Enhancement of Hydrogels' Properties for Biomedical Applications: Latest Achievements

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Abstract

Currently, there are many hydrogels used in many important biomedical fields such as therapeutic delivery, contact lenses, corneal prosthesis, bone cements, wound dressing, 3D tissue scaffolds for tissue engineering, etc., due to their excellent biocompatibility and water sorption properties. Many of these hydrophilic polymers have been already approved by the US Food and Drug Administration (FDA) for various applications. However, many of their potential uses required for many biomedical applications often are hindered by their low mechanical strength, antimicrobial and/or antifouling activity, biological interactions, water sorption and diffusion, porosity, electrical and/or thermal properties, among others. Thus, new advanced hydrogels have been developed as multicomponent systems in the form of composite or nanocomposite materials, which are expected to exhibit superior properties to increase the potential uses of these materials in the biomedical industry. Even though the great advances achieved so far, much research has to be conducted still in order to find new strategies to fabricate novel hydrogels able to overcome many of these problems.

Keywords: hydrogels, polymers, composites, nanocomposites, biomedical, properties

1. Introduction

Hydrogels are used in many fields of the biomedical industry such as therapeutic delivery [1], intraocular lenses, contact lenses and corneal prosthesis in ophthalmology [2], bone cements for orthopedics [3], wound dressing [4], 3D tissue scaffolds in regenerative medicine [5], etc., due to their excellent properties such as biocompatibility, water sorption and suitable mechanical performance, among others [6]. Many of these hydrogels have been approved by the US Food and Drug Administration (FDA) for diverse applications and are currently
produced massively. However, many of their potential uses required for many biomedical applications are sometimes hindered by their low mechanical strength, biological interactions, electrical and/or thermal properties, water sorption and diffusion, antimicrobial and/or antifouling activity, porosity etc. Thus, new advanced hydrogels have been developed and are currently under intensive research to solve all these problems by means of multicomponent polymeric systems or by combination with other materials and/or nanomaterials to form composites or nanocomposites with enhanced required properties.

2. Mechanical properties

The enhancement of mechanical properties is one of the most desirable achievements in the field of hydrogel engineering and many researchers are currently working in this complex scientific area. Most hydrogels possess very low mechanical properties, especially in the swollen state. Thus, hydrogels can be reinforced through many established kinds of methods and techniques: block copolymers, in which hydrophobic and hydrophilic domains alternate [7], increasing crosslinking density [8], by means of binary systems composed of two or more mixed polymers as interpenetrating polymer networks [9], by plasma grafting of a hydrogel onto a hydrophobic substrate [10–12], self-reinforced composite materials composed of fibers embedded in a matrix of the same polymer [13] and with the sol–gel reaction to produce nanosilica reinforcement [14]. However, more recent studies have shown new procedures to improve the mechanical properties of hydrogels with the incorporation of nanomaterials such as graphene (2010 Nobel Prize in Physics) and their derivatives: carbon nanotubes (CNT) [15], graphene oxide (GO) [16, 17], reduced graphene oxide (rGO) [18], etc.

2.1. IPNs

Interpenetrating polymer networks (IPN) have gained greater attention during last decades, mainly due to their biomedical applications as reinforced polymer networks. In 2003, Gong et al. [19] reported their discovery of a new hydrogel architecture that produced extraordinarily materials with enhanced mechanical properties, which they termed a double-network (DN) hydrogel. The DN hydrogel was originally believed to be an interpenetrating polymer network (IPN) of a soft neutral polymer network within a more highly crosslinked network prepared by a two-step sequential free-radical polymerization. The first step consisted of the synthesis of a highly crosslinked network, and the second step involved swelling this first network with a water soluble monomer that was then polymerized within it. The second polymerization step was conducted with or without adding a crosslinking agent. Thus, the use of an IPN, which consists of two separate but interwoven polymer networks, is a chemical procedure that is often used in polymer science to control, enhance, and/or combine functional properties. These advanced multicomponent polymeric systems are composed of crosslinked polymer networks without any covalent bonds between them, where at least one of them is synthesized and/or crosslinked within the immediate presence of the other. It is important to differentiate between the six basic multicomponent polymeric structures: mechanical blends, graft copolymers, block copolymers, AB-crosslinked copolymer, semi-IPNs and full-IPNs (see Figure 1) [20].
If a crosslinker is present in the polymeric system, fully-IPN [21] result, while in the absence of crosslinking, a network having linear polymers embedded within the first crosslinked network is formed (semi- or pseudo-IPN) [22, 23]. IPNs are prepared usually in the form of simultaneous interpenetrating polymer networks (SINs), in which the precursors of both networks are mixed and the two networks are synthesized at the same time, or in the form of sequential IPNs, by swelling of a single-polymer network into a solution containing the mixture of monomer, initiator and activator, usually with a crosslinker. Thus, poly(2-hydroxyethyl methacrylate) (PHEMA) networks were greatly reinforced by poly(ethylene glycol) in SINs and semi-SINs composed of both polymers [24]. Full-IPNs and semi-IPNs of weak gelatin hydrogels were also prepared by the sequential mode of synthesis with polyacrylic acid (PAA) to be evaluated for tissue response in rats [25]. The mechanical properties of pseudo-SIPNs and pseudo-IPNs hydrogels, where the prefix pseudo denotes connectivity of the two network, showed that non-linear tensile properties of pseudo-SIPNs are rate-dependent, but for pseudo-IPNs they are not, which is a consequence of the viscoelastic behavior of a pseudo-SIPN versus elastic performance of the pseudo-IPN [26]. In that study, the mechanical properties of triple-network (TN) hydrogels synthesized from pseudo SIPNs and pseudo-IPNs showed that the presence of a loosely crosslinked third network changes the mechanical behavior of pseudo-SIPNs and pseudo-IPNs by homogenizing the stress within the sample for finite deformations.

