Polymeric nanoparticles: Recent development in synthesis and application

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Abstract. Nanosized particles have attractive characteristics, which have received considerable attention in the last decade. Polymeric nanoparticles (PNP)s are solid particles or particulate dispersions with size in the range of 10–1000 nm. Due to the very small size, the surface area is very large so the percentage of atoms or molecules on the surface is significantly increased, which is expected to have extensive applications in various fields such as drug delivery systems, biosensors, catalysts, nanocomposites, agriculture and environment. The aim of the present paper is to critically review enhancement in the field of synthesis and different application of novel PNPs in various area from drug delivery to composite fabrication. Literature sources were mainly taken from the publications of 2011 and later; though, for a basic depiction of the structural principles, older publications have also been cited.

Keywords: biopolymers, biocomposites, polymeric nanoparticles, drug delivery systems, biosensors

1. Introduction to polymer nanoparticles (PNP)s

Particles with diameters below the micron dimension: generally, in the range 10–100 nm are nanoparticles (NP)s [1]. Polymer-based NP (PNP) is a collective term which is given to any kind of polymer NP, but specifically is applied for nanospheres and nanocapsules [2]. The historical development of PNPs was created by Paul Ehrlich with the first experimental efforts by Ursula Scheffel. Extensive works were conducted by the group of Peter Speiser at ETH Zürich in the late 1960s and early 1970s [3].

The field of PNPs is quickly growing and playing a key role in extensive field of areas ranging from photonics, electronics, sensors, medicine, pollution control and environmental technology. PNPs have long

been used as main components in established everyday coatings, paints and adhesives products. More recently, they have found applications in biomedical fields such as bio-imaging, drug delivery and diagnostics. PNP-based materials with unique physical and chemical characteristics might become future commands for the progress of new nanomaterials [4–7]. As a contribution to updating the state of knowledge and due to importance of PNPs, the present review focuses on PNPs. The aim of this review article is primarily to provide short information about traditional preparation ways of PNPs. Then, we would like to show some recently reported methods like using ultrasonic and microwave tools as other environmentally friendly approaches for the PNPs preparation in the first section. From our point of view, the use

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of these methods as low cost and safe ways should be highlighted. Furthermore, their importance according to their applications discusses. We will also show some properties of them such as morphology and biological activity.

2. Green techniques in synthesis of NPs

The manufacturing techniques of PNPs are classified due to whether the particle formation involves a polymerization reaction or NPs are produced directly from a preformed polymer or by direct polymerization of monomers using classical polymerization or polyreactions [7, 8]. Direct polymerization of monomers can be accomplished through different polymerization techniques such as micro-emulsion, mini-emulsion, surfactant-free emulsion and interfacial polymerization. The preparation of PNPs from preformed polymers can be carried out via methods like solvent evaporation, salting-out, dialysis and supercritical fluid technology. Methods like rapid expansion of supercritical solution and rapid expansion of supercritical solution into liquid solvent and surfactant-free emulsion polymerization can be successfully applied for manufacturing surfactant-free PNPs and moreover they are environment friendly [2]. In this section we want to introduce ultrasonic and microwave tools as another environmentally friendly approaches for the PNPs preparation.

2.1. Ultrasonication

Ultrasound (US) is presently a common laboratory tool applied to disperse NPs and colloids and to nebulize solutions into fine mixtures [9]. This method is advantageous because it is nontoxic, rapid in reaction rate, and produces very small particles [10]. US provides rather unusual reaction conditions (such as: temperatures of ~ 5000 K, pressures of ~ 1 GPa, and cooling rates of ~ 1010 K $\cdot$ s $^{-1}$) in contrast to the traditional energy sources. In fact, acoustic cavitation causes sonochemistry. Irradiation of liquids with acoustic waves of US creates the bubbles and makes the bubbles to oscillate. The bubbles collect ultrasonic energy while growing. A bubble can overgrow and collapse within a very short lifetime and a large energy concentration is attained. Consequently, various chemical reactions can proceed at room temperature using US irradiation [11, 12]. For example, the synthesis of colloidal silver NPs by using starch as

reducing and stabilizing agent under sonication was accomplished by Kumar *et al.* [13]. Sonochemical reduction showed a remarkable potential for producing desired particle size colloidal silver NPs. It was more environmentally friendly and safer than other synthetic methodology. A variety of 1,3,5-triaryl-1,3,5-hexahydrotriazine was synthesized using ultrasound assisted reactions from the reactions of aryl amines with aqueous formaldehyde by Singh *et al.* [14]. The use of ultrasound provided an efficient, clean and rapid methodology for the synthesis of various 1,3,5-hexahydrotriazine derivatives. In addition, it caused greater yields than the previously reported conventional methods.

2.2. Microwave (MW)

A fast technique of heating materials for industrial, domestic, and medical usages is MW heating. Reduction of the reaction time, controlling the reaction conditions, monitoring of temperature, pressure, and reaction times, higher yields in shorter reaction time are key advantages of MW apparatus [15, 16]. Medium needs to have a high dielectric constant for performing reaction in a solvent under MW irradiations. There are excellent organic solvents such as 1-methyl-2-pyrrolidone (NMP), dimethylsulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) for carrying out the reaction but solvents should be removed at the end of the reaction and they are also toxic [16, 17]. Room temperature ionic liquids (IL)s efficiently absorb MW energy due to their high polarity. ILs are green organic salts consisting only of ionic species that melt being below 100°C or even at room temperature which have attracted much attention as solvent for the polymerization [18]. The combination of MW-assisted reactions with IL has been applied for the synthesis of various nanomaterials [19].

Recently, Sun *et al.* [20] synthesized fluorescent carbon dots using single precursor, ammonium citrate dibasic using cheap home-use microwave oven as a facile and ultrafast method for the first time. In 2015, Hasanpoor *et al.* [21] obtained ultrafine zinc oxide (ZnO) particles with controlled morphology using microwave irradiation by various methods. They examined the effect of precursor type as well as the time and the microwave irradiation power on the structure and size of ZnO NPs. By increasing the time of synthesis needle-shaped particles with a diameter of 50–

150 nm could be attained and with increasing the microwave power flower-shaped particles were obtained.

3. Recent development in synthesis of PNPs

In this section, novel and modified processes for the production of PNPs through the polymerization of monomers are discussed. Till 2013, emulsion polymerization is the best-proven and most generally used method [22]. In nano-emulsion formation, the spontaneous emulsification occurs with mixing of an aqueous phase and organic phase. The aqueous phase consists of hydrophilic surfactant and water, whereas the organic phase is a homogeneous solution of lipophilic surfactant, oil and water-miscible solvent. At the end of the reaction, PNPs with very small droplets (50–100 nm) will form [23]. It is known that this method requires large amounts of surfactant/co-surfactant to make small NPs which increases cost and causes difficulty of purification [8]. So, ‘acoustic emulsification’ as one of the powerful tools for fast and environmentally friendly emulsion production was applied by Nakabayashi *et al.* [22] to obtain size-controlled poly(methyl methacrylate) (PMMA) NPs. They developed a novel synthesis method for size-controlled PNPs under surfactant free conditions using sequential ultrasonic irradiