Chapter

Acrylic-Based Hydrogels as Advanced Biomaterials

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Abstract

Acrylate based hydrogels are one of the most promising soft biocompatible material platforms that significantly contribute to the delivery of therapeutics, contact lenses, corneal prosthesis, bone cements and wound dressing, and are being explored widely for potential applications in the field of regenerative medicine. A significant number of these materials, which possess excellent water sorption properties, have been supported by the Food and Drug Administration (FDA) of the United States for different applications. Nonetheless, many of their physical and biological properties required for certain biomedical and bioengineering applications are often poor when they are in the hydrated state at the body temperature: tensile/compression performance, water diffusion, antimicrobial activity, antifouling capacity, biological response, porosity for the fabrication of supports or *scaffolds* for tissue engineering, electrical and/or thermal properties, among other properties. Consequently, new acrylic-based hydrogels have been designed as multicomponent systems such as interpenetrated polymer networks, composites and nanocomposite materials, which have exhibited superior properties able to substantially enhance potential uses of these materials in the biomedical and bioengineering industry.

Keywords: acrylic-based hydrogels, polymers, composites, nanocomposites, biomedicine, bioengineering

1. Introduction

Hydrogels are hydrophilic polymer networks that are capable of absorbing large amounts of water and retaining them, which make them a versatile class of materials especially for biomedical applications. The physical and biological properties largely depend on composition, polymerisation methods and crosslinking but in general are mechanically weak materials. Acrylic-based hydrogels are utilised in numerous fields of biomedicine and examples include therapeutic delivery [1], intraocular lenses, contact lenses and corneal prosthesis in ophthalmology [2], bone cements for orthopaedics [3], wound dressing [4], and tissue *scaffolds* for regenerative medicine [5], due to their diverse properties. Owing to their propensity to absorb large amounts of water or biological fluids, they tend to exhibit properties like the extracellular matrix. The ability to tune physical and mechanical properties of hydrogels and the inherent properties that facilitate diffusion of oxygen, biomolecules and waste metabolites make them a versatile group of polymers [6]. Many of these hydrogels have been supported by the US Food and Drug Administration (FDA) for differing applications. Nonetheless, their potential use in biomedical applications are sometimes limited by their low mechanical strength, biological interactions, electrical

and/or thermal properties, water sorption and diffusion, antimicrobial and/or antifouling activity, porosity, etc. [7]. These shortcomings have led to the development of suitable advanced acrylic-based hydrogels and research is ongoing to find solutions. Thus, the approach of developing multicomponent polymeric systems or combination of materials and/or nanomaterials to form composites or nanocomposites with enhanced physical and biological properties is of interest.

2. Mechanical properties of hydrogels

Hydrogels form a versatile platform for a large number of biomedical applications; however, they are in general mechanically weak and improvement of these properties is one of the most desirable aims in the field of hydrogel engineering. Current research is focussing in this complex scientific field [8] especially as the mechanical integrity drops rapidly in the hydrated state. Thus, hydrogels have been reinforced through many established kinds of methods and techniques: forming block copolymers, in which hydrophobic and hydrophilic domains alternate [9], increasing crosslinking density [10], using binary systems composed of two or more mixed polymers as interpenetrating polymer networks [11], plasma grafting of a hydrogel onto a hydrophobic substrate [12–14], self-reinforced composite materials composed of fibres embedded in a matrix [15] and by reinforcement through sol-gel reactions [16]. Nevertheless, new procedures to enhance the mechanical performance of acrylics have been performed by incorporating 2D materials such as graphene (2010 Nobel Prize in Physics) [17] and other outstanding carbon-based materials such as carbon nanotubes (CNT) [18]. Graphene derivatives, such as graphene oxide (GO) [19–21] or reduced GO (rGO) [22], have also shown excellent reinforcement for acrylics, especially in the hydrated state, and for the enhancement of many other physical and biological properties.

2.1 Interpenetrating polymer networks

Interpenetrating polymer networks (IPNs) lead to reinforced polymer networks that enhance the mechanical properties of hydrogels. In 2003, the first double-network (DN) hydrogel with enhanced mechanical properties was reported [23]. This type of DN interwoven hydrogel architecture consisted of an interpenetrating polymer network (IPN) of a soft neutral polymer network within a more highly cross-linked network prepared by a two-step sequential free-radical polymerisation. This two-step chemical procedure consisted of synthesising a highly cross-linked polymer network, and subsequent swelling of this network in a water soluble monomer that was then polymerised inside. The second polymerisation step was conducted with or without the incorporation of a cross-linking agent. Therefore, an IPN is an advanced polymeric system that is often utilised in polymer engineering to enhance physical and biological properties by combination of functional properties. These multicomponent polymeric networks are composed of cross-linked polymers without covalent bonds between polymer networks. However, at least one of these networks is synthesised and/or cross-linked within the presence of the second network. In this field, six basic multicomponent polymeric morphologies can be distinguished: mechanic blends, graft copolymers, block copolymers, AB-cross-linked copolymers, semi-IPNs and full-IPNs [24]. Both polymer networks are cross-linked in a full-IPN [25], while an IPN having a polymer network embedded within the first cross-linked network produces a semi- or pseudo-IPN [26, 27]. IPNs can be produced while the two networks are synthesised at the same time as simultaneous interpenetrating polymer

