We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Latest Improvements of Acrylic-Based Polymer Properties for Biomedical Applications

Ángel Serrano-Aroca

Additional information is available at the end of the chapter

Abstract

Acrylic-based polymers have many currently important biomedical applications such as contact lenses, corneal prosthesis, bone cements, tissue engineering, etc. due to their excellent biocompatibility and suitable performance in mechanical properties, among many other applications. Many of these biomaterials have been approved by the US Food and Drug Administration (FDA) for various applications. However, the potential uses of these polymeric materials in the biomedical industry could be increased exponentially if some of their acrylic properties (mechanical strength, electrical and/or thermal properties, water sorption and diffusion, biological interactions, antibacterial activity, porosity, etc.) are enhanced. Thus, acrylics have been fabricated as multicomponent polymeric systems in the form of interpenetrated polymer networks or combined with other advanced materials such as fibers, nanofibers, graphene and its derivatives and/or many other kinds of nanoparticles to form composite or nanocomposite materials, which are expected to exhibit superior properties. Besides, in regenerative medicine, acrylic scaffolds need to be designed with the required extent and morphology of pores by sophisticated techniques. Even though the great advances have been achieved so far, much research has to be carried out still in order to find new strategies to improve the above-mentioned properties.

Keywords: biomedical applications, hydrogels, acrylic properties, nanocomposites, latest improvements

1. Introduction

Acrylics are currently used in many important fields of the biomedical industry such as corneal prosthesis, intraocular lenses and contact lenses in ophthalmology [1], bone cements for orthopedic applications [2], tissue engineering [3], etc. due to their excellent properties such as biocompatibility and suitable mechanical performance, among others [4]. Many of these acrylic

products for various applications have been approved by the US Food and Drug Administration (FDA) and are expected to produce 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, antibacterial activity, porosity, etc. when they are synthesized as scaffolds for tissue engineering applications. Thus, new advanced acrylic-based materials 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 or without interconnected porous morphology.

2. Mechanical properties

The improvement of the mechanical properties of acrylics is one of the *hot topics* in the field of bioengineering, and many research groups have been working on this topic for many years. Acrylics can be reinforced through many kinds of methods and techniques: polymers with microphase-separated morphologies such as block copolymers, in which hydrophobic and hydrophilic domains alternate [5], increasing crosslinking density [6], by means of binary systems composed of two or more mixed polymers as interpenetrating polymer networks (IPNs) [7], self-reinforced composite materials composed of fibers embedded in a matrix of the same acrylic polymer [8], by plasma grafting of a hydrophilic acrylic polymer onto a hydrophobic acrylic substrate [9, 10] and with the sol-gel reaction to produce nanosilica reinforcement [11]. However, more recent studies have shown new procedures to improve the mechanical properties of acrylics with the incorporation of graphene (GN) (2010 Nobel Prize in Physics) and other carbon nanomaterials such as carbon nanotubes (CNT) [12]. Chemically modified graphenes (CMGs) such as graphene oxide (GO) [13, 14] or reduced graphene oxide (rGO) [15], have also been shown to be very good nanofillers to reinforce acrylics and improve many other properties, especially acrylic hydrogels which, in the swollen state, show very low mechanical properties.

2.1. IPNs

Acrylic-based interpenetrating polymer networks (IPN) have gained greater attention during last decades, mainly due to their biomedical applications as reinforced polymer networks. 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 are advanced multicomponent polymeric systems 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 (**Figure 1**).

If a crosslinker is present in the polymeric system, fully IPN [17] result, while in the absence of crosslinking, a network having linear polymers embedded within the first crosslinked network is formed (semi- or pseudo-IPN) [18, 19]. Acrylic-based IPNs are prepared usually in the form
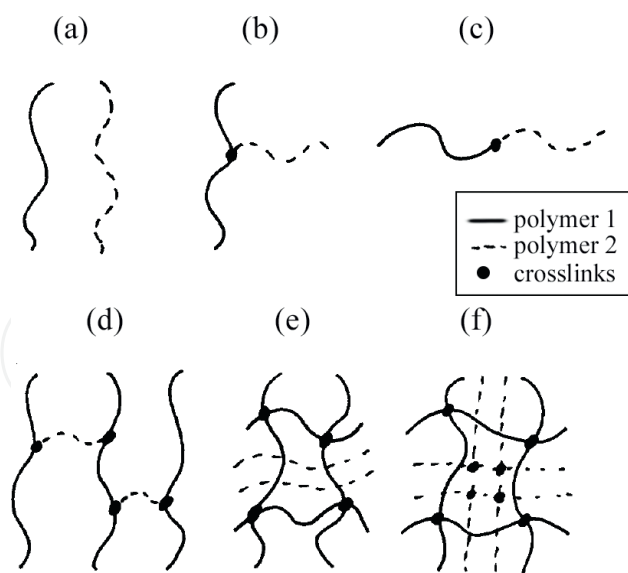
Figure 1. Schematic representation of (a) mechanical blends, (b) graft copolymers, (c) block copolymers, (d) AB-crosslinked copolymer, (e) semi-IPNs and (f) full-IPNs. Modified from Sperling and Mishra [16].

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, urethane acrylate resin networks were greatly reinforced by epoxy networks in SINs composed of both resins [20]. Full IPNs and semi-IPNs of the epoxy resin and poly(ethyl methacrylate) (PEMA) were also prepared by the sequential mode of synthesis, and these showed a gradual decrease of modulus and tensile strength properties with consequent increase in elongation at break and toughness for both types of IPNs with increases in PEMA content [21]. Combinations of different kinds of IPNs have been synthesized using simultaneous photopolymerization, which gave rise to simultaneous semi-interpenetrating polymer networks (semi-SINs) of epoxy resin-acrylate polyurethane semi-interpenetrating networks having very high compatibility [22].

Pseudo-SIPNs were prepared by melt blending of poly(methyl methacrylate) (PMMA), and double-C_{60}-end-capped poly(ethylene oxide) (FPEOF) exhibited a storage modulus of 16 times larger than that of PMMA, which are as good as those of PMMA/carbon nanotube nanocomposites [19].

Acrylic-based IPN hydrogels are also developed with the aim of enhancing the mechanical strength and swelling/deswelling response of these acrylic hydrogels [23]. For example, interpenetrating polymer network (IPN) hydrogels composed of chitosan and poly(acrylic acid) (PAA) are synthesized by employing the UV irradiation method and showed that even in the swollen state, the present chitosan/PAA IPNs possessed good mechanical properties [24].

'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, most of them focussing on biological and therapeutic demands [25, 26] and sensing applications [27].

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 [28].

2.2. Composites

Several kinds of chemical modifications of acrylic hydrogels do not have a significant change of the overall mechanical strength because the main structural skeletons of these polymers or copolymers are still weak. On the contrary, the method of fiber reinforcement to produce composites is different because the added fabrics impart high strength to the networks which not only just embed inside the membranes but also form the main skeleton of the composites. A fiber-reinforced polymer is a composite material consisting of a polymer matrix imbedded with high-strength fibers such as glass, aramid and carbon [29]. In such kind of materials, the mechanical properties are presumed to be improved and the biocompatible characteristics of the acrylic polymer should remain the same. Thus, acrylic resin polymers have been reinforced with glass fibers for dental applications [30], and acrylic hydrogels such as poly(2-hydroxyethyl methacrylate), which is one of the most popular biomaterials, have been manufactured by adding various kinds of weaved and knitted fabrics and fibers, in order to improve overall qualities of the poly(2-hydroxethyl methacrylate) (PHEMA)-based artificial skin for advanced wound dressing usage [31]. 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 [32]. 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 biodegradability [33]. Thus, ultra-long chitin natural fibers were incorporated into PMMA resin to prepare PMMA/chitin nanocomposites with improved properties [34]. This achievement is a significantly environmental move toward the sustainable utilization of marine-river crab shell wastes for biomedical applications.

2.3. Nanocomposites

Another alternative and very promising way of reinforcing acrylic polymers consists of the incorporation of nanomaterials such as silica, graphene and its derivatives, nanofibers or many other nanoparticles. Silica is a biocompatible material and has been reported to possess bioactive properties [35]. Silica can improve the mechanical properties of acrylics 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 [36].

