Overview of Hydrogels and Hydrogels based Actuators for Biomedical Applications

Rohit Sharma[1], Iqbal Singh[2], Ajay Vasishth[3], Sourbh Thakur[4]

[1]Satyam Engineering & Technology, Amritsar, Punjab, India-143107

[2]Satyam Polytechnic & Pharmacy College, Amritsar, Punjab, India-143107

[3]University Institute of Sciences, Chandigarh University, Mohali,

Punjab, India- 140413

[4]Department of Organic Chemistry, Bioorganic Chemistry and Biotechnology,

Silesian University of Technology, B. Krzywoustego 4, 44-100 Gliwice, Poland

Email: rohitsharma3940@gmail.com

Abstract

Hydrogels are three-dimensional polymeric chains that are widely employed in many applications due to their extraordinary and unique abilities. Nowadays, hydrogels are being incorporated more and more into various bio-medical applications because of their characteristics like biocompatibility, biodegradability, imitation of extracellular matrices, and bioactive molecules. This paper aims to provide a brief overview of hydrogels, their classifications, and types of hydrogel actuators based on their response to different types of stimuli like electric fields, light, magnetic fields, pressure, temperature, solvent composition, ions, pH, and specific molecular recognition. Applications of hydrogel actuators in the biomedical field and current challenges have also been discussed.

Keywords: Hydrogel, polymer, stimuli-responsive, actuator, biomedical applications

1. INTRODUCTION

Hydrogels are three-dimensional polymeric networks that contain water in their structure and show the property of swelling without dissolving in water [1]. The tendency to hold water in hydrogels depends upon the presence of hydrophilic

groups, cross-linking degree, polymer-polymer and polymer-water physical interactions, temperature, pH, and ionic strength. Its characteristics, like softness, elasticity, biodegradability, and the ability to expand and contract, make it a potential candidate for various biomedical applications [2]. The polymeric network of hydrogels is formed through the chemical or physical interactions between homopolymers and copolymers. Hydrogels can be moulded into any shape and size, such as nanoparticles, microparticles, coatings, slabs, and films. The use of hydrogels in biomedical applications has increased significantly in recent years due to their phenomenal stretching and flexibility, biocompatibility, and stimuli sensitivity. Furthermore, new hydrogel nanocomposites are being explored because the already present hydrogels have many limitations and inabilities, such as poor mechanical strength, low strain, and low thermal stability. So, to address most of these problems, scientists are synthesizing new hydrogel nanocomposites from various nanomaterials [3]. This paper sheds light on hydrogels, their classification, hydrogel actuators, their biomedical applications and current challenges.

2. CLASSIFICATION OF HYDROGELS

Hydrogels are classified into several types. Based on sources, hydrogels are classified into natural and artificial/synthetic origins [4]. Hydrogels can be obtained naturally from proteins of natural products such as collagen and gelatine and polysaccharides and using chemical compositions in synthetic ways. Though synthetic polymers are much stronger than natural polymers, but in recent years, the usage of natural hydrogels in various applications has significantly increased. Further, according to polymeric compositions, hydrogels are also defined into three categories: homopolymeric hydrogels, copolymers, and multi-polymers (interpenetrating polymeric hydrogels). First, homopolymeric hydrogels are polymer networks produced from only one type of monomer. On the basis of the type of monomer and the polymerization process, they may result in a cross-linked skeletal structure [5]. Second, copolymers are formed from at least two or more distinct species of monomers having one hydrophilic constituent which are then organised with polymeric network chains in a pseudorandom, block, or alternating pattern [6]. Third, hydrogels are defined as multipolymer interpenetrating polymeric hydrogels (IPH). In this type, hydrogels are constructed using two freely cross-linked synthetic and/or natural polymer components, whereas semi-interpenetrating polymeric hydrogels contain one cross-linked and another the non-cross-linked polymeric component [7, 8]. Further, depending on the type of cross-linking, hydrogels are defined as chemically cross-linked and physically cross-linked. Apart from this, based on chemical composition and physical interactions, hydrogels through cross-linking are classified as amorphous, semi-crystalline, and crystalline. Moreover, according to the presence or absence of electrical charge located on the cross-linked chains, hydrogels are classified as non-ionic, ionic, amphoteric electrolyte and zwitterionic. Furthermore, it is possible to tailor the mechanical strength, biodegradability, and response of

hydrogels to different stimuli by choosing the right combination of monomers and cross-linking agents for a specific biomedical application.

