Hindawi
Advances in Materials Science and Engineering
Volume 2018, Article ID 4368910, 13 pages
https://doi.org/10.1155/2018/4368910

Review Article

Hydrogels for the Application of Articular Cartilage Tissue Engineering: A Review of Hydrogels

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Received 27 June 2017; Revised 19 December 2017; Accepted 25 December 2017; Published 3 April 2018

Academic Editor: Jun Liu

The treatment of articular cartilage damage is a major task in the medical science of orthopedics. Hydrogels possess the ability to form multifunctional cartilage grafts since they possess polymeric swellability upon immersion in an aqueous phase. Polymeric hydrogels are capable of physiological swelling and greasing, and they possess the mechanical behavior required for use as articular cartilage substitutes. The chondrogenic phenotype of these materials may be enhanced by embedding living cells. Artificial hydrogels fabricated from biologically derived and synthesized polymeric materials are also used as tissue-engineering scaffolds; with their controlled degradation profiles, the release of stimulatory growth factors can be achieved. In order to make use of these hydrogels, cartilage implants were formulated in the laboratory to demonstrate the bionic mechanical behaviors of physiological cartilage. This paper discusses developments concerning the use of polymeric hydrogels for substituting injured cartilage tissue and assisting tissue growth. These gels are designed with consideration of their polymeric classification, mechanical strength, manner of biodegradation, limitations of the payload, cellular interaction, amount of cells in the 3D hydrogel, sustained release for the model drug, and the different approaches for incorporation into adjacent organs. This article also summarizes the different advantages, disadvantages, and the future prospects of hydrogels.

1. Introduction

1.1. Introduction to Articular Cartilage. Articular cartilage is a thin layer that covers joint surfaces. In a young and normal joint, the articular cartilage is called hyaline articular cartilage, a dense, translucent, and white connective tissue. Articular cartilage is a specialized tissue that can offer shock and impact absorption, which serves to further protect bone tissue [1, 2].

Chondrocytes are cells that are distributed in articular cartilage, and they account for less than 10% of the volume of the tissue [3]. Even though chondrocytes are distributed in the articular cartilage, they are responsible for production, secretion, organization, and maintenance of the organic component of the extracellular matrix (ECM) [3–5]. In the body, the most abundant protein is collagen [6, 7]. Collagen accounts for a large amount of the fibrous ultrastructure in articular cartilage [8–10]. The fibrils that polymerize via rod-like tropo-collagen molecular structure (1.4 mm in diameter and 300 nm in length) [6, 7] have a mean diameter around 25 to 40 nm. Type II collagen is the main component of cartilage, and it is present in articular cartilage, sternal cartilage, and the meniscus. From a physiological viewpoint, articular cartilage is an isolated organ with no lymphatic channels, blood vessels, and neurologic innervation, and its density of cell is below that of other tissues [11].

The principal purpose of articular cartilage is for offering a lubricated, smooth surface, decreasing the frictional coefficient and stresses sustained by the contacting joint surface, and facilitating the transmission of loadings

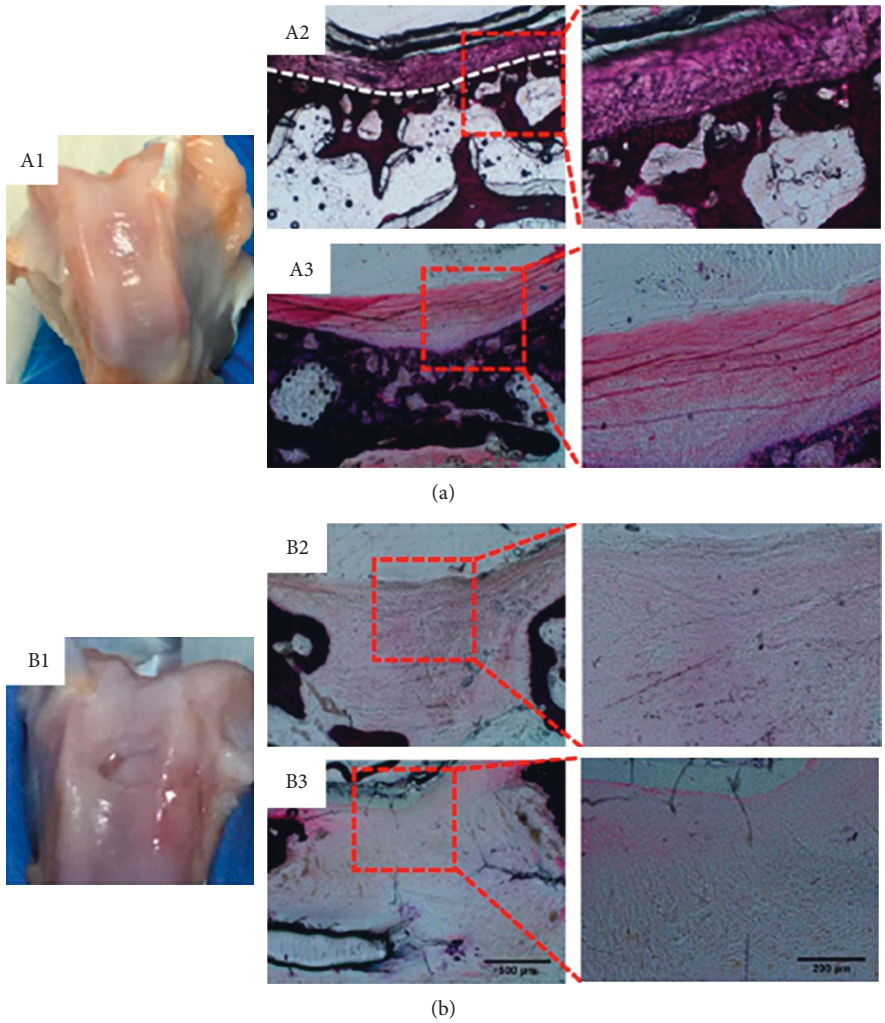

Figure 1: Histological examination in a rabbit articular cartilage study. Adapted with permission from [15], copyright 2017 ACS Publications.

to the underlying subchondral bone as indicated in Figure 1 [12–14].

