Chapter 12
Elasticity, Strength, and Biocompatibility of Hydrogels

Arunima Reghunadhan, Athira Johnson, and A. R. Ajitha

Abstract Hydrogels have been a familiar term in the current biomedical research. Generally, hydrogels are swollen polymer networks with water. Biocompatibility and ease of preparation are the key properties which enable them to be used in a variety of biomedical applications. Hydrogels can be classified in a number of ways depending on a wide range of properties. The chapter discusses in detail about the general properties, classification, mechanical properties, and biocompatibility of hydrogels. The special emphasis is on the biocompatibility. The factors affecting the elasticity and mechanical strength will be discussed along with the characterization techniques.

Keywords Hydrogels · Elasticity · Biocompatibility · Mechanical properties

1 Introduction

Hydrogels are by definition, polymeric gel consisting of crosslinked molecules which are capable of holding large amounts of water. That means a three-dimensional system of polymers made from natural or synthetic materials with a high degree of flexibility owing to increased water content is called hydrogels. Hydrogels are like solids and also like liquids. Water fills the voids in the crosslinked three-dimensional networks. Particles can diffuse to these structures. They may be firm or dissociate or dissolve in water. Even though water molecules can diffuse or penetrate into the hydrogels, they are normally water-insoluble materials. The insolubility is a result

A. Reghunadhan (✉) · A. R. Ajitha
International and Interuniversity Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, P.D. Hills P.O., Kottayam, Kerala, India
e-mail: arunimarenjith02@gmail.com

A. Reghunadhan
Department of Chemistry, TKM College of Engineering, Karicode, Kollam-5, Kerala, India

A. Johnson
Department of Food Science, College of Life Science, National Taiwan Ocean University, Keelung, Taiwan

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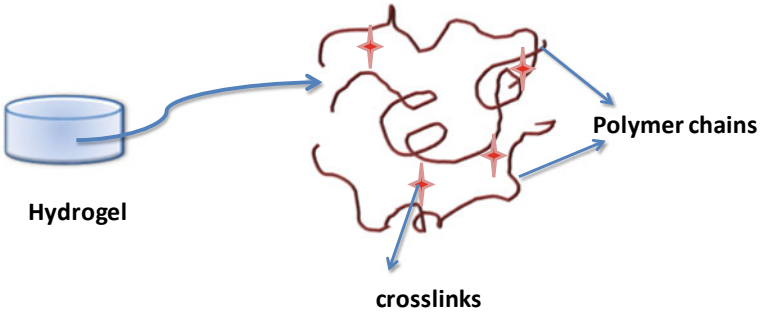

Fig. 1 Schematic representation of hydrogels

of the 3D crosslinks. At the molecular level, water in a hydrogel either binds to polar hydrophilic groups as bond water or fills the space between the network chains, pores, or voids as free water [1]. The presence of hydrophilic groups like $–NH_2$, –COOH, –OH, $–CONH_2$, –CONH, etc., is the reason behind the hydrophilicity (Fig. 1).

2 Classification of Hydrogels

Hydrogels can be classified in a variety of ways [2]. A large classification is possible in the case of these materials. The classification depends on many factors such as their physical properties, nature of swelling, methods of preparation, origin, charges, different sources, biodegradation, and nature of crosslinking.

Based on the origin or source, hydrogels can be divided into natural and synthetic.

The second division is based on the composition of the polymer involved. According the polymeric composition, hydrogels are classified into homopolymeric, co-polymeric, and multipolymeric IPNs.

1. Homopolymeric: These are polymer networks obtained from a single monomer species, a fundamental structural unit consisting of any polymer network. Homopolymers may have cross-linked skeletal structure based on the nature of the method of monomer and polymerization.
2. Copolymeric: They are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network.
3. Multipolymer Interpenetrating polymeric: A significant class of hydrogels consists of two fully independent cross-linked synthetic and/or natural polymer components embedded in a network form. In semi-IPN hydrogel, one part is a cross-linked polymer and another part is a non-cross-linked polymer.

Next classification is based on crosslinking, and normally, two types exist: physical crosslinking and chemical crosslinking. Also based on configuration, they can be divided into crystalline, semi-crystalline and amorphous.