3. HYDROGEL ACTUATORS AND THEIR TYPES

A simple actuator is defined as a device that converts any sort of energy, such as electrical, optical, air, or hydraulic energy, into mechanical energy to achieve physical movements, whereas hydrogel actuators convert the received energy into mechanical energy with a soft motion like a living being. Hydrogel actuators are sensitive to external stimuli. There are different types of stimuli. One is physical stimuli, which contain electric fields, light, magnetic fields, pressure, solvent composition, sound, and temperature, whereas the other is chemical or biochemical stimuli having ions, pH, and specific molecular recognition. Hydrogel actuators can be optimized by changing the variety of input stimuli. Based on input stimuli, hydrogel-based soft actuators are divided into six types.

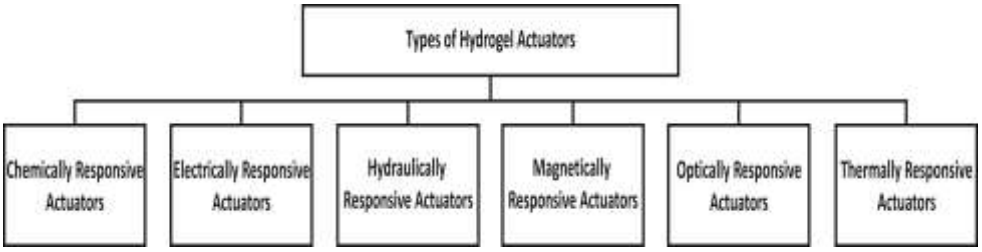

Figure 1. Schematic classification of hydrogel actuators on the basis of input stimuli

3.1. Chemically Responsive Actuators

This type of hydrogel actuator can convert the chemical energy of the surroundings directly into mechanical motion [9]. These actuators are fabricated with chemically responsive hydrogels and depend on the volumetric adjustments that occur in hydrogels in reaction to chemical stimuli. They are further divided into three types of actuators; solvent-responsive, pH-responsive and biomolecule-responsive. In solvent-responsive actuators, the differential in hydrophobicity between the polymer network and the solvent determines how much volume can be changed by this actuator [10]. Further, in pH-responsive hydrogel actuators under the required pH environment, the volumetric changes rely on the ionization of the polymer network [11]. Further, the biomolecular-responsive actuators are based on the reversible association and dissociation of biomolecular complexes to change the volumetric quantity [12].

3.2. Electrically Responsive Actuators

These types of hydrogel actuators change their shape according to electrical stimuli. Without the need for any complex conversion of stimuli, only computational circuits are required to control the volumetric changes very efficiently and accurately [13]. Electrically responsive actuators are further divided into electrically induced osmotic pressure actuators and dielectric elastomer actuators. In these actuators, osmotic pressure is created via the formation of an ion gradient, which leads to the swelling of hydrogel asymmetrically. Second, the dielectric elastomer actuator consists of a dielectric elastomer layer between the two ionic conductive hydrogels. The hydrogel/elastomer interfaces along each hydrogel accumulate opposite-charged ions when a high voltage is placed between the two materials. This creates Maxwell tension between the hydrogels, and resultantly, the elastomer layer shrinks in thickness and enlarges in area. [14].

3.3. Hydraulically Responsive Actuators

Hydraulic pressure plays a pivotal role in changing the shape of the hydrogel in hydraulically responsive actuators. In comparison with other types of actuators, hydraulically responsive actuators can achieve higher speeds and actuation forces. Furthermore, they are transparent by nature, so they are widely used in underwater activities owing to the same refractive index of these actuators as hydrogel and water. Moreover, they can easily eschew the sonic radars because of their same impedance as water, so they are also used in applications where stealth purposes are required [15].

3.4. Magnetically Responsive Actuators

In magnetically responsive actuators, external magnetic fields are responsible for the shape change of the hydrogels. They typically contain nano- or micro-sized magnetic particles and can be controlled remotely without a physical connection. When a magnetic field is applied externally, the hydrogel matrix changes shape as a result of the magnetic force being transmitted to it through the scattering of magnetic particles in the hydrogel. Nowadays, magnetically responsive hydrogels are used in artificial muscles and the manufacturing of implantable medical devices [16].

3.5. Optically Responsive Actuators

Light irradiation is used for volumetric changes of the hydrogels in optically responsive actuators. Energy can be transferred wirelessly with this type of actuator, and no physical connection is required. These actuators are also responsive to multiple wavelengths. Further, in response to specific wavelengths, reversible isomerization occurs in photoswitchable molecules like spiropyran and azobenzene. Under ultraviolet (UV) light, spiropyran dissociates, and under visible light, it changes back into a ring-closed structure. Hydrophobicity changes are

directly responsible for the reverse isomerization that leads to changing the shape of the hydrogels. Furthermore, an optically responsive actuator which involves spiropyran can function as a reversible photo-valve for microfluids [17].