IPN hydrogels are also developed with the aim of enhancing the mechanical strength and swelling/deswelling response [27]. For example, interpenetrating polymer network (IPN) hydrogels of chitosan/poly(acrylic acid) (PAA) synthesized by the UV irradiation method showed that even in the swollen state, the present chitosan/PAA IPNs possessed good mechanical properties [28].

![Figure 1. Schematic representation of (a) mechanical blends, (b) graft copolymers, (c) block copolymers, (d) AB-crosslinked copolymer, (e) semi-IPNs and (f) full-IPNs. Modified from [20].](image)
“Smart” hydrogels are able to significantly change their volume/shape in response to small alterations of certain parameters of the environment. These responsive hydrogels have numerous applications, being the most of them focused on biological and therapeutic demands [29, 30], and sensing applications [31].

Encapsulation of cells in interpenetrating network (IPN) hydrogels of two biocompatible materials-agarose and poly(ethylene glycol) (PEG) diacrylate with superior mechanical integrity has been developed [32].

Although IPNs based on hydrogels have been extensively reported, the combination of liquid crystalline (LC) property based hydrogels has been rarely explored. In this case, the anisotropic and molecular order of liquid crystals can be combined with the responsive isotropic properties of hydrogels. Thus, advanced stimuli-responsive materials based on interpenetrating liquid crystal-hydrogel polymer networks have been recently fabricated consisting of a cholesteric liquid crystalline network that reflects color and an interwoven poly(acrylic acid) network that provides a humidity and pH response [33].

2.2. Composite hydrogels

Diverse types of chemical modifications of hydrogels do not have a significant change of the overall mechanical strength because of the main structural skeleton of these polymers or copolymers are still weak. However, by fiber reinforcement, the addition of fabrics imparts high strength to the polymer networks, which form the main skeleton of the composites. Thus, fiber-reinforced hydrogels usually consists of a polymer matrix imbedded with high strength fibers, such as glass, aramid and carbon [34]. In such kind of materials, the mechanical properties are presumed to be improved and the biocompatible characteristics of the polymer should remain the same. Thus, hydrogels such as PHEMA, which is one of the most popular biomaterials, has been manufactured by adding various kinds of weaved and knitted fabrics and fibers, in order to improve overall qualities in advanced wound dressing usage [35]. However, in the recent decades, natural fibers as an alternative reinforcement in polymer composites have attracted the attention of many research groups due to their advantages over conventional glass and carbon fibers [36]. These natural fibers include flax, hemp, jute, sisal, kenaf, coir, kapok, banana, henequen and many others, which offer various advantages over man-made glass and carbon fibers such as low cost, low density, comparable specific tensile properties, non-abrasive to the equipment, non-irritation to the skin, reduced energy consumption, less health risk, renewability, recyclability and bio-degradability [37]. Thus, ultra-long chitin natural fibers were incorporated into hydrophobic Poly(methyl methacrylate) (PMMA) to prepare PMMA/Chitin composite hydrogels with improved properties [38]. This achievement is a significantly environmental move toward the sustainable utilization of marine-river crab shell wastes for biomedical applications in good agreement with green chemistry principles.

2.3. Nanocomposite hydrogels

Another alternative and very promising way of reinforcing hydrogels consist of the incorporation of nanomaterials such as silica, graphene and its derivatives, nanofibres or many other nanoparticles. Silica is a biocompatible material which has been reported to possess
bioactive properties [39]. Silica can improve the mechanical properties of hydrogels through nanosilica filling or the well-known sol–gel process, which offers a new approach to the synthesis of nanocomposite materials with domain sizes approaching the molecular level [40]. Thus, for example, a biphasic matrix of a hybrid (inorganic–organic) nanocomposite materials of poly(2-hydroxyethyl acrylate) (PHEA) with a silica network obtained by an acid catalyzed sol–gel process of tetraethoxysilane (TEOS) showed a very significant improvement of the mechanical properties of the pure hydrogel [41].

Another reinforcement strategy that can be used consists of the combination of interpenetrated polymer networks and nanosilica filling. Thus, for example, poly(acrylic acid) and alginate IPN material with the incorporation of nanosilica greatly increased the compressive strength of the pure components [42].

