Applications of Hydrogels in Biomedicine

Subjects: Cell & Tissue Engineering

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Hydrogels are crosslinked polymer chains with three-dimensional (3D) network structures, which can absorb relatively large amounts of fluid. Because of the high water content, soft structure, and porosity of hydrogels, they closely resemble living tissues. Research in recent years shows that hydrogels have been applied in various fields, such as agriculture, biomaterials, the food industry, drug delivery, tissue engineering, and regenerative medicine. Along with the underlying technology improvements of hydrogel development, hydrogels can be expected to be applied in more fields.

Keywords: hydrogel ; medical application ; 3D cell culture ; drug delivery ; wound dressing ; tissue engineering

1. Introduction

Hydrogels comprise a three-dimensional (3D) network which can absorb a large amount of water and swell in the water due to their hydrophilic groups, such as -NH_2, -COOH, -OH, -$CONH_2$, -CONH, and -SO_3H [1][2][3][4][5][6][7][8][9]. Its network is usually constructed by crosslinked polymer chains that sometimes can be formed through crosslinked colloidal clusters [10][11][12][13][14][15][16][17]. They can be flexible and soft, which are results of their water absorption ability [18]. Chemical or physical crosslinking of natural or synthetic polymer chains can be used to design the hydrogels [19][20][21][22][23]. Because of the high water content, soft structure, and porosity of hydrogels, they closely resemble living tissue. Wichterle and Lim first developed hydrogels for biomaterials in 1960. They produced a synthetic poly-2-hydroxyethyl methacrylate (PHEMA) hydrogel, which was then used as a filler for eye enucleation and contact lenses [24]. Since then, the expense of hydrogels in drug delivery and bioactive compound release has been elevated in several early studies from the 1970s to the 1990s [25][26][27][28][29]. In the 1990s, hydrogels were applied in tissue engineering [30][31][32][33]. The application of hydrogels was restricted to only the surface environment from the 1970s to the 1990s, for applications in the eye or open wounds, for example. The properties (e.g., swelling–deswelling rate, stiffness, degradability, mech size) of hydrogels can be adjusted by changing the hydrophilic and hydrophobic ratios, the initiator or polymer concentrations, and the reaction conditions (time, temperature, container, etc.) [34][35][36][37]. The biomedical application of hydrogels is not limited to the surface environment due to in situ gelation after infection and the stimuli responsiveness of the hydrogel [38][39].

Over the past 60 years, hydrogels have been engineered to be implantable, injectable, and sprayable for many organs and tissues [38][39]. Recently, hydrogels have gained attention in the field of environmental engineering [40], soft robotics [41], and wastewater treatment [42]. With the underlying technological improvement of hydrogel generation, hydrogels can be expected to be used in more fields.

2. Biomedical Applications of Hydrogels

2.1. 3D Cell Cultures

Three-dimensional cell cultures provide a useful platform for the cell to grow in vitro in all directions. Compared with the 2D culture system, it is easier to understand the in vivo cell behavior, since cells form a 3D structure in living tissue. The 3D cell culture is achieved by culturing the cells on a 3D scaffold. In the in vivo 3D cell structures, the cells are embedded in the extracellular matrix (ECM) and form a 3D structure. ECM is known to play an important role in regulating the cell behavior [43]. Hydrogels have a 3D structure and a hydrophilic polymer network capable of absorbing water in addition to biological fluid [1][2][3][4][5][6][7][8][9][44][45]. Thus, they can construct the soft and wet 3D structure which is like the extracellular matrix (ECM), which is available to encapsulate the cells. This results in those hydrogels which have gained increasing attention in the application of scaffolds for 3D cell cultures [46][47].

Hydrogels can comprise natural, synthetic, and semi-synthetic polymers. These hydrogels provide distinct biochemical, physical, and mechanical properties for the 3D cell culture [43]. **Table 1** describes the recent application of these hydrogels

for 3D cell culture. Natural hydrogels have good biocompatibility, endogenous factors, and the similar viscoelasticity and fibrils of the ECM. These hydrogels can support cell activity for 3D cell cultures.

Table 1. Natural, synthetic, and semi-synthetic hydrogels for 3D cell cultures.