1.2. Articular Cartilage Damage. Lesions of the articular cartilage may restrain joint function by preventing the lesion from healing spontaneously, and it may further lead to osteoarthritis (OA) [16, 17]. Articular cartilage lesions can be briefly classified into four types: (1) localized focal osteochondral or chondral lesion, (2) OA, (3) osteochondritis dissecans, and (4) other types [18]. The medial femoral condyle and patellar articular surface are locations where cartilage lesions often occur because of their presence in a weight-bearing area. Cartilage lesions can be systematically classified through the Outerbridge method [19]. This system divides cartilage lesions into four grades: Grade I is cartilage with swelling and unstiffening. Grade II is particle thickness damage with a crack on the surface where the defects do not stretch the bone located at the subchondral region or surpass 15 mm in diameter. Grade III is slitting of the layer of bone located at the subchondral region exceeding 15 mm. Grade IV is bare subchondral bone [20]. However, this classification system seems more suitable for the classification of OA rather than for cartilage injury classification [21]. Additionally, other different classification methods have been developed, such as magnetic resonance imaging evaluation [22–28] and the ICRS hyaline cartilage lesion classification system [29].

1.3. Different Treatments for Articular Cartilage Damage (Healing Methods). Articular cartilage injury does not heal instantly, unfortunately, and the methods for articular cartilage repair are few. Slight cartilage damage can be treated by strengthening the surrounding muscles by physiotherapy, and pain and swelling can be reduced by anti-inflammatory drugs [30–32]. However, if the cartilage injury is more serious, surgical treatment may be considered. From the point of view of pain reduction, arthroscopic lavage/debridement can be used to wash the cartilage by an injection of saline solution [33, 34].

Microfracture is one regeneration technique. The hematoma that contains mesenchymal stem cells (MSCs) are

formed by small fractures created on the bone. These MSCs can differentiate into chondrocytes and create new cartilage [35, 36]. Although this method is relatively fast, the hematoma cannot totally fill the defect [37]. Furthermore, the cartilage formed by the microfracture method is fibrocartilage; this fibrocartilage is weaker, denser, and possesses lower stiffness in comparison with hyaline cartilage [38]; these weaknesses lead to an increase in the probability of recurring damage [39, 40].

A second method, osteochondral autograft transplantation (mosaicplasty), involves the transfer of cartilage and subchondral bone from a nonload-bearing site to the damaged load-bearing site. Unfortunately, this method is only applicable to a small defect because of the small amount of possible donor sites [41–43]. The donor cartilage that is transplanted from a nonload-bearing site to the load-bearing site is more susceptible to damage because of the structural difference between the two regions of cartilages. To overcome this problem, osteochondral allograft transplantation is used. Cartilage from a donor cadaver may, however, pose a risk to the immune system of the recipient.

A third method is autologous chondrocyte implantation technique. This technique uses chondrocytes that have been harvested from healthy and nonweight-bearing cartilage. The cartilage is introduced into the damaged site or inserted into the scaffold of the damaged site before cells are introduced by matrix-induced autologous chondrocyte implantation [44, 45]. This autograft method can reduce the risk of rejection and can supply cells continuously. Nevertheless, this method is very slow, and the patient must undergo multiple surgeries.

The fourth method involves total joint replacement. This method is used only for cartilage that has been damaged beyond repair. In recent years, the survival rate of total knee replacements is between 90% and 95% [46, 47]. An artificial joint has a certain period of use; thus, young patients may require more surgery for further replacements during their lifetime, resulting in increased medical expenses.

Tissue engineering is a novel method that has great potential use in cartilage repair. Cell, scaffold, and signal are the three elements of tissue engineering. In this context, the general method for cartilage tissue engineering is placing the cells and/or growth factor (signal) into the hydrogel (scaffold) in order to repair the damaged cartilage. However, cartilage that has been repaired using the tissue-engineering method does not possess sufficient mechanical properties that confer load-bearing capability [48].

Once the cartilage damage has interacted with the underlying bone marrow, a case in which there is a full-thickness crack, self-healing repair may be achievable; however, the subsequent tissues undergo fibrosis and are physically or automatically disadvantaged in the injured cartilage of patients; finally, deterioration results from overloading of the knees [49]. The microfractural subchondral method, the transplantation of cartilage plugs, and the living chondrocyte seeding method are used as surgical procedures focusing on trying to induce the self-healing repair process [17, 50–52]. On the other hand, biomaterials that are used act as artificial cartilage substitutes and encourage the renewal of newborn tissue are designed for addressing the shortcomings of other presently applied procedures [53–56]. The cartilage tissues are composed of a long chain polymeric substance such as typical collagen and glycosaminoglycan, which swells in an excess of aqueous phase and thus results in behavior similar to that of hydrogels. This also creates a three-dimensional (3D) water-soluble polymeric network that has the ability to swell to an extreme extent in an aqueous phase [57, 58]. Since investigations on biological applications of methacrylate-based hydrogel about 60 years ago, hydrogels have been used as drug carrier systems, chemically modified implants for biomedical uses, devices used for diagnostic purposes, and for various purposes in engineered tissue [59]. Hydrogels possess biocompatibility, although many factors influence the response of the immune system to hydrogels. Some of these factors are the type of polymer, the choice of crosslinking approaches, the manner of biodegradation of the material, and the products that exist after degradation through an enzymatic process, as well as the cellular interactions involved and the behavior of the released active substance aspects [60]. The usage of hydrogels as biomaterials can be enhanced through the use of diverse factors such as the polymeric ingredients, crosslinker concentration, morphological change of the polymeric filaments, and the profile of degradation using the bioenzyme [57, 58, 60].