Thus, a biphasic matrix of a hybrid (inorganic-organic) nanocomposite materials of poly(2-hydroxyethyl acrylate) 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 [37].

The combination of the reinforcement through interpenetrated polymer networks and nano-silica filling is another strategy that has also been used in the past. For example, simultaneous polyurethane/poly(ethyl methacrylate) interpenetrating polymer network with silica filler consisting of very fine powders with an approximate diameter of 5 nm also showed an important improvement of material strength [38].

Graphene (GN) is a two-dimensional (2D) monolayer of sp^2-bonded carbon atoms, which has attracted increasing attention [39] owing to its excellent electrical and thermal conductivities [40, 41] and great mechanical strength [42]. Besides, graphene promotes adherence of human osteoblasts and mesenchymal stromal cells [43], which render this nanomaterial also very promising material in the biomedical field. Thus, it has shown potential applications in nanocomposites such as magnetite-GNs/poly(arylene-ether-nitrile) nanocomposites because their mechanical properties were significantly enhanced by the incorporation of magnetite-GNs hybrids [44]. Besides, GN enhances the shape memory of poly(acrylamide-co-acrylic acid) and self-healing ability when the content of graphene is in the range of 10–30%, even though this copolymer itself has poor shape memory ability [45]. There are some reports that graphene oxide (GO) nanosheets can also enhance the mechanical strength of polymer substrates such as poly(acrylamide) (PAM) hydrogels [46]. GO is also a 2D nanomaterial prepared from natural graphite that can be easily exfoliated into monolayer sheets. GO has many hydrophilic oxygenated functional groups, including hydroxyl (-OH), epoxy (-C-O-C-), carbonyl (-C=O) and carboxyl (-COOH), which enable its dispersion in water solution [47]. The diversity of unique properties of GO, including great tensile modulus (1.0 TPa), ultimate strength (130 GPa) and electrical and thermal properties [48], renders graphene oxide an ideal carbon nanomaterial for variety of applications toward the development of new advanced materials. Thus, GO added into PAM hydrogels improved very much the mechanical performance of the original PAM hydrogels, which generally exhibit pronounced weakness and brittleness [46]. In the same way, the addition of GO nanosheets increased the Young's modulus and maximum stress of poly (acrylic acid)/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 suggested that the application of GO nanosheets could be used to improve mechanical properties of hydrogel materials, which is very beneficial for tissue engineering applications [14]. The other derivatives of graphene such as chemically modified graphene (CMG) fillers have been used in nanocomposites of PMMA and were compared with the GO filling. These results showed an elastic modulus of GO/PMMA and RG-O/PMMA composites improved by 28% by just loading 1 wt.%. Fracture strength increased for GO/PMMA composites but decreased for RG-O/PMMA composites [49].

Single-wall carbon nanotubes (SWCNTs), multi-wall carbon nanotubes (MWCNTs) as well as carbon nanofibers (CNFs) are being used for reinforcing polymer matrices such as poly(methyl

methacrylate) by melt blending. Thus, for example, using an amount of carbon nanofibers of 5 wt.%, the nanocomposites improved over 50% of their axial tensile modulus as compared to the control PMMA. The PMMA/CNFs nanocomposite fibers also show enhanced thermal stability, significantly reduced shrinkage and enhanced modulus retention with temperature, as well as improved compressive strength [50]. The electrical properties and electromechanical responses of acrylic materials such as acrylic elastomers and styrene copolymers can be improved toward electroactive applications such as artificial muscle and/or micro-electro-mechanical systems (MEMS) devices [51].

The other novel nanocomposite hydrogels such as those prepared with polyacrylamide (PAM) as a matrix material reinforced with natural chitosan nanofibers via *in situ* free-radical polymerization showed that these nanofibers acted as a multifunctional crosslinker and a reinforcing agent in the hydrogel system producing a compression strength and a storage modulus significantly higher than those of pure PAM [52].

Reinforcement can be also performed with plant fiber-based nanofibers 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 resin [53].

The other nanoparticles such as clay have been employed to reinforce acrylic polymers. These polymer-clay nanocomposites such as PMMA/clay 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 nanometre scale and exhibiting enhanced mechanical and thermal properties when compared to pure polymer or conventional composites [54].

3. Electrical properties

The electrical properties are very important in some biomedical fields because various types of electrical stimulation can regulate cell physiological activities such as division [55], migration [56], differentiation and cell death [57]. The electrical stimulation also has been employed in promoting healing for spinal cord repair and cancer therapy due to its non-invasiveness of these polymers [58–60]. For these reasons, much emphasis was given in developing these new acrylic-based materials in biomedical application where the conductivity of the biomaterials is essential. Recently, nanocarbon materials such as graphene had been considered to be very effective electrode material with very high conductivity. The graphene has high transmittance and excellent conductivity [40] as was mentioned earlier. But, its production is still very expensive, and more studies are expected to carry out with its derivative, graphene oxide. However, in order to develop electrically conductive acrylic-based resins, GO, which has a very low conductivity due to their oxygen-containing functional groups, must be modified to obtain reduced graphene oxide (rGO). 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 an acrylic resin [61]. The transparent conductive films were also produced by grafting poly(acryl amide)/poly(acrylic acid) on the

GO surface followed by a reduction to rGO nanosheets by a two-step chemical reduction with increased conductivity [62]. The inorganic-organic double network (DN) flexible and conductive hydrogel of rGO and poly(acrylic acid) has also been prepared by a two-step synthesis with a reduction-induced *in situ* self-assembly [63]. Even more recently, a nacre-inspired acrylic-based nanocomposite of rGO and PAA has been prepared *via* a vacuum-assisted filtration self-assembly process (**Figure 2**). The abundant hydrogen bonding between GO and PAA results in both high strength and toughness of the bioinspired nanocomposites, which are 2 and 3.3 times higher than that of pure reduced GO film, respectively. Moreover, this nanocomposite also displays high electrical conductivity of 108.9 S·cm^{-1}, which renders it very promising material in many biomedical applications such as flexible electrodes, artificial muscles, etc.

Carbon nanotubes (CNTs), discovered by Iijima [65], have also been attracting intensive attention because of their excellent electrical properties with a superb conductivity, remarkable mechanical strength and modulus with many potential technological applications [66]. CNTs offer the possibility of developing ultrasensitive electrochemical biosensors due to unique electrical properties. Thus, nanofibrous membranes filled with multi-walled carbon nanotubes (MWCNT) were electrospun from the mixture of poly(acrylonitrile-co-acrylic acid) (PANCAA) and MWCNT to develop a glucose biosensor for diabetics [67].

The other nanocomposites of poly(methyl methacrylate) containing various multi-walled carbon nanotube (MWCNT) contents have been prepared using melt mixing to achieve high conductivity levels in the nanocomposites [68].
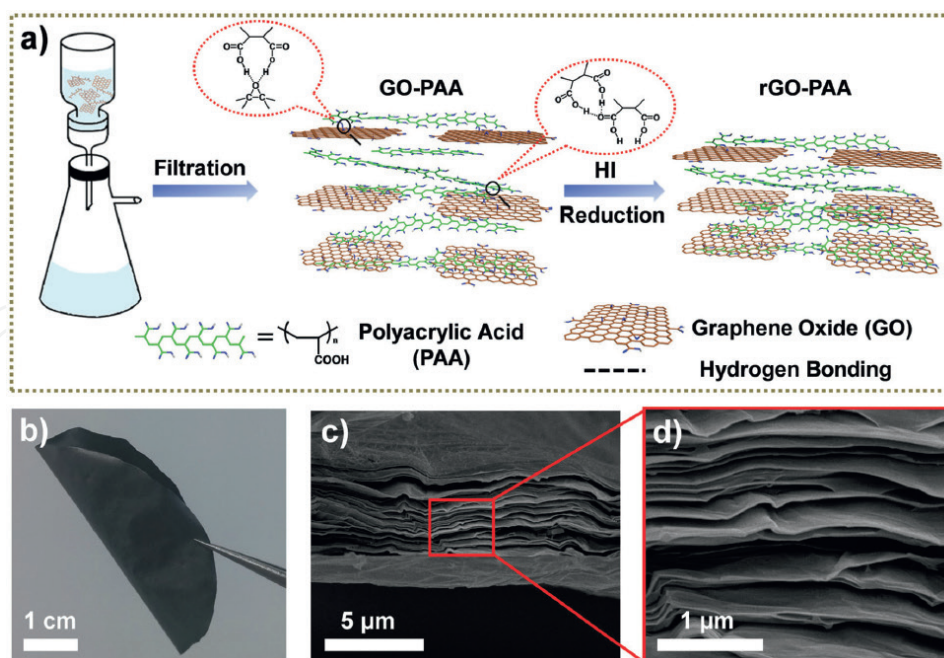
Figure 2. Fabrication process of rGO–PAA nanocomposites: (a) The GO nanosheets/PAA homogeneous solution was filtered by vacuum-assisted filtration into GO–PAA nanocomposites. Then after HI reduction, the rGO–PAA nanocomposites were obtained. (b) A digital photograph of rGO–PAA nanocomposites. (c) and (d) The cross-section surface morphology with different magnifications of rGO–PAA nanocomposites. Reprinted with permission from Ref. [64].