3.6. Thermally Responsive Actuators

These kinds of hydrogel actuators change their shape according to variations in temperature. These actuators create large deformations by selectively reacting to a specific temperature range. Due to their tunable temperature range, they can be widely used in applications such as soft robotics. Thermally responsive hydrogel actuators are divided into lower critical solution temperatures (LCST) and upper critical solution temperatures (UCST). LCSTs generally shrink when temperatures rise above critical and swell when temperatures fall, whereas UCSTs expand when temperatures rise above critical and contract to their normal position at lower temperatures [18].

4. BIOMEDICAL APPLICATIONS OF HYDROGEL ACTUATORS AND CURRENT CHALLENGES

The hydrogel-based actuators have proven productive in biomedical field and are becoming popular for various applications such as navigating medicine in the arteries and holding and releasing drugs in drug delivery systems [19]. They are widely employed in biomedical industries, such as implanting chips on human body organs (heart, liver, skin, kidneys) via microfluidic devices [20]. Moreover, microfluidic devices are also employed in cell culture, medical examination, wound healing and dressing, and the manufacturing of pharmaceutical devices in a quick, precise, and high-throughput manner [21]. In addition to this, smart robotics arms, or usually microrobotics arms, are becoming very popular in the biomedical field. Microactuators are also employed in smart robotic arms using polypyrrole. Furthermore, hydrogel actuators are playing tremendous role in bioprinting applications such as tissue engineering and steriolithography via 3D bioprinting and 4D bioprinting of neural stem cell attachments and natural collagen fibre imitation [22, 23]. Hydrogel scaffolds are extremely useful to repair or regrow damaged biological tissue and are essential for providing a supportive matrix for embedded cells. Scaffold matrices serve a significant role in development of new tissue morphogenesis by directing the growth of cells placed inside them. Scaffolding is used to deliver cardiac cells into cardiac muscles and it plays a pivotal role in the tissue regeneration process [24].

5. CURRENT CHALLENGES

Hydrogel actuators have evolved with the passage of time and undergone significant advancements, but they are still facing some challenges in contemporary times. Firstly, the biggest limitation of hydrogel actuators is related to their power efficiency. It is observed that hydrogel actuators that work on the expansion/shrinking phenomenon yield low power conversion efficiency. Till

date, much research has been carried out to improve the energy efficiency of hydrogels, but the obtained efficiency is not as high as required for feasible biomedical applications. Another limitation of hydrogel actuators is related to their fabrication techniques. For practical biomedical applications, it is required to muster different hydrogels with multiple properties and fuse them into one material, but in fact, it is a hectic task to amass distinct hydrogel properties into one material and create an advanced hydrogel actuator. So far, much research has focused on tailoring the properties related to stimulus response of hydrogel actuators; however, there are still some challenges, such as lower mechanical power, UV carcinogenesis, stability factors, and the virulence of some materials that need to be addressed. Further, all the present hydrogels have a longer response time to stimuli. This response time creates a bottleneck in many practical biomedical applications that require a very fast response time in nanoseconds.

6. CONCLUSION

In summary, hydrogel-based biomaterials are widely used in many interdisciplinary fields but over the past decade, the usage of hydrogels in the biomedical area has grown significantly owing to their biocompatibility with human organs/tissues. Hydrogel actuators are used in drug delivery, bioprinting, microrobotics, microfludic devices and tissue scaffold fabrication. So far tremendous progress has been made in development of hydrogel based actuators but few issues should be addressed to use hydrogel actuators in efficient manner. In the stimulus-responsive hydrogels, there is need of fabricating actuators that can work with minimal input of stimuli. Furthermore, reducing the response time to stimuli from several minutes to the millisecond level especially in applications that require a quick response is still a challenge that provides scope for future research.

7. REFERENCES

[1] E.M. Ahmed, et. al., ‘An innovative method for preparation of nanometal hydroxide superabsorbent hydrogel’, Carbohydrate Polymers, vol. 91, pp. 693-698, 2013.

[2] E. Caló, V.V. Khutoryanskiy, ‘Biomedical applications of hydrogels: a review of patents and commercial products’, European Polymer Journal, vol. 65, pp. 252-267, 2015.

[3] A.K. Gaharwar, N. A. Peppas, A. Khademhosseini, ‘Nanocomposite hydrogels for biomedical applications’, Biotechnology and Bioengineering, vol. 111, pp. 441-453, 2014.

