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Poly(L-Lactide) Bionanocomposites

Ali Nabipour Chakoli

Abstract

A variety of natural, synthetic, and biosynthetic polymers such as poly(L-lactide), polyhydroxyalkanoate, and poly(ϵ -caprolactone) are biocompatible and environmentally degradable. Biodegradability can therefore be engineered into polymers by the judicious addition of chemical linkages such as anhydride, ester, or amide bonds, among others. Poly(L-lactide) (PLLA) has attracted increasing attention due to the combination of its bioresorbability, biodegradability, biocompatibility, and shape memory effect. It has been widely applied to biomedical fields such as bone screws, surgical sutures, tissue engineering, and controlled drug delivery. Nevertheless, the PLLA is weaker than that of natural cortical bones in mechanical strength. Additionally, the ability of PLLA in cell attachment and bioactivity are weak due to its hydrophobic properties. In order to overcome the unsuitable properties of PLLA, various techniques have already been applied to modify the physical and mechanical properties of PLLA. The most significant method is to introduce some various kinds of fillers into PLLA matrix to provide reinforcing filler/PLLA composites, such as hydroxyapatite (HA), b-tricalcium phosphate, bioglass, silica gel, amorphous carbon, carbon nanotubes (CNTs), and so on.

Keywords: poly(L-lactide), nanocomposites, nanomaterials, tissue engineering

1. Introduction

Nowadays, nanoscience and nanotechnology have increased the scope of polymeric materials application, with the ultimate goal of dramatically enhanced performance [1, 2]. The most popular performance is to introduce nanoparticles into the polymer matrix to treat the polymer/nano-sized particles composites. The second is the fabrication of polymeric nanoscale materials [3, 4]. Both the mentioned approaches have been applied for various polymeric systems [5]. Based on the revolutionary researches, nanotechnology has been successfully applied to produce different kinds of biopolymer materials with valuable quality and high performance in various fields [6].

The tissue engineering, which is considered as a multidisciplinary field in medicine and industry, is emerging as the promising new approach in the reconstruction of imperfect or damaged body tissues [7, 8]. Also, tissue engineering is multidisciplinary field of integrating materials science, biotechnology, industrial engineering, and medical engineering [9]. This chapter focuses on the development of biotechnical substitutes for restoration, replacement, maintaining, or enhancing tissue and organ functionalities. The artificial scaffolds like framework play a basic role in supporting the structural cells to settle and guide their growth to find the

specific tissue with acceptable structure [10]. Therefore, designation of artificial scaffolds has a great importance in tissue engineering. An artificial scaffold that covers the preferred characteristics such as biocompatibility, biodegradability, and high porosity structure could provide as template for bone growth [11]. In the same case, fibrous artificial scaffolds, biodegradable and biocompatible polymers, which are frequently used as artificial scaffold materials, are naturally soft in order to mimic the rigidity of natural tissues [12, 13].

Using fillers as a reinforcing agent is not a new idea in the world. Straws were used to reinforce mud bricks since 4000 BC [14]. Now, fibers made from so many kinds of materials in mesoscale such as glass, boron, silicon carbide, alumina, and especially carbon has been used as fillers in composites. Polymer nanocomposites are combination of a polymer matrix and inclusions that have at least one dimension (i.e., length, width, or thickness) in the nanometer size range (**Figure 1**).

In order to achieve ultimate effective properties, the fabrication of nanoparticle reinforced polymers must be optimized [15, 16]. Nowadays, there are several issues that are not well understood in this area and need more theoretical and experimental researches. However, individual research groups have made significant processing advances for particular nanoparticle-polymer systems, universal guidelines regarding the fabrication of nanocomposites do not exist [17]. This is in part due to the complexity of the polymer chemistry, the lack of detailed models describing the processing conditions, and the large list of parameters (specific to the types of polymer and nanotube under consideration) that can influence the polymer/nanoparticle interaction and impact the effective reinforcement properties.

There are four main system requirements for effective reinforcement. These are a large aspect ratio (1), good dispersion (2), alignment (3), and interfacial stress transfer (4).

Reinforcement of biodegradable and biocompatible polymers is a possible approach to overcome some natural limitations of mentioned polymers such as in adequate mechanical properties, insufficient stiffness, high brittleness, and low toughness [18–22]. Also, some researches were focused on evaluation of the properties of biopolymer blends and copolymers [23–27]. Some kinds of polyesters are widely studied as matrix polymer in biocomposites that reinforced with many kinds of reinforcing fillers for improving their applications. Biopolymers are used to produce harmless fluorescent microparticles for in-vivo material penetration researches.

Biodegradable and biocompatible nanomaterials, because of their properties such as controlled release, low toxicity, and enhanced encapsulation effect, are used frequently as drug delivery systems. Nanotechnology highlighted the impact of nanoencapsulation of various disease-related drugs on biodegradable nanoparticles such as poly(L-lactide-co-glycolide) (PLGA), poly lactic acid (PLA), chitosan, gelatin, poly caprolactone, and poly-alkyl-cyanoacrylates [3].

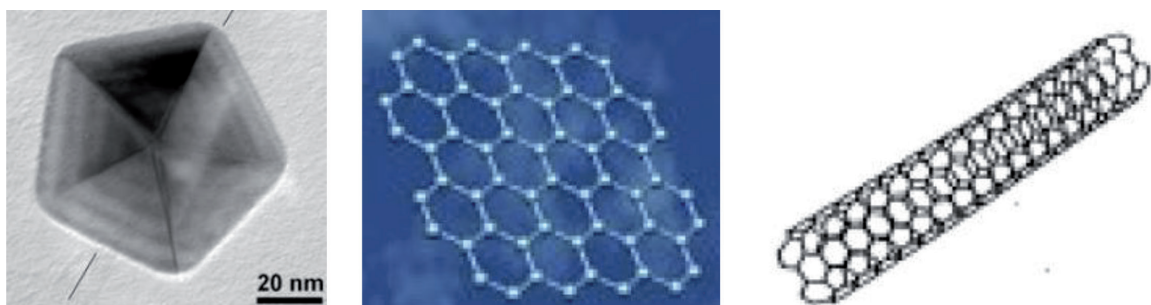


Figure 1.
The scheme of nanofillers for polymer nanocomposites.

2. Polymer nanocomposites fabrication

The methods for fabrication of nanocomposite have considered on improvement of nanomaterials dispersion because significantly higher distribution in the biopolymer matrices to improve the properties of polymeric nanocomposite. Like nanoparticle suspensions in solvents, pristine nanoparticles have not valuable dispersion in polymers illustrating the extreme difficulty to overcome the inherent thermodynamic driving of nanoparticles to agglomerate. The dispersion of nanoparticles in polymer should be evaluated over a various size scales of nanoparticles. The solution blending, melt blending, and in situ polymerization are widely applied to produce nanomaterial/polymer nanocomposites.