4. Thermal properties

Even though biomaterials 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 networks enhanced the thermal properties of these semi-IPNs due to higher crosslink density imparted by the hard segment content [18]. Though silica can improve the mechanical properties of acrylic polymers, the differential scanning calorimetry results of PHEMA/SiO_2 hybrids are complicated, showing two glass transition temperatures, and it was shown that the SiO_2 content is an important factor in influencing the shift of the Tg transition [69]. However, polymer nanocomposites with functionalized graphene sheets (FGNS) showed an unprecedented shift in glass transition temperature of up to 40 and 30°C in poly(acrylonitrile) with 1 wt.% of FGNS and in poly(methyl methacrylate) with only 0.05 wt.%, respectively [70]. Besides, the thermal stability of magnetite-graphene/poly(arylene-ether-nitrile) nanocomposites were significantly enhanced by the incorporation of magnetite-graphene hybrids [44]. The nanocomposites of PMMA with chemically modified graphene (CMG) and GO fillers made by *in situ* polymerization showed large shifts in the glass transition temperature with loadings as low as 0.05 wt.% [49].

Another strategy to improve the thermal properties of acrylic polymers is by nanoparticle filling. Thus, the thermal performance of well-known acrylic polymers such as PMMA can be significantly improved by filling of nanometric particles (5, 10 15 and 20%) of titanium oxide (TiO_2) and ferric oxide (Fe_2O_3) by the solvent casting method [71, 72].

Thermal degradation can also be improved in acrylic-based materials by nanoparticle filling. For example, the experimental results obtained by thermogravimetric analysis (TGA) of PMMA with TiO_2 and Fe_2O_3 showed that these nanoparticles can improve the thermal stability of PMMA by about 50°C by loading 5 wt.% of fillers [72]. The TGA also showed that the presence of small amounts of Pd nanoparticles (0.0005–0.005 vol%) in PMMA/Pd nanocomposites significantly improved the thermal stability of PMMA, as shown by a degradation initiation retarded by 75°C and a gain of 32°C at the maximum decomposition rate [73].

Acrylic hydrogels are hydrophilic polymers and are able to absorb large amounts of water in their biomedical applications 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. Thus, many studies have been done in this way with acrylic hydrogels such as PHEMA [74], bulk and plasma-polymerized poly(2-hydroxyethyl acrylate) (PHEA) [75], Poly(ethyl acrylate) [76], etc.

5. Water sorption and diffusion

Water sorption and diffusion are also very important in biomedicine because these properties play a very important role in cell survival, especially in tissue engineering applications [3].

Thus, acrylic hydrogels such as poly(2-hydroxyethyl methacrylate) or poly(2-hydroxyethyl acrylate), are very important hydrophilic materials as these polymers were able to absorb and swell retaining large amounts of water within their structure[77–80]. The excellent water sorption property has made these types of materials very promising in a wide range of biomedical applications such as controlled drug delivery, tissue engineering, wound healing, etc. [4, 81]. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymeric backbone, while their resistance to dissolution arises from crosslinks between network chains [82]. However, these single-network hydrogels have weak mechanical properties and slow response at swelling. Therefore, they are in need of reinforcement, as already mentioned, which can also modify their water sorption properties. For example, the combination of hydrophilic and hydrophobic functional groups of acrylic polymers as multicomponent polymeric systems is shown in **Figure 1**.

The reinforcement of acrylics through GO loading can modify the water sorption behavior of the polymers. 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. Therefore, these GO-based superabsorbent acrylic hydrogels have very potential applications in many fields such as biomedical engineering and hygienic products [47].

The mechanism of water diffusion [83] can also be altered by the reinforcement of acrylics through any of the methods shown in Section 1. Thus, poly(acrylic acid)-GO nanocomposite hydrogels shows non-Fickian anomalous diffusion and the deswelling ratio decreases with increasing GO content [48].

A new method (ultrasound synthesis) has been developed to prepare superabsorbent polymers of sodium lignosulfonate-grafted poly(acrylic acid-co-acryl amide). This superabsorbent acrylic-based polymer exhibited also a non-Fickian water diffusion transport and a maximum water absorbency of 1350 $g \cdot g^{-1}$ [84].

There are many acrylic hydrogels, which exhibit a non-Fickian diffusion behavior such as poly(2-hydroxyethyl acrylate) [79, 80]. Even though water sorption is not classically Fickian, it has been observed in a variety of polymers such as PHEMA, that an important water-swellable biomedical polymer is controlled by Fickian diffusion [85]. Thus, copolymeric hydrogels based on 2-hydroxyethyl methacrylate (HEMA) and epoxy methacrylate (EMA) synthesized by bulk polymerizations showed that the swelling process of these polymers also follows Fickian behavior and the equilibrium water content (EWC) decreased with increase in EMA content due to its hydrophobicity [86].

It is remarkable that the pH has a big influence in the swelling properties and diffusion mechanism of acrylic-based materials. Thus, the swelling properties of semi-interpenetrating polymer networks of acrylamide-based polyurethanes decreased in acidic pH, while a reverse trend was seen in basic pH. However, these semi-IPNs were found to be hydrolytically stable in phosphate buffer solution, which makes them to be a potential material for biomedical applications [18].

Polyacrylic acid is a pH-sensitive and biocompatible polymer that is being used in many biomedical fields [26]. It 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 [87]. 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(acryl amide-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 pH of the swelling media [88].

The effect of temperature on swelling properties of acrylic hydrogels is also very important [86], and they can be modified to exhibit fast temperature sensitivity, and improved oscillating swelling-deswelling properties as, for example, in thermosensitive poly(N-isopropyl acrylamide-co-acrylic acid) hydrogels [89].

6. Antibacterial activity

In biomedicine, bacterial 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 antibacterial materials are urgently needed for medical uses [90]. However, acrylics itself do not have antibacterial activity intrinsically, and therefore some fillers and antibacterial agents need to be incorporated by physical blending in order to produce an acrylic-based antibacterial material [91]. Thus, graphene has emerged as a novel green broad-spectrum antibacterial material, with little bacterial resistance and tolerable cytotoxic 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 graphene-based nanocomposites have a wide range of biomedical applications such as wound dressing due to its superior antibacterial properties and good biocompatibility [92].