networks (SINs), or by swelling of the first polymer network into a solution containing the mixture of monomer, initiator and activator, usually with a cross-linker, as sequential IPNs. Thus, reinforced SINs and semi-SINs of hydrophilic poly(2-hydroxyethyl methacrylate) (PHEMA) networks have been synthesised with hydrophobic poly(ethylene glycol) polymer chains [28]. The sequential mode of synthesis has been employed to produce reinforced hydrogels as full IPNs and semi-IPNs of weak gelatin with polyacrylic acid (PAA) for studies of biological response in rats [29]. The mechanical properties of triple-network (TN) hydrogels synthesised from pseudo-SIPNs and pseudo-IPNs have exhibited that the presence of a loosely cross-linked third network modifies the mechanical performance of pseudo-SIPNs and pseudo-IPNs [30]. Many types of IPN hydrogels have been also developed with the goal of improving the mechanical behaviour and swelling/deswelling response [31]. For instance, IPN hydrogels of chitosan/poly(acrylic acid) (PAA) synthesised by UV radiation showed significant enhancement of mechanical properties, even in the hydrated state [32]. 'Smart' hydrogels possess the special property of being able to modify their volume/shape in response to small alterations of certain parameters of the surrounding ambient. These responsive hydrogels find application in numerous biomedical and bioengineering fields such as biological and therapeutic demands [33, 34] and sensing applications [35]. Encapsulation of cells for cartilage tissue engineering was reported using two biocompatible materials-agarose and poly(ethylene glycol) (PEG) diacrylate to form an IPN with superior mechanical integrity [36]. Under unconfined compression, these hydrogel networks were found to be fourfold higher in their shear modulus relative to a pure PEG-diacrylate network (39.9 vs. 9.9 kPa) and a 4.9-fold increase relative to a pure agarose network (8.2 kPa). In the field of hydrogel materials, advanced stimuli-responsive materials based on interpenetrating liquid crystal-hydrogel polymer networks have been engineered by combination of cholesteric liquid crystalline network that reflects colour and an interwoven poly(acrylic acid) network that provides humidity and pH response [37].

2.2 Acrylic-based composite hydrogels

Fibre reinforcement is known to enhance mechanical properties and the incorporation of fabrics produces significant mechanical improvement to polymer hydrogels. Thus, hydrogels consisting of a polymer matrix embedded with high-strength fibres, such as glass, aramid and carbon, have exhibited significant reinforcement [38]. In these kinds of materials, the mechanical properties are significantly enhanced and the biocompatibility of the acrylic polymer phase should remain unmodified. Thus, PHEMA hydrogels, which are one of the most studied hydrogel biomaterials, have been synthesised by incorporating various types of weaved and knitted fabrics and fibres, in order to enhance overall qualities in advanced biomedical wound dressing usage [39]. Nevertheless, in the last decades, natural fibres have attracted much interest as reinforcement agents for polymer-based composites due to their advantages over other type of conventional fibres such as those made from glass or carbon [40]. Thus, natural fibres such as flax, hemp, sisal, kenaf, jute, coir, kapok and banana, among many others, have shown many advantages over man-made glass and carbon fibres: lower cost, lower density, comparable specific tensile behaviour, less energy cost, non-abrasive, not irritating, lower health risk and sustainable properties such as renewability, biodegradability and recyclability [41]. Thus, natural ultra-long chitin natural fibres obtained from marine-river crab shell wastes have been added into PMMA resins to produce nanocomposites with outstanding properties for biomedical and bioengineering applications [42].