Graphene (GN) is a two-dimensional monolayer of sp²-bonded carbon atoms [43], which has attracted increasing attention in the last decade owing to its excellent electrical and thermal conductivities [44, 45] and great mechanical strength [46]. Furthermore, graphene promotes adherence of human osteoblasts and mesenchymal stromal cells [47], which render this nanomaterial and its derivatives very promising in the biomedical research field. It has been recently reported that its oxidized form, graphene oxide (GO), can greatly enhance the compression performance of alginate hydrogels even in a minuscule concentration [48]. The improvement of mechanical strength of poly(acrylamide) (PAM), which generally exhibit pronounced weakness and brittleness, by incorporating GO to the polymer matrix has also been reported [49]. GO is also a 2D nanomaterial obtained from natural graphite that can be easily exfoliated into monolayer sheets. GO has many hydrophilic oxygenated functional groups, including hydroxyl (−OH), epoxy (−C=O−), carbonyl (−C=O) and carboxyl (−COOH), which groups enable its dispersion in water solution [50] and render possible its use in many synthetic procedures. The diversity of unique properties of graphene oxide, including great tensile modulus (1.0 TPa), ultimate strength (130 GPa), electrical and thermal properties [51], render GO an ideal carbon nanomaterial for variety of applications toward the development of new advanced materials. Thus, the addition of GO nanosheets increased the Young’s modulus and maximum stress of poly (acrylamide)/gelatin composite hydrogels significantly as compared with control (0.0 wt. % GO). The highest Young’s modulus was observed for hydrogel with GO (0.2 wt. %)/PAA (20 wt. %), whereas the highest maximum stress was detected for GO (0.2 wt. %)/PAA (40 wt. %) specimen. These results suggests that GO nanosheets could be used to improve mechanical properties of hydrogel materials, which are very promising for tissue engineering applications in regenerative medicine [17]. In the biomedical area, a very innovative strategy for three-dimensional self-assembly of graphene oxide sheets and DNA to form multifunctional hydrogels with high mechanical strength, environmental stability, and dye-loading capacity, has also been recently reported [52]. Furthermore, the promising properties of GO with the availability of oxygen-containing functional groups has led the synthesis of 3D crosslinked GO networks able to improve the mechanical properties of alginate hydrogels even more than single GO nanosheets (Figure 2) [53].

Other derivatives of graphene, such as carbon nanotubes (CNTs), discovered by Iijima [54], in the form of single wall carbon nanotubes (SWCNTs) and multi-wall carbon nanotubes (MWCNTs), as well as carbon nanofibres (CNFs) are being used for reinforcing and enhancement of many other hydrogels’ properties [55–59].
Reinforcement can be also conducted with plant fiber-based nanofibres by a successful fibrillation of wood pulp fibers into nanofiber bundles, which are thin enough to work as well as bacterial cellulose in maintaining the transparency of materials [60]. Other novel nanocomposite hydrogels such as those prepared with polyacrylamide (PAM) as a matrix material reinforced with natural chitosan nanofibres via in situ free-radical polymerization showed that these nanofibres acted as a multifunctional cross-linker and a reinforcing agent in the hydrogel polymer system producing a compression strength and a storage modulus significantly higher than those of the pure hydrogel [61].

Figure 2. Confocal microscopy of (a) GO/alginate (GO/Alg) (b & d) crosslinked GO/alginate (cGO/Alg), (c) dynamic mechanical analysis (storage modulus (E') and loss tangent (tan δ)) (e) morphology after swelling in water for 3 hours. Modified from Ref [53].
Other nanoparticles such as clay have been employed to reinforce hydrogels such as polyvinyl alcohol (PVA) [62]. These polymer-clay nanocomposite hydrogels, fabricated for wound healing, constitute a class of materials in which the polymer matrix is reinforced by uniformly dispersed inorganic particles (usually 10 wt.% or less) having at least one dimension in the nanometer scale and exhibiting superior mechanical and thermal properties when compared to pure polymer or conventional composites [63].

3. Electrical properties

The electrical properties are very important in some biomedical areas because it has been demonstrated that various types of electrical stimulation can regulate cell physiological activities such as division [64], migration [65], differentiation and cell death [66]. The electrical stimulation has also been useful in promoting healing for spinal cord repair and cancer therapy due to its non-invasiveness of these polymers [67–69]. Therefore, much emphasis is being done in the development of new conductive hydrogels for biomedical applications. Graphene has been considered to be very effective electrode material due to its excellent conductivity [44], but its production is still very expensive and more new composite materials are expected to be developed with its derivative graphene oxide. However, GO has a very low conductivity due to their oxygen-containing functional groups and must be modified to reduce graphene oxide (rGO) in order to develop electrically conductive hydrogels. Thus, for example, following a single-step procedure starting from a homogeneous water dispersion of GO, it is possible to undergo reduction induced by the UV radiation during the photopolymerization of a resin [70]. Recently, transparent conductive films have been produced by grafting poly(acrylamide)/poly(acrylic acid) on the GO surface followed by a reduction to rGO nanosheets by a two-step chemical reduction with increased conductivity [71] and inorganic–organic double-network (DN) conductive hydrogel of rGO and poly(acrylic acid) has been prepared by a two-step synthesis with a reduction-induced in situ self-assembly [72]. Even more recently, a nacre-inspired nanocomposite of rGO and PAA has been prepared via a vacuum-assisted filtration self-assembly process (see Figure 3). The abundant hydrogen bonding between GO and PAA results in both high strength and toughness of the bioinspired nanocomposites, which are higher than that of pure reduced GO. Moreover, this composite also displays high electrical conductivity, which renders it very promising material in many biomedical applications such as flexible electrodes and artificial muscles.