In the field of dental materials, since methyl methacrylate was firstly used in tooth restoration in 1937, methacrylate monomers having good biocompatibility and adhesive property have been extensively used as dental materials [91]. The most commonly used methacrylate monomers in commercial dental resin-based materials are methyl methacrylate (MMA), 2,2-bis[4-(2-hydroxy-3-methacryloyloxypropyl)-phenyl]propane (Bis-GMA), 1,6-bis-[2-methacryloyloxyethoxycarbo nylamino]-2,4,4-trimethylhexane (UDMA) and tri-ethylene glycol dimethacrylate (TEGDMA) [93]. However, the dental materials produced with these monomers are not of antibacterial nature, which is very important in this biomedical field. Thus, another strategy to design acrylic hydrogels with desired antibacterial performance consists of adding silver nanoparticles (Ag NPs). This modification produced a strong antibacterial activity against *Escherichia coli* and also

improved the mechanical properties of acrylic resins for dental applications. Such antibacterial effects were mainly attributed to the release of silver ions upon immersion of the dental composite in water, which appeared to be fairly nontoxic to humans [94]. Poly(methyl methacrylate) (PMMA) nanofibers containing silver nanoparticles were synthesized by radical-mediated dispersion polymerization and also showed enhanced antimicrobial efficacy compared to that of silver sulfadiazine and silver nitrate at the same silver concentration [95].

Infections are also frequent and highly undesired occurrences after orthopedic procedures. Besides, the growing concern caused by the rise in antibiotic resistance progressively decreased the efficacy of such drugs. Thus, in this area, the integration of silver nanoparticles in the polymeric mineralized acrylic-based nanocomposites also provides antibacterial activity against bacteria [96].

The combination of both previous strategies (graphene and Ag NPs) to design antibacterial 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 days of healing of impaired wounds [97]. 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 [98].

7. Porosity in scaffolds for tissue engineering

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 of their biocompatibility and similarities to native extracellular 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. Emerging technologies have demonstrated the ability to control porosity and morphology in hydrogels, creating engineered tissues with structure and function similar to native tissues [99].

The applications of porous materials are nowadays widespread. The interconnection and geometry of pores, which depend on the tissue to regenerate, physicochemical properties and mechanical resistance of the material, play in these biomedical applications a major role. Thus, there are several methods to produce *scaffolds*, which include gas foaming [100], sintering fiber meshes [101], solvent casting [102], polymerization in solution [80, 103], porogen

technique [104, 105], freeze-drying techniques [106, 107], electrospinning [108], 3D printing [109], 3D bioplotting of scaffold with cells [110], etc. For example, acrylic 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 physicochemical properties of the resulting material can be controlled in an independent way. Copolymerization of hydrophobic ethyl acrylate 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 3**) [105].

Another example is the novel preparation of gelatin-PHEMA porous scaffolds by freeze-drying technique, in which morphology was assessed by SEM and μ-CT (**Figure 4**). 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 in this study, and the results indicated that the HEMA content in the initial polymerization mixtures modulates 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 in the case of higher HEMA loaded materials. It is important to notice that the covalently bound gelatin sequences significantly improve the biocompatibility of PHEMA-based hydrogels, which is very convenient for tissue engineering purposes.

Superporous acrylic scaffolds can also be prepared by the salt-leaching technique using NaCl or $(NH_4)_2SO_4$ as a porogen [111] or with many other porogenic agents such as ammonium oxalate crystals [112].

By submitting carbon dioxide (CO_2) to supercritical conditions (P = 160–260 bar, T = 60°C) after certain time and then rapidly depressurize, it is also possible to fabricate porous structures that are related to the supercritical parameters and to the polymer blend composition [113]. The use of carbon dioxide (CO_2) to create such scaffolds has received some attention in the past. But, many researchers believe that although CO_2 processing of polymers can lead to porous scaffolds, there is limited interconnectivity between the pores. However, highly porous (greater than 85%) and well-interconnected scaffolds were obtained in a blend of poly(ethyl methacrylate) and tetrahydrofurfuryl methacrylate (PEMA/THFMA) showing promise for potential applications in cartilage repair [114].

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, and for example, biodegradable nanofibrous poly(ʟ-lactic acid) (PLLA) scaffolds have been prepared by this process for use in tissue regeneration [115]. 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, must still be overcome. The common 3D printing technologies such as three-dimensional printing, fused deposition modeling, selective laser sintering, stereolithography and 3D Plotting/Direct-Write/Bioprinting, are still
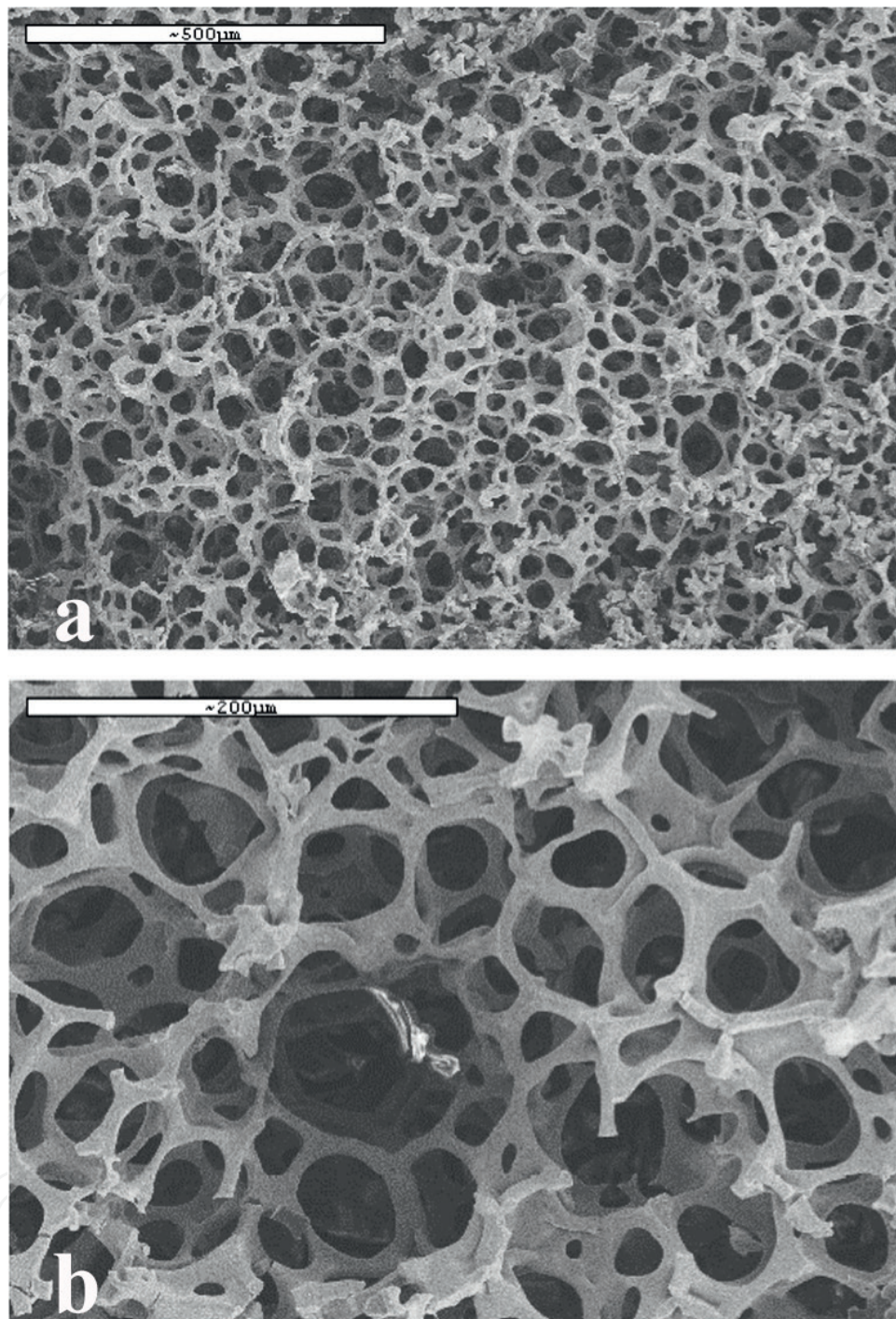
Figure 3. SEM micrographs of EA/HEMA copolymer scaffolds (30% HEMA) at different magnifications. Reprinted with permission from Ref. [105].

under deep research for the progress of each technology 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 [109].