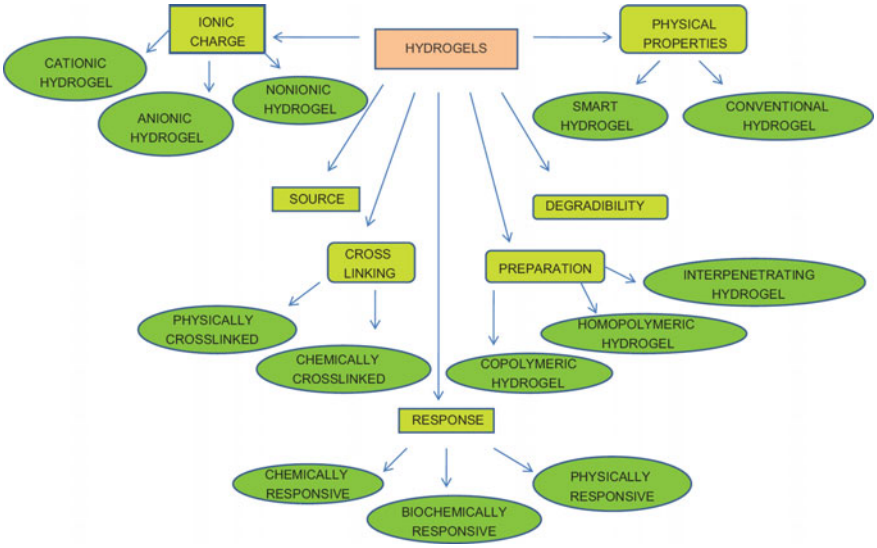

Fig. 2 Classification of hydrogels

Depending on appearance, they can be matrix, films, or microspheres. Based on the charge of the species, hydrogels may be grouped into four based on the presence or lack of electrical load situated on the crosslinked chains as nonionic (neutral), ionic (including cationic or anionic), amphoteric electrolyte (ampholytic) comprising acidic and basic groups and zwitter ionic comprising both anionic and cationic units in each structural repeating unit. Based on physical properties, they are subdivided into smart hydrogels and conventional hydrogels. A very important and broad classification is based on the response of the gels. Chemically responsive, biochemically responsive, and physically responsive hydrogels are there. Degradability is also considered as a measure to divide the hydrogels. Hydrogels can be biodegradable and non-biodegradable. All these classifications can be simply represented by a diagram as show in Fig. 2.

3 Properties of hydrogels

The general properties of hydrogels include the response, swelling, permeability, surface, optical, and mechanical properties. Rapid response to external stimuli is a crucial property in the view of applications. The swelling and mechanical properties depend on the degree of crosslinks in the polymeric material. All the properties of hydrogel materials depend on the environment too. Here, the detailed discussion will be for the elasticity, mechanical strength, and surface properties.

4 Elasticity of hydrogels

Elasticity is the physical entity of a substance by means of which it returns to its initial form after removing the force under which it deforms. The applied force is termed as stress, and the response is termed as strain. The stress-to-strain ratio is constant for a specified material and is defining mechanical property. The stresses and strains may be axial or shear based on whether the force applied is perpendicular or parallel to the supporting region. The elastic regime is characterized by a linear relationship between stress and strain. The theory of elasticity assumes that the strain reaction is instantaneous when stress is applied to the hydrogel. Hydrogels usually convey a non-purely elastic conduct owing to the viscoelasticity of the polymer chains and the poroelasticity caused by the presence of fluid.

5 Mechanical Properties of Hydrogels

As explained earlier, since the hydrogels are swollen with water, they have poor mechanical strength. There are a few explanations for the poor mechanical properties of hydrogel along with the random fiber arrangement and large water content inside the hydrogel. Monomer composition, crosslinking density, polymerization conditions, and degree of swelling play important role in determining the strength of gels. Crosslinks in the swollen structure are the main variable in evaluating strength. Mechanical properties are generally material dependent. The mechanical properties measured in the case of hydrogels are Young's modulus, Poisson's ratio, and viscoelastic properties. From the obtained Young's modulus, the crosslink density can also be measured [3]. The viscoelastic properties are better explained by Maxwell's model or theory. The relation between stress and deformation can be related as