For the purpose of articular cartilage substitution, the hydrogels are created to be either resident substitutes for the replacement of injured cartilage or to be constituents loaded into cell that encourage or stimulate the regeneration of new tissue. Hydrogels can automatically form cartilage tissues that have physically comparable qualities, and they permit the effective loading for transfer as cellular empty grafts [61, 62]. Hydrogels possess other valuable qualities, for instance, their ability to enhance the stimulation of chondrocyte adhesion, which affects the ECM of cartilage such that a bioscaffold exists where the cellular seeding can be considered for tissue engineering [63]. These substances also possess the ability to preserve the behavior of a chondrocyte phenotype in difficult cultures, which appear in the given cellular structure [64–66]. They are also viscoelastic, allowing the transfer of support to the chondrocyte according to the mechanical requirements for survival [67, 68].

Numerous development variables can be adjusted to modify the properties of the hydrogels used as a substitute for cartilage or scaffold for tissue engineering. The major factors that need to be adjusted are the polymeric classification, crosslinking condition or method, manner of biodegradation and limitation of the payload, cellular interaction, amount of cells in the 3D hydrogel, sustained release time for the model drug, and approaches for inducing incorporation into adjacent organs. In the use of functional hydrogel for treating articular cartilage damage, suitable manufacture approaches and superb bio-materials act as important parts in developing perfect injectable polymeric hydrogels which could be considered as bio-scaffolds for bone and articular cartilage tissue engineering uses. A choice of biomedical materials, either synthetic or natural, has been elucidated to fabricate injectable polymeric hydrogels; those materials comprise poly(vinyl alcohol) [69], poly(ethylene glycol) (PEG) [70] or collagen, hyaluronic acid [71] (Figure 2, [72]), alginate [73],

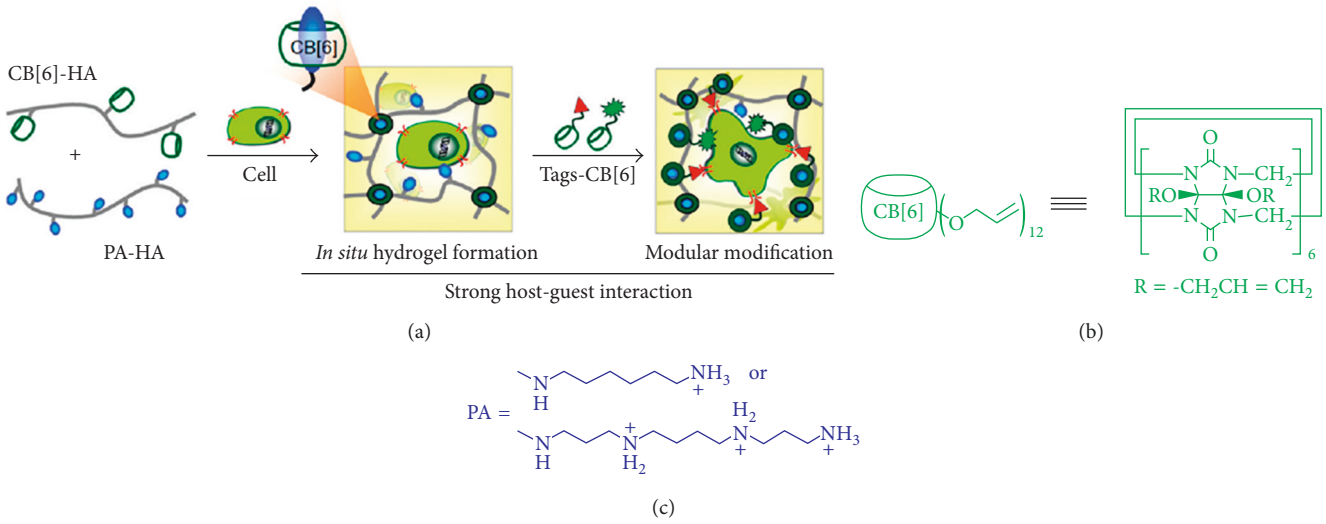

Figure 2: The functional hydrogel containing hyaluronic acid. Adapted with permission from (p. 2961) [72], copyright 2012 ACS Publications.