Mechanical resistance depends both on the material properties and on the interconnected pore structure of the scaffold. This problem is more serious in the case of porous acrylic hydrogels, which exhibit very poor mechanical properties in their swollen state [80]. Therefore, it is
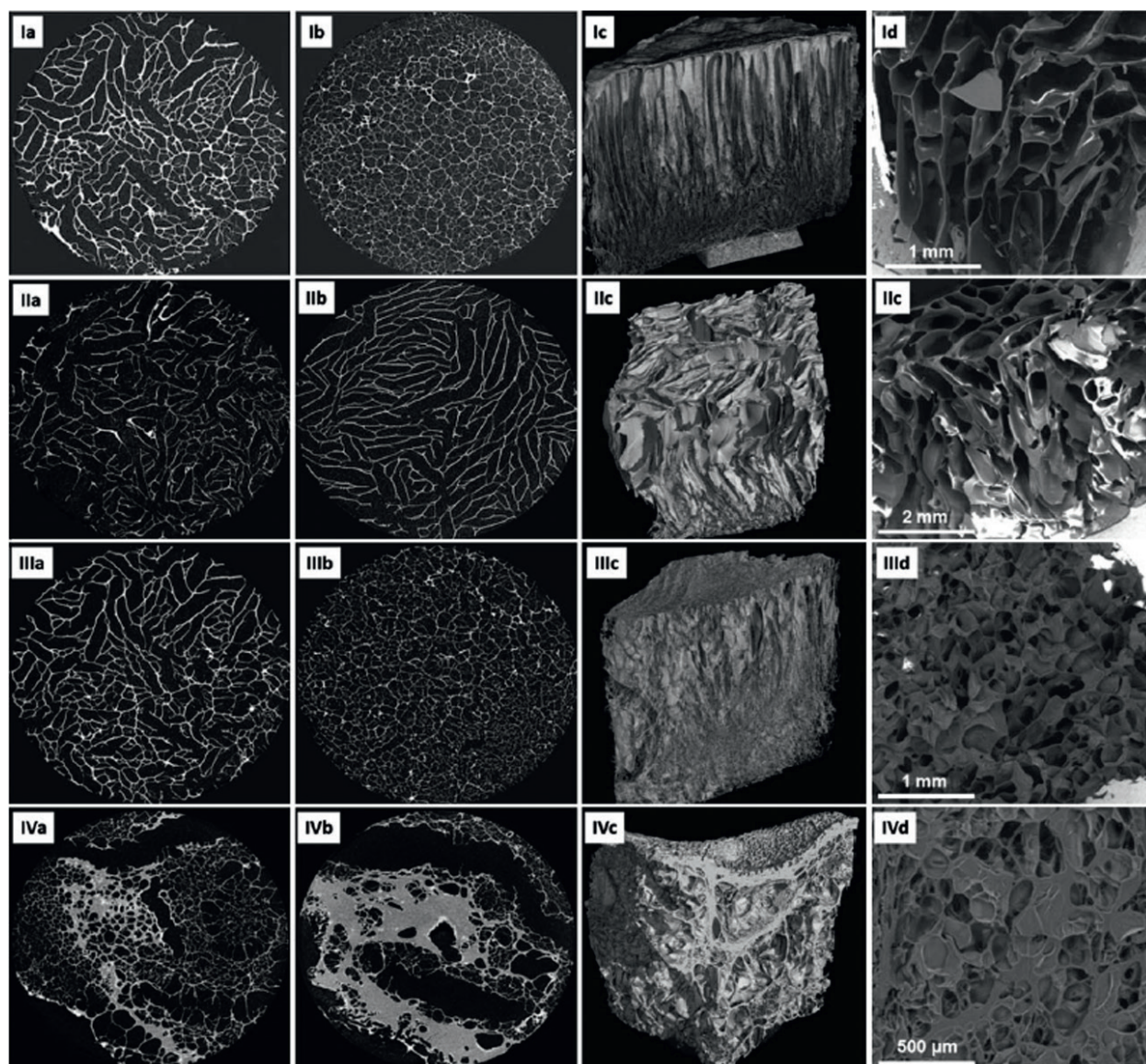
Figure 4. Morphology of the gelatin-PHEMA porous scaffolds as obtained through μ-CT (panels (a)–(c): (a), top view; (b), bottom view; (c), side view) and SEM (panel (d)) analyses: panel (I), C0; panel (II), C1; panel (III), C2; panel (IV), C3. Reprinted with permission from Ref. [107].

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/poly(2-hydroxyethyl acrylate) as scaffold material matrix greatly improves the mechanical properties, and the silica phase of the scaffold was effectively interconnected and continuous, able to withstand pyrolysis without losing the pore architecture of the scaffold [37].

Other modifications of acrylics 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 [116]. PHEMA has also been modified with laminin-

derived Ac-CGGASIKVAVS-OH peptide sequences to construct scaffolds that promote cell adhesion and neural differentiation. With the same goal, nanofiber scaffolds 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 [115].

Recent studies of 3D microenvironment comprising fibronectin-coated PMMA/PC-based multicomponent polymeric systems promoted differentiation of primary human osteoblasts, which hereby renders a promising tool for tissue-specific *in vitro* preconditioning of osteoblasts designated for clinically oriented bone augmentation or regeneration. Furthermore, morphogenesis and fluorescence dye-based live/dead staining revealed homogenous cell coverage of the microcavities, whereas cells showed high viability up to 14 days, and Azur II staining proved formation of uniform sized multi-layered aggregates, exhibiting progressive intracellular deposition of extracellular bone matrix constituents comprising fibronectin, osteocalcin and osteonectin from day 7 onwards [117].

Polysaccharide hydrogels have become increasingly studied as matrices in soft-tissue engineering due to their known cytocompatibility. Thus, for example, crosslinkable 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 kinds of hydrogels could be controlled by the polysaccharide structure and the crosslinking density. Furthermore, under *in vitro* conditions, these materials had no cytotoxic effects against fibroblasts, and the use of composite gels improved the adherence of cells [118].

Even though the great advances have been achieved in scaffold design of acrylic-based materials, much research has to be conducted still in order to find new ways and methods capable of providing suitable advanced porous materials for tissue engineering applications.

Acknowledgements

Author details

Ángel Serrano-Aroca

Address all correspondence to: angel.serrano@ucv.es

Bioengineering and Cellular Therapy Group, Department of Applied and Technological Sciences, Faculty of Veterinary and Experimental Sciences, San Vicente Mártir Catholic University of Valencia, Valencia, Spain

References

[1] Chirila T, Harkin D. Biomaterials and Regenerative Medicine in Ophthalmology. 2nd ed. UK, Elsevier; 2016

[2] Shalaby S, Nagatomi S, Peniston S. Polymeric Biomaterials for Articulating Joint Repair and Total Joint Replacement. Polymers for Dental and Orthopedic Applications; Boca Raton, CRC Press; 2007

[3] Van Blitterswijk C, De Boer J. Tissue Engineering. United States of America, Academic Press; 2014

[4] Ratner BD, Hoffman AS, Schoen FJ, Lemons JE. Biomaterials Science: An Introduction to Materials in Medicine. Canada, Academic Press; 2012

[5] Stoy V, Climent C. In Hydrogels: Speciality Plastics for Biomedical and Pharmaceutical Applications. Basel: Technomic Publishers; 1996

[6] Serrano-Aroca Á, Monleón-Pradas M, Gómez-Ribelles JL. Effect of crosslinking on porous poly(methyl methacrylate) produced by phase separation. Colloid and Polymer Science. 2008;**286**(2):209-216

[7] Ramaraj B, Radhakrishnan G. Modification of the dynamic swelling behaviour of poly(2-hydroxyethyl methacrylate) hydrogels in water through interpenetrating polymer networks (IPNs). Polymer (Guildf). 1994;**35**(10):2167-2173

[8] Gilbert JL, Ney DS, Lautenschlager EP. Self-reinforced composite poly (methy1 methacrylate): Static and fatigue properties. Journal of Applied Polymer Science 1995;**16**(14): 1043-1055

[9] Serrano-Aroca Á, Gómez-Ribelles JL, Monleón-Pradas M, Vidaurre-Garayo A, Suay-Antón J. Characterisation of macroporous poly(methyl methacrylate) coated with plasma-polymerised poly(2-hydroxyethyl acrylate). European Polymer Journal. 2007;**43**(10):4552-4564

