DOI: 10.26717/BJSTR.2018.05.001144
Shree R Singh. Biomed J Sci & Tech Res

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574-1241

Mini Review

Open Access

Advanced Hydrogels for Biomedical Applications

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Received: May 24, 2018; **Published:** May 30, 2018

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Abstract

Gels or hydrogels are described as the matrix of cross-linked polymers. Hydrogels are naturally a part of the body in the form of collagen, gelatin, mucous, tear films, cartilage, vitreous humor, cornea, and tendon. Collagen, gelatin, and nanofillers can be used to modify the strength of hydrogels. Use of biodegradable hydrogel scaffold is ideal for tissue regeneration, where the scaffold degrades as the tissue regeneration occurs. The hydrogel can be lone or composition of fundamental properties such as edible, non-edible, biodegradable, non-biodegradable, injectable, topical, natural, synthetic, physically crosslinked, chemically cross-linked. During past three decades hydrogels due to various factors such as biodegradable, absorbent, tissue resemblance and easy use, have received the enormous attention from researchers around the globe. Although hydrogels have become part of a variety of industries but quest for biomedical application of hydrogels is ongoing. This review addresses the recent advances in different forms of hydrogels and their biomedical use.

Keywords: Hydrogel; Biomedical; Biodegradable; Polymer; Cross-linked

Introduction

Researchers are working on hydrogels over decades and according to researchers a water-swollen, network of cross-linked polymers produced by the reaction between one or more monomers or by hydrogen bonding or by large van der Waals interaction between chains [1-3]. It has also been reported that the hydrogel is a superabsorbent material that absorbs water over 99% of its capacity without dissolving itself and swells to form a gel called hydrogel [2,3]. The hydrogel is a colloidal material involving disperse phase and dispersion medium combined to yield a semisolid material like jelly [4]. Over 70 years ago the process of methacrylic acid polymerization was patented [5], and now hydrogels are existing in a variety of forms. In the biomedical field, the hydrogels have entered in the mainstream due to interesting porous structure, biocompatibility and easy of production [6,7].

The hydrogel can be lone or combinations of different source, composition, charge, and structure [1]. Hydrogels are broadly classified as chemical and physical hydrogels by their crosslinking ability [1]. Chemical crosslinking involves the conversion of hydrophobic polymers into the hydrophilic polymeric gel to form a network with the aid of crosslinking agents. However, the crosslinking agent can often be toxic and cannot be used in the biological application. Hence their removal is required before its implementation in bio logical systems [3,7]. Chemically cross-linked hydrogels can be pre pared either by high irradiation energy or by photo-polymerization [1]. Physically cross-linked gels do not possess toxicity like chemically cross-linked gels. Mechanism of physically cross-linked gel formation is a molecular entanglement or use of secondary force such as ionic interaction, hydrogen bonding, crystallization, hydrophobic interaction and protein interaction [3,8].

Advances in Hydrogels

Hydrogels are widely used in the field of drug delivery, tissue engineering, regenerative medicine, food industries as well as fashionable showcase materials providing safety cushion and identity to the biomedical device [9,10]. In pharmaceuticals, the peptide, MIP, nanofiller enhanced hydrogels are being considered as drug delivery system [11,12]. Designing of the biomaterial surface can turn the material into smart biomaterial, and this surface modulation, e.g., for cell adhesion[13], chemo-selective conjugation of biologicals [14], etc. are gaining more attention of researchers in fields like material science as well as bioscience [9]. Swelling nature of the gels mainly depends on their network structure, but the latter part is significantly related to the condition under which the gel has formed [15].

Hydrogels have become omnivorous, the pharmaceutical, nutraceutical, agricultural, medical devices and cosmetic industries have formulations or developing formulation based on hydrogels (Table 1). Modulation of material surface with stimuli-responsive polymers can show considerable changes in properties in response to various stimuli's [9,10]. Use of such stimuli-responsive polymers in hydrogel preparation can make it stimuli-responsive hydrogel and such hydrogel can undergo considerable change in their structure upon a small change in external environment; such hydrogels are called as stimuli-responsive hydrogels [9]. These environmental changes could be changed in pH, temperature, light and hormonal secretion and have different applications mentioned further in Table 1.

Table 1: Hydrogels and their biomedical applications.

Application	Hydrogel	Application	Ref.
Wound healing	Methacrylate, nanofiller enhanced	Dressing, cream	[61-63]
Dental	Peptide and collagen-based	Implant, dressing, cream	[64-66]
Drug and Vaccine Delivery	Stimuli-responsive, nanofiller enhanced, peptide-based, collagen-based, molecularly imprinted polymer (MIP) based	Implant, dressing, contact lenses, soft-gel capsules	[8, 11, 12, 42, 67-70]
Ophthalmic	Methacrylate, gelatin	Micro emulsion eye drop, contact lenses	[68, 71]
Orthopedic	Collagen, nanofiller enhanced, methacrylate	Implants, microgel	[53, 72, 73]
Cardiac	Nanofiller enhanced, gelatin, stimuli-responsive, self-oscillating	Bio-actuator, implant	[9, 74-76]
Organ Culture	Gelatin, collagen, peptide, stimuli responsive	Scaffold	[7, 39, 77-80]
Plastic surgery	Hyaluronic acid (HA), stimuli-responsive, methacrylate	Trans-dermal implant	[81-83]
Cosmetics	HA, stimuli responsive, methacrylate	Cream, dressing	[56, 57, 84]
Diapers/ Sanitary Pad	Methacrylate	Pads, Diapers	[85, 86]
Medical Devices	HA, stimuli responsive	Robotic dispensers,	[7, 87, 88]
Agricultural	Methacrylate	Powder	[48, 89]
Nutraceutical	Peptide	Micro-particles	[27-29]