2.1 Solution blending of nanocomposites

Solution blending is a common technique for fabrication of polymeric nanocomposites because it is both amenable for various sizes and effectiveness. The solution blending includes three steps: dispersion of nanoparticles in a solvent, mixing with the polymer solution at effective temperature, and finally recover the composite after precipitation or casting the film. Solution-based casting methods provide an advantage through low viscosities, which facilitate mixing and dispersion of the nanoparticles. Many studies have used these methods for processing both thermoset and thermoplastic polymers.

As mentioned earlier, it is difficult to disperse nanoparticles in solvents by simple stirring. The instruments such as ultrasonicator are suitable for making metastable suspensions of reinforcing filler/polymer mixtures in solvents. It is necessary to consider that ultrasonication for a long time affects the nanoparticles. When using solution blending, nanoparticles tend to agglomerate during slow solvent evaporation, leading to inhomogeneous distribution of the nanoparticles in the polymer matrix.

2.2 Melt blending

The melt blending need heat and high shear pressure to disperse the nanoparticles in polymer matrix and it is well-matched with present industries. In comparison with solution blending, the melt mixing has less effective at dispersion of nanoparticles in polymer matrix and has limitation for low concentration of nanoparticle because of high viscosities of the composites at higher nanoparticles loadings.

Melt mixing of nanoparticles into thermoplastic polymer matrix using conventional processing techniques, such as extrusion, injection molding, and blow molding are particularly desirable, due to the speed, simplicity, and availability of the process in plastic industries. These methods are also benefit due to free of solvent and related contaminant. The nanoparticles has a unique advantage in thermoplastic polymer compounding and molding, because less fiber cutting or breaking occurs, and a high aspect ratio is maintained for one dimensional fillers in contrast to larger, microscale fillers. Application of shear mixing with long processing time may improve the dispersion of fillers, and when coupled with elongating extrusion, should yield adequate aligned nanofillers. Increasing in viscosity is higher for nanofibers than that of large diameter fibers such as carbon black, so shear mixing is necessary to overcome the high viscose polymer/nanofibers composites. Additionally, another advantage is the vision of recycling thermoplastic nanocomposites to decrease the financial expenses and to become safe for environment. Nevertheless, much needs to be learned about the ability of nanofibers to withstand

high shear and elongation flow processing and about optimization of processing parameters to provide good nanofibers dispersion.

Controlling the alignment of nanofibers in polymer matrix is possible using melt mixing methods. For example, spinning of extruded melt samples is used for alignment of fillers in nanofibers/polypropylene nanocomposites with high dispersion of nanofibers. Up to now, various methods of nanofiber alignment techniques have been developed such as using further increment in residence time in the die channel or die design to control the orientation of nanofibers. Injection molding was also found to induce significant alignment in nanofibers/ polypropylene composites, as demonstrated by measurement of thermal expansion and electrical conductivity.

2.3 In situ polymerization

The nanoparticles are dispersed in monomer and then the polymerization process starts. As solution blends, functionalized nanoparticles can improve the initial dispersion of the nanoparticles in the liquid (monomer and solvent) and consequently in the nanocomposites. Furthermore, in situ polymerization methods enable covalent bonding between nanoparticles and the polymer matrix using various condensation reactions. Noteworthy extensions of in situ polymerization include infiltration methods in which the reactive agents are introduced into a nanoparticle structure and subsequently polymerized.

3. Biopolymers

A variety of natural, synthetic, and biosynthetic polymers such as poly(L-lactide) (PLLA), polyhydroxyalkanoate (PHA), poly(ϵ -caprolactone) (PCL), poly glycolic acid (PGA), poly ethylene glycol (PEG), polyesteramide (PEA), and aliphatic copolyesters (PBSA). The biodegradability is capable of undergoing decomposition into carbon dioxide, methane, water, inorganic compounds, or biomass in which the predominant mechanism is the enzymatic action of microorganisms. The biodegradability of polymer depends on the chemical structure of the materials and on the constitution of the final product, and also depends on the raw materials used for its production. The polymer based on the C-C backbone tends to be nonbiodegradable, whereas heteroatom containing polymer backbones confer biodegradability. It is possible to engineer biodegradability of polymers using the judicious addition of chemical linkages such as anhydride, ester, or amide bonds, among others (**Figure 2**). The properties of some commercial biodegradable polymers are summarized in **Table 1**.

The most biomedical application of polymers are surgical dressings, sutures, adhesives, polymeric screws and nails, fiber/polymer composite bone plates, tendons/ligaments, reinforcing meshes, heart valves, joint reconstruction and bone cement, tubular devices, soft-tissue replacement materials for cosmetic reconstruction, drug delivery implants, artificial kidney/blood dialysis, artificial lung/blood oxygenator, and artificial heart.

3.1 Poly(L-lactide)

Among the aliphatic polyesters, poly(L-lactide) (PLLA) is considered to be the most promising biodegradable material, not only because it has excellent biodegradability, compatibility, and high strength but also due to the fact that it can be obtained totally from renewable resources. PLLA is a bio-based,

biodegradable polymer which can be produced from renewable sources such as corn and has found numerous applications in the medical and pharmaceutical fields.