[4] W. Zhao, et. al., ‘Degradable natural polymer hydrogels for articular cartilage tissue engineering’, Journal of Chemical Technology & Biotechnology, vol. 88, pp. 327-339, 2013.

[5] T. Iizawa, et. al., ‘Synthesis of porous poly (n-isopropylacrylamide) gel beads by sedimentation polymerization and their morphology’, Journal of Applied Polymer Science, vol. 104, pp. 842-850, 2007.
[6] L.Yang, J.S. Chu, J.A. Fix, ‘Colon-specific drug delivery: New approaches and in vitro/in vivo evaluation’, International Journal of Pharmaceutics, vol. 235, pp. 1-15, 2002.
[7] Z. Maolin, et. al., ‘The swelling behavior of radiation prepared semi-interpenetrating polymer networks composed of polynipaam and hydrophilic polymers’, Radiation Physics and Chemistry, vol. 58, pp. 397-400, 2000.
[8] F. Machado, E. L. Lima, J. C. Pinto, ‘A review on suspension polymerization processes’, Polimeros, vol. 17, pp. 166-179, 2007.
[9] P. Techawanitchai, et. al., ‘Photo-switchable control of pH-responsive actuators via pH jump reaction’, Soft Matter, vol. 8, pp. 2844-2851, 2012.
[10] P. Etienne, et. al., ‘Reversible patterning and actuation of hydrogels by electrically assisted ionoprinting’, Nature Communications, vol. 4, pp. 2257, 2013.
[11] J. Duan, et. al., ‘Bilayer hydrogel actuators with tight interfacial adhesion fully constructed from natural polysaccharides’, Soft Matter, vol. 13, pp. 345-354, 2017.
[12] J. Kim, et. al., ‘Review of soft actuator materials’, International Journal of Precision Engineering and Manufacturing, vol. 20, pp. 2221-2241, 2019.
[13] E. Acome, et. al., ‘Hydraulically amplified self-healing electrostatic actuators with muscle-like performance’, Science, vol. 359, pp. 61-65, 2018.
[14] P. J. Glazer, et. al., ‘Role of pH gradients in the actuation of electro-responsive polyelectrolyte gels’, Soft Matter, vol. 8, pp. 4421-4426, 2012.
[15] H. Yuk, et. al., ‘Hydraulic hydrogel actuators and robots optically and sonically camouflaged in water’, Nature Communications, vol. 8, pp. 14230, 2017.
[16] S.Y. Chin, et. al., ‘Additive manufacturing of hydrogel-based materials for next-generation implantable medical devices’, Science Robotics, vol. 2, pp. eaah6451, 2017.
[17] J. T. Schiphorstet. et. al., ‘Molecular design of light-responsive hydrogels, for in situ generation of fast and reversible valves for microfluidic applications’, Chemistry of Materials, vol. 27, pp. 5925-5931, 2015.
[18] W. J. Zheng, et. al., ‘Tough Al-Alginate/Poly (N-Isopropylacrylamide) hydrogel with tunable LCST for soft robotics’, ACS Applied Materials & Interfaces, vol. 7, pp. 1758-1764, 2015.
[19] S. Fusco, et. al., ‘Self-folding mobile microrobots for biomedical applications’, Proc. of IEEE Int. Conf. on Robotics and Automation, pp. 3777-3782, 2014.
[20] Q. Wu, et. al., ‘Organ-on-a-Chip: Recent breakthroughs and future prospects’, Biomedical Engineering Online, vol. 9, pp. 19, 2020.

[21] M. Ibrahim, M. K. Richardson, ‘Microfluidic devices for cell, tissue and embryo culture’, Recent Patents on Regenerative Medicine, vol. 3, pp. 249-263, 2013.

[22] S. Shin, H. Kwak, J. Hyun, ‘Melanin nanoparticle-incorporated silk fibroin hydrogels for the enhancement of printing resolution in 3d-projection stereolithography of Poly(Ethylene Glycol)-Tetraacrylate bio-ink’, ACS Applied Materials & Interfaces, vol. 10, pp. 23573-23582, 2018.

[23] J.M. McCracken, et. al., ‘3D-printed hydrogel composites for predictive temporal (4D) cellular organizations and patterned biogenic mineralization’, Advanced Healthcare Materials, vol. 8, pp. 1800788, 2019.

[24] C. Lin, C.S. Ki, H. Shih, ‘Thiol-Norbornene photo-click hydrogels for tissue engineering applications’, Journal of Applied Polymer Science, vol. 132, pp. 41563, 2015.