hydrogels prevent their fast entrance in the dressing market, where hydrogel are obtained as saturated gauze, gels or sheets.

Polymers for hydrogel fabrication

Hydrogel consist of polymers either natural or synthetic with or without non-polymers particles (Table 1). In a gel the polymeric and non-polymeric particles are dispersed in liquid medium and cross-linked to provide steady state. This 3D cross-linked or interconnected polymeric network of fibers within the fluid system form sol-gel formless structure.16 Therefore, the stiffness, strength and stickiness of the materials play an essential role in stabilization and flow rate of gel.[17] Bio-polymers or natural polymers have received immense considerable over the past decade due to their safe nature, biodegradable nature, biocompatibility and hydrophillic properties.[18] Wide variety of bio-materials used for hydrogel preparation is classified into three groups: 1) protein based materials, 2) polysaccharide based materials,

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3) Decellularized tissue. Bio-polymers such as collagen, gelatin, Fibrin, Elastin, Skin fibroin have proteins in the ECM structure that provide strength, elasticity and making them future material for cell culture system and tissue engineering.[19] Polysaccharide based material include Glycosaminoglycans; Chitosan and Alginate are also used for the encapsulation of bio-molecule, drug and cells. Collagen is naturally proteins exclusively found in animals. In mammals it is the most abundant protein found in connective tissue and about 25% to 35% protein content of the whole body. It was reported that two third of the amino acids of collagen helix have less flexibility, stringent the overall structure of the proteins and hold its forms.[20] Therefore, collagen fibers can holds up together at temperature above it take for natural collagen to fall apart.

Table 1 Polymers for hydrogel preparation and their properties

Polymers	Properties
Collagen	Main component of ECM (Extracellular matrix), triple helical fibrous protein provides strength to the tissue, act as matrix for cell attachment, biocompatible, non-immunogenic and biodegradable.
Gelatin	Partial hydrolyzed form of collagen, peptide mixture rich with RGD amino acids, having gelatinization property, biocompatible, non-immunogenic and biodegradable.
Fibrin	Insoluble protein found in the blood, good strength and stability, helps in clotting and sealing of wound
Hyaluronic acid	Negatively charged non-sulfated glycosaminoglycans (GAG) found in ECM, induce inflammation, lubricate the tissue and helps in wound healing,
Cellulose	Bio-polymer consists of glucose moieties (branched, linear or non-linear), obtained from plant and bacterial cells, have good mechanical strength, degrability, biocompatible, less toxic, promote hemostasis.
Alginate	Another form of polysaccharide obtained from brown seaweed, hydrophilic, form gel with Calcium ions, from agglomerates, biocompatible and biodegradable.
Chitosan	It is a linear polysaccharide consists of amino sugars found in chitin shells of shrimp, crabs etc., biocompatible, biodegradable, anti-microbial and less toxic in nature.
Silk	Natural fibrin protein obtained from silkworm cocoons, rich in RGD amino-acids, having excellent strength, hydrophilicity, biocompatible, bio-degradable, non-immunogenic,
Polycaprolactone (PCL)	PCL is a synthetic bio-degradable, hydrophobic, good strength and biocompatibility.
Polylactic acid (PLA)	Polymer found in agro-waste act as thermoplastic, having good strength, biocompatibility and biodegradability.
poly(glycolic acid) (PGA)	Linear thermoplastic, semi-crystalline structure, having good strength and stability.
Poly Lactic-co-Glycolic Acid (PLGA)	It's a co-polymer consist of PLA and PGA, good solubility, biocompatibility and bio-degradability.
Polyethylene glycol (PEG)	Synthetic polyether, also called poly(ethylene oxide) (PEO), hydrophilic, good gelatinization and strength