2.3 Acrylic-based nanocomposite hydrogels

Nanoparticles have generated significant interest and are a promising strategy of reinforcing hydrogels. Nanocomposites made with nanomaterials such as silica, graphene and its derivatives, nanofibres and various other nanoparticles have been reported for biomedical applications. Silica is a biocompatible material which has been reported to possess bioactive properties [43]. Silica possesses high biocompatibility and bioactive properties [43] and can also enhance the mechanical performance of hydrogels through filling or by the sol-gel process [44]. Thus, for example, biphasic matrices of hybrid acrylic-based nanocomposite hydrogels consisting of an organic phase of poly(2-hydroxyethyl acrylate) and an inorganic phase of silica network obtained by the sol-gel process of tetraethoxysilane (TEOS) showed improved physical properties [45]. Another reinforcement approach consists of combining IPNs with nanosilica filling. Thus, for instance, poly(acrylic acid) and alginate in the form of IPNs with the incorporation of nanosilica have shown improved compressive strength of the pure components [46]. On the other hand, the development of graphene-based nanocomposite hydrogels has exponentially increased during the last decade. Thus, graphene (GN) is a two-dimensional monolayer of sp2-bonded carbon atoms [47], which has attracted increasing interest owing to its excellent electrical and thermal conductivity [48, 49] and superior mechanical performance [50]. In addition, in the field of biomedicine, graphene is able to promote adherence of human osteoblasts and mesenchymal stromal cells [51]. The addition of small amounts of the oxidised form of GN, graphene oxide (GO), can significantly improve the mechanical strength of poly(2-hydroxyethyl acrylate) (PHEA) hydrogels [21]. Polyacrylamide (PAM) is generally a weak and brittle material; however, when reinforced with GO, it was reported to exhibit improved of mechanical properties [52]. GO is also a 2D nanomaterial with excellent physical properties [53] like graphene, usually produced from natural graphite that can be easily exfoliated into monolayer sheets. Nevertheless, GO is more utilised than GN in the synthesis of composite materials because it possesses hydrophilic oxygenated functional groups, such as hydroxyl (-OH), epoxy (-C-O-C-), carbonyl (-C=O) and carboxyl (-COOH), which render easier its dispersion in water [54–57]. Thus, the incorporation of GO nanosheets into poly(acrylic acid)/gelatin composite hydrogels significantly increased their Young's modulus and maximum stress. In addition, the hydrogel with GO (0.2% w/w)/PAA (20% w/w) showed the highest Young's modulus, whereas GO (0.2% w/w)/PAA (40% w/w) composites exhibited the highest maximum stress. These results suggest that GO nanosheets can be successfully used as reinforcing agents to improve the mechanical properties of hydrogel materials, which are often required for certain applications in tissue regeneration [20]. Multifunctional hydrogels with high mechanical performance, environmental stability, and dye-loading capacity has also been proposed as innovative synthetic approach for the 3D self-assembly of GO nanosheets and DNA [58]. Furthermore, the available oxygen-containing functional groups of GO have led to the synthesis of 3D cross-linked GO networks by coordination chemistry, as reinforcement micro-meter size carbon nanomaterials (CNMs) are able to enhance the mechanical performance of hydrogels, such as alginate, even more than single GO nanosheets [59]. Other CNMs such as carbon nanotubes (CNTs), discovered by Iijima [60], in the form of single wall carbon nanotubes (SWCNTs) and multi-wall carbon nanotubes (MWCNTs), as well as carbon nanofibres (CNFs) are being explored for the enhancement of mechanical and other physical and biological properties of hydrogels [61–68]. Plant fibre-based nanofibres

are used as reinforcement agents to produce transparent hydrogels [69]. Novel PAM-based nanocomposite hydrogels produced with natural chitosan nanofibres via in situ free-radical polymerisation exhibited that this type of nanofibres can act simultaneously as a multifunctional cross-linker and as a reinforcing agent achieving higher compression strengths and storage modulus than those of the pure hydrogel [70]. Popular hydrogels such as polyvinyl alcohol (PVA) has been reinforced with nanoparticles of clay (usually 10 wt.% or less) for wound healing applications [71]. These polymer-clay nanocomposite hydrogels with uniformly dispersed inorganic particles with at least one dimension in the nanometre scale exhibited superior mechanical and thermal properties when compared to pure polymers or conventional composites [72].