[10] Serrano-Aroca Á, Monleón-Pradas M, Gómez-Ribelles JL. Plasma-induced polymerisation of hydrophilic coatings onto macroporous hydrophobic scaffolds. Polymer (Guildf). 2007;**48**(7):2071-2078

[11] Amerio E, Fabbri P, Malucelli G, Messori M, Sangermano M, Taurino R. Scratch resistance of nano-silica reinforced acrylic coatings. Progress in Organic Coatings, 2008;**62**:129-133

[12] Kugler S, Kowalczyk K, Spychaj T. Progress in organic coatings hybrid carbon nanotubes / graphene modified acrylic coats. Progress in Organic Coatings. 2015;**85**:1-7

[13] Cha C, Shin SR, Gao X, Annabi N, Dokmeci MR, Tang XS, et al. Controlling mechanical properties of cell-laden hydrogels by covalent incorporation of graphene oxide. Small. 2014;**10**(3):514-523

[14] Faghihi S, Gheysour M, Karimi A, Salarian R. Fabrication and mechanical character-
ization of graphene oxide-reinforced poly (acrylic acid)/gelatin composite hydrogels.
Journal of Applied Physics. 2014;**115**(8)

[15] Ha H, Shanmuganathan K, Ellison CJ. Mechanically stable thermally crosslinked
poly(acrylic acid)/reduced graphene oxide aerogels. ACS Applied Materials & Interfaces.
2015;**7**(11):6220-6229

[16] Sperling LH, Mishra V. The current status of interpenetrating polymer networks.
Polymers for Advanced Technologies. 1996;**7**(4):197-208

[17] Maity J, Ray SK. Enhanced adsorption of methyl violet and congo red by using semi and
full IPN of polymethacrylic acid and chitosan. Carbohydrate Polymers. 2014;**104**(1):8-16

[18] Merlin DL, Sivasankar B. Synthesis and characterization of semi-interpenetrating poly-
mer networks using biocompatible polyurethane and acrylamide monomer. European
Polymer Journal. 2009;**45**(1):165-170

[19] Wang M, Pramoda KP, Goh SH. Mechanical behavior of Pseudo-Semi-Interpenetrating
polymer networks based on Double-C 60 -End-Capped poly (ethylene oxide) and Poly
(methyl methacrylate). Chemistry of Materials. 2004;**16**:3452-3456

[20] Hua F, Hu C. Interpenetrating polymer networks of epoxy resin and urethane acrylate resin
2. Morphology and mechanical property. European Polymer Journal. 2000;**36**(1):27-33

[21] Chakrabarty D, Das B, Roy S. Epoxy resin-poly (ethyl methacrylate) interpenetrating
polymer networks: Morphology, mechanical. 1997;**105**:1-9

[22] Vabrik R, Czajlik I, Tury G, Rusznak I, Ille A, Vig A. A study of epoxy resin-acrylated
polyurethane semi-interpenetrating polymer networks. Journal of Applied Polymer
Science. 1998;**68**(1):111-119

[23] Dragan ES. Design and applications of interpenetrating polymer network hydrogels. A
review. Chemical Engineering Journal. 2014;**243**:572-590

[24] Lee J, Kim S, Kim S, Lee Y, Lee K. Synthesis and characteristics of interpenetrating poly-
mer network hydrogel composed of chitosan and poly (acrylic acid). Polymer (Guildf).
1998;**73**:113-120

[25] Bajpai AK, Shukla SK, Bhanu S, Kankane S. Responsive polymers in controlled drug
delivery. Progress in Polymer Science. 2008;**33**(11):1088-1118

[26] Zhao Y, Kang J, Tan T. Salt-, pH- and temperature-responsive semi-interpenetrating
polymer network hydrogel based on poly(aspartic acid) and poly(acrylic acid). Polymer
(Guildf). 2006;**47**(22):7702-7710

[27] Richter A, Paschew G, Klatt S, Lienig J, Arndt K-F, Adler H-JP. Review on Hydrogel-
based pH sensors and microsensors. Sensors. 2008;**8**(1):561-581

[28] Stumpel JE, Gil ER, Spoelstra AB, Bastiaansen CWM, Broer DJ, Schenning APHJ. Stimuli-responsive materials based on interpenetrating polymer liquid crystal hydrogels. Advanced Functional Materials. 2015;**25**(22):3314-3320

[29] Groover MP. Fundamentals of Modern Manufacturing_ Materials, Processes, and Systems. 4th ed. J. Wiley & Sons; United States of America, 2010

[30] Stipho HD. Repair of acrylic resin denture base reinforced with glass fiber. Journal of Prosthetic Dentistry. 1998;**80**(5):546-550

[31] Young CD, Wu JR, Tsou TL. High-strength, ultra-thin and fiber-reinforced pHEMA artificial skin. Biomaterials. 1998;**19**(19):1745-1752

[32] Saheb DN, Jog JP. Natural fiber polymer composites: A review. Advances in Polymer Technology. 1999;**18**(4):351-363

[33] Ku H, Wang H, Pattarachaiyakoop N, Trada M. A review on the tensile properties of natural fiber reinforced polymer composites. Composites Part B: Engineering. 2011;**42**(4):856-873

[34] Chen C, Li D, Hu Q, Wang R. Properties of polymethyl methacrylate-based nanocomposites: Reinforced with ultra-long chitin nanofiber extracted from crab shells. Materials & Design. 2014;**56**:1049-1056

[35] Kokubo T. Design of bioactive bone substitutes based on biomineralization process. Materials Science and Engineering: C. 2005;**25**(2):97-104

[36] Hench LL, West JK. The sol-gel process. Chemical Reviews. 1990;**90**(1):33-72

[37] Rodríguez-Hernández JC, Serrano-Aroca Á, Gómez-Ribelles JL, Monleón-Pradas M. Three-dimensional nanocomposite scaffolds with ordered cylindrical orthogonal pores. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2008;**84**(2):541-549

[38] Trakulsujaritchok T, Hourston DJ. Damping characteristics and mechanical properties of silica filled PUR/PEMA simultaneous interpenetrating polymer networks. European Polymer Journal. 2006;**42**(11):2968-2976

[39] Novoselov KS, Geim AK, Morozov SV, Jiang D, Zhang Y, Dubonos SV, et al. Electric field effect in atomically thin carbon films. Science. 2004;**306**(5696):666-669

[40] Geim AK, Novoselov KS. The rise of graphene. Nature Materials. 2007;**6**:183-191

[41] Balandin AA, Ghosh S, Bao W, Calizo I, Teweldebrhan D, Miao F, et al. Superior thermal conductivity of single-layer graphene. Nano Letters. 2008;**8**(3):902-907

[42] Lee C, Wei X, Kysar JW, Hone J. Measurement of the elastic properties and intrinsic strength of monolayer graphene. Science. 2008;**321**(5887):385-388

[43] Kalbacova M, Broz A, Kong J, Kalbac M. Graphene substrates promote adherence of human osteoblasts and mesenchymal stromal cells. Carbon N Y. 2010;**48**(15):43234329

[44] Zhan Y, Meng F, Yang X, Liu X. Magnetite-graphene nanosheets (GNs)/poly(arylene ether nitrile) (PEN): Fabrication and characterization of a multifunctional nanocomposite film. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2011;**390**(1-3):112-119

[45] Dong J, Ding J, Weng J, Dai L. Graphene enhances the shape memory of poly (acrylamide-co-acrylic acid) grafted on graphene. Macromolecular Rapid Communications. 2013;**34**(8):659-664

[46] Shen J, Yan B, Li T, Long Y, Li N, Ye M. Study on graphene-oxide-based polyacrylamide composite hydrogels. Composites Part A: Applied Science and Manufacturing. 2012;**43**(9):1476-1481

[47] Huang Y, Zeng M, Ren J, Wang J, Fan L, Xu Q. Preparation and swelling properties of graphene oxide/poly(acrylic acid-co-acrylamide) super-absorbent hydrogel nanocomposites. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2012;**401**:97-106

[48] Shen J, Yan B, Li T, Long Y, Li N, Ye M. Mechanical, thermal and swelling properties of poly(acrylic acid)-graphene oxide composite hydrogels. Soft Matter. 2012;**8**(6):1831-1836