$$\sigma(t) = \frac{\varepsilon_0}{t_1}\left[E_0 t_1 + \sum_{i=1}^{N} \eta_i \mathrm{e}^{-\frac{E_i}{\eta_i}\cdot t}\left(\mathrm{e}^{\frac{E_i}{\eta_i}\cdot t} - 1\right)\right]$$

where t is time, η_i an E_i represent the generalized Maxwell model parameters, N is the number of Maxwell elements considered (apart from the pure elastic element characterized by E_0), and t_1 is the time required to get the deformation ε_0.

Graci and coworkers used the above equation in order to relate the crosslink density and mechanical properties. They fitted the experimental data with the above theory and concluded that the Young's modulus and the crosslink density increased with increasing concentration of the polymer. From the mechanical properties, they calculated the network average mesh size [4].

Good mechanical strength is the utmost important property in biocompatible systems. As mentioned earlier, the hydrogels are poor in strength. Sometimes in order to increase the mechanical strength of hydrogels they are converted into composites with other materials having high strength. Such a modification was reported in the

case of super porous hydrogel used for gastric retention devices. Chen and Park introduced a sol for making composite [5].

6 Analysis of Mechanical Properties

A good number of techniques are available for characterizing hydrogels in terms of their mechanical strength. Microindendation proved as the most successful technique to determine the tensile properties of hydrogels.

6.1 Compression Tests

Compression test is a common practice used to examine the mechanical characteristics of several distinct kinds of hydrogels. Suitability of this method is owed to the cylindrical shape of the hydrogels. In this test, a disk is compressed between two flat platens and can be expanded in the radial direction (sliding boundary conditions) [6]. As in this laboratory module, this test setup is usually conducted under displacement control. By considering the geometry of the disk sample (radius and thickness), the Young's modulus can be calculated. The pressure applied to the hydrogel's surface and the distance compressed by the hydrogel can be used to calculate the mechanical properties of the hydrogels using a theoretical model (Fig. 3).

6.2 Bulging Tests

The experiment includes deflating the hydrogel in the substratum across a window and measuring the corresponding displacement as a function of the stress applied. The displacement can be measured using either a camera or a laser. A finite element

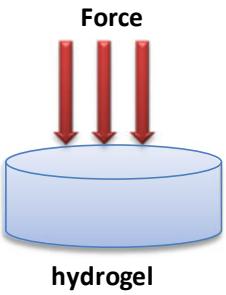

Fig. 3 Schematic representation of compression test

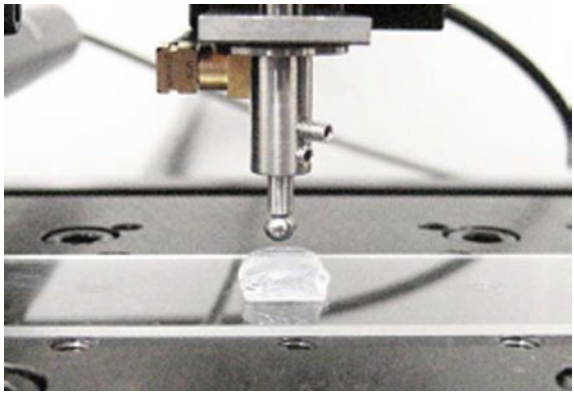

Fig. 4 Indentation on a hydrogel sample

template is then used to assess the information and compute values for the hydrogel's mechanical characteristics [7, 8].

6.3 Indentation

Indentation tests are the most favorable mechanical property analysis in the case of hydrogel and is the most successful technique [9–11]. This technique works by indenting a hydrogel at a single point to a predetermined displacement depth and measuring the reaction force required to cause the indentation. Indentation test are non-destructive approach in the field of mechanical characterization (Fig. 4).

6.4 Rheology

Rheological analysis is a common procedure to analyze the properties of polymer gels and viscous liquids. Rheology is generally considers as the study of the flow or it is considering the flow behaviour of substances. The rheological analysis can be done in different modes and all the modes generally deals with the shearing forces. The mechanical properties of hydrogels can be determined by rheological analysis. The hydrogels are subjected to shear force, and the response is measured (Fig. 5). The change in viscosity, storage and loss modulus are considered and related to the mechanical strength and processability.