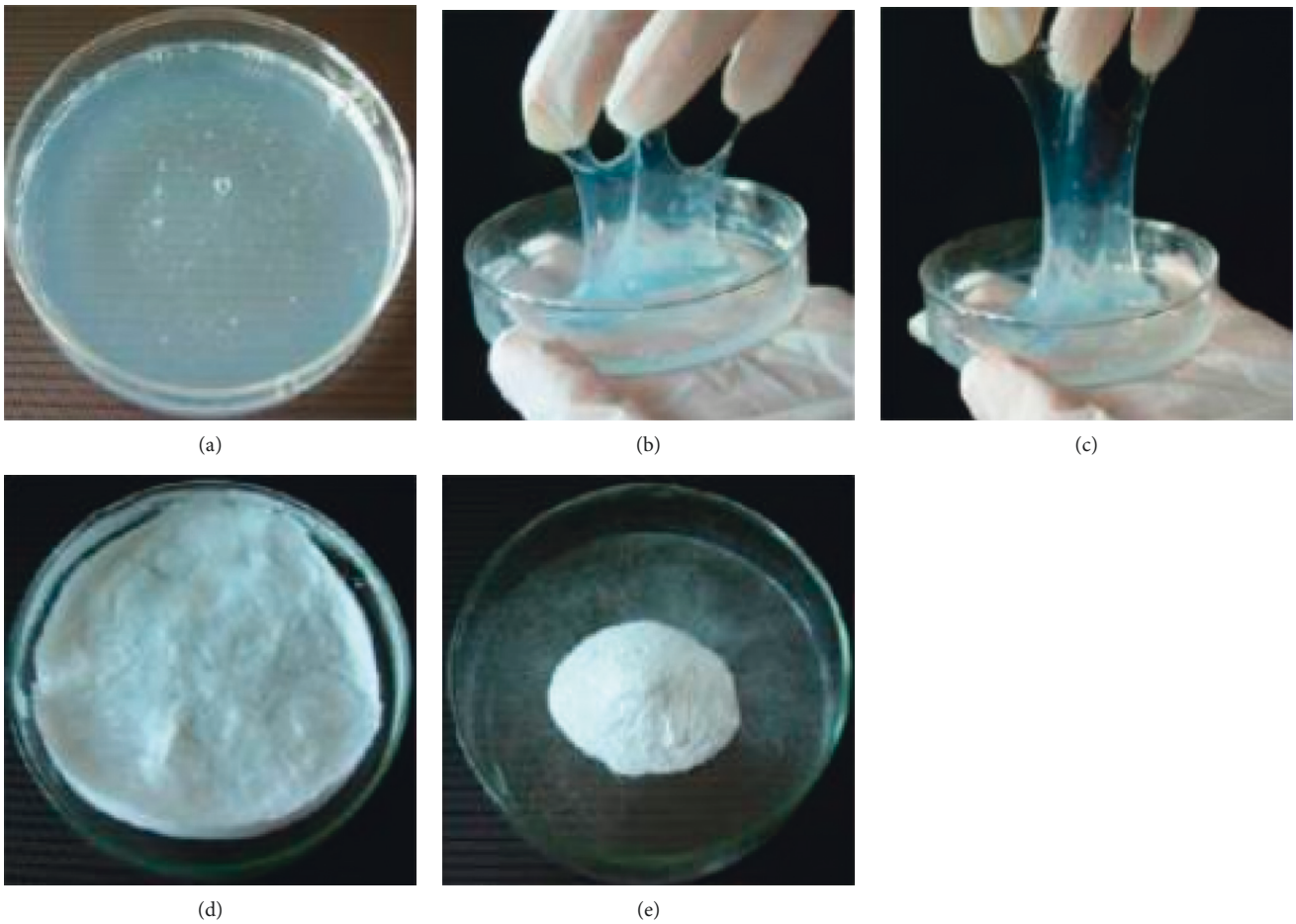

Figure 3: The fabrication of γ-PGA/gelatin hydrogel. Adapted with permission from (p. 692) [78], copyright 2014 ACS Publications.

chondroitin sulfate [74], heparin [75], gelatin [76, 77] (Figure 3, [78]), and chitosan [79]. Injectable polymeric hydrogel enables to be prepared via both chemical and physical ways. Chemical hydrogel is typically generated by covalent conjugation under crosslinking process, while injectable physical hydrogel is naturally made by feeble

secondary bonding of force [80]. Additionally, the binding peptides noncovalently attach on chondroitin sulfate and hyaluronic acid to biomimic the natural instincts of extracellular matrix and potentially enhance performance. [81, 82]. These water-soluble, vastly charged GAGs have been acknowledged for assistance in moisturizing tissue and donated to the mechanical property of enhancement for the natural articular cartilage tissue [83]. A detailed discussion regarding the classification, advantages, disadvantages, and future outlooks of these applied hydrogels is provided below.

2. Crosslinking Approaches for Fabricating Hydrogel

2.1. Crosslinking Approaches Using Chemically Modified Process. Hydrophilic polymers usually have functional groups (mainly hydroxyl, carboxyl, and amine) that may be utilized for the fabrication of hydrogels. Covalent conjugations between polymeric chains may be created by chemical modification of functional groups with affinity for one another, such as in a carboxyl acid–amine or a hydroxyl/NH_2–isocyanate interaction, or by Schiff base generation.

Crosslink in hydrogels may also be achieved by other methods such as condensation, crosslinking using an additional reagent, and linkage by irradiation or by using protease.

2.2. Crosslinking Approaches Using a Crystallization Process. Poly(vinyl alcohol) (PVA) is one kind of hydrophilic polymeric materials that has the feature of adhesion. When the liquid aqueous phase of PVA is kept at room temperature, they eventually transform into a gel without the requisite mechanical properties. Once the aqueous polymeric materials undergoes lyophilization, a robust and elastic hydrogel forms [84]. This feature of the gum is influenced by the PVA molecular weight, concentration, environmental temperature, and time of exposure to the lyophilization process. The development of the gel is attributed to the generation of crystallized PVA that serves as space of a physically crosslinking procedure within the complex. These gels obtained via the applied circumstances can be stable at least up to half a year at body temperature [85].