[49] Potts JR, Lee SH, Alam TM, An J, Stoller MD, Piner RD, et al. Thermomechanical properties of chemically modified graphene/poly(methyl methacrylate) composites made by *in situ* polymerization. Carbon N Y. 2011;**49**(8):2615-2623

[50] Zeng J, Saltysiak B, Johnson WS, Schiraldi DA, Kumar S. Processing and properties of poly(methyl methacrylate)/carbon nano fiber composites. Composites Part B: Engineering. 2004;**35**(2):173-178

[51] Kunanuruksapong R, Sirivat A. Electrical properties and electromechanical responses of acrylic elastomers and styrene copolymers: Effect of temperature. Applied Physics A: Materials Science & Processing. 2008;**92**(2):313-320

[52] Zhou C, Wu Q. A novel polyacrylamide nanocomposite hydrogel reinforced with natural chitosan nanofibers. Colloids Surfaces B Biointerfaces. 2011;**84**(1):155-162

[53] Iwamoto S, Nakagaito AN, Yano H, Nogi M. Optically transparent composites reinforced with plant fiber-based nanofibers. Applied Physics A: Materials Science & Processing. 2005;**81**(6):1109-1112

[54] Meneghetti P, Qutubuddin S. Synthesis, thermal properties and applications of polymer-clay nanocomposites. Thermochimica Acta. 2006;**442**(1-2):74-77

[55] Zhao M, Forrester J V, McCaig CD. A small, physiological electric field orients cell division. Proceedings of the National Academy of Sciences of the United States of America. 1999;**96**:4942-4946

[56] Yao L, Shanley L, Mccaig C, Zhao M. Small applied electric fields guide migration of hippocampal neurons. Journal of Cellular Physiology. 2008;**216**(2):527-535

[57]   Woo DG, Shim MS, Park JS, Yang HN, Lee DR, Park KH. The effect of electrical stimulation on the differentiation of hESCs adhered onto fibronectin-coated gold nanoparticles. Biomaterials. 2009;**30**(29):5631-5638

[58]   Sisken BF, Walker J, Orgel M. Prospects on clinical applications of electrical stimulation for nerve regeneration. Journal of Cellular Biochemistry. 1993;**51**(4):404-409

[59]   Zhao M. Electrical fields in wound healing-An overriding signal that directs cell migration. Seminars in Cell and Developmental Biology. 2009;**20**(6):674-682

[60]   Kirson ED, Dbalý V, Tovaryš F, Vymazal J, Soustiel JF, Itzhaki A, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**(24):10152-10157

[61]   Fabbri P, Valentini L, Bittolo Bon S, Foix D, Pasquali L, Montecchi M, et al. In-situ graphene oxide reduction during UV-photopolymerization of graphene oxide/acrylic resins mixtures. Polymer (Guildf). 2012;**53**(26):6039-6044

[62]   Huang YL, Tien HW, Ma CC, Yang SY, Wu SY, Liu HY, et al. Effect of extended polymer chains on properties of transparent graphene nanosheets conductive film. Journal of Materials Chemistry. 2011;**21**(45):18236

[63]   Huang P, Chen W, Yan L. An inorganic-organic double network hydrogel of graphene and polymer. Nanoscale. 2013;**5**(13):6034-6039

[64]   Wan S, Hu H, Peng J, Li Y, Fan Y, Jiang L, et al. Nacre-inspired integrated strong and tough reduced graphene oxide-poly(acrylic acid) nanocomposites. Nanoscale. 2016;**8**(10):56495656

[65]   Iijima S. Helical microtubules of graphitic carbon. Nature. 1991;**354**(6348):56-58

[66]   Rao CNR, Satishkumar BC, Govindaraj A. Nanotubes. ChemPhysChem. 2001;**2**:78-105

[67]   Wang ZG, Wang Y, Xu H, Li G, Xu ZK. Carbon Nanotube-Filled nanofibrous membranes electrospun from Poly(acrylonitrile- co -acrylic acid) for glucose biosensor. The Journal of Physical Chemistry C. 2009;**113**(7):2955-2960

[68]   Logakis E, Pandis CH, Pissis P, Pionteck J, Pötschke P. Highly conducting poly(methyl methacrylate)/carbon nanotubes composites: Investigation on their thermal, dynamic-mechanical, electrical and dielectric properties. Composites Science and Technology. 2011;**71**(6):854-862

[69]   Huang ZH, Qiu KY. The effects of interactions on the properties of acrylic polymers/silica hybrid materials prepared by the *in situ* sol-gel process. Polymer (Guildf). 1997;**38**(3):521-526

[70]   Ramanathan T, Abdala AA, Stankovich S, Dikin DA, Herrera-Alonso M, Piner RD, et al. Functionalized graphene sheets for polymer nanocomposites. Nature Nanotechnology. 2008;**3**(6):327-331

[71] Laachachi A, Cochez M, Ferriol M, Lopez-Cuesta JM, Leroy E. Influence of TiO2 and Fe2O3 fillers on the thermal properties of poly(methyl methacrylate) (PMMA). Materials Letters. 2005;**59**(1):36-39

[72] Laachachi A, Leroy E, Cochez M, Ferriol M, Lopez Cuesta JM. Use of oxide nanoparticles and organoclays to improve thermal stability and fire retardancy of poly(methyl methacrylate). Polymer Degradation and Stability. 2005;**89**(2):344-352

[73] Aymonier C, Bortzmeyer D, Thomann R, Muelhaupt R. Poly (Methyl methacrylate)/Palladium nanocomposites: Synthesis and characterization of the morphological, thermomechanical, and thermal properties. Chemistry of Materials. 2003;**15**(25):4874-4878

[74] Roorda WE, Bouwstra JA, de Vries MA, Junginger HE. Thermal analysis of water in p(HEMA) hydrogels. Biomaterials. 1988;**9**(6):494-499

[75] Serrano-Aroca Á, Monleón-Pradas M, Gómez-Ribelles JL, Rault J. Thermal analysis of water in reinforced plasma-polymerised poly(2-hydroxyethyl acrylate) hydrogels. European Polymer Journal. 2015;**72**:523-534

[76] Tanaka M, Mochizuki A. Effect of water structure on blood compatibility--thermal analysis of water in poly(meth)acrylate. Journal of Biomedical Materials Research Part A. 2004;**68**(4):684-695

[77] Serrano-Aroca Á, Campillo-Fernández AJ, Gómez-Ribelles JL, Monleón-Pradas M, Gallego-Ferrer G, Pissis P. Porous poly(2-hydroxyethyl acrylate) hydrogels prepared by radical polymerisation with methanol as diluent. Polymer (Guildf). 2004;**45**(26):8949-8955

[78] Clayton AB, Chirila T V, Lou X. Hydrophilic Sponges based on 2-Hydroxyethyl methacrylate. V. Effect of crosslinking agent reactivity on mechanical properties. Polymer International. 1997;**44**:201-207

[79] Monleón-Pradas M, Gómez-Ribelles JL, Serrano-Aroca Á, Gallego-Ferrer G, Suay-Antón J, Pissis P. Interaction between water and polymer chains in poly(hydroxyethyl acrylate) hydrogels. Colloid and Polymer Science. 2001;**279**(4):323-330

[80] Monleón-Pradas M, Gómez-Ribelles JL, Serrano-Aroca Á, Gallego Ferrer G, Suay Antón J, Pissis P. Porous poly (2-hydroxyethyl acrylate) hydrogels. Polymer (Guildf). 2001;**42**(10):4667-4674

[81] Ahmed EM. Hydrogel: Preparation, characterization, and applications: A review. Journal of Advanced Research. 2015;**6**(2):105-121

[82] Tanaka T. Gels. Scientific American. 1981;**244**(1):124-136, 138

[83] Williams MMR. The mathematics of diffusion. Annals of Nuclear Energy. 1977;**4**(4-5):205-206

[84] Wang X, Zhang Y, Hao C, Dai X, Zhu F, Ge C. Ultrasonic synthesis and properties of a sodium lignosulfonate–grafted poly(acrylic acid-co-acryl amide) composite super absorbent polymer. New Journal of Chemistry. 2014;**38**(12):6057-6063