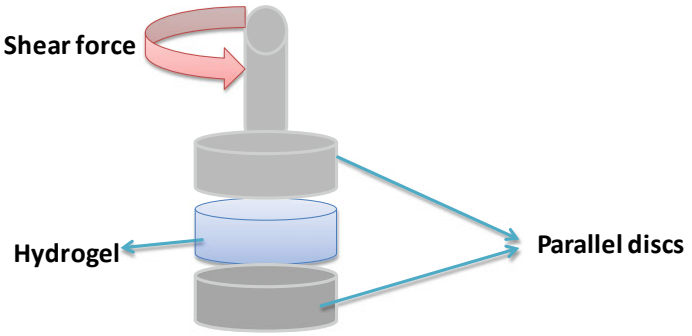

Fig. 5 Experimental setup for the rheological analysis of hydrogel

6.5 Particle Image Velocimetry

The method is based on the fact that small particles implemented in a fluid flow would move with the velocity of the local fluid. Basic measurements in particle image velocimetry (PIV) relate particle displacement over a period of time in such a manner that speed is measured as displacement proportion and time interval [12] (Fig. 6).

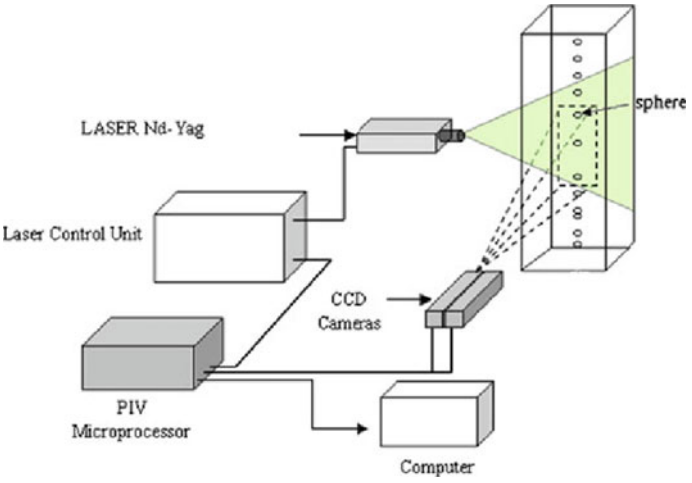

Fig. 6 Experimental setup of PIV

7 Biocompatibility of Hydrogels

7.1 Biocompatibility

"Biocompatibility" is an important term that considered during the preparation and execution of a biomaterial. In recent years, the advancement of biotechnology and tissue engineering facilitate the practice of novel biomaterials for clinical applications. According to the definition, a biomaterial is defined as "a substance that has been engineered to take a form which is used to direct, bycontrol of interactions with components of living systems, the course of any therapeutic or diagnostic procedure" [13]. The interaction between the biomaterial and living tissue is an important parameter because of the incompatibility. All of the biomaterials are considered as a foreign material when it will introduce into the body and that exerts certain immunological response known as foreign body responses (FBRs). Macrophages, dendritic cells, and adsorbed proteins are known as the key players that initiate the interaction between biomaterials and cells [14]. The need for non-toxic materials for therapeutic applications initiates the usage of term biocompatibility. It is defined as "the ability of the chosen material to achieve the best therapeutic performance in the target physiological environment, without adverse effects of the health of the host [15]." It creates significant challenges to the manufactures of the biomaterial in terms of the FBRs. Biocompatibility is also defined as the interdependent interaction mechanism between the biomaterial and living tissue, and it is categorized into interfacial (biological) and mechanical (bulk) biocompatibility [16]. A biocompatible material has an appropriate density, strength, rigidity, non-toxicity, and non-inflammatory response together with long-term storage capacity [17]. The biocompatibility is different from materials to materials, tissues to tissues, and cells to cells. So, the designing of a material with good biocompatibility is a challenge to researchers and manufacturers.