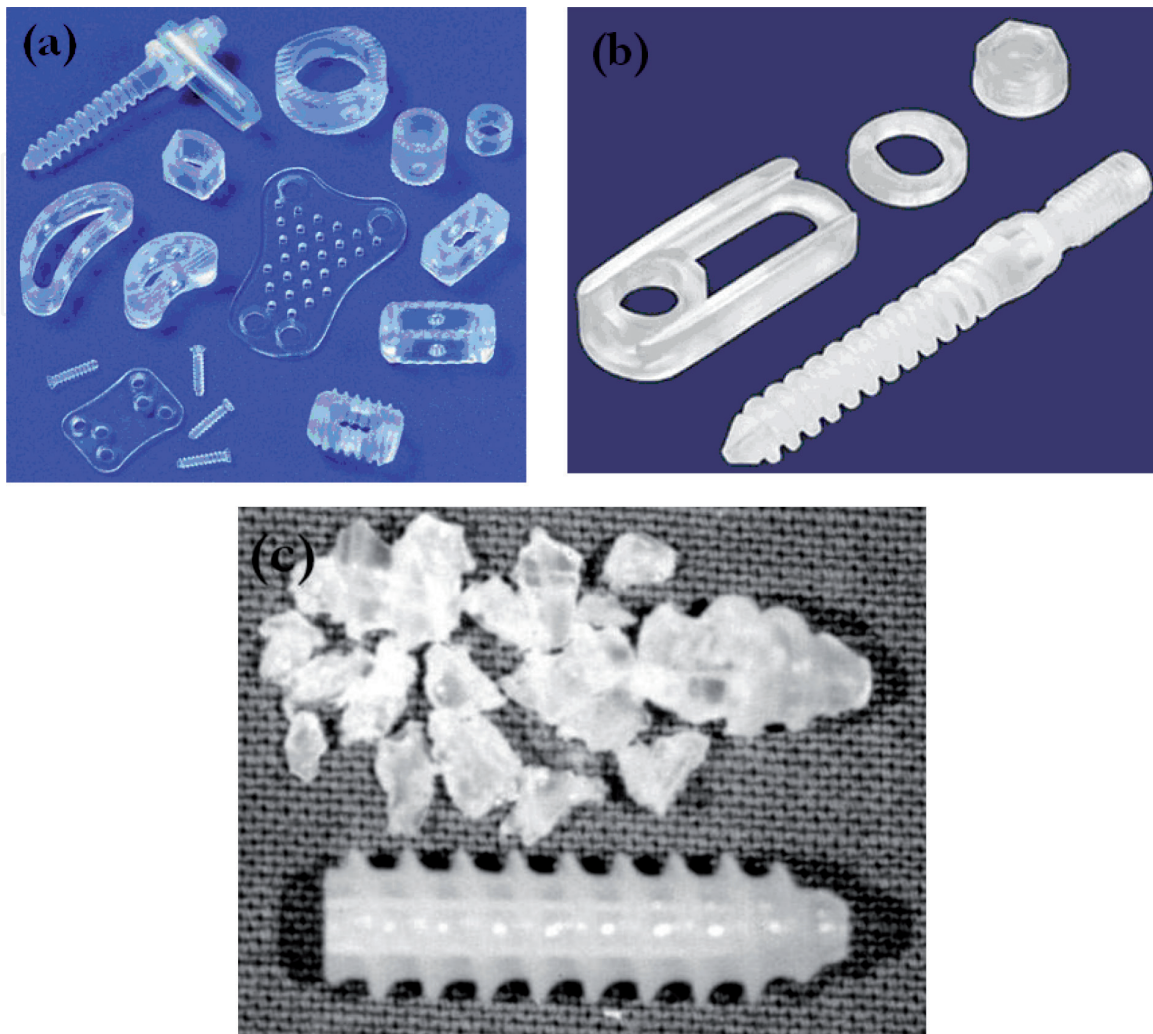


Figure 2. Bioabsorbable implants that have potential applications throughout the spine (a), an example of a bioabsorbable plate and pedicle screw, washer (b), and the in-vitro degraded bioabsorbable screw.

	PLLA*	PHA*	PCL	PEA*	PBSA*	PBAT*
Density (g/cm ³)	1.25	1.25	1.11	1.07	1.23	1.21
Melting point (°C) (DSC)	152	153	65	112	114	110–115
Glass transition (°C) (DSC)	58	5	–61	–29	–45	–30
Crystallinity (%)	0–1	51	67	33	41	20–35
Elastic modulus (MPa)	2050	900	190	262	249	52
Elongation at break (%)	9	15	>500	420	>500	>500
Tensile stress at break or max (MPa)	—	—	14	17	19	9
Biodegradation mineralization (%)	100	100	100	100	90	100
Water permeability WVTR at 25°C (g/m ² /day)	172	21	177	680	330	550

*Abbreviations: Poly(L-lactide) (PLLA), polyhydroxyalkanoate (PHA), poly(ϵ -caprolactone) (PCL), polyesteramide (PEA), aliphatic copolyesters (PBSA), aromatic copolyesters (PBAT).

Table 1. Properties of some commercial biopolyesters.

The PLLA has important characteristics over other biopolymers such as:

- Using renewable resources for production,
- Considered as energy saver,
- Recyclable to lactic acid,
- Using carbon dioxide for manufacturing,
- Improving the farm economics by composting,
- Decline of landfill volumes, and
- Possible modification of physical and mechanical properties using copolymerization and blending.

The commercialization of PLLA has been affected from three factors:

- High cost in comparison to other polymers due to its immature technology,
- Moisture absorption of in environment, and
- Modified processing conditions are needed.

Copolymerization of LA with other monomers like glycolide or CL can significantly enhance the properties and broaden the use of PLLA. The PLLA is produced from polylactic acid. The asymmetric polylactic acid has two stereo isomeric forms, L- and D-isomers. The L-isomer exists in normal human carbohydrate metabolism, and the D-isomer is detectable in urine and in acidic milk. If a polymer formed by one type of monomer, it is called homopolymer PLLA. A copolymer consists of two types of monomers named g. poly(D, L)-lactic acid (PDLLA) (**Figure 3**).

Some large scale manufacturers are beginning to favor PLLA because it is renewable, conserves energy, and degrades easily. The ring-opening polymerization of L-lactide oligomers (LAs) yields the PLLA semi-crystalline polymer with a melting point of 180–190°C and a glass transition temperature of 55–60°C (**Figure 4**).

Up to now, the PLLA has limited biomedical applications as implanting devices because of its biodegradation effect. If incorporating different nanoparticles into the PLLA matrix could enhance the properties of this material significantly, this process would increase its applicability further. In addition, the PLLA showed shape memory effect and the original shape could be recovered up to glass transition temperature. However, the recovery strain of PLLA was relatively low and the

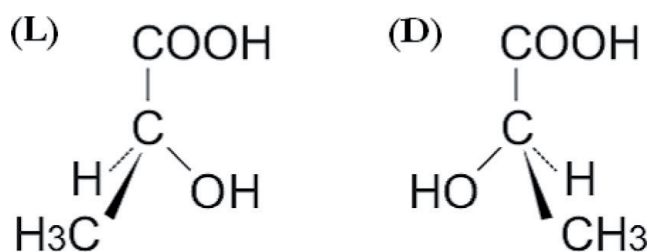


Figure 3. Stereoisomeric forms of lactic acid: lactic acid occurs in two, L(+) and D(-). Note the difference in location of the hydroxyl group in the chiral carbon.

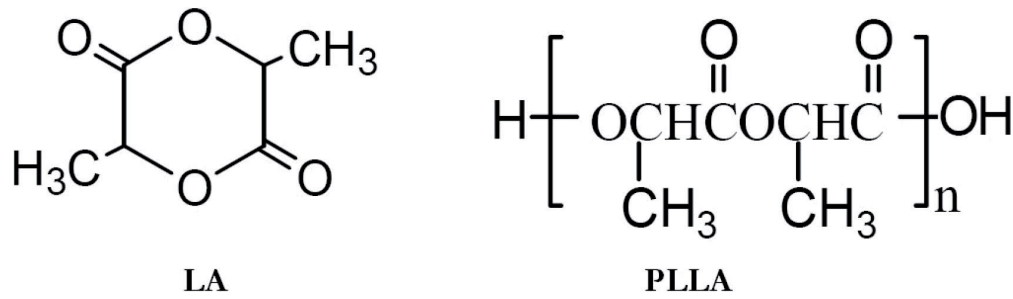


Figure 4.
Molecular scheme of L-lactide as oligomer and poly(L-lactide) as homopolymer.

recovery temperature was high for using in the human body. In order to improve the shape memory and decrease the recovery temperature, copolymers with PCL has been considered.