Another category is synthetic or man-made polymers such as Silicon, Polyester, Polycaprolactone (PCL), Polylacticacid (PLA) etc are widely used for fabrication of grafts due their good mechanical stability and strength. For hydrogel preparation synthetic polymer used have different characteristics and chemical structures for prolonged water retention capacity.[21] Synthetic polymers have precise control and ultrastructure that can be tailored to give a wide range of properties.[22] Therefore, it's easy and feasible to designed polymeric matrix according to the specific needs and applications. In several study it was also found that some synthetic polymers e.g., Polyethylene oxide (PEO) and Polyethylene glycol (PEG) have excellent solubility, low immunogenicity, biocompatibility, and also minimize the risk of contaminants and biological pathogens.[21,23] Bioabsorable hydrogels were prepared by used using copolymers that are structurally semi crystalline and crystalline by gel sol transition and evaluated for healing process.24 The natural hydrogel have some limitations, they don't have strong mechanical properties and not easily controllable. Thus, consequently widely experimental study has been conducted to creating composite polymers and blends by mixing bio-polymers with synthetic for better stability and controlled biomechanism.[25]

Hydrogel preparation techniques

There are various techniques for synthesizing hydrogel such as chemical crosslinking, physical crosslinking, polymerization; radiation crosslinking has been used for preparation of hydrogel.[26] The fabrication of Hydrogels involves, a diversity of crosslinking techniques comprising amide crosslinking, enzyme mediated crosslinking, thiol disulfide exchange, click chemistry, schiff base reactions (Figure 1). Especially the polymer precursor's nanogel has been used for the fabrication of Hydrogels.[27] Crosslinking: Polymeric chain either linear or branched having covalently bond to form a polymer network done by the process of crosslinking.[28] It is the main process for the preparation of hydrogel dressing. Dissolving in an aqueous environment is formed a spatial network by crosslinking to prevent the hydrophilic polymer chain. Crosslinking methods involve chemical and physical crosslink for hydrogel synthesis. Chemically crosslinking formed by covalent bonds between polymeric chains. The characterization of chemical hydrogels can be done by better stability and enhanced mechanical properties. The design of sophisticated material systems have been enabled by doing advancement in modern polymer chemical transformation which have

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broad range of applications.[29] However, the physical crosslinking occur by the supramolecular interaction between the molecules, due to these crosslinking it's called as supramolecular hydrogels.[30] There are different types of supramolecular interaction forms like ionic, van der Waals forces and hydrogen bonds in the formation of hydrogel.[31] These weak interaction forms polymer aggregates in the microstructure region of hydrogel polymers chains and seize them together.[32] Polymerization: It's a common method to generate elongated chain of monomer linked together to form macromolecules.[33] In this process three basic steps i.e., initiation, propagation and termination of process are required to generate polymer. For the initiation of reaction specific reagent or initiator required to generate free radicals. Subsequently, free-radicals forms crosslinkage between the monomeric units, chain elongation, and leading to the formation of polymeric chain. In case of hydrogel, chemical cross-linking e.g., bifunctional or multifunctional cross linkers, is used to design heterogeneous polymeric hydrogels for better effects.[31] Ionic interaction: It was reported that, except covalent interaction, electrostatic force helps to crosslink the polymers fibers or particles in hydrogel for better healing and sealing of wound.[34] In case of automatically self-repair, after sometime Zwitter Ionic Fusion form like carboxybetaine acrylamide (AAZ), 7-acrylamidoheptanoate acid (AAS) have anionic charge from ziwtter ionic likage with nonionic hydroxyhexylacrylamide (AAN).[35] The self-healing behavior is vary due to the variation in chemical structures, charges of polymers and the migration of the free ions part of the polymer chain. Radiation crosslinking: In some case to reduce the toxic effect of crosslinking reagents, in hydrogel crosslinking done by radiation, especially to polymerise unsaturated compounds.[36] Radicals are form by high radiation treatment in an aqueous solution initiates free radicals polymerization and recombined with different polymer chain to form covalent bonds. Hence, the Hydrogels are non-toxic, cheap and having a sterilization formulation for clinical application.[11]