Carbon nanotubes (CNTs) have also been attracting intensive attention because of their excellent electrical properties with a superb conductivity, remarkable mechanical properties with many potential technological applications [74]. CNTs offer the possibility of developing ultrasensitive electrochemical biosensors due to their unique electrical properties. Thus, nanofibrous membranes filled with multiwalled carbon nanotubes (MWCNT) have been electrospun from the mixture of poly(acrylonitrile-co-acrylic acid) (PANCAA) and MWCNT to develop a glucose biosensor for diabetics [75]. Other hydrogels with very promising biomedical applications consists of dielectrophoretically aligned carbon nanotubes, which control electrical and mechanical properties of gelatin methacrylate (GelMA) hydrogels [76]. The contractile muscle
cells cultured on these materials demonstrated higher maturation compared with cells cultured on pristine and randomly distributed CNTs in GelMA hydrogels.

4. Thermal properties

Even though hydrogels do not need to endure temperatures higher than that of the human body, the improvement of thermal properties can increase its long-term operation. Thus, for example, the incorporation of polyurethane into polyacrylamide network in the form of an interpenetrating polymer network enhanced the thermal properties due to higher crosslinking density imparted by the hard segment content [22]. Though silica can improve the mechanical properties of hydrogels, the differential scanning calorimetry results of PHEMA/SiO₂ hybrids are complicated, showing two glass transition temperatures (Tg) [77]. However, composite hydrogels with functionalized graphene sheets (FGNS) showed an unprecedented shift in Tg of up to 40 and 30°C in poly(acrylonitrile) with 1 wt. % of this nanomaterial [78].

Another strategy to improve the thermal properties of hydrogels is by nanoparticle filling. Thus, crosslinking metal nanoparticles added into the polymer backbone of PHEMA...
hydrogels enabled the preparation of thermally stable, soft, magnetic field-driven actuators with muscle-like flexibility [79]. Furthermore, thermal degradation can also be improved by this filling procedure. For example, the mechanical and thermal properties of a renewable and biocompatible hydrogel of gelatin were improved through cross-linking by cellulose nanowhiskers [80].

In the biomedical field, hydrogels are hydrophilic polymers, which are able to absorb large amounts due to contact with cells or tissue in the human body. Therefore, the thermal analysis of water and its influence on the swollen hydrogel properties becomes essential [12, 81, 82].

5. Water sorption and diffusion

Water sorption and diffusion of hydrogels are also very important in biomedical applications because these properties play a very important role in cell survival, especially in tissue engineering [5]. Thus, synthetic hydrogels such as PHEMA or PHEA are very important hydrophilic materials as these polymers were able to absorb and swell retaining large amounts of water within their structure [83–86]. The excellent water sorption property has made these kind of biomaterials very promising in a wide range of biomedical applications such as controlled drug delivery, tissue engineering, wound healing, etc. [6, 87]. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymeric backbone, while their resistance to dissolution arises from cross-links between network chains [88]. However, these single-network hydrogels have weak mechanical properties in the swollen state and slow response at swelling. Therefore, although reinforcement of hydrogels is absolutely necessary, as already mentioned, the improvement of mechanical properties can significantly affect water sorption. For example, water sorption can be dramatically reduced by the reinforcement produced by the combination of hydrophilic and hydrophobic functional groups of polymers as multicomponent polymeric systems (Figure 1).

Reinforcement of hydrogels by GO loading can enhance significantly water sorption and diffusion. Thus, the swelling rates of graphene oxide / poly(acrylic acid-co-acrylamide) nanocomposite hydrogels increased with increase in the GO loadings to 0.30 wt. % and then decreased with further increasing GO loadings. It is worth noting that the hydrogel with only 0.10 wt. % GO exhibited significant improvement of swelling capacity in neutral medium, and could also retain relatively higher swelling rates to a certain degree in acidic and basic solutions. Furthermore, it has been reported very recently that a very low filling of GO can produce a very significant increase of water diffusion (almost 6 times faster) in crosslinked alginate (Figure 4) [48]. Therefore, these GO-based super-absorbent hydrogels have very potential applications in many fields such as biomedical engineering and hygienic products [50].