The PLLA with high performance biodegradable and biocompatible homopolymer is under various studies due to significant properties. PLLA crystallization happens very slowly, even if nanoparticles are incorporated and treat heterogeneous nucleation point [23, 25, 26].

In some researches, the thermo mechanical properties of PLLA nanocomposites reinforced with functionalized multi-walled carbon nanotubes (MWCNT-g-PLLAs) were determined. For functionalization, PLLA chains were grafted from the surface of MWCNTs. Then, the func.MWCNTs/PLLA composite is prepared by solution casting. The results show that the MWCNT-g-PLLAs were dispersed in PLLA matrix adequately. With increasing the weight percentage of MWCNT-g-PLLAs, up to 2 wt% led to gradual enhancement of the mechanical properties of nanocomposite. The thermal analysis also revealed the func.MWCNTs increase the melting point and the glass transition temperature of nanocomposite. Also, the DMA analysis results show that incrementing the concentrations of func.MWCNTs is also accompany with increasing Young modulus and the transition temperature of PLLA. The chain stiffness in amorphous phase of PLLA can also increase due to the van der Waals force and the homogenous dispersion of func.MWCNTs. In addition, the crystallinity of PLLA could be increased due to func.MWCNTs as heterogeneous nucleation points [19, 28].

3.2 Poly(L-lactide-co-ε-caprolactone)

Poly(ε-caprolactone) (PCL) is another important aliphatic polyester that is considered as a potential material in both biomedical and environmental fields. PCL is a biodegradable and nontoxic polyester. The ring-opening polymerization of ε-caprolactone oligomers (CLs) yields the PCL semi-crystalline polymer with a melting point of 59–64°C and a glass transition temperature of –60°C. The glass transition temperature can be increased by copolymerization with L-lactide, which also enhances the biodegradation of the polymer. PCL has good permeability to many therapeutic drugs and has been studied for long-term contraceptive delivery (Figure 5).

The polymer has been regarded as tissue compatible and used as a biodegradable suture. PCL exhibits a low glass transition temperature and melting point, high crystallinity and permeability, and good flexibility with a high elongation at break and low modulus. However, modification is highly necessary when it is applied to different requirements. Because the homopolymer has a degradation time on the order of 2 years, copolymers have been synthesized to accelerate the rate of bioabsorption.

For example, copolymers of CL with LA have yielded materials with more rapid degradation rates. Also, combining nanoparticles with PCL is an effective and operable approach to improving the properties of PLLA significantly. The copolymers of PLLA with other biopolymers such as PCL may increase its applications because with this procedure, it becomes possible to fabricate a various kinds of bioabsorbable polymers and composites with soft and elastic properties. Because the PCL has a low melting point, if PCL is introduced into segmented polyurethane as a soft segment, the shape memory effect would be expected. Hydrolysis of PCL yields 6-hydroxycaproic acid which enters the citric acid cycle and is metabolized.

PLLA is a biocompatible and biodegradable homopolymer with good mechanical properties and its copolymers with PCL may expand its applications. The CL appears to be a suitable comonomer for the preparation of copolymers with PLLA and PGA with mechanical properties ranging from rigid to elastomeric. The copolymer of PLLA and PCL possessed properties partly like that of PLLA and partly like that of PCL (**Figure 6**).

The poly(L-lactide-co-ε-caprolactone) PLACL has a lower tensile strength than higher elongation and substantially more rapid degradation time than PLLA. But PLACL has not enough sufficient characters for hard tissue engineering. The synthesis of LA/CL copolymers and other lactone polymers have been widely studied in recent years. Most studies have focused on random, diblock, and triblock copolymers. Both PLLA and PCL have shape memory properties. Hence the PLACL must have shape memory effect. It is found that the mechanical properties of PLACL are significantly affected by the polymer compositions. With the increment of CL content, the maximum stress decreases linearly and the strain at break increases gradually as can be seen in **Figure 6**. By adjusting the compositions of monomers, the copolymers exhibit excellent shape memory effects.

There are many research on reinforcing the PLACL using nanomaterials. As an example, PLACL reinforced with well-dispersed multi-walled carbon nanotubes (MWCNTs) were prepared using functionalized MWCNT by in situ polymerization. The surface functionalization of MWCNTs can effectively improve the

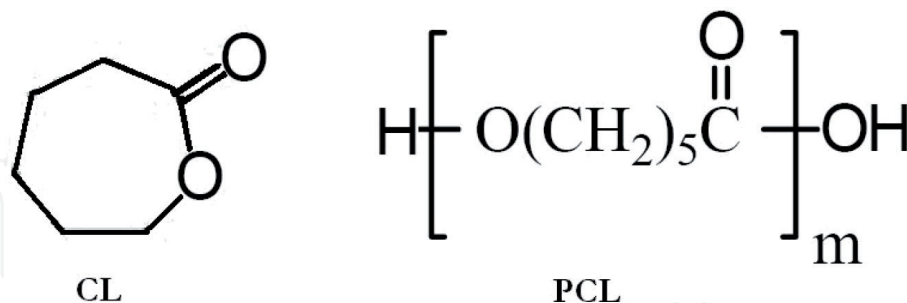


Figure 5.
Molecular scheme of ϵ -caprolactone as oligomer and poly(ϵ -caprolactone) as homopolymer.

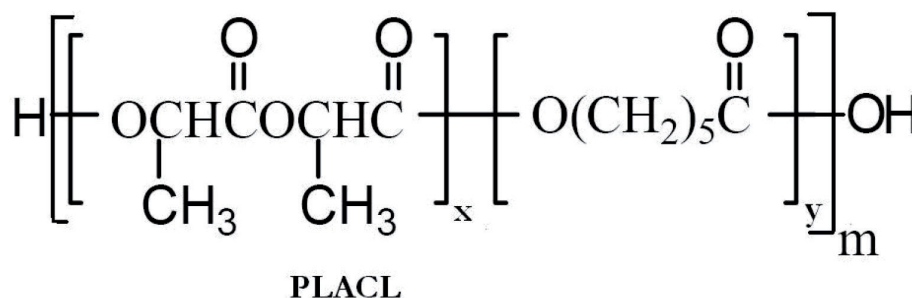


Figure 6.
Molecular scheme poly(L-lactide-co- ϵ -caprolactone) as copolymer.