3. Electrical properties

Stimulus responsive biomaterials are highly desirable in biomedicine and bioengineering. Electrical stimulation can regulate physiological activities such as cell division [73], migration [74], differentiation and death [75]. It has been reported that electrical stimulation helps both in spinal cord repair and cancer therapy. The ability to use electrically conducting polymers endogenously enables spatial control of stimulation [76–78]; hence, there is much focus on developing new conductive hydrogels for biomedical applications. Graphene is well-known for its excellent electrical conductivity [48]. However, its current cost is still very high. Therefore, more new composite materials are expected to be developed using reduced graphene oxide (rGO), which is produced from GO. GO cannot be utilised for the design of conductive composite hydrogels because it possesses very low electrical conductivity due to the oxygen-containing functional groups located at the basal planes and edges. A recent paper reported a single-step procedure starting from a homogeneous water dispersion of GO, to form rGO during photopolymerisation of a resin induced by UV radiation [79]. Grafting of poly(acryl amide)/poly(acrylic acid) onto the surface of GO followed by a reduction to rGO nanosheets by a two-step chemical reduction with increased conductivity has been performed in order to fabricate transparent conductive films [80]. Advanced conductive DN hydrogels composed of rGO and poly(acrylic acid) have been synthesised by a two-step procedure with a reduction-induced in situ self-assembly [81]. A nacre-inspired nanocomposite of rGO and PAA prepared via a vacuum-assisted filtration self-assembly process exhibited abundant hydrogen bonding between GO and PAA that resulted in both high strength and toughness, which are higher than that of pure reduced GO. Moreover, this composite also displayed high electrical conductivity with potential in many biomedical applications such as flexible electrodes and artificial muscles. Carbon nanotubes (CNTs), on the other hand, are being exploited for biosensing units because of their excellent electrical properties with a superb conductivity and remarkable mechanical properties [82]. Ultrasensitive electrochemical biosensors have been developed with CNTs because of their unique electrical properties. Glucose biosensors for diabetics have been developed with nanofibrous membranes filled with multiwalled carbon nanotubes (MWCNTs) electrospun from mixtures of poly(acrylonitrile-co-acrylic acid) (PANCAA) and MWCNT [83]. Dielectrophoretically aligned carbon nanotubes were proposed to control the electrical and mechanical properties of gelatin methacrylate (GelMA) hydrogels [84]. In addition, in the field of biomedicine, these GelMA-based hydrogels exhibited excellent maturation of contractile muscle cells.

4. Thermal properties

Hydrogels placed in the human body do not need to endure temperatures higher than that of body temperature; however, it is of importance to have an understanding of the thermal properties and improvements can enhance its long-term performance. For instance, semi-IPNs of polyurethane incorporated into a polyacrylamide network showed improved thermal properties [26]. Differential scanning calorimetry of PHEMA/SiO_2 hybrids exhibited two glass transition temperatures (*Tg*). In addition, the SiO_2 content have shown to be able to modify the *Tg* shift of the thermal transition [85]. However, polymer nanocomposites with functionalized graphene sheets (FGNSs) showed a *Tg* shift of up to 40 and 30°C in poly(acrylonitrile) with the addition of 1% *w/w* of this carbon-based material [86]. Another successful enhancement of thermal properties of hydrogels, in terms of thermal behaviour and degradation, can be achieved by incorporating nanoparticle fillers. Thus, thermally stable, soft and magnetic field-driven actuators with muscle-like flexible PHEMA-based hydrogels were prepared with crosslinking metal nanoparticles added into the polymer backbone [87]. In this research line, the mechanical and thermal performance of renewable and biocompatible hydrogels of gelatin has been enhanced through cross-linking with cellulose nanowhiskers [88]. Acrylic-based hydrogels are hydrophilic polymers that are able to absorb large amounts of water in biomedicine and bioengineering due to their contact with fluids in cells or tissue in the human body. Therefore, the thermal analysis of water and its influence on the hydrated hydrogel properties becomes essential in this field. In this regard, many studies have been reported with acrylic hydrogels such as PHEMA [89], bulk and plasma-poly(2-hydroxyethyl acrylate) (*pl*PHEA) [14].

5. Water sorption/diffusion

The behaviour of water in hydrogels is also very important for any biomedical applications because properties such as water sorption and water diffusion play a very important role in cell survival, especially relevant in tissue regeneration [5]. Thus, acrylic hydrogels such as PHEMA or PHEA are important due to their unique properties of hydrophilicity, swelling and deswelling [90–92]. Their excellent water sorption behaviour has rendered this type of hydrophilic materials very promising for a wide range of biomedical and bioengineering applications such as wound healing, controlled drug delivery, regenerative medicine, etc. [6, 93]. Their hydrophilic functional groups attached to the polymeric backbone provide the ability to absorb water, while their resistance to dissolution arises from cross-linking of polymer chains [94]. Nevertheless, these single-network hydrogels possess very weak mechanical properties and slow swelling response. Therefore, reinforcement of hydrogels is deemed necessary to exponentially increase their potential applications in biomedicine and bioengineering. However, the enhancement of mechanical properties can significantly affect the water sorption and diffusion of polymer hydrogels. Thus, reinforcement approaches combining hydrophilic and hydrophobic functional groups as multicomponent polymeric systems can yield to a decrease of water sorption. The enhancement of mechanical properties of hydrogels through the addition of GO nanosheets can also modify their water sorption performance. Thus, for instance, the swelling rates of graphene oxide/poly(acrylic acid-co-acrylamide) nanocomposite hydrogels increased with increasing GO content to about 0.30% *w/w* and then decreased with further increase in GO contents. It is worth noting that the hydrogel with only 0.10% *w/w* GO exhibited significant enhancement in swelling capacity in a neutral medium and could retain relatively higher swelling rates in