Hydrogels obtained from physical crosslinking are usually either graft copolymers or multiblock copolymers. The former may be formed from a hydrophilic polymer backbone, such as a natural polysaccharide, to which water-insoluble units or water-insoluble chains containing hydrophilic sections are bonded. Crosslinking may also be achieved by the contribution of hydrogen bonding through van der Waals forces [86], dispersion polymerization [87], and attachment functional groups by photochemical reaction [88]. It may also be achieved by enzymatically crosslinking processes for peptides [89], which involves the usage of a cross-linking reagent that is usually seriously cytotoxic and raises issues about the dependability of the prepared gel. To address these issues, hydrogels fabricated by physical crosslinking, which may be prepared by the use of some crosslinking means, for example, van der Waals interactions, crystallized process, ionic interactions, water-insoluble interactions, or peptide molecular interactions with pH-responsive property [90], are now discussed.

As a consequence of the swollen property of hydrogel materials, they have become of interest to investigators of the vital characteristics of swollen polymers in bulk, and they have been extensively applied in other scientific fields. Other applications include their use as a novel material for disposable contacts and protein/peptide purification, a matrix for cell incubation, an artificial filler, a drug carrier for the sustained release of medicine and peptide drugs, a substance nanocarrier for nutrients, and an agent in chemical or enhanced waste recovery.

On the basis of the reactivity of the functional residuals, the fabricated hydrogels would be categorized as ion or neutral; thus, neutral hydrogels possess a dynamic role in inflammation as a result of hydrophilic-polymer physical mixing. Such mixing is caused by the net Gibbs free energy, and the polymeric property of these substances is for clinical use [85]. The intricate features of the networked filaments include their crystallizations, structures of the hydrogen bonds, ultrastructures, and colloid aggregation [91].

2.3. Crosslinking Way Using Free-Radical-Interaction Polymerization. The swelling features of a hydrogel material may be adjusted using the desired amount of crosslinker. Triggerable materials can be acquired by the use of a crosslinker with the desired characteristics. One way of achieving the crosslinking process is through radical polymerized process, in which crosslinking hydrogels by chemical modification may also be achieved by free radical polymerization of hydrophilic polymeric materials with functional groups. Various hydrophilic polymers (natural, semiartificial, and synthetic) have been studied for the development of hydrogels through this method.

2.4. Crosslinking Approaches Using Ionic Polymerization. Alginate, a natural polymer, is a biopolymer that may be crosslinked by ionic polymerization. Alginate is one kind of polysaccharides that contains negatively charged glucuronic and mannuronic acid moieties and can undergo conjugation upon addition of calcium ions. This crosslinking process is performed at a room temperature and at neutral pH. The natural polymers can used as an extracellular matrix for embedding of living cells [68] and can be used as a drug carrier system to controllably release medicine [92]. It should also be noted that these hydrogels enable to be unstabilized by using the removal of the calcium ions from the hydrogel using a chelator. The release of a drug from a designed alginate microcarrier system can be controlled by coating the particles with positively charged polymers such as chitosan/chitin-based materials [93]. Gel microbeads are formulated by mixing an aqueous polychloro phenoxy phenol (PCPP) polymer in a water phase of Ca^{2+} ions.

3. Classification of Hydrogel

3.1. Homo- (Single-) Based Hydrogel Materials. Polymeric networks based on a single type of monomer are referred to as homo-based polymers. This is the fundamental structural

element for any polymeric network [94]. A crosslinked structure defined by the polymerization procedure or the property of the monomer used is observed in homogeneous polymers. For example, polyethyleneglycol- (PEG-) established hydrogel materials are sensitive to an environmental stimulant; thus; these hydrogels have been extensively applied in controlled release of model drugs. As chemically crosslinked PEG hydrogels may act as functional artificial scaffolding for protein drug encapsulation and useful tissue repair, they are candidates for use in this area. This is a biomaterial with potential use in the sustained release of medicine, peptide drugs, growth factors, and living cells [95].

3.2. Copolymeric-Based Hydrogel Materials. Natural hydrogels constituted of dual kinds of monomers of which more than one is water soluble are referred to as copolymeric hydrogels. An example of this is the novel triblock polycaprolactone polyethylene glycol copolymer (PECE) polymeric hydrogel matrix, which was designed for medicine carrier systems [96]. The ring-opening polymerization of co-caprolactone was achieved using the synthetic mechanisms. mPEG has been applied as the starting agent; stannous ions were used to be an activator of another chemical compound of hexamethylene diisocyanate was used for coupling the reagent in this triblock polymer modification. Such a multipolymeric block enables the production of a hydrogel in living tissue.

3.3. Thermosensitive Hydrogel Materials. Hydrogel materials that are capable of swelling and shrinking upon thermal exposure of bulk solution of the hydrogel are classified as thermoresponsive. The deswelling and swelling properties of these hydrogels are mainly decided by the environmental temperature [97]. Thermally sensitive hydrogels should be defined as negative or positive thermosensitive carrier systems [98].

The upper critical solution temperature (UCST) is noted as a property of positive thermal sensitive hydrogels [99]. This property indicates that once the bulk temperature is lower than the UCST, the hydrogel contracts and subsequently squeezes out the solvents or interstitial fluids from within the hydrogel matrix (a process also known as dehydration). Once the bulk temperatures return above the UCST, swelling behavior occurs. As described previously, this type of hydrogel reverts to its previous state once it is in a negative temperature environment. Because of the generation of the intricate structural interactions of the hydrogen bonds, positive temperature hydrogels shrink at lower environmental temperatures. As a consequence of loose hydrogen (H) bonding, molecular structure of the hydrogel disintegrates at high temperature. Additionally, this gel tends to swell to maximum and expands suddenly upon reaching the UCST. Many polymers and their copolymers possess such behavior, for instance, the stochastic copolymeric gel structure, ABA-type triblock copolymer [100].