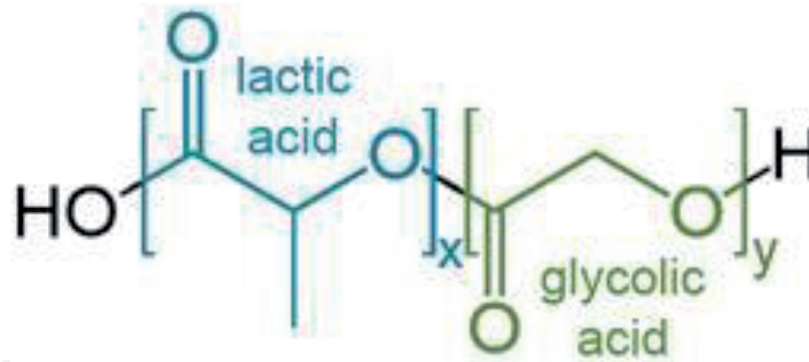


Figure 7.
Molecular scheme poly(D,L-lactide-co-glycolide) as copolymer.

dispersion and adhesion of MWCNTs in PLACL and hence, it will have a significant effect on the physical, thermomechanical, and degradation properties of MWCNT/PLACL nanocomposites [29].

3.3 Poly(D,L-lactide-co-glycolide) (PLGA)

The next nanocarrier that has been considered for sustained and targeted delivery of different agents is poly[L-lactide-co-glycolide] (PLGA)-based nanoparticles. Although PLGA have been applied many years ago, but the task of nanoparticles in mechanism of intercellular uptake, their trafficking, and sorting into different intercellular compartments, as well as their procedure of action for therapeutic efficacy of nanoparticles encapsulated agent at cellular level is recently considered [30] (**Figure 7**).

In addition, we know that the PLGA nanoparticles have deeper in vitro and in vivo effects in comparison with industrial nanoparticles in similar range such as ferrous oxide and zinc oxide. The effect of PLGA nanoparticles on cell viability was characterized by in vitro cytotoxicity analysis via a WST assay. The PLGA, silica, and ferrous oxide have a cell viability up to 75%, but for zinc oxide, particles cell viability significantly reduced [31]. The researchers found that nanoparticle mean size correlates linearly with polymer concentration is between 70 and 250 nm [32].

The PLGA/MWCNT composite was considered as a scaffold material to treat artificial bloods. PLGA/MWCNT nanocomposite is prepared using electrostatic technique, in which layers of MWCNTs are deposited on the PLGA. For in vivo and in vitro analysis, the fibrinogen is immobilized on PLGA/MWCNT composite and incubated in non-stimulated platelet-rich plasma (PRP) for platelet studies. The interaction of fibrinogen and PRP, are characterized on the prepared PLGA/MWCNT nanocomposite [33].

4. Nanoparticles

Nanomaterials consists of materials that the size of particle is less than 100 nm. All kinds of materials could be treating to be nanomaterials such as metallic, nonmetallic, ceramics, polymeric and so on..

4.1 Metal-based nanoparticles

The widely used metallic nanoparticles in the field of medicine and biotechnology are gold (Au), platinum (Pt), silver (Ag), selenium (Se), copper (Cu), palladium (Pd), and gadolinium (Gd), also, the widely used metal oxide nanoparticles

in the field of medicine and biotechnology are iron oxide (Fe_2O_3), titanium oxide (TiO_2), and zinc oxide (ZnO). The metallic nanomaterials can be prepared and modified with appropriate chemical functional groups to bind with drugs, antibodies, and ligands.

4.1.1 Gold-based nanomaterials (AuNPs)

The AuNPs have many characteristics such as biocompatibility, optical properties, and electrical behavior. Now-a-days, AuNPs have been considered in bioimaging and tissue engineering. Electrospinning and metal nanoparticles (Nps) can create a scaffold that will trigger muscle cell elongation, orientation, fusion, and striation. Traumatic injuries can interrupt muscle contraction by damaging the skeletal muscle and/or the peripheral nerves. The healing process results in scar tissue formation that impedes muscle function. Poly(L-lactic acid) (PLLA) and Nps were electrospun to create nanocomposite by Fischer et al. [34]. They found that low amounts of AuNps may be utilized to create a biodegradable, biocompatible, and conductive scaffold for skeletal muscle repair.

4.1.2 Silver-based nanomaterials (AgNPs)

Silver nanoparticles have antimicrobial activity and useful as antimicrobial agent, hence, it is a proven killer of bacteria [35]. Silver is far more efficient antibiotic than any allopathic pharmaceutical materials. Colloidal silver is effective in killing more than 600 bacteria in less than 5 min. AgNPs also find application in ointment and cream used to prevent infection in burns and open wounds anticancer particles with paclitaxel inhibits the growth of hep G2 cell more effectively [36–38].

Biodegradable PLLA ultrafine fibers containing AgNps were prepared via electrospinning by Xu et al. [39]. These fibers showed antibacterial activities (microorganism reduction) of 98.5 and 94.2% against *Staphylococcus aureus* and *Escherichia coli*, respectively, because of the presence of the silver nanoparticles.

4.1.3 Copper-based nanomaterials (CuNPs)

The polymer/CuNPs loading is proposed as a biostatic coating and systematic correlations between material properties and biological effects are established. The experimental result of the nanocomposite capability to release metals in a controlled manner and to slow or inhibit the growth of living organisms are proofed [40].

Using the electrospinning method, Badaraev et al. produced biodegradable scaffolds from PLLA. Using DC magnetron sputtering of the copper target, they modified the surface of the scaffolds. The diameters of fibers range from 0.8 to 2 μm . Testing for antibacterial features indicated that the modified scaffolds are capable to have a bacteriostatic effect [41].

4.1.4 Selenium-based nanomaterials (SeNPs)

The major biomedical applications of SeNPs include, targeted drug delivery [42–44], drug delivery vehicles and artificial enzymes [45, 46], anti-cancer therapy [47–49], anti-bacterial activities [50], biosensors and intracellular analysis [51].

For bone tissue engineering, application of bioactive glass scaffolds because of bone bonding ability is present interests. Of course the bioactive glass scaffolds do not have some functionalities to enable the successful formation of new bone. For bone tissue engineering, application of Se due to significant role in antioxidant

protection enhanced immune surveillance and modulation of cell proliferation is a solution for problem. Also, the SeNPs possess antibacterial as well as antiviral activities. Stevanović et al., in their recent research, synthesized uniform, stable, amorphous SeNPs, and additionally immobilized within spherical PLGA particles (PLGA/SeNPs). These particles were used to coat bioactive glass-based scaffolds synthesized by the foam replica method. The prepared composite showed a considerable antibacterial activity against Gram-positive bacteria, *Staphylococcus aureus* and *Staphylococcus epidermidis*, one of the main causative agents of orthopedic infections [52].

4.1.5 Palladium-based nanomaterials (PdNPs)

The major biomedical applications of PdNPs include targeted drug delivery [53, 54], anti-cancer therapy [55, 56], anti-microbial activities [57], biosensors and intracellular analysis-hydrogen sensors [58, 59], biocatalysts [60], and catalysis [61]. Graphene oxide (GO) has treated to create an anchoring OH site on the surface of GO. The subsequent GO-g-PLA was synthesized by the polymerization reaction in the presence of GO-MDI-OH and PLA. Finally, GO-g-PLA-Pd NPs was used for the electrochemical detection of serotonin [62].