acidic and basic solutions. Furthermore, a very low filler volume of GO can produce a very significant increase in water diffusion (almost 6 times faster) in cross-linked alginate [95]. Therefore, these GO-based super-absorbent hydrogels have potential applications in many fields such as biomedical engineering and hygiene products [54]. The water diffusion mechanisms [96] can also be altered by the modification of mechanical properties of hydrogels. Thus, poly(acrylic acid)-GO nanocomposite hydrogels, which are potential carriers for drug release, can be manipulated by changing the concentration of GO and tend to exhibit non-Fickian anomalous diffusion with decrease in deswelling ratio with increasing GO content [53]. Superabsorbent polymer hydrogels of sodium lignosulfonate-grafted poly(acrylic acid-co-acryl amide), synthesised by a ultrasonic method, also exhibited a non-Fickian water diffusion transport with a maximum water absorbency of 1350 $g \cdot g^{-1}$ [97]. There are many acrylic hydrogels, which have shown non-Fickian diffusion mechanism such as PHEA [92, 98]. Nevertheless, a well-known water-swellable biomedical polymer hydrogel such as PHEMA has shown to be governed by Fickian diffusion, even though water sorption is not classically Fickian [99]. Thus, advanced hydrogels based on 2-hydroxyethyl methacrylate (HEMA) and epoxy methacrylate (EMA) produced via bulk polymerisation exhibited also a Fickian swelling behaviour, and the equilibrium water content (EWC) decreased with increasing the hydrophobic EMA content as expected [100]. The pH of the environment influences also the swelling capacity and diffusion mechanism of acrylic-based hydrogels. Hence, for example, the swelling properties of semi-IPNs of acrylamide-based polyurethanes decreased in acidic pH, while a reverse trend was observed in alkaline medium. However, these semi-IPNs were hydrolytically stable in phosphate buffer solution, which render them potential hydrogel materials for biomedical and bioengineering applications [26]. PAA is a pH-sensitive and biocompatible polymer that is being used in a wide range of biomedical fields [34] and has attracted considerable interest due to its capacity to swell reversibly with changes in pH. Thus, the functionalization of GO nanosheets with PAA (GO-PAA) by in situ atom transfer radical polymerisation (ATRP) have demonstrated great potential as intracellular protein carriers using bovine serum albumin (BSA) [101]. This achievement is very important because proteins participate in all vital body processes and perform an essential function inside cells as enzymes, transduction signals and gene regulation. Poly(acryl amide-co-2-acrylamido-2-methyl-1-propanesulfonic acid-co-acrylamido glycolic acid) is another pH-sensitive terpolymer hydrogel suitable for drug release, which has shown a quasi-Fickian diffusion mechanism. These hydrogels showed a strong change of water sorption and molecular weight between cross-links of the network with a change in pH of the swelling media [102]. Temperature affects also very significantly the swelling properties of acrylic hydrogels [100]. Thus, for example, thermosensitive poly(N-isopropyl acrylamide-co-acrylic acid) hydrogels can be designed in order to exhibit fast temperature sensitivity and enhanced oscillating swelling-deswelling properties [103].

6. Antimicrobial and antifouling capacity

Microbial infections are becoming more and more serious because they often lead to implant failure, which may cause major economic losses and suffering among patients in spite of using antibiotics and aseptic conditions. Therefore, novel antimicrobial approaches are becoming more and more necessary in biomedicine in this antibiotics resistant era [104]. Thus, much effort is being made on the development of new advanced biomaterial hydrogels with high antimicrobial activity and non-toxic for human beings. Thus, antibacterial hydrogels of polydextran aldehyde