Source of Hydrogels	Properties	Materials	Cell	Applications
Natural	Provide comparable viscoelasticity and fibrils to the ECM; having good biocompatibility; endogenous factors can support cellular activity	Collagen	Rat chondrocyte [48], hMSCs [49][50], rMSC [51], HUVECs/hASCs [52]	Maintain the chondrocyte phenotype [48]; facilitate chondrogenic differentiation of hBMSCs [49] and rBMSCs [51]; form stable EC networks [52]; promote cell viability; promote growth of hMSCs [50].
		HA	hiPSC-NPCs [53], hiPSCs [54], rMSCs [55], human breast cancer MCF-7 cells [56], HepG2 cells [57], human dental pulp stem cells [58], hNS/PC [59], and hMSCs [60]	Promote the neural differentiation of hiPSC-NPCs [53]; cardiac differentiation of hiPSCs [54]; osteogenic differentiation of human dental pulp stem cells [58]; the adhesion and proliferation of HepG2 cells [57]; cell spreading, fiber remodeling, and focal adhesion of hMSCs [60]; maintain the stemness of rMSCs and induce the direct cartilage differentiation [61]; enhance the tumorigenic capability of MCF-7 cells [56]; increase the oligodendrocytes and neural differentiation of hNS/PC and support long-term cell viability [59].
		Fibrin	HUVECs/hMSCs [62], porcine cumulus–oocyte complexes (COCs) [63], primary human chondrocytes [64], mHPSCs [65], and hiPSCs/HUVECs/human dermal fibroblast [66]	Prevascular formation of HUVECs, improve cell viability and proliferation of hMSCs and enhance their osteogenic differentiation and bone mineral deposition [62]; maintain the functional relationship between oocytes and follicular cells [63]; induce the production of glycosaminoglycans and collagen type II of primary human chondrocytes [64]; enhance the murine hematopoietic stem/progenitor cells (mHPSCs) expansion and differentiation [65]; no effect viability and prevascular formation of encapsulated cells [66].
		Alginate	hESCs/hiPSCs [67], hiPSCs-derived neurons [68]	Enhance the generation of retinal pigmented epithelium and neural retina of hESCs/hiPSCs [67]; form complex neural networks [68].
Synthetic	Have the good mechanical strength to provide structural support for various cell types in 3D cell culture	PVA	mHSCs [69], mSCCs [70], human glioma cell lines LN299, U87MG and Gli36 [71], human breast cancer Hs578T cells, and human pancreatic cancer cell lines Sui67 and Sui72 [72]	Enhance the expansion of murine hematopoietic stem cells (mHSCs) [69]; promote the meiotic and post-meiotic differentiation rate of mSCCs [70]; form tumor spheroids [71][72].
		PEG	hiPSCs [73], mMSCs [74], chondrocyte [75], and hMSCs [76]	Enhance the hematopoietic differentiation of hiPSCs [73]; evaluate the behavior of mMSCs [74] and hMSCs at the specific condition [76]; prolong the oxygen release of chondrocytes [75].
Semi-synthetic	Have a feature of ECM microenvironment and faster stress relaxation	HA–PEG	hiPS-HEPs [77] and HUVECs [78]	Enhance viability and functionality of hiPS-HEPs [77]; promote the capillary-like sprouts formation of HUVECs spheroids [78].
		RGD–alginate–PEG	Fibroblasts and mMSCs [79]	Increase the spread and proliferation of fibroblasts and the osteogenic differentiation of mMSCs [79].

2.2. Drug Delivery

Polymers are one of the most promising substances for the preparation of drug delivery systems. Polymers can be prepared for various nanostructures, including polymeric micelles, polymeric vesicles, and hydrogels. Those

nanostructures are great for drug delivery [80]. Increased interest in hydrogels is focused on smart hydrogels due to the stimuli-responsive properties of polymeric moieties. Stimuli-responsive properties can enable the formulation of novel targeted drugs and control drug release through non-intravenous administration. It can also delay the effect of opsonization by low blood contact.

The basic advantage is the ability of a smart hydrogel to change its properties (such as mechanical properties, swelling capacity, hydrophilicity, or permeability of bioactive molecules) under the effect of surroundings, including temperature, pH, electromagnetic radiation, magnetic field, and biological factors. Smart hydrogels can be prepared by the natural or synthetic polymers. There is a problem with natural hydrogels, which is that its mechanical properties make it difficult to maintain consistency.

Although this problem with natural hydrogel can be overcome by extensive chemical modification for natural polymers, it is very difficult to process [81]. In contrast, synthetic polymers are easy to alter their chemical or physical properties. The biodegradable and hydrophilic synthetic polymers are the most competitive substances for the synthesis of smart hydrogels for drug delivery. Those synthetic polymers endow smart hydrogels with low toxicity, low side effects, and low blood material adhesion. Of these, the low blood material adhesion can slow the effect of opsonization and reduce the phagocyte elimination. **Table 2** shows the application of those synthetic smart hydrogels for drug delivery.

Table 2. Smart hydrogels for drug delivery.