The mechanism of water diffusion [89] can also be altered by the reinforcement of hydrogels through any of the methods shown in Section 2. Thus, very promising biomaterials
Figure 4. Cryo-scanning electron micrograph of crosslinked alginate synthesized with a minuscule amount of GO and 18 wt.% of calcium chloride (with respect to the mass of sodium alginate) in the swollen state after 2 minutes of immersion in water at 24 ± 0.5°C (a). Apparent diffusion coefficients of liquid water (mean ± standard deviation) in calcium alginate hydrogels with different crosslinker contents with (black columns) and without (gray columns) 0.1 wt.% of GO (b). Reprinted with permission from Ref [48].
for drug-releasing such as poly(acrylic acid)-GO composite hydrogels exhibit non-Fickian anomalous diffusion and their deswelling ratio decreases with increasing GO content [51]. Superabsorbent polymers of sodium lignosulfonate-grafted poly(acrylic acid-co-acrylamide), prepared by a new ultrasound synthetic method, shows also a non-Fickian water diffusion transport with a maximum water absorbency of 1350 g·g⁻¹ [90]. PHEA hydrogels exhibit also a non-Fickian diffusion behavior s [83, 86]. However, other polymer chemically very similar, PHEMA, which is a very important water-swellable biomedical polymer, is controlled by Fickian diffusion [91]. Thus, copolymerized hydrogels based on 2-hydroxyethyl methacrylate (HEMA) and epoxy methacrylate (EMA) synthesized by bulk polymerizations showed that the swelling process of these polymers is also Fickian and the equilibrium water content (EWC) decreased with increasing EMA content due to its hydrophobicity [92].

It is remarkable that pH has a big influence in the swelling properties and diffusion mechanism of hydrogels. Thus, the swelling properties of semi-interpenetrating polymer networks of acrylamide-based polyurethanes decreased in acidic pH while a reverse trend was observed in basic pH. Nevertheless, these semi-IPNs were found to be hydrolytically stable in phosphate buffer solution, which render them potential materials for biomedical applications [22]. PAA is a pH-sensitive and biocompatible polymer that is being used in many biomedical fields [30] and has attracted considerable interest because of its therapeutic use, due to its ability to swell reversibly with changes in pH. Thus, GO functionalized with PAA (GO-PAA) by in situ atom transfer radical polymerization (ATRP) showed potential use as an intracellular protein carrier using bovine serum albumin (BSA) as a model protein [93]. This application is very important because proteins participate in all vital body processes and these perform an essential function inside cells as enzymes, transduction signals, and gene regulation. Another pH-sensitive terpolymer hydrogel, poly(acrylamide-co-2-acrylamido-2-methyl-1-propanesulfonic acid-co-acrylamido glycolic acid), with applications in drug release showed a quasi-Fickian diffusion mechanism with partly chain relaxation controlled diffusion. These hydrogels demonstrated a sharp change in its water absorbency and molecular weight between crosslinks of the network with a change in the swelling media pH [94].

The effect of temperature on swelling properties of hydrogels is also very important [92]. Thus, hydrogels can be modified to exhibit fast temperature sensitivity, and improved oscillating swelling-deswelling properties as for example the thermosensitive poly(N-isopropyl acrylamide-co-acrylic acid) hydrogels [95].

6. Antimicrobial and antifouling activity

Microbial infections can lead to implant failure, which may cause major economic losses and suffering among patients despite the use of preoperative antibiotic prophylaxis and the aseptic processing of materials. Therefore, novel antimicrobial materials are urgently in need for medical uses [96]. For that reason, much effort is being done in the development of advanced hydrogels with inherent antimicrobial properties. Thus, syringe-injectable bioadhesive hydrogels prepared from mixing polydextran aldehyde and branched polyethyleneimine, able
to kill both Gram-negative and Gram-positive bacteria, while sparing human erythrocytes [97] and injectable conductive self-healed hydrogels based on quaternized chitosan-g-polyaniline (QCSP) and benzaldehyde group functionalized poly(ethylene glycol)-co-poly(glycerol sebacate) (PEGS-F) with antibacterial, anti-oxidant and electroactive dressing for cutaneous wound healing have been developed [98].

Other hydrogels such as chitosan and its derivatives has been widely used as implant coatings for its intrinsic properties such as non-toxic, osteoconductive, pH responsive, anti-microbial, biocompatible and cell adhesive [99, 100]. Nevertheless, the development of new chitosan derivatives or composites with superior antimicrobial activity is still under research. Thus, for example, a novel hydrogel coating produced by electrophoretic co-deposition of chitosan/alkynyl chitosan showed high antibacterial effect against *Escherichia coli* and *Staphylococcus aureus* [101] by disk diffusion method [102] (see Figure 5). Antibacterial polymer coating adhered on the surface of medical implants and devices have attracted great interests in the last decades for its ability to reduce implant-associated infections [103, 104].