4.2 Metal oxides-based nanomaterials

Biodegradation and biocompatibility of metal oxide nanoparticles (MONPs) are investigated medical applications. It is vital that the surface modification of MOPs must be adequate stable to resist against the salts and proteins in vivo and also become water soluble. It is elucidated that super paramagnetic iron oxides nanoparticles (SPIONPs) are significantly biocompatible. The behavior of SPIONPs for drug delivery applications based on their surface structure and conjugated targeting ligands/proteins [63–66].

The most important application of SPIONPs are include targeting of drug by engineered delivering system [67, 68], for cancer therapeutic [69, 70], diagnosis of many kinds of cancers [67], contrasting agents for bioimaging [71], ultra-sensitive in vivo molecular imaging [72], anti-microbial activities [73, 74], bio-sensing and inter cellular analysis [75], and cancer therapy using photo thermal technique [76, 77]. The distinctive properties of iron oxide MNPs are appropriate for biocatalysis [78, 79].

ZnO NPs are used as anti-microbial, anti-biotic, and anti-fungal (fungicide) agents by incorporating them in coatings, bandages, nanofiber, nanowire, plastics, alloy, and textiles. They possess suitable electrical, dielectric, magnetic, optical, imaging, catalytic, biomedical, and bioscience properties. ZnO is a white powder that insoluble in water. ZnO is applicable in many kinds of ointments that used to treat skin irritations. Also, ZnO has many industrial applications such as in semi-conductors, ceramics, and glass compositions [80, 81]. The well-known biomedical applications of ZnO NPs are found as targeted drug delivery destruction of tumor cells [82, 83], biomedical imaging and drug delivery systems [84], tumor characterization [85, 86], anti-cancer therapy [87], contrast agent in medical imaging [88], anti-microbial activities [89], biomarkers [90], and biosensors [91–94].

A suitable food packaging can increase the shelf life of food products in addition to save their initial quality. The biodegradable polymer has various limitations such as fragility due to their low mechanical properties. Due to high aspect ratio of nanoparticles, their properties have significant differences from conventional size particles. ZnO nanostructured materials have presented valuable properties which have led to variety of applications such as food packaging applications.

Combination of ZnO nanoparticles and polyvinyl alcohol results a more effective and environmentally friendly material for food stuff packaging [95].

Titanium oxide (TiO₂) nanoparticles can enhance cell attachment and proliferation on its composite surfaces. The polymer/TiO₂ composite films exhibit enhanced cell adhesion and a tendency to increased Ca-containing mineral deposition. Also, TiO₂ nanoparticles might act as interfacial bonding to tissue by means of the formation of a biologically active hydroxyapatite layer on implant surface. Boccaccini fabricated PDLLA films contain TiO₂ nanoparticles. Thus, if TiO₂ NPs are introduced in PLLA matrix, some disadvantages are anticipated to be improved. However, one of the most problems in master batch production of TiO₂ is the agglomeration in the PLLA matrix. The aggregated TiO₂ NPs in the composite reduce the mechanical properties and hence is necessary more researches to solve the TiO₂ agglomeration [96].

Deterioration of fresh fruits and vegetables during storage treat microorganisms breeding such as *Aspergillus niger* (*A. niger*) and *Bacillus subtilis* (*B. subtilis*), which can be a seriously danger for human health. For antibacterial and preservative properties, a self-assembled film of graphene oxide (GO) and chitosan (CS) with titanium dioxide (TiO₂) nanoparticles are introduced. These non-cytotoxic nanometer-scale films, with the ratio of 1:20:4 for graphene oxide, chitosan, and titanium dioxide nanoparticles, respectively, exhibited valuable antibacterial activity against the biofilm forming strains *A. niger* and *B. subtilis*. Also, the nanocomposites did not show any cytotoxicity against mammalian somatic cells and plant cells. Nanocomposites disrupted microbial film formation while avoiding internalization by animal and plant cells. Due to their selectivity and safety, these nanocomposites demonstrate potential as antimicrobial coatings for food preservation [97].

4.3 Silica nanoparticles (SNPs)

The performance of SNPs as nanofillers in polymer nanocomposite has significant attention, because of increased in demand for new materials with enhancement in thermal, mechanical, physical, and chemical properties of various kinds of composites (**Figure 8**). Synthesis of SNPs using sol-gel treatment has significant improvement in the development of SNPs/polymer nanocomposites [98].

Gardella et al. developed a novel catalytic system, consisting of palladium nanoclusters homogeneously dispersed on the surface of nanostructured polymer fibers based on poly(L-lactide) (PLLA) and polyhedral oligomeric silsesquioxanes (POSS). In fact, PLLA nanofibers that contain amino silsesquioxane molecules (POSS-NH₂) have capability to interact with metal precursor prepared by electrospinning. The prepared system proves a relevant catalytic activity toward the hydrogenation of stilbene under heterogeneous conditions [99].

4.4 Carbon-based nanomaterials

4.4.1 Carbon nanotubes

The carbon nanotubes (CNTs) have been investigated for a variety of applications based on their unique electrical, optical, and mechanical properties. The exceptional mechanical properties of CNTs have led to their use as effective reinforcing filler for polymer composites. It was expected that CNTs would display superlative mechanical properties by analogy with graphite. The inside of CNTs can be filled with some elements or compounds, such as C₆₀, to produce hybrid nanomaterials which possess unique intrinsic properties. The properties of the CNTs/

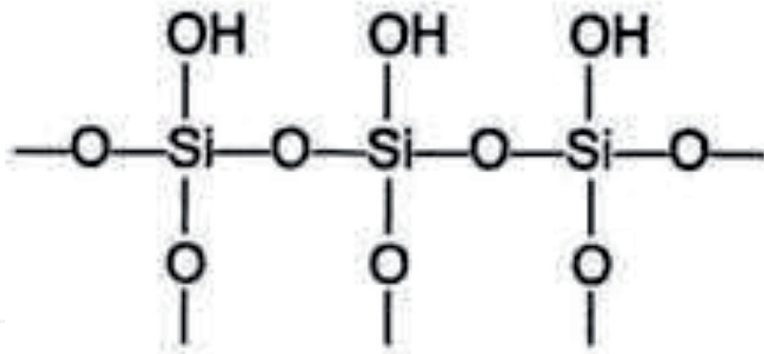


Figure 8.
Chemical scheme of silica.

polymer composites will vary significantly depending on the distribution of the type, diameter, and length of the nanotubes.