Hydrogels	Drug	Materials	Sustained-Release Time	Proposed Applications	Ref.
Thermoresponsive hydrogel	Dexamethasone	HPMA	More than 30 days	Osteoarthritis and rheumatoid arthritis	[81]
	Topotecan	Poloxamer 407 and poloxamer 188	28 days	Colorectal cancer	[82]
	Lamivudine and zidovudine	Pluronic® F-127	168 h	AIDS	[83]
	Antibody	PEGMA	13 days	Enhance the efficacy of antibody treatment	[84]
pH-responsive hydrogel	Bortezomib	mPEG-LUT	50 h	Colorectal cancer	[85]
	Amifostine (S-2(3-aminopropylamino) ethyl phosphorothioate	MAC-g-PCL	6 h	Acute radiation syndrome	[86]
Photoresponsive hydrogel	Doxycycline	SPCOOH modified-silicone-hydrogel (poly(HEMA-co-PEGMEA))	42 h	Inflammation disease	[87]
	Insulin	BP, pNIPAM, PEG, and ETPTA	Not detected	Diabetic disease	[88]
Daul-responsive hydrogel					
pH/thermo	Doxorubicin chemosensitizer curcumin	poly (NIPAAm-co-DMAEMA)	168 h	Colon cancer	[89]
	Methotrexate		50 h	Breast cancer	[90]
pH/redox	Magnesium ions	poly (NIPAAm-co-DMAEMA) PLP-CDE	6 h	Ionic therapeutics	[91]

2.3. Wound Dressings

The skin is the largest human organ and consists of epidermis, endothelium, and subcutaneous tissue from outside to inside. Skin is attacked by physical, chemical, or thermal damage, which results in wounding. Wounds lead to the destruction of skin structure and function [92]. The creation of a wound will trigger a series of physiological responses that promote wound repair, known as wound healing [93]. Wounds can be categorized by the nature of the repair as acute and chronic wounds. Acute wounds are mainly caused by mechanical injuries, such as abrasions, cuts, burns, scalds, or surgical incisions, and can heal completely in about 8–12 weeks [94]. Chronic wounds are wounds with delayed healing,

12 weeks after the initial injury [89]. These wounds are mainly caused by repeated tissue damage, underlying physiological factors (such as diabetes, impaired angiogenesis, innervation, or cell migration), or acquired physiological factors (such as malignancy or infection) [95][96]. Once a chronic wound forms, it can eventually lead to amputations or even mortality [97]. The wound healing process is dynamic and complicated. It involves four phases: hemostasis, inflammation, proliferation, and remodeling [98]. The hemostasis phase occurs within minutes of the injury. During this period, platelets stick to the wound site, engage with collagen, and release thrombin, which activates fibrin to form a network that stops blood loss. The inflammation phase occurs when immune cells (especially neutrophils and macrophages) are recruited to the wound site by platelets. Immune cells engulf damaged cells, dead cells, bacteria, and other pathogens at the wound site. At the same time, various peptide growth factors are released by platelets and inflammatory cells, which promote the migration of fibroblasts to the wound site.

During the proliferation phase, fibroblasts proliferate at the wound site and rebuild the dermal tissue, employing granulation tissue formation and extracellular matrix protein deposition. Within the granulation tissue, blood vessel networks will be formed, providing sufficient oxygen and nutrients to improve cell survival. Epithelial cells then migrate from the wound edge to the center to cover the defect: this process is termed re-epithelialization. During the remodeling phase, excess collagen fibers are degraded in the dermis, and the wound shrinks and heals rapidly. Therefore, the use of wound dressings to quickly stop bleeding, prevent infection, and promote repair can speed up wound healing and reduce unnecessary mortality.

Characteristics of an ideal wound dressing should (1) provide and maintain a moist environment, (2) permit the easy transmission of gases, (3) remove exudates and absorb blood from the wound, (4) have low adherence to skin, (5) reduce wound necrosis, (6) prevent infection, (7) allow heat insulation, (8) enhance epidermal migration, (9) promote angiogenesis, (10) have low toxicity and be biocompatible and biodegradable [98]. Several studies have shown that hydrogels can form a physical barrier and remove excess exudate. They also provide a moist environment to promote the process of wound healing. In addition, hydrogels can be applied as a sprayable or injectable wound dressing, which may fill irregularly shaped wounds [99][100][101]. They also present with similar properties as the natural extracellular matrix (ECM), biocompatibility, biodegradability, and tunable properties (such as shape, gel state, and mechanical strength). These advantages of hydrogels can simulate the development of hydrogels for different dressings for different types of wounds. Recently, functional hydrogels have received a lot of attention in wound dressing research. These hydrogels can exhibit high-performance biological activities, such as antibacterial properties, promoting blood coagulation, or promoting blood regeneration, etc. [102].