Biocompatibility is influenced by various biological pathways such as chemotaxis, neutrophil activation, and complement activation. The presence of foreign material (here: biomaterial) initiates neutrophil aggregation due to complement activation and leads to pulmonary dysfunction [18]. The incompatibility of the materials is marked by clotting and thrombosis. Host proteins such as blood proteins (fibronectin, fibrinogen, and vitronectin), opsonins(immunoglobin G), and the complement-activated fragment C3b were adsorbed onto the material when the material comes in contact with blood [19]. At the same time, frustrated phagocytosis occurred due to the large size of the biomaterial. As a result, leukocyte products (e.g., lysosomal proteases and oxygen-free radicals) are released to degrade the foreign material. After the neutrophil clearance, the chronic inflammation is arised due to the prolonged accumulation of monocytes, macrophages, and lymphocytes together with the proliferation of blood vessels and connective tissue [20]. This will initiate a foreign body response.

Both in vivo and in vitro methods are used to evaluate the biocompatibility of a material. The response of cells or tissues toward the biomaterials is roughly classified into (i) strong effects (cytotoxicity, genotoxicity), (ii) moderate to nearly negligible

effects (complement activation, pharmacological effects), and (iii) the absence of measurable effects [21]. Cytotoxicity, sensitization, irritation or intracutaneous reactivity, mucous membrane irritation, systemic and subchronic toxicity, genotoxicity, reproductive or developmental toxicity, blood biocompatibility/complement activation, immune response, carcinogenicity, biodegradation, etc., are the some of the standards related to biocompatibility [21]. Final finished form of medical devices (ISO 10993–12), evaluation of the biological response due to device mechanical failure (specific to FDA), preparation of test article samples or test extracts (ISO 10993–12), evaluation of submicron or nanotechnology components (ISO 10993–22), testing of in situ polymerizing and/or absorbable materials (ISO/TR 37137), and the strategy for testing of extracts from multiple component devices (specific to FDA) are the major biocompatibility testing considerations [22]. The evaluation of the biocompatibility helps to predict whether the material is toxic or nontoxic to the living tissue. The hydrophilicity/hydrophobicity, wettability, surface energy, lubricity, chemical functions, smoothness, surface roughness, protein adsorption, swelling, and electrostatic effects are the important surface parameters of the biomaterials that are considered during the assessment of biocompatibility [23]. Both in vitro and in vivo tests are carried out to evaluate the cytotoxicity of the biomaterials. The prolonged exposure of biomaterials toward the target cell line is a widely accepted way to check the biocompatibility/toxicity of the material. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, methylcellulose toxicity test, and nitro blue tetrazolium chloride (NBT) assay, etc., are some of the experiment that frequently used to evaluate the biocompatibility of the material in vitro. The subcutaneous implantation with histological and morphological evaluations are common in in vivo biocompatibility assessment [24].

7.2 Biocompatibility of the Hydrogel

Hydrogels are the network of polymer chains that swollen extensively in water. It is categorized according to cross-linking (physical and chemical crosslinking), physical state (solid, semisolid, and liquid), stimuli-responsive (pH-responsive, temperature, etc.), source (natural and synthetic), polymer composition (homopolymer, copolymer, and multipolymer), electric charge (nonionic, ionic, zwitterionic, and amphoteric), and configuration (amorphous, crystalline) [25–27]. The synthetic polymer-based hydrogels are considered to have low biocompatibility as compared to the natural one. The polymeric biomaterials are classified into biostable, bioabsorbable, and partially bioabsorbable based on their behavior in contact with the living tissue [23]. Hydrogel-related oral drug delivery has a wide application due to the strong pH variation from the mouth to the intestine and elimination from the body through feces. The degradation rate of the hydrogel is affected by the degree of crosslinking. An increase in the degree of crosslinking reduces the degradation rate of the material [28]. The physiochemical similarity to the extracellular matrix (ECM) and higher water content make the hydrogel become more biocompatible.