It has been suggested that temperature-responsive hydrogels that form through physical crosslinking experience a solution-gelation phase transformation rather than a capacity alteration at critical bulk solution temperature, as has been reported upon previously [101]. Polysaccharide-modified polymeric materials such as *N*-isopropylacrylamide, methylcellulose, and hydroxypropyl methylcellulose are temperature-responsive hydrogels that have been widely examined [102–105]. The most well-known thermally sensitive polymeric material, poly(N-isopropylacrylamide) or named poly(PNIPAAm), shows a narrow transitional phase at a bulk aqueous temperature of 34.3°C, which is close to body temperature for use in biological applications. The lower critical solution temperature (LCST) of poly(PNIPAAm) can therefore be adjusted by performing copolymerization conjugation with other reactive monomers [106]. Through the addition of hydrophilic monomers, the LCST of synthesized hydrogel can be increased. The LCST of this substance also decreases upon combination with water-insoluble monomers. It is also known that the substitution of hydrophobic or hydrophilic monomers may not result in any substantial alteration of the LCST.

In contrast, another type of hydrogel has the LCST as the critical parameter, which implies that this hydrogel shrivels once the bulk temperature exceeds the LCST, swelling or expanding at a temperature under the LCST. For negative temperature-sensitive hydrogels, the LCST is the most crucial parameter that can be transformed through distinct methods, for example, by blending a tiny concentration of ionic copolymeric materials into the test gel materials or by exchanging dispersed ingredient. Generally, the polymeric LCST is shifted to lower temperatures if there is a greater amount of water-insoluble components in the system, as this shifts the ratio of water-soluble to water-insoluble components [107]. These hydrogels develop in two segments: the first is the water-soluble section, such as hydrophilic functional groups-, and the second is the water-insoluble section, such as –R– [108, 109]. The fluid or aqueous medium interacts with the water-soluble region by generating hydrogen bonds at temperatures below the LCST. The swelling and dissolution properties of the hydrogel are enhanced by the generated hydrogen bonds. The hydrophobic interactions with the water-insoluble region are stronger once the temperature approaches or surpasses the LCST, when the region composed of hydrogen bonds simultaneously becomes weaker. Because of the interpolymer-chain elongation, the shrinking of the hydrogel is inevitable [110], resulting in extrusion of the interfluid via a dehydration process. An example of this type of hydrogel is polyvinylpyrrolidone (PVP)/PNIPAAM, which is applied in a controlled drug-release system.

Some IPN-based hydrogels display positive thermosensitivity a behavior in which they contract in some conditions such as low temperature and would be swollen in high temperature. As noted in the literature [110], polyacrylamide, P(AAm-*co*-BMA), and poly(acrylic acid) are thermosensitive hydrogel materials. Adding the more amount of BMA raises the observed transitional temperature of the middle polymer. The stepwise temperature changes are reversible in terms of the swelling property of the hydrogels. For example, reversibly changed properties in a rate of ketoprofen release from the monolithic device have been studied. Copolymeric hydrogels that act as negative-temperature-responsive hydrogels have been discussed previously [111, 112]. The active substance has been noted to be released at a sustained rate mediated by the LCST [113]. The reduction of the transitional temperature upon the addition of a crosslinker was

examined, and the most prominent swelling behavior was observed at temperatures greater than the transitional temperature for both types of copolymeric materials. Since the test gel material was shown in absent of shrink or swell because of complementary hydrophobic-hydrophilic interactions, the model drug is released from the hydrogel at a steady rate.

Positive- and negative-temperature sensitive hydrogels possess similar structural compositions. The type of bonds they possess is the main difference between these two kinds of thermally responsive hydrogels. The crosslinking process between polymeric chains is achieved through noncovalent bonding. Rather than form a transitional state of swelling-shrinking, these types of gels undergo solution-gelation phase transitions.

Instead of a solution-gelation phase transitional state, the thermal response of hydrogels with chemically crosslinking components undergoes volume alterations. Certainly, hydrophobicity associated with molecular interactions or van der Waals force related to hydrogen bonds acts as a key factor in a swift volumetric alteration of the given hydrogel materials as they approach a critical solution temperature (CST). At the situation of swelling, H_2O-molecular H-bond interacted with the polar group of a polymer chain inside the hydrogel and coordinated with the surrounding hydrophobic moiety, such as cold water. When the CST is reached, the hydrogen bonds at the interface between polymer and water break, which in turn forces the rapid dehydration of the gel system. As the water is discharged, the entropy substantially changes because of shrinkage of the polymeric structure [114]. An example of such a polymer is poly (ethylene oxide) and poly(p-phenylene oxide) derivative (PEO–PPO–PEO), which is based on a thermally reversible hydrogel. It is vital that these thermally reversible hydrogels for clinical use possess biodegradability. In order to study the biodegradability, the polymeric material PEO–PPO–PEO, which contains a PPO segment, is commonly substituted with PLA. The suitable molecular weight and suitable structure combination caused by a hydrogel structure with changeable LCST points at either body or room temperature.

Hydrogels that possess thermal reversibility characterize the utmost imperative category of hydrogel materials. The water phase of these materials is subject to the gelation transitional state in solution in response to real stimuli. The hydrophobic region of the polymeric structure can be crosslinked in an aqueous state through a reversible thermal gelation process in which the hydrophobic derivative is integrated into the hydrophilic domain by attachment or copolymerization, and the surfactant-like substances are water soluble at relatively low temperatures. The solvent's entropy is therefore increased besides their hydrophobicity region is aggregated in order to reduce its surface area once the temperature is increased. The gelation process via thermal effect is decided by the hydrophobic and hydrophilic interactions, polymer concentration, and the chemical intrinsic quality of the polymer. The solution-gelation process related to the reversible transitional property has been discussed previously [115]. The most generally used thermally reversible hydrogels have been adopted by the Environmental Protection Agency (EPA) and Food and Drug Administration (FDA) for applications in agronomic goods, food ingredients, and medicinal additives.