In CNTs, only few concentrated acids are capable of breaking the bonds between carbon atoms. Consequently, when CNTs reinforce a composite, the mentioned stability becomes a problem at the interaction between the matrix and CNTs. Uncontrolled agglomeration is another noticeable difficulty that can interfere on CNTs due to its nanometer size. To increase the interaction between matrix and reinforcement is submitting CNTs to a process called functionalization. Functionalization of CNTs is a mix of physical and chemical processes that inserts functional groups on the sidewall of CNTs. The introduction of this procedure can also be helpful to obtain better dispersion of carbon nanotubes into relevant matrices (**Figure 9**).

4.4.2 Functionalization of CNTs

Functionalization is one of the most effective methods in improving the surface properties of CNTs so that the application potentials can be fully realized. The methods of functionalization for CNTs range from chemical modification to physical interaction, and mechanical manipulations (**Figure 10**).

4.4.3 Functionalization in chemical base

In chemical base, there are two methods for functionalization of CNTs:

1. Covalent functionalization.
2. Noncovalent functionalization.

Each method has some advantages and some disadvantages.

The carbon nanotubes (CNTs) are another important and novel category of NPs that has been investigated extensively in medicine and drug delivery systems. The CNTs can interact with various bio-macromolecules such as DNA and proteins by physical adsorption. Additionally, in order to conjugate covalently targeting moieties or therapeutic molecules to CNTs, numerous chemical modifications were developed [117, 118].

In the field of research on medical application of CNTs, Zheng et al. elucidated the interactions between DNA molecules and CNTs [119]. In the case of single-stranded DNA, CNTs could disperse effectively in aqueous media. Up to date, the improvement of mechanical properties of CNTs might be counted primarily for

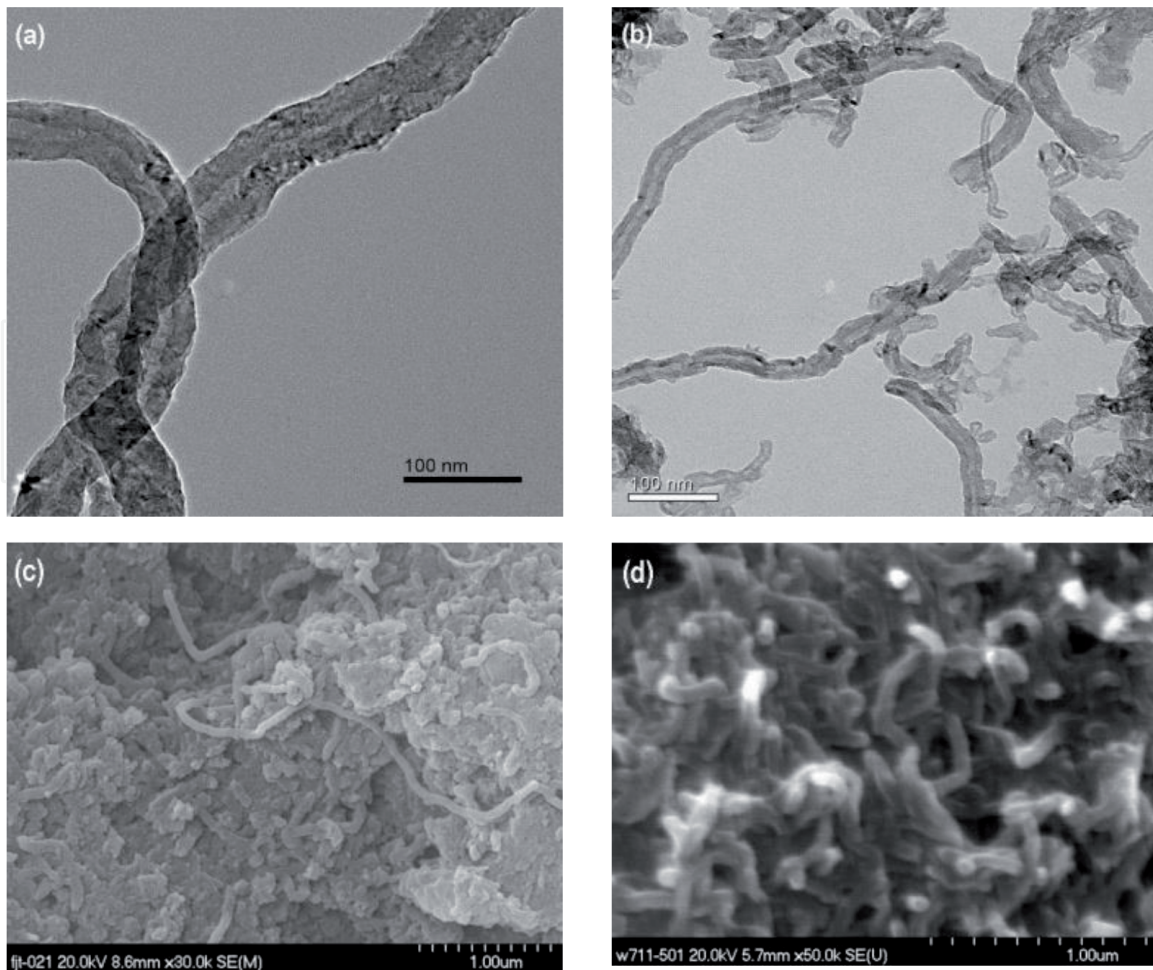


Figure 9. TEM micrograph of pristine MWCNTs (a), MWCNT-COOHs (b), MWCNT-OHs (c, d), and MWCNT-OH-graft-PLACL (e, f) [100].

their using as composite reinforcements for tissue engineering and preparation of artificial scaffolds [120]. More recently, researchers have considered their attention to utilizing the multi-functional nature of CNTs in engineering tissue scaffolds. Most particularly, the CNTs were incorporated to fabricate electrically conductive artificial scaffolds.

4.4.4 Graphene nanoparticles

Due to the similarity between graphene and CNTs, several medical applications such as drug delivery systems, scaffold reinforcements, and injectable cellular labeling agents have been committed using graphene and graphene oxide (GO) [121]. For reinforcement of biodegradable polymers by graphene, in one case, the PLLA/GO nanocomposites were prepared by solution mixing. The results show that the crystallization of PLLA enhanced and the spherulite morphology change were insignificant when the content of GO exceeded 0.5 wt%, because the extreme GO increased the number of nucleation sites while restricting the PLA crystal growth. Thus, the arrangement of nanopores did not mimic the spherulites because of imperfect crystal morphology [122].