The polymers used to develop hydrogels are versatile in nature. They are capable of form hydrogels with good flexibility and softness. Like cells, the hydrogel maintains a hydrated nature and the elastic property that helps to reduce the irritation to the surrounding tissue. The negative immune response of the host cell is reduced by the low interfacial tension between the hydrogel surface and the body fluid. Furthermore, the mucoadhesive and bioadhesive characteristics of hydrogel enable the tissue permeability [29]. A biomaterial has the ability to perform desired functions without causing any toxicity to the cells/tissues. It must be immunocompatible and should not undergo significant functional changes during sterilization. The three-dimensional structure of the hydrogels is provided by cross-linking of the polymers. The mechanical properties also affect the cell migration, proliferation, and differentiation of the cells. Another important parameter is the degradation of the hydrogels. The hydrogels are mainly degraded via ester cleavage, enzymatic cleavage, photolytic cleavage or the combinations of this mechanism. The by-products formed after degradation must be non-toxic to the cells and the degradation kinetics is needed to be stable [18]. Alginate, dextran, hyaluronic acid, pectin, and xanthan are some of the natural polymers used for the preparation of hydrogels. The synthetic polymers such as acrylic acid (AA), poly(vinylalcohol), methacrylic acid (MAA), and poly(styrene) (PS) are used for the preparation of biocompatible hydrogels (Fig. 7).

A good hydrogel has the ability to control the specific molecular interaction such as receptor-ligand complexes, bound or soluble molecule interactions, and focal adhesion interactions at the cell-material interface. Poly(ethylene glycol) (PEG) hydrogel mimic collagenase substrates found in natural ECM proteins. Controlled resorption or dissolution is essential for the degradation of hydrogels [31]. At the macroscopic level, the physical texture of the hydrogels is altered by environmental parameters like temperature, pH, an electric signal, the presence of an enzyme or other ionic species. Biosafety and bio-functionality are the two elements of biocompatibility that

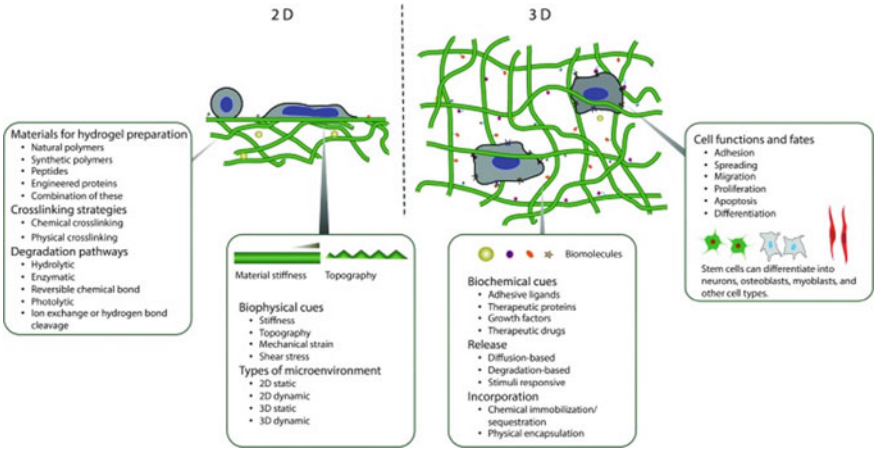

Fig. 7 Schematic illustration of parameters considered during hydrogel preparation [30]

ensure safe use and the ability to perform the desired task. In the case of hydrogels, the organic solvents, emulsifiers, initiators, crosslinkers, and unreacted monomers bring the toxicity toward cells. The purification of the hydrogels by dialysis or solvent washing reduces the toxicity of the hydrogel [32].

7.3 Biocompatibility of Natural Hydrogels

Natural polymers are known to have better interactions with the living tissues and promote them to exhibit high performance. Collagen, gelatin, agarose, alginate, chitosan, hyaluronic acid, etc., are widely used for biomaterial preparation. Alginate is a hydrophilic anionic polysaccharide obtained primarily from brown seaweed. It is composed of (1–4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G)monomers. Due to the variations in the distribution of M and G residues and molecular mass in each algal source, the biocompatibility of the alginate is not guaranteed. So, the biocompatibility of alginate is depending on the purity, distribution of M and G residue, viscosity, and molecular weight [33]. Because of the gel-forming characteristics, alginate is generally used in the pharmaceutical field. The slower degradation rate of alginate is facilitated by the higher molecular weight. Because of the presence of the carboxyl group, alginate hydrogels are able to show a high swelling ratio at increasing pH values. Alginate-based hydrogels have a potential application in drug delivery and regenerative medicine. It was used for bone regeneration, wound healing, cartilage repairing, and drug delivery, etc. [34]. The hydrogel composed of N,O-carboxymethyl chitosan and oxidized alginate possesses good biocompatibility toward NH3T3 cells after 3-dayincubation [35]. In the case of calcium cross-linked alginate hydrogels, the stiffness and toughness improved with increasing cross-linking density [36]. Studies show that the high content of M contributes to the immune response by producing cytokines such as TNF-α, IL-1, and IL-6 [37]. Rapid release of the loaded drugs and low entrapment efficiency are the major disadvantages of alginate-based hydrogels.