The crosslinking substances, as well as nonbiocompatibie and nonbiodegradabile monomers, that are used to fabricate thermally responsive hydrogels based on PNIPAAM and its derivatives represent the main limitations for these hydrogels. They result in immune response, as well as toxic, teratogenic, and carcinogenic effects. Clinical data are still unclear as to whether the metabolism of PNIPAAM and acrylamide constructed polymeric materials could trigger the activation of platelets once contacting with systemic blood; detailed toxicity results are required before further application. In addition, it is needed to study the valuable features of thermal hydrogels in terms of the improvement and development of fabrication of new biocompatible and biodegradable thermally responsive hydrogels.

3.4. pH-Sensitive Hydrogels. Hydrogels that are responsive to outside stimuli undergo switches in their developmental activities, linkage construction, mechanical properties, and solubility. These systems are therefore termed environmentally responsive, intelligent hydrogel systems [116, 117]. Nonchemically induced changes are considered to be those caused by thermal effects, electric force, light, magnetic change, mechanical force, and the strength of numerous energy sources, in which transfer molecular interactions play an important role. Chemical stimuli include chemical reagents, ionic strength, and pH value, which influence the interfaces between the solvents, polymeric molecules, and within the 3D structure of the polymer molecule.

Another type of hydrogel, known as a multisensitive hydrogel, is made by consolidation of the two stimulus-sensitive characteristics of the hydrogel model. Polyacrylic acid-*co*-polyvinyl sulfonic acid has been considered as this case [118]. The biological response takes in a reaction with protease, ligands bonding, antibodies, or some active substances [116, 117]. Therefore, these stimuli make this type of hydrogel interesting for biomedical, therapeutic, and living applications [101].

Polymer hydrogel materials in the presence of ionic side residuals which could receive and provide H^+ in reply to an alteration in the pH value were studied by this research group [119]. At a given pH value, the amount of ions present in a pH-sensitive polymeric hydrogel, denoted as pK or PI, changes dramatically relative to another pH value. A swift capacity transition in opposition to the repulsively interacted force among the ionic residuals results in a quick transformation in the final charged characters of the ionic functional residuals, which generates large permeable swelling driving force. A common example is two classes of pH-sensitive hydrogels: one with a negative charge and one with a positive charge. Negatively charged hydrogels have side groups such as sulfonic or carboxylic acid, in which the deprotonated state exists when the test pH value is beyond the *isoelectric point*, which indicates the ionizations of the side groups. Here, the swelling behavior of the polymeric solution occurs [120–122]. Alternatively, positively charged hydrogels include functional groups such as those that are amine bound, in which

the ionic state exists below the pK_b, resulting in swelling behavior due to the enhanced electric repulsive force. The extent of the swelling behavior of the soluble hydrogels is subject to many factors, as suggested by previous research [90, 123]. The characteristics of the polymeric substance, for instance, ionic strength, hydrophilicity or hydrophobicity, dosage, isoelectric point of the functional groups, crosslinker concentration, and solubility, should be of primary concern. The states of the swelling solution such as the ionic concentration, environmental pH, repulsive ions, and the valence of the special polymer are included in the secondary factor to be considered [124, 125]. The capability of a novel methacrylate-based polymer with a copolymeric structure to be functioned to a pH value has been proven previously [126, 127] and has been applied to a designed alginate-/chitosan-mixed gel particle decorated with chitosan that was used in a given drug delivery system targeting the colon. The above investigations suggest that the degree of swelling at neutral pH is noticeably greater than that at lower pH (1.2) and thus imply the pH responsiveness of these hydrogels. The swelling behavior has been noted to drop because of the presence of the alginate-/chitosan-mixed gel particles and by chitosan decorating due to the ionic change and the hydrogen bonding of the side groups of the polymeric moiety. As noted, chitosan has been considered as a potential biomedical material for wide use. The relative study of chitosan hydrogel was previously published (Figure 4).

A hydrogel composed of a starch-based polymer, sodium acrylate-*co*-acrylamide, possesses ultra-absorbent property along with pH sensitivity. The ibuprofen-release behavior of this hydrogel has been previously studied in a simulated intestinal and gastric pH environment [129]. The rate of swelling of this hydrogel in relation to different size of particle was studied; then it has been determined if burst release of the drug is much faster at pH 7.4 when compared with release at lower pH. Although a polymeric matrix with low degradability should not be a main issue when considering real-world uses of this substance, such as in oral administration, it may be a dangerous limitation when this substance is used for other purposes, such as drug-targeted release and use within a surgically implantable biochip. Thus, the development of these hydrogels should be focused toward the improvement of pH-responsive hydrogels with biodegradability and biocompatibility and is developed from extracellular matrix (ECM) proteins, functional peptides, and positively or negatively charged polysaccharides.