4.5 Nano hydroxyapatite (HANs)

Owing to its biocompatibility and osteoconductive properties, nano hydroxyapatite (nHA) is widely used bioceramic for bone graft substitute. nHA with

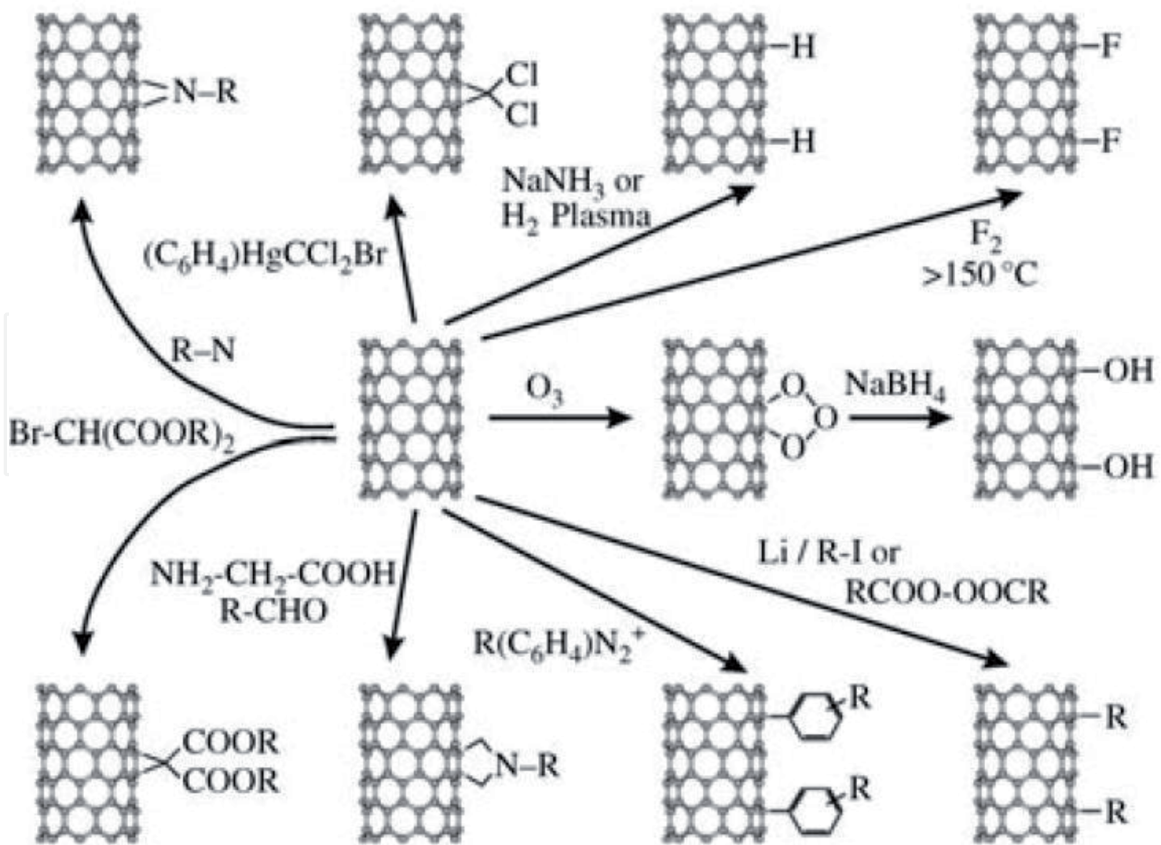


Figure 10.
 Scheme of possible addition reactions for the functionalization of CNTs [101–116].

biodegradable and biocompatible polymer-based composite scaffolds have been explored for bone grafting. Hence, the nHA/biopolymer nanocomposites proved to be promising for bone tissue engineering [123]. Composite fibers composed of PLA-g-HANs and PLA matrix was prepared by electro-spinning for tissue engineering [124].

4.6 Magnetic nanoparticles (MNs)

The MNs are a class of nanomaterials which can be performed using adequate magnetic field. The MNs can be conjugated with any protein, drug and gene, and by that MNs serve as contrast agent for magnetic resonance imaging (MRI) by changing the MRI signal. Additionally, MNs serve as a therapeutic tool by improving drug delivery to the target organ. Drug controlled releasing using nanostructured functional materials are attracting increasing attention in some diseases such as cancer therapy and other ailments. The potential of MNs stems from the intrinsic properties of their magnetic cores combined with their drug loading capability and the biochemical properties [125]. Therapeutic compounds are attached to MNs and magnetic fields generated outside the body are focused on specific targets [126].

In the field of biopolymer nanocomposites, iron oxide MNs with sizes less than 10 nm have been successfully deposited on multi-walled CNTs (MWCNTs) by in situ high temperature decomposition of iron(III) acetylacetonate and MWCNTs in polyol solution [127]. The PLLA has been covalently grafted onto the surface of mMWCNTs. The mMWCNTs/PLLA nanocomposite possess significant mechanical, electronic, super paramagnetic, and biocompatible properties, which means that the mMWCNTs/PLLA will have great potential applications in the fields of nanobiomaterials and nanotechnology, and the addition of mMWCNTs/PLLA can treat novel properties to PLLA and other biodegradable polymers [128] (**Figure 11**).

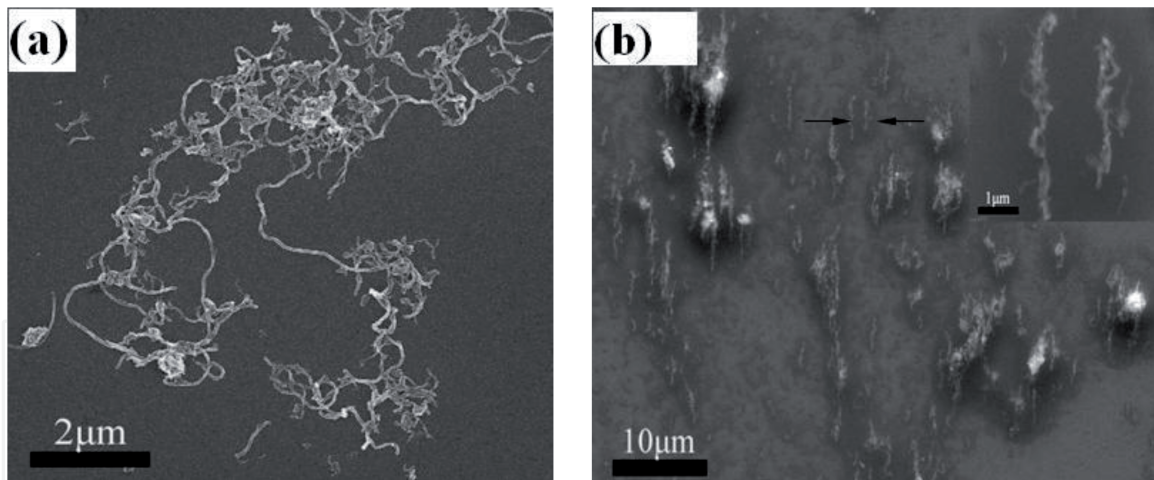


Figure 11. SEM images of *m*-MWCNTs-*g*-PLLA in the absence (a) and presence (b) of an external magnetic field [128].

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Author details

Ali Nabipour Chakoli
Nuclear Science and Technology Research Institute, Tehran, Iran

*Address all correspondence to: anabipour@aeoi.org.ir

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