Antimicrobial hydrogels formed by crosslinking polyallylamine with aldaric acid derivatives exhibited complete kill within 4 hours against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* suspended in culture medium [105] and a facile strategy to fabricate antibacterial ultrathin hydrogel films via a layer-by-layer (LbL) technique and “click” chemistry was reported by Wang et al. [106]. This hydrogels consisted of poly[oligo(ethylene glycol)glyfurate]-co-poly[dodecyl bis(2-hydroxyethyl)methylammonium fumarate] (POEGDMAM) containing multi-enes and poly[oligo(ethylene glycol)mercapto-succinate] (POEGMS). These ultrathin films exhibited excellent antibacterial activity against both *Staphylococcus aureus* and *Escherichia coli* due to the presence of ammonium groups with long alkyl chains in the POEGDMAM.

**Figure 5.** Antimicrobial results of chitosan and alkynyl chitosan against *E. coli* and *S. aureus* by using disk diffusion method. Images (a–e) are paper disks containing 1 wt. % chitosan, 1 wt. % alkynyl chitosan (ACS1, ACS2, ACS3 and ACS4), respectively against *E. coli*; images (f–j) correspond to paper disks containing 1 wt. % chitosan, 1 wt. % alkynyl chitosan (ACS1, ACS2, ACS3 and ACS4), respectively against *S. aureus*. Alkynyl chitosan coded as ACS1, ACS2, ACS3 and ACS4 were prepared by changing the molar ratio of chitosan 0 unit to 3-bromopropyne monomer as 1:0.5, 1:1, 1:1.5 and 1:2. Reprinted with permission from Ref [101].
Antibacterial properties can also be imparted to a hydrogel by doping in an exogenous antibiotic for eventual release [107]. In these delivery systems, the active agent is released from the polymer matrix over time. However, the material’s antibiotic activity is eventually exhausted with the remaining matrix being left inactive and the remaining vehicle may become a substrate for colonization by bacterial biofilms once the payload is depleted, which can become life threatening. For this reason, secondary surgeries are typically performed to remove these empty depots as a means of preventing this type of infection. To avoid this second surgery, a hydrogel drug delivery system in which the drug release rate of vancomycin and degradation rate of the hydrogel are linked via covalent incorporation of vancomycin in the hydrogel backbone was successfully developed [108].

However, many hydrogels themselves do not have any antimicrobial activity and therefore some fillers, and antimicrobial agents need to be incorporated by physical blending in order to produce antimicrobial materials [109]. Thus, graphene has emerged as a novel green broad-spectrum antimicrobial nanomaterial, with little bacterial resistance and tolerable cytoxic effect on mammalian cells. It exerts its antibacterial action via physical damages through direct contact of its sharp edges with bacterial membranes and destructive extraction of lipid molecules. The antimicrobial activity of GO against two bacterial pathogens (*Pseudomonas syringae* and *Xanthomonas campestris pv. undulosa*) and two fungal pathogens (*Fusarium graminearum* and *Fusarium oxysporum*) showed that GO had a powerful effect on the reproduction of all these four pathogens because it killed nearly 90% of the bacteria and repressed 80% macroconidia germination along with partial cell swelling and lysis at 500 μg/mL. The graphene-based nanocomposites have a wide range of biomedical applications, such as wound dressing due to its superior antimicrobial properties and good biocompatibility [110].

Another strategy to design hydrogels with desired antimicrobial performance consists of adding silver nanoparticles (Ag NPs). Hence, silver nanoparticles have emerged up with diverse medical applications ranging from silver based dressings, silver coated medicinal devices, such as nanogels, nanolotions, etc. [111].

Infections are also frequent and highly undesired occurrences after orthopedic procedures. Thus, for example, medicated hydrogels of hyaluronic acid derivatives have been developed [112] to address this problem. However, the growing concern caused by the rise in antibiotic resistance is progressively dwindling the efficacy of such drugs and the integration of silver nanoparticles in hydrogels has become a very promising alternative [113].

The combination of both previous strategies (graphene and Ag NPs) to design antimicrobial hydrogels with good water maintaining ability is of particular significance to promote the development of wound dressing. Thus, a series of hydrogels were synthesized by crosslinking of Ag/graphene composites with acrylic acid and N,N’-methylene bisacrylamide at different mass ratios. In this study, prepared hydrogel with an optimal Ag to graphene mass ratio of 5:1 exhibited much stronger antibacterial abilities than other hydrogels and showed excellent biocompatibility, high swelling ratio, and good extensibility at the same time. Besides, *in vivo* experiments indicated that this nanocomposite hydrogel could significantly accelerate the healing rate of artificial wounds in rats, and it helped to successfully reconstruct intact and
thickened epidermis during 15 day of healing of impaired wounds [114]. In the same way, acrylic acid (AA) grafted onto poly(ethylene terephthalate) (PET) film through gamma-ray induced graft copolymerization with silver nanoparticles on the surface showed strong and stable antibacterial activity [115].