Tissue regeneration and drug delivery are the focused applications of peptide-based hydrogels [16]. Supramolecular structure of the peptides capable of self-gelation (gelating peptides) can be used to deliver and control the release of the drugs physiological conditions [17-20]. Peptide-based hydrogel as cochlear implants describes the advancement of hydrogels in biomedical applications [21,22]. Recent findings point the possibility of the peptide-based hydrogels as functionalized biomaterials scaffold to attract projections from neurons, its attachment and stability providing an uninterrupted interface between cochlear implants and audio-neurons [21]. Peptide-based hydrogels can mimic extracellular matrix (ECM), where the peptides and related derivatives self-assemble to form a gel [23,24]. During early 90's Zhang et al. described that peptides can be staggered using their structure, for example, ionic bonds formed between alanine side chains facing each other and the charged lysine and glutamic acid chains facing each other [25]. These hydrophilic/hydrophobic nanosheets then form a fibrous hydrogel in the presence of salts [21].

Moreover, even the shortest peptide comprised of natural amino acids found capable of creating the transitional α-helices inside hydrophilic environment as well as self-assembled into fibrous structure [26]. Use of peptide-based hydrogels has begun for nutraceutical purposes too [27-29]. Molecularly imprinted polymer (MIP) based hydrogels are getting popular in biomedical applications as smart hydrogels systems [24]. The MIP based hydrogels are non-covalently bonded hydrogels formed by hydrogen bonding between the monomer and imprint template [24]. The imprints of the MIPs formed as a result of template monomer interaction [30]. The application of this system involves recognition of target molecules at the molecular level [31]. Precisely, the claims of these MIPs prominently associated with microfluidic devices [32,33].

Addition of nanofillers can substantially influence material's mechanical, optical and thermal properties [34]. Based on the dimensions the nanofillers can be classified as one dimensional, e.g., clay nanoplates [35], two dimensional, e.g., nanofibers (nanotubes and nanofibers) [36] and three dimensional, e.g., metallic nanoparticles [34,37]. Clay nanoplates or nanoclays are the basic nanofillers to be used in the hydrogels and can be natural, e.g., montmorillonite [38], or synthetic, e.g., hydrotalcite [34]. Clays are used as catalysts, absorbents, metal chelating agents as well as polymer nanocomposites to make the hydrogel mechanically stronger than conventional hydrogels [39]. The water absorption is controlled with the inclusion of clay nanofillers in the hydrogels for wound dressing [40]. However, other nanostructures like carbon nanotubes (CNT) and graphene are one of the novel nanofillers to be used in hydrogels [41,42]. Both graphenes, as well as CNT, are being studied for their use in tissue engineering as well as in drug delivery [42]; moreover, it can be used to coat the electrodes in solar cell operated medical devices [43]. Similarly, graphene-enhanced hydrogel actuators [44], a small amount of graphene could increase the conductivity four times benefiting conductive tapes [45,46], element sensor [47].

Super absorbent hydrogels are another example of smart hydrogels. Swelling of hydrogel could result in complications in case of implants, but the superabsorbent hydrogels withstand the swelling [48,49]. Super absorbent hydrogels can also be referred as super porous hydrogels [49]. Hydrophilic polymers can adsorb water up to 90 % of their weight without dissolving. This property of hydrogels has been addressed for dressings for wound healing, e.g., alginate-based hydrogel dressing [50]. The research on collagen product has broadened in past two decades, and the collagen-based hydrogel is part of that development [51]. The skin, bone, cartilage, tendon, and vasculature are the different collagen [51]. The network of collagen fibers and related components is recognized as ECM [52]. Although collagen itself is water-insoluble, it can be blended with other hydrophilic polymers to form hydrogels scaffolds mimicking skin, bone, etc. [53]. Multilayered collagen hydrogel can be prepared for retaining the cellular functions [54]. Moreover, collagen hydrogels have found less toxic compared to many others and most efficient in proliferation [7]. The inclusion of polysaccharides like Beta-glucan (beta-1,6-branched beta-l,3-glucan) has been reported biocompatible and effective in encouraging cell growth as well as rejuvenate the collagen [55].

Hyaluronic acid (HA) is a polysaccharide-based component of the natural ECM [3]. Hydrophilic nature of the HA helps in water binding, but on the other side, HA has a short half-life of 1-2 days due enzymatic degradation and over-hydration [56]. HA could be low molecular weight or high molecular weight [6]. However, the low molecular weight HA renders the cell functions and could develop cancer [57]. On the other side, high molecular weight HA is nonimmunogenic, aids in nutrient transportation as well penetration of fibers, cells, and vesicles [58]. HA-based implants have promising results, e.g., CNS scaffold implantation aids neural rejuvenation [59], elastic nature of HA reduces bone friction [60-80], HA gel filler restores skin elasticity and gives uniformity [56].

Conclusion

Hydrogels have become one of the essential and vital players of biomedical sector. Since chemically cross-linked hydrogels are toxic, the physically cross-linked hydrogels are in demand. Hydrogels based on peptides, HA, acrylamide are patented and marketed. However, the quest for monomers and cross-linkers will remain to invent and modify biological applications of hydrogels [81-89].

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