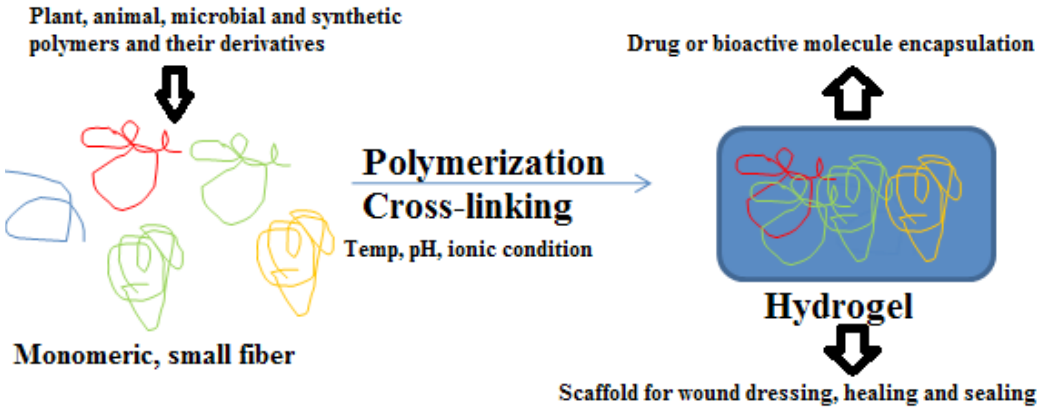

Figure 1 Basic outline of hydrogel synthesis.

Applications and advances

Hydrogel demands increases in the bio-medical fields due to its self-healing, free adaptable form and stabilize structure. Hydrogel have great attention for application and uses because of their unique properties such as flexibility, biocompatibility, softness, high water content.[6] Application of Hydrogel extensively forum in agriculture, wound healing, pharmaceutical, diagnostic, drug delivery systems, tissue engineering, biomedicine, environmental science, hygiene products, microelectronics industry, food industries.[37,38] In case of drug-delivery or controlled release of bio-molecules smart and intelligent hydrogels are used for the delivery of various drugs from micro molecular to macromolecular level including growth factors and enzymes.[30,39] In addition, the encapsulation ability of wide size range bio-molecules and their release can be achieved due the water sorption capacity of hydrogel. Thus, the swollen polymeric fibers makes dry networks with drug molecules and effectively enters or absorbed through the oral, buccal, nasal, vaginal, intestinal tissue.[40] Hydrogel also have ability to receive, transmit, and respond to external stimulus and produce a beneficial effect on bio-mechanism for healing. The nano to micro porous matrix of the hydrogel is an important feature that permits drug loading and the diffusion coefficient results in controlled drug release at a specific rate.[41] Besides, the application of hydrogels on drug-delivery or as therapeutic agent, they are also used for tissue regeneration. In tissue engineering, bio-materials and synthetic polymers along with novel techniques for fabrication has been used to improve the quality of hydrogel specifically for tissues or organs regeneration.[42] Hydrogel scaffold is useful for cell transplantation and tissue engineering (cartilage, bone and smooth muscles). There are some applications that have been reported for hydrogels are micropumps and microvalves, antimicrobial and antibacterial products, timed release of growth factors and other nutrients to ensure proper tissue growth, good transport properties and also easy to modify and can be injected. A potential treatment for resistant bacterial infection and wound healing can be treated by silver nanoparticles loaded hydrogels.[30] Horseradish peroxidase-catalyzed hydrogelation for biomedical application such as wound closure and peritoneal prevention, HRP excluded hydrogels, cell selective separation and cryopreservation.[43] Advanced hydrogel is applicable for delivery of active compounds in wounds and dressing for sensor and imaging of wound healing under controlled temperature, pH parameters and infection biomarkers.[44,45]

Conclusion

Hydrogel shows significant out and play an important in biological sector either in treatment or testing. Natural polymers such as ECM protein based hydrogel potential used for scar-less and faster healing of any size or shape. But the wide range of wound types needs to focus to design self-modulating hydrogel according to the types of wounds. Therefore, many researchers have been continuously working to design smart and intelligent hydrogel for faster healing at cheaper level.

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Conflicts of interest

The author declares that there is no conflict of interest.

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