and branched polyethylenimine have been prepared in the form of syringe-injectable bioadhesive [105]. These hydrogels have shown effective antibacterial activity against both Gram-negative and Gram-positive bacteria. Conductive injectable self-healed hydrogels based on quaternized chitosan-g-polyaniline (QCSP) and benzaldehyde group functionalized poly(ethylene glycol)-co-poly(glycerol sebacate) (PEGS-FA) have also shown antibacterial, antioxidant and electroactive action for cutaneous wound healing [106]. Hydrogels based on chitosan and its derivatives have been broadly utilised as implant coatings because of their intrinsic non-toxic, osteoconductive properties, pH response, antimicrobial activity, biocompatibility and cell adhesive capacity [107, 108]. Novel hydrogel coatings produced by electrophoretic co-deposition of chitosan/alkynyl chitosan exhibited high antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [109] by the disk diffusion test [110, 111]. Antibacterial polymer coating tethered to the surface of medical implants and devices has attracted great interest in the last few decades for its ability to reduce implant-associated infections [112, 113]. Antimicrobial hydrogels of polyallylamine cross-linked with aldaric acid derivatives are very powerful weapons against a broad range of microorganisms: *Pseudomonas aeruginosa*, *E. coli*, *S. aureus* and *Candida albicans* [114]. Antibacterial ultrathin hydrogel films have been fabricated via a layer-by-layer (LbL) method and 'click' chemistry by Wang et al. [115]. This ultrathin hydrogel film consisted of poly[oligo(ethylene glycol) fumarate]-co-poly[dodecyl bis(2-hydroxyethyl) methyl ammonium fumarate] (POEGDMAM) containing multi-enes and poly[oligo(ethylene glycol) mercaptosuccinate] (POEGMS), and showed excellent antibacterial activity against both *S. aureus* and *E. coli*, due to the action of the ammonium groups with long alkyl chains present in the POEGDMAM. Doping antibiotics exogenously for eventual release in hydrogels has shown to be also an efficient antimicrobial strategy [116]. In these delivery systems, the antibacterial agent is released from the polymer matrix over time. Nevertheless, these systems present associated problems because the material's antibiotic release is eventually exhausted and the remaining polymer matrix may become a substrate for bacterial biofilm colonisation, which can become a concerning health threat. In these cases, secondary surgeries are carried out in order to remove these empty depots to prevent this type of infection risks. This second surgery can be avoided if a biodegradable hydrogel drug delivery system with a degradation rate linked via covalent incorporation of vancomycin in the hydrogel backbone [117]. Some antimicrobial fillers and/or agents need to be usually incorporated through physical blending in order to produce antimicrobial materials because most hydrogels themselves do not possess any antimicrobial action [118]. In this regard, graphene has emerged as a promising wide-spectrum antimicrobial nanomaterial, with unknown bacterial resistance so far and tolerable cytotoxic effect on mammalian cells. Through physical damage by direct contact of the sharp nanosheets' edges with bacterial membranes, graphene produces destructive extraction of lipid molecules. GO has also demonstrated to possess high antimicrobial activity against bacterial pathogens such as *Pseudomonas syringae* and *Xanthomonas campestris* pv. *undulosa*, and fungal pathogens such as *Fusarium graminearum* and *Fusarium oxysporum*. Thus, antimicrobial and biocompatible graphene-based nanocomposites have found application in a broad range of biomedical applications such as wound dressing [119], and silver coated medicinal devices, such as nanogels, nanolotions, etc. In the field of nanotechnology, silver nanoparticles (AgNPs) are also well-known for their antimicrobial activity and thus have been used to develop antimicrobial hydrogels with diverse biomedical applications such as silver-based dressings and silver coated medicinal devices, such as nanogels, nanolotions, etc. [120]. Microbial infections are frequent and are very undesired occurrences that may have occurred after orthopaedic procedures. Thus, medicated hydrogels of hyaluronic acid derivatives

have been proposed [121] to address this problem. Nevertheless, there is a growing worldwide concern caused by the exponential increase in antibiotic resistance, which has open new alternative approaches such as the incorporation of AgNPs [122] or AgNPs combined with graphene [123] into hydrogels. Thus, an optimal mass ratio (5:1) of AgNPs with graphene showed excellent biocompatibility, high swelling ratio, good extensibility and much higher antimicrobial activity than other hydrogels. In addition, in vivo experiments performed in rats demonstrated that these nanocomposite hydrogels can accelerate the healing rate of artificial wounds. Similarly, 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 [124].

In the field of implanted biomedical devices, it is important to modify the hydrogel surface to achieve antifouling properties that make it resistant to protein adsorption and cell adhesion. Thus, for example, the antifouling activity of poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) hydrogels was enhanced by surface grafting of a brush of poly(oligoethylene glycol methyl ether acrylate) [poly(OEGA)] [125]. Copolymerisation 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 by UV radiation has produced novel antifouling highly wettable hydrogels with superior mechanical performance and self-healing capacity [126]. In this field, it is highly desirable to produce hydrogels bearing antifouling properties and biocompatibility in order to prolong the lifetime of implanted materials, switchable antimicrobial property to eliminate infection and inflammation and outstanding mechanical performance to avoid the failure of the implanted material. To address these points, derivatives of zwitterionic carboxybetaine were developed with hydroxyl group(s), which can switch between the lactone form (antimicrobial) and the zwitterionic form (anti-fouling) [127]. Besides, the intramolecular hydrogen bonds enhance the mechanical property of the zwitterionic hydrogel, making it a viable material for coatings. However, the current increasing rates reported by the World Health Organisation of antibiotic resistance in pathogenic microbes are becoming a global health threat. Therefore, more resources and efforts must be done worldwide in order to develop new antimicrobial approaches such as antimicrobial hydrogels, because they have shown to be very effective in preventing and treating clinically relevant multidrug-resistant pathogens.