It is highly desired to have a hydrogel material bearing the excellent antifouling property/biocompatibility to prolong the lifetime of implanted materials, switchable antimicrobial property to eliminate infection and inflammation, and good mechanical properties to avoid the failure of the implanted material. We hypothesize derivatives of zwitterionic carboxybetaine with hydroxyl group(s) can switch between the lactone form (anti-microbial) and the zwitterionic form (anti-fouling) and the intramolecular hydrogen bonds will enhance the mechanical property of the zwitterionic hydrogel. It is highly desired to have a hydrogel material bearing the excellent antifouling property/biocompatibility to prolong the lifetime of implanted materials, switchable antimicrobial property to eliminate infection and inflammation, and good mechanical properties to avoid the failure of the implanted material. We hypothesize derivatives of zwitterionic carboxybetaine with hydroxyl group(s) can switch between the lactone form (anti-microbial) and the zwitterionic form (anti-fouling) and the intramolecular hydrogen bonds will enhance the mechanical property of the zwitterionic hydrogel.

On the other hand, the surface of hydrogels must be modified to make it resistant to protein adsorption and cell adhesion to avoid fouling. Thus, there is a need for coatings with antifouling properties that are able to improve the performances of implanted biomedical devices. Thus, the antifouling properties of poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) hydrogels were improved by the surface grafting of a brush of poly(oligoethylene glycol methyl ether acrylate) [poly(OEGA)] [116]. Novel antifouling highly wettable hydrogels with superior mechanical and self-healing properties have also been developed by UV-initiated copolymerization of non-fouling zwitterionic carboxybetaine methacrylamide (CBMAA-3) and 2-hydroxyethyl methacrylate (HEMA) in the presence of uniformly dispersed clay nanoparticles (Laponite XLG) in water [117].

Therefore, it would be highly desired to have a hydrogel material bearing the excellent antifouling property/biocompatibility to prolong the lifetime of implanted materials, switchable antimicrobial property to eliminate infection and inflammation, and good mechanical properties to avoid the failure of the implanted material. Thus, derivatives of zwitterionic carboxybetaine have been developed with hydroxyl group(s), which can switch between the lactone form (anti-microbial) and the zwitterionic form (anti-fouling) [118]. Besides, the intramolecular hydrogen bonds enhance the mechanical property of the zwitterionic hydrogel.

Nevertheless, the rapid emergence of antibiotic resistance in pathogenic microbes is becoming an imminent global public health problem because they are highly prone to develop resistance through mutation and the treatment with conventional antibiotics often leads to resistance development leaving the bacterial morphology intact. Therefore, much research is currently being done in the development of new antimicrobial hydrogels because they have been demonstrated to be very effective in preventing and treating multidrug-resistant infections.
7. Porosity

Porous polymers have received an increased level of research interest because of their potential to merge the properties of both porous materials and polymers [119]. Porous polymers have potential applications in many fields such as gas storage and separation materials [120, 121], drug delivery [122], catalysts [123], supports for electrochemical sensing [124], low-dielectric constant materials [125], packing materials in chromatography [126], scaffolds or three-dimensional porous matrices for tissue engineering in regenerative medicine [5, 41, 127, 128] and many others. These high value applications have driven much emphasis on development of reliable methods for preparation of porous polymers with designed pore architectures in the last decades (see Figure 6).

Tissue engineering holds great promise for regeneration and repair of diseased tissues, making the development of new porous supports as scaffolds for tissue regeneration a topic of great interest in biomedical research. Hydrogels have emerged as leading candidates for engineered tissue scaffolds due to their good biocompatibility and similarities to native extracellular

![Figure 6](http://dx.doi.org/10.5772/intechopen.71671)

**Figure 6.** Different porous polymers prepared by different preparation methods to obtain diverse pore architectures. Reprinted with permission from Ref [12, 41, 48, 128–130].
matrix. However, precise control of hydrogel properties, such as high porosity, remains a challenge. Traditional techniques for creating bulk porosity in polymers have demonstrated success in hydrogels for tissue engineering. However, some problems related to direct cell encapsulation often occur. Thus, emerging technologies have demonstrated the ability to control porosity and morphology in hydrogels, creating engineered tissues with structure and function similar to native tissues [131]. The interconnection and geometry of pores, which depends on the tissue to regenerate, physicochemical properties, and mechanical resistance of the material play a major role in these biomedical applications. Thus, there are several methods to produce scaffolds, which include gas foaming [132], sintering fiber meshes [133], solvent casting [134], polymerization in solution [86, 135], porogen technique [129, 136], freeze-drying techniques

Figure 7. Scanning electron micrographs of EA/HEMA copolymer scaffolds (30% HEMA) at different magnifications. Reprinted with permission from Ref. [129].
electrospinning [139], 3D printing [140], 3D bioplotting of scaffold with cells [141], etc. For example, scaffolds with interconnected spherical pores and controlled hydrophilicity with interconnected porous structure were synthesized using a template of sintered PMMA microspheres of controlled size. In these scaffolds, the geometric characteristics (pore size, connectivity and porosity) and the physico-chemical properties of the resulting material can be controlled in an independent way. Copolymerization of hydrophobic ethyl acrylate (EA) and hydrophilic hydroxyethyl methacrylate comonomers in the free space of the template and subsequent solution of the PMMA microspheres gave rise to the scaffold with the designed pore architecture (see Figure 7) [129].