Wound dressings with hemostasis, angiogenesis, antibacterial infection, and anti-inflammation characteristic have a good impact on wound healing. Natural polymers, such as cellulose, chitosan, collagen, and HA, contain endogenous bioactivation factors. These natural hydrogels are a good wound dressing for wound healing. For example, an in-situ-formed collagen–HA hydrogel was adapted to promote spontaneous wound healing. In addition, this hydrogel inhibited the growth of planktonic *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) [103]. PEG-modified collagen–chitosan hydrogels further reduce the zone diameters of *E. coli* and *S. aureus* biofilms. This hydrogel also exhibits hemostatic ability, which can enhance wound healing [104]. Zhu L. and Chen L. developed CF-encapsulated graphene–silk fibroin macromolecular hydrogel dressings, which have functions of antibacterial (both planktonic and biofilm *S. aureus* and *Pseudomonas aeruginosa* (*P. aeruginosa*)) and enhanced fibroblasts growth. These have a great healing ability for burn wounds [105]. Khaliq T et al. used the chitosan HCl, κ-carrageenan, and PVA-based, physically crosslinked hydrogel to load cefotaxime sodium (CTX), which displays a high oxygen permeability and antibacterial capacity for inhibiting the biofilm size of *S. aureus, P. aeruginosa*, and *E. coli*. This hydrogel provided higher re-epithelialization and good granulation tissue formation for healing burn wounds in a diabetic rat model [106]. In addition, the silver-nanoparticle-loaded pH hydrogel also showed the effective elimination of *P. aeruginosa* and *Staphylococcus epidermidis* (*S. epidermidis*) in in vitro antibacterial biofilm studies. This hydrogel provides a promising strategy to enhance the healing of drug-resistant-bacteria-infected wounds [107]. The in vivo effect of this hydrogel needs further investigation. Collagen–PEG injectable hydrogels containing umbilical cord stem cell factor (SCF) can induce neovascularization and skew toward M2 macrophages in diabetic wounds. They can promote diabetic wound repair based on their angiogenesis and anti-inflammation abilities [108]. It is unknown whether this hydrogel has functions in the inhibition of bacterial growth due to the lack of antibacterial activity assay studies. A 3-carboxy-phenylboronic-acid-grafted gelatin–PVA hydrogel exhibits excellent hemostasis properties enhancing cell adhesion. This hydrogel further encapsulates the vancomycin-conjugated silver nanoclusters (VAN-AgNCs) and nimesulide (NIM), endowing an anti-inflammatory effect. It also has the capacity to inhibit the planktonic *S. aureus* and *P. aeruginosa* growth in a VAN-AgNCs dose-dependent manner. In an in vivo experiment, this VAN-AgNCs- and NIM-loaded 3-carboxy-phenylboronic-acid-grafted gelatin–PVA hydrogel can induce the sequential healing processes to promote the healing of chronically infected diabetic wounds [109]. Plasma-exosomes-loaded, pH-responsive carboxymethylcellulose (P-Exos-loaded CMC) hydrogel stimulates the activation of the vascular endothelial

growth factor (VEGF) signaling pathway. This pathway further enhances angiogenesis and re-epithelialization to promote the wound healing process in diabetic type 1 mice [110]. Another study uses the umbilical-cord-derived mesenchymal stem cell exosomes combined with Pluronic F127 hydrogel to demonstrate that this hydrogel can induce the expression of transforming growth factor beta-1 (TGFβ-1) and cell proliferation in addition to VEGF production. Based on the above ability, it can enhance the regeneration of granular tissue and angiogenesis in chronic diabetic wound healing [111]. However, the antibacterial activity of exosomes-loaded hydrogels is unclear in these two studies [110][111].

2.4. Tissue Engineering

Tissue engineering is a promising and challenging strategy to treat patients who suffer functional failure and irreparable tissue destruction [112]. The aim of tissue engineering is to develop a scaffold mimicking an in vivo extracellular matrix to support tissue regeneration. Hydrogels have gained great interest in tissue engineering due to their mechanical strength, biocompatibility, biodegradability, and the resemblance to in vivo extracellular matrix [113].

A hydrogel scaffold can be useful in tissue regeneration of nerves, cardiac tissue, cartilage, and bone. For example, the 3D printing of collagen–chitosan is beneficial in decreasing scar and cavity formation and can improve the regeneration of nerve fibers, as well as functional recovery, when tested in an animal model [114]. Another example is HA combined with alginate and fibrin. This was applied as an ink ingredient of 3D printing in peripheral nerve tissue regeneration [115]. In addition, the HA–cellulose hydrogels can repair the central nerves [116]. Li J et al. used horseradish peroxidase (HRP) and choline oxidase (ChOx) crosslinked gelation hydrogel to encapsulate the mMSCs. This hydrogel displays a high capacity to promote cellular viability, neural differentiation, and neurotrophic secretion of loaded mMSCs. Based on that capacity, it can enhance the survival and proliferation of endogenous neural cells and neurological function recovery of traumatic-brain-injured mice [117].

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