7. Porosity

The development of new advanced porous polymers has received much interest due to their potential to combine the properties of porous materials and polymers [128]. Many industrial fields such as gas storage and separation materials [129, 130], control drug delivery [131], catalysts [132], supports for electrochemical sensing [133], low-dielectric constant materials [134], packing materials for chromatography [135], and engineered three-dimensional porous matrices (*scaffolds*) for tissue regeneration in regenerative medicine [5, 45, 136, 137] require porous polymers. These advanced applications have driven much effort on developing new reliable techniques for fabricating porous polymers with specific pore architectures in the last few decades. Tissue engineering constitutes a promising alternative for tissue regeneration and even be able to bioengineer whole organ in the near future. Therefore, the development of new *scaffolds* has become a hot topic in biomedical research. Hydrogels have been proposed as leading candidates for engineered tissue *scaffolds* because of their good biocompatibility and close similarities to native

extracellular matrix. Nevertheless, precise design of hydrogel properties, such as high and interconnected porosity suitable for specific cells, remains a challenge. Traditional methods for bulk porosity formation in hydrogels have demonstrated success for tissue engineering purposes. Nevertheless, some difficult issues related to direct cell encapsulation often occur. Thus, advanced technologies have shown to be able to produce hydrogels with suitable morphologies and function for tissue engineering applications [138]. In addition to the physicochemical properties and mechanical performance of the *scaffold* materials, the degree of interconnection and pore geometry, which depends on the tissue to be regenerate, plays a major role in these biomedical applications. Therefore, several methods and techniques have been developed so far to produce *scaffolds* with controlled morphology: gas foaming [139], fibre mesh sintering [140], solvent evaporation [141], polymerisation in the presence of a solvent [98, 142], porogen method [143, 144], freeze-drying [145, 146], electrospinning [147], 3D printing [148] and bioplotting [149], among many others. Thus, for instance, *scaffolds* of copolymerized hydrophobic ethyl acrylate (EA) and hydrophilic hydroxyethyl methacrylate comonomers with controlled hydrophilicity and interconnected morphology were prepared with a sintered template of controlled size PMMA microspheres [144]. On the other hand, porous *scaffolds* of gelatin with PHEMA have been synthesised by freeze-drying [146]. The HEMA content added in the initial mixtures before polymerisation modulated the porous architecture of the *scaffolds.* In addition, the covalently bound gelatin sequences significantly enhanced the biocompatibility of the PHEMA-based hydrogels. *Scaffolds* of high porosity can also be synthesised by the salt-leaching technique, utilising salts of NaCl or $(NH_4)_2SO_4$ as porogen agents [150] or with many other porogenic compounds such as sugar or ammonium oxalate crystals [151]. Carbon dioxide submitted to supercritical conditions and followed by rapid depressurization allows the fabrication of highly porous *scaffolds* [138]. Thus, *scaffolds* consisting of a blend of poly(ethyl methacrylate) and tetrahydrofurfuryl methacrylate with well interconnected and high porosity (greater than 85%) have been developed through this technique [152]. This gasification method has received significant attention in the past. Nevertheless, many scientists believe that the degree of pore interconnectivity is low. Electrospinning utilises a high-voltage DC power supply, infusion pumps and a syringe with a needle tip to produce fibres of varying diameters. For instance, a 3D aligned nanofiber-collagen type I hydrogel scaffold for controlled non-viral drug/gene delivery to direct axon regeneration in spinal cord injury treatment has been developed recently [153]. Nowadays, sophisticated biomedical devices designed by computer using patient-specific anatomical data can be easily fabricated by 3D printing. Thus, one-of-a-kind devices, surgical implants, *scaffolds* for tissue regeneration, and drug delivery systems have been fabricated by this relatively recent technique. Nevertheless, especially two technological limitations need still to be overcome: low choice of commercially available printable materials and very slow printing speed. Fused deposition modelling, selective laser sintering, stereolithography and 3D plotting/direct-write/bioprinting are also 3D printing techniques that are being progressively developed to suit tissue engineering applications. Bioprinting is the more advanced 3D printing technology because it consists of printing cells combined with custom 3D *scaffolds* for personalised regenerative medicine [148]. One of the important aspects in porous *scaffolds* is the mechanical resistance, which depends on the chemical and physical properties of the *scaffold* material and on its porosity. This aspect is even more relevant in hydrated porous polymer hydrogels at the body temperature in biomedical applications. Therefore, it is usually necessary to improve the mechanical properties of these porous hydrophilic materials by means of the mentioned reinforcing methods. Thus, for example, hybrid hydrogel nanocomposite *scaffolds* of silica/PHEA have shown enhanced mechanical performance in comparison with neat PHEA [45].