[85] Gehrke SH, Biren D, Hopkins JJ. Evidence for Fickian water transport in initially glassy poly(2-hydroxyethyl methacrylate). Journal of Biomaterials Science Polymer Edition. 1995;**6**(4):375-390

[86] Wang J, Wu W. Swelling behaviors, tensile properties and thermodynamic studies of water sorption of 2-hydroxyethyl methacrylate/epoxy methacrylate copolymeric hydrogels. European Polymer Journal. 2005;**41**(5):1143-1151

[87] Kavitha T, Kang IK, Park SY. Poly(acrylic acid)-grafted graphene oxide as an intracellular protein carrier. Langmuir. 2014;**30**(1):402-409

[88] Krishna-Rao KSV, Ha CS. PH Sensitive hydrogels based on acryl amides and their swelling and diffusion characteristics with drug delivery behavior. Polymer Bulletin. 2009;**62**(2):167-181

[89] Zhang XZ, Yang YY, Wang FJ, Chung TS. Thermosensitive poly(N-isopropylacrylamide-co-acrylic acid) hydrogels with expanded network structures and improved oscillating swelling-deswelling properties. Langmuir. 2002;**18**(6):2013-2018

[90] Shi L, Chen J, Teng L, Wang L, Zhu G, Liu S, et al. The antibacterial applications of graphene and its derivatives. Small. 2016; **12**(31):4165-4184

[91] He J, Söderling E, Lassila LVJ, Vallittu PK. Incorporation of an antibacterial and radiopaque monomer in to dental resin system. Dental Materials Journal. 2012;**28**(8):e110–e117

[92] Ji H, Sun H, Qu X. Antibacterial applications of graphene-based nanomaterials: Recent achievements and challenges. Advanced Drug Delivery Reviews. 2016;**105**:176-189

[93] Moszner N, Salz U. New developments of polymeric dental composites. Progress in Polymer Science. 2001;**26**(4):535-576

[94] Guo C, Zhou L, Jianxiong L. Effects of expandable graphite and modified ammonium polyphosphate on the flame-retardant and mechanical properties of wood flour-polypropylene composites. Polymer Composites. 2013;**21**(7):449-456

[95] Kong H, Jang J. Antibacterial properties of novel poly(methyl methacrylate) nanofiber containing silver nanoparticles. Langmuir. 2008;**24**(5):2051-2056

[96] González-Sánchez MI, Perni S, Tommasi G, Morris NG, Hawkins K, López-Cabarcos E, et al. Silver nanoparticle based antibacterial methacrylate hydrogels potential for bone graft applications. Materials Science and Engineering: C. 2015;**50**:332-340

[97] Fan Z, Liu B, Wang J, Zhang S, Lin Q, Gong P, et al. A novel wound dressing based on Ag/graphene polymer hydrogel: Effectively kill bacteria and accelerate wound healing. Advanced Functional Materials. 2014;**24**(25):3933-3943

[98] Ping X, Wang M, Xuewu G. Surface modification of poly(ethylene terephthalate) (PET) film by gamma-ray induced grafting of poly(acrylic acid) and its application in antibacterial hybrid film. Radiation Physics and Chemistry. 2011;**80**(4):567-572

[99] Annabi N, Nichol JW, Zhong X, Ji C, Koshy S, Khademhosseini A, et al. Controlling the porosity and microarchitecture of hydrogels for tissue engineering. Tissue Engineering Part B: Reviews. 2010;**16**(4):371-383

[100] Arora KA, Lesser AJ, McCarthy TJ. Compressive behavior of microcellular polystyrene foams processed in supercritical carbon dioxide. Polymer Engineering & Science. 1998;**38**(12):2055-2062

[101] Thomson RC, Wake MC, Yaszemski MJ, Mikos AG. Biodegradable polymer scaffolds to regenerate organs. Advances in Polymer Science. 1995;**122**:247-277

[102] Andrianova GP, Pakhomov SI. Porous materials from crystallizable polyolefins produced by gel technology. Polymer Engineering & Science. 1997;**37**(8):1367-1380

[103] Serrano-Aroca Á, Monleón-Pradas M, Gómez-Ribelles JL. Macroporous poly(methyl methacrylate) produced by phase separation during polymerisation in solution. Colloid and Polymer Science. 2007;**285**(7):753-760

[104] Flynn L, Dalton PD, Shoichet MS. Fiber templating of poly(2-hydroxyethyl methacrylate) for neural tissue engineering. Biomaterials. 2003;**24**(23):4265-4272

[105] Brígido-Diego R, Pérez-Olmedilla M, Serrano-Aroca Á, Gómez-Ribelles JL, Monleón-Pradas M, Gallego-Ferrer G, et al. Acrylic scaffolds with interconnected spherical pores and controlled hydrophilicity for tissue engineering. Journal of Materials Science: Materials in Medicine. 2005;**40**(18):4881-4887

[106] Kang HW, Tabata Y, Ikada Y. Fabrication of porous gelatin scaffolds for tissue engineering. Biomaterials. 1999;**20**(14):1339-1344

[107] Dragusin DM, Van Vlierberghe S, Dubruel P, Dierick M, Van Hoorebeke L, Declercq HA, et al. Novel gelatin–PHEMA porous scaffolds for tissue engineering applications. Soft Matter. 2012;**8**(37):9589

[108] Agarwal S, Wendorff JH, Greiner A. Use of electrospinning technique for biomedical applications. Polymer (Guildf). 2008;**49**(26):5603-5621

[109] Chia HN, Wu BM. Recent advances in 3D printing of tissue engineering scaffolds. Journal of Biological Engineering. 2015;**9**(4):2-14

[110] Derby B. Printing and prototyping of tissues and scaffolds. Science. 2012;**338**(6109): 921-926

[111] Horák D, Hlídková H, Hradil J, Lapčíková M, Šlouf M. Superporous poly(2-hydroxyethyl methacrylate) based scaffolds: Preparation and characterization. Polymer (Guildf). 2008;**49**(8):2046-2054

[112] Kubinová Š, Horák D, Kozubenko N, Vaněček V, Proks V, Price J, et al. The use of superporous Ac-CGGASIKVAVS-OH-modified PHEMA scaffolds to promote cell adhesion and the differentiation of human fetal neural precursors. Biomaterials. 2010;**31**(23):5966-5975

[113] Velasco D, Benito L, Fernández-Gutiérrez M, San Román J, Elvira C. Preparation in supercritical CO_2 of porous poly(methyl methacrylate)-poly(l-lactic acid) (PMMA-PLA) scaffolds incorporating ibuprofen. The Journal of Supercritical Fluids. 2010;**54**(3):335-341

[114] Barry JJA, Silva MMCG, Cartmell SH, Guldberg RE, Scotchford CA, Howdle SM. Porous methacrylate tissue engineering scaffolds: Using carbon dioxide to control porosity and interconnectivity. Journal of Materials Science. 2006;**41**(13):4197-4204

[115] Park K, Hyun JJ, Kim JJ, Ahn KD, Dong KH, Young MJ. Acrylic acid-grafted hydrophilic electrospun nanofibrous poly(L-lactic acid) scaffold. Macromolecular Research. 2006;**14**(5):552-558

[116] Kubinová Š, Horák D, Syková E. Cholesterol-modified superporous poly(2-hydroxyethyl methacrylate) scaffolds for tissue engineering. Biomaterials. 2009;**30**(27):4601-4609

[117] Altmann B, Steinberg T, Giselbrecht S, Gottwald E, Tomakidi P, Bächle-Haas M, et al. Promotion of osteoblast differentiation in 3D biomaterial micro-chip arrays comprising fibronectin-coated poly(methyl methacrylate) polycarbonate. Biomaterials. 2011;**32**(34):8947-8956

[118] Möller S, Weisser J, Bischoff S, Schnabelrauch M. Dextran and hyaluronan methacrylate based hydrogels as matrices for soft tissue reconstruction. Biomolecular Engineering. 2007;**24**(5):496-504