Dextran is a bacterial polysaccharide consist of linear α-1,6-linked glucopyranose unit with some degree of 1,3 branching. Dextran has a molecular weight below than 100 kDa which is used as a plasma expander because of its relatively inert and nontoxic nature [38]. Different dextranases present in the liver, colon, and spleen have the capacity to metabolize the dextran. The reticuloendothelial system is able to degrade high molecular weight dextran [39]. Ferreira et al. showed that dextran-acrylate hydrogels have biocompatibility in both in vitro (human foreskin fibroblasts) and in vivo (subcutaneous and intramuscular implantation in Wistar rats for up to 40 days) [40]. It increases the longevity of therapeutic drugs and eliminates through the renal clearance (Mw < 40 kDa) [41].

Hyaluronic acid (HA) is a glycosaminogly can consist of repeating non-sulfated disaccharide units (α-1,4-D-glucuronic acid and β-1,3-*N*-acetyl-D-glucosamine) [42]. It is a major element in the ECM and involved in several biological functions such as regulation of cell adhesion, cell motility, and differentiation, etc. [43]. HA itself or

association with other materials has been used to develop nanoparticles, hydrogels, microparticles, and other drug carriers [44]. Because of the high rate of elimination, modification of HA is needed for drug delivery. High structural analogy and poor interaction with blood facilitate the non-antigenic and nonimmunogenic effects [45]. Literature indicated that the HA is degraded by both reactive oxygen intermediates and hyaluronidases synthesized by endothelial cells, fibroblasts, and macrophages [46]. HA-based hydrogels are biologically inert, non-allergic, and non-carcinogenic during the degradation process. The non-toxicity of the HA hydrogels was confirmed by Kim et al. 2013 [47].

Pectin is an anionic polysaccharide found in the cell wall of the most plant and linked by 1,4-α-D-galacturonic acid residues [48]. It has a good gelling property and improves drug loading and releasing. The intermolecular interaction between pectin and tissues is determined by the presence of positive or negative charges on the pectin [49]. Pectin forms ionic interaction via calcium ions [50]. After the formation of hydrogels, these charges are partially or fully engaged. So that the further molecular interactions are reduced. Currently, pectin is used in tissue engineering, dentistry, and wound-healing applications, etc. [49].

Chitosan is a semi-synthetic polymer obtained from the deacetylation of chitin-whic is known as the analogous of the glycosaminoglycans (GAG) found in ECM of the cartilage [51]. It is approved by the FDA as a wound dressing material. This positively charged chitosan is known to stimulate the granulation and rebuilding of the tissues [52]. The positive charge of chitosan enables them to interact highly with the cells due to ionic interchanges between the intracellular and extracellular medium mediated by the Na+ /K+ pump [53]. Encapsulation of the drug within the chitosan carrier reduces the positive charge, thereby limiting the cellular uptake, and contribute toxicity [53]. The antibacterial and anticancer effect of chitosan is made then a suitable drug delivery system. In mammalian implantation model, the early migration of neutrophils was observed, and it was resolved with an increase in implantation time. The endotoxins were absent, and new blood vessels were formed [54].