Another acrylic-based hydrogel, PHEMA, combined with cholesterol methacrylate (CHLMA) and lamina, has been synthesised in presence of ammonium oxalate crystals to produce *scaffolds* with interconnected pores that are able to promote cell-surface interaction [154]. The modification of PHEMA *scaffold*s with laminin-derived Ac-CGGASIKVAVS-OH peptide sequences has shown an enhanced effect to promote cell adhesion and neural differentiation. Cell adhesion and proliferation have also been improved in nanofiber *scaffolds* of poly(L-lactide) (PLLA) prepared by electrospinning by plasma treatment and simultaneously in situ grafting of hydrophilic acrylic acid to obtain PLLA-g-PAA [155]. Polysaccharide-based hydrogels have become increasingly proposed as matrices in soft tissue engineering because of their well-known cytocompatibility [68]. Thus, for instance, cross-linkable dextran methacrylates and hyaluronan methacrylate hydrogel matrices have been reported as leading candidates for soft tissue reconstruction and have shown that their in vitro degradation can be controlled by the polysaccharide morphology and cross-linking density. Besides, under in vitro conditions, these novel biomaterials had no toxic effects against fibroblasts and the use of composite gels improved cell adherence [156]. Therefore, proven advances have been reported in scaffold hydrogel design so far for tissue engineering applications. However, the need to develop viable *scaffolds* for clinical applications exists and new ways to find methods capable of providing suitable materials able to fulfil all the necessary requirements for different applications in regenerative medicine is a challenge.

8. Applications and future trends

Acrylate-based hydrogels are being widely investigated for their use in biomedical applications such as tissue engineering and systems for controlled delivery of biologically active agents. Hydrogels have been derivatized to enable crosslinking and photo-polymerisation, form electro-conducting networks and confer degradability to suit different biomedical applications. The pioneering work by Hubbel et al. [157] on bioerodible hydrogels based on copolymers of polylactic acid (PLA), copolymers of alpha hydroxyacids and polyethylene glycol (PEG) with acrylate end groups facilitated new tools for controlled release formulations and delivery platforms. These systems could be tuned to vary the degradation times from very short to long periods by changing composition of the hydrophobic ester block. Rational design using pH and thermoresponsive polymers have also been reported for drug delivery applications. A novel pH-responsive hydrogel based on carboxymethyl cellulose/2-hydroxyethyl acrylate was synthesised [158] as a transdermal delivery system for naringenin. The polymer exhibited different swelling ratio at different pH with Fickian diffusion characteristics, while mechanical properties could be controlled by varying cross-linking density and grafting. Photo-cross-linked hydrogels have also been used for the controlled release of various hydrophobic and hydrophilic drugs, including hydrogels based on methacrylate-terminated PEG [159] and PEG-poly(ε-caprolactone) multiblock copolymers [160]. Another family of hydrogels that is being explored for possible applications is thiol-acrylate hydrogels that were tailored to vary degradation rates and enhance cell viability particularly for cranial defects [161, 162]. A study of the multiscale modelling of the reaction kinetics of these thiol-acrylates with the mechanical properties revealed that the stiffness was related to light intensity, concentration of thiol groups and pH, thereby making it possible to tune the hydrogel properties. More recently, the synthesis and characterisation of novel acrylate-terminated amide-linked PEG-PDLA and PEG-PLLA star block copolymers were reported by Buwalda et al. [163]. Using PEG-PLA star block copolymer hydrogels through physical cross-linking and combining with photopolymerization, in situ gelation was achieved. Selected

copolymers were initially physically cross-linked by stereocomplexation that on subsequent photopolymerization generated robust and stable hydrogels. This system was injectable and the hydrogels that were formed in situ were stable over periods of time that would be appropriate for long-term drug delivery.

9. Conclusions

Due to their versatile properties, acrylic-based hydrogels are currently used or proposed for a wide range of biomedical and bioengineering fields such as tissue engineering, orthopaedics, ophthalmology and dental materials. However, the number of applications of this type of biomaterials could be significantly increased if their properties would be improved, such as their mechanical strength in the hydrated state at the body temperature. In this regard, acrylic-based biomaterials have been developed as interpenetrating polymer networks, composites with incorporated particles such as fibres and/or advanced nanomaterials such as graphene, graphene oxide and carbon nanofibers, among many others, in order to improve their mechanical performance, electricity, thermal behaviour/degradation, water sorption/diffusion, biological interaction, antimicrobial activity and porosity values, required for certain applications. Furthermore, acrylic-based hydrogel scaffolds have been produced with the suitable morphology of pores and porosity for tissue regeneration by following developed protocols and sophisticated techniques. Nevertheless, in spite of the impressive advancements achieved so far, which are presented in this book chapter, many challenges still remain to design acrylate hydrogels with specific polymers for advanced applications in biomaterial science.

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