3.5. Protein-/Polypeptide-Constructed Hydrogel Materials. The mentioned hydrogels are specially developed with special considerations, using the DNA stereochemistry technology to molecularly engineer recombinant and defined molecular structures for use in tissue engineering, organ transplantation, and controllable drug-release applications. Another example of these techniques makes use of the coiled-coil structure, which is found in protein-/polypeptide-based hydrogels. Coiled-coil proteins with hydrophobic amino acid parts are used as physical crosslinking agents to construct protein/polypeptide artificial hydrogels. The coiled-coil

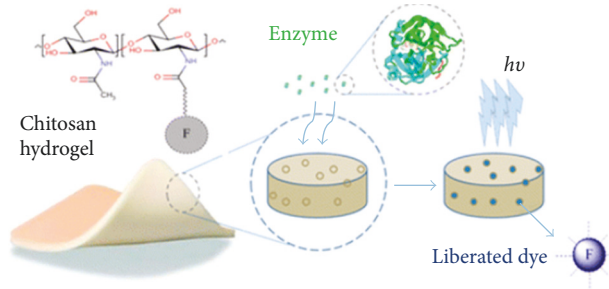

Figure 4: Illustration of the hydrogels composed of chitosan. Adapted with permission from [128], copyright 2014 ACS Publications.

domains of the triblock copolymers that exist at the end of the polymer and in the hydrophilic protein residues in the center of the polymer can be used to develop physically crosslinked protein-based hydrogels, and this has been studied previously [130–132]. With these hydrogels, both the pH and environmental temperature can affect the hydrogel in different ways according to the placement of the coiled-coil segments' amino acid structure and the hydrophilic protein domains, which can be manipulated to improve cell interactions. To fabricate the 3D polymeric hydrogel structure, a hydrophilic linear typical polymer such as coiled-coil protein may be used as a crosslinking agent [133].

The utilization of fluorescence correlation spectroscopy in order to estimate the protein motion rates, along with the intensity profiles on the cellular membranes and the cell junctional structure of capillary endothelial cells in living tissue, has been previously investigated [134]. When applied as protein delivery carrier systems, these hydrogels display the ability to produce a physical steric hindrance barrier in relation to the distribution of the test proteins or polypeptides. These reacted chains are also "attachable" to these polypeptides or proteins, and the feeble interaction between them additionally determines the motional behavior of the polypeptides or proteins [134, 135].

3.6. Blood-Sugar-Sensitive Hydrogel Materials. In a clinical study on the treatment of diabetic patients, a glucose-sensitive carrier composed of a hydrogel that is designed for biomedical use should be established. Glucose-sensing hydrogel materials are candidates that would be used as a glucose monitoring system for diabetic patients [136, 137]. Researchers have found a suitable category of such material, known as "bio-smart" material, which combines the artificial molecular identification with actuation and contains poly (methyl acrylate) and (hydroxyethyl) methacrylate [138, 139]. To use functional hydrogel in diabetic study, when the glucose oxidation enzyme in the presence of oxygen transforms blood sugar to gluconic acid, the local pH value of the bulk medium decreases, where change rises the swelling property of positively charged hydrogels and thus discharges the insulin. In order to reduce the burst release of insulin from the carrier system and to enhance the controllable encapsulation of insulin, the oxidation enzyme for blood sugar has been covalently conjugated within the hydrogel carrier system.

As previously investigated [140], possible molecular mechanisms resulting from blood sugar may be used as a smart sensor. The use of concanavalin A as a crosslinking agent has also been investigated in order to optimize glucose-sensitive hydrogels [141]. Because glucose oxidase enables the oxidization of blood sugar into gluconic acid, it is commonly used as a digestion enzyme in glucose sensing, which therefore influences the pH value of this carrier system and allows the use of pH-responsive hydrogels for the controlled triggered release of insulin. Because of the ionic state, the enhanced solubility of the released insulin or other drugs may be achieved by reducing the pH in poly(dimethylaminoethyl methacrylate)-(PDEAEM-) based hydrogels in order to improve the swelling behavior. To immobilize glucose oxidase and to use a porous membrane filter conjugated with polyanionic materials such as methacrylic acid-*co*-butyl methacrylate, this model of a drug carrier system should be designed in the use of a glucose-responsive hydraulic flow controller. At physiologic pH, the chain swells. As the pH drops, however, the chains are disrupted and the carboxyl groups protonated by the blood sugar may be being transformed into gluconic acid by way of the oxidant enzyme of blood sugar.

4. Conclusion

This review covers previously published articles from earlier in the decade that are related to polymeric hydrogels. The hydrogels are categorized in terms of the various physical and chemical features that allow them to be triggered in carrier systems in environmental, industrial, and biomedical applications (articular cartilage tissue in particular). Polymeric hydrogels formed from distinct procedures are influenced by the fabrication of the desired hydrogels and by the development of a protocol of fabrication, in which a highly sensitive material is necessary and must be defined. This review illustrates that the constitution of polymeric substances that respond to distinct stimulants such as biochemical, physical, or chemical stimulants should be recognized. Hydrogels for development that either do or do not spontaneously swell when in contact with living cells should be studied. The novel classification of such substances should be considered for future studies regarding these materials. In order to facilitate in organizing cartilage tissue engineering, hydrogels that possess biocompatibility, improved stability, mechanical strength, and biodegradability should be investigated on a nanomanufacture scale for current uses. Understanding medical needs and concurrently lessening the difficulty of hydrogel construction should therefore be the goal for future research in this field.

Conflicts of Interest

All authors declare no conflicts of interest.

Authors' Contributions

Er-Yuan Chuang and Chih-Wei Chiang contributed equally to this reviewed paper. Er-Yuan Chuang and Chih-Wei Chiang collected researched literatures and arranged the outline of the collected document; Er-Yuan Chuang, Chih-Wei Chiang, Pei-Chun Wong, and Chih-Hwa Chen discussed the content of the paper and wrote the article. All authors reviewed and commented on the entire manuscript.

Acknowledgments

This reviewed article was financially helped from a grant of Taipei Medical University (Hospital) (TMU105-AE1-B09 and TMU101-AE1-B63) and the government project of Ministry of Science and Technology (MOST) of Taiwan (MOST105-2314-B-038-015-MY3 and MOST106-2314-B-038-022-MY2).

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