8 Biocompatibility of Synthetic Hydrogels

Synthetic polymers do not occur in nature and made artificially through the process of polymerization. They got great acceptance because of its ease of modification. Generally, these kinds of polymers show less biocompatibility than natural polymers. Biocompatibility of some prominent synthetic polymers is given in Table 1. It gives an overall idea of the comparison between the biocompatibility of polymers based on tissue engineering applications [55]. Localized inflammation is observed during poly(lactic and glycolic) acid hydrogels, while polyethylene oxide and polyethylene glycol shows no inflammation during treatment. Polycaprolactone is degraded via hydrolysis, and it shows minimal inflammation to the tissues. Polyethylene glycol (PEG) is a synthetic polymer widely used for drug delivery applications. It was noted

Table 1 Biocompatibility nature of different types of synthetically manufactured hydrogels

Hydrogels from synthetic polymers	Biocompatibility nature	TE applications
Poly (lactic and glycolic) acid	Products degrade during metabolic pathway, lacalized inflammation	Bne, nerves, skin, ligament, tendon, vessels, cartilage, kindney, tumor, bladder, liver cells
Polyethyline oxide and plyethylene glycol	Hydrolysis, mild foreign in PEO and minimal foreign in PEG body reaction, no inflammation	Bone, skin, muscles, vessels, cartilage, nerves, cardiovascular, intraperitoneal, liver cells
Polycaprolactone	Hydrolysis, minimal inflammation	Sini, ligament, tendon, vessels, nerves, cartilage, bone, retina

that polyethylene glycol acts as a surface protector by reducing protein adsorption and cell adhesion [56]. It has been approved as a preservative additive by the U.S. Food and Drug Administration. Modification of nanoparticle with PEG helps them to escape from the recognition of the immune system and slowdown their removal. Apart from this, it was understood that PEG is able to inhibit the inflammatory response and will not accumulate in the body [57]. Covalent attachment of PEG to a molecule is called PEGylation. This kind of attachment will improve pharmacokinetics and biological functions [58] together with less protein adhesion. The coating with PEG limits protein adhesion, tissue damage, and antigenic activity [56]. The ability to resist protein adsorption is proportional to the polymer chain length and surface density. This is achieved by high mobility, steric hindrance effect, hydrophilicity, and large excluded volume [59].

Polyacrylic acid hydrogels are called superabsorbents because it has the capacity to absorba large amount of water [60]. Acrylic acid biomaterials are used widely in the pharmaceutical field and have been approved by the Food and Drug Administration (FDA). The hydrogels obtained by grafting the acrylic acid on cellulose was non-toxic to human embryonic kidney cells when cross-linked with ethylene glycol [61].

Polyvinyl alcohol is a water-soluble synthetic polymer widely used pharmaceutical field. Alexandre et al. reported that the PVA can be used as a vascular graft with good biocompatibility and hemocompatibility [62]. PVA-based artificial arteries, cartilage, muscle, etc., were reported. The strong hydrophilic nature of PVA-based gel contributes to bio-inert behavior [63]. It is a non-toxic material which has the ability to form films and exhibit emulsifying and cell adhesive properties. It is biodegradable, with high tensile strength and flexibility [64].

Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable polymer which consists of polylactic acid and polyglycolic acid. It was approved by the FDA and currently used for various applications such as tissue engineering, drug delivery, and wound healing. During hydrolysis, the monomers are produced by the breaking of the ester bond and that can easily be metabolized by the Krebs cycle [65]. The biocompatibility is altered by initiating the inflammatory condition by lowering the pH value of the surrounding tissue. Hydration, initial degradation, constant degradation, and

solubilization are the important steps involved in the degradation of the PLGA [66]. The biocompatibility of the PLGA was improved by incorporating various nanoparticle into it [67]. The previous study reported that the biocompatibility of PLGA with low concentration is satisfactory and the highest concentration of degradation product caused a toxic effect [68]. High lactide content of PLGA make them more hydrophobic and absorb less water. The crystallinity behavior of PLGA is directly linked to swelling behavior, mechanical strength, hydrolysis, and degradation property [69].

Polycaprolactone (PCL) is obtained by the ring opening polymerization of ε-caprolactone monomers. PCL is a biodegradable and biocompatible polymer widely used for biomedical applications. Under physiological condition, it will undergo degradation by hydrolytic mechanism and take more than 24 months for complete degradation [70]. The degradation of PCL is faster in the alkaline environment than acidic environment [71].

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