Figure 8. Morphology of the gelatin-PHEMA porous scaffolds as obtained through μ-CT (panels (a)–(c): (a)—top view, (b)—bottom view, and (c)—side view) and SEM (panel (d)) analyses: panel (I)—C0; panel (II)—C1; panel (III)—C2; panel (IV)—C3. Reprinted with permission from Ref. [138].
A novel preparation of gelatin-PHEMA porous scaffolds by freeze-drying technique was developed recently [138]. Their morphology was assessed by SEM and μ-CT (Figure 8). In this study, four types of novel hydrogels using different methacrylamide-modified gelatin/2-hydroxyethyl methacrylate ratios between 1/0 and 1/2 (w/w) (samples from C0 to C3) were prepared and the results indicated that the HEMA content in the initial polymerization mixtures modulate the architecture of the porous scaffolds from straightforward, top-to-bottom oriented channels for hydrogels possessing the lowest HEMA content to a complex and dense internal porosity of the channels the case of higher HEMA loaded materials. Besides, the covalently bound gelatin sequences significantly improve the biocompatibility of PHEMA based hydrogels, which is very desirable for tissue engineering purposes.

Superporous scaffolds can be also prepared by the salt-leaching technique using NaCl or (NH₄)₂SO₄ as a porogen [142] or with many other porogenic agents such as ammonium oxalate crystals [143].

By submitting carbon dioxide to supercritical conditions after certain time and then rapidly depressurized is also possible to fabricate porous structures that are related to the supercritical parameters and to the polymer blend composition [131]. The use of CO₂ to create such scaffolds has received some attention in the past but many researchers believe that there is limited interconnectivity between the pores, which is required for tissue engineering. However, highly porous (greater than 85%) and well interconnected scaffolds with very promising applications for cartilage repair have been obtained in a blend of poly(ethyl methacrylate) and tetrahydrofurfuryl methacrylate [144].

Probably the most sophisticated techniques to produce scaffolds are electrospinning, 3D printing and bioprinting. Electrospinning is composed of a high-voltage DC power supply, an infusion pumps and a syringe with a needle tip usually with a diameter of 0.5 mm. For example, a three-dimensional aligned nanofibers-collagen type I hydrogel scaffold for controlled non-viral drug/gene delivery to direct axon regeneration in spinal cord injury treatment has been reported very recently [145].

3D printing promises to produce complex biomedical devices according to computer design using patient-specific anatomical data. This 3D printing technique has slowly evolved to create one-of-a-kind devices, implants, scaffolds for tissue engineering, and drug delivery systems among other important applications. However, several technological limitations, related to the kind of commercially printable materials available and other technical printing aspects such as printing speed, must still be overcome. The common 3D printing technologies are three-dimensional printing, fused deposition modeling, selective laser sintering, stereolithography, and 3D plotting/direct-write/bioprinting, and are still under deep research for the progress of each technology applied in tissue engineering. Bioprinting is the more advanced 3D printing technology because it consists of printing cells combined with custom 3D scaffolds for personalized regenerative medicine [140].

Mechanical resistance depends both on the material properties and on the interconnected pore structure of the scaffold. This problem is more important in polymer hydrogels, which
exhibit even poorer mechanical properties when they are porous and hydrated. Therefore, it is usually necessary to enhance the mechanical properties of these porous structures by means of the methods, shown in chapter 2, with nanomaterials or other techniques. For example, the use of a hybrid hydrogel nanocomposite of silica/PHEA as scaffold material matrix greatly improves the mechanical properties [41].

Other modifications of scaffolds such as those of PHEMA with cholesterol methacrylate (CHLMA) and laminin have been developed in the presence of ammonium oxalate crystals to introduce interconnected superpores in the matrix in order to design superporous scaffolds that promote cell-surface interaction [146]. PHEMA has also been modified with laminin-derived Ac-CGGASIKAVS-OH peptide sequences to construct scaffolds that promote cell adhesion and neural differentiation. With the same goal, nanofiber scaffolds of poly (L-lactide) (PLLA) prepared by electrospinning were treated with oxygen plasma and then simultaneously in situ grafted with hydrophilic acrylic acid to obtain PLLA-g-PAA with a modified surface, which significantly improved cell adhesion and proliferation [130].

Polysaccharide hydrogels have become increasingly studied as matrices in soft tissue engineering due to their known cytocompatibility. For example, cross-linkable dextran methacrylates and hyaluronan methacrylate hydrogels, which are candidates as matrices for soft tissue reconstruction, were synthesized showing that the in vitro degradation behavior of these types of hydrogels could be controlled by the polysaccharide structure and the cross-linking density. Furthermore, under in vitro conditions, these novel materials had no cytotoxic effects against fibroblasts and the use of composite gels improved the adherence of cells [147].

Therefore, great advances have been achieved so far in scaffold design of new advanced porous hydrogels for tissue engineering applications. Nevertheless, much research has to be conducted still in order to find new ways and methods capable of providing suitable materials able to fulfill all the necessary requirements of this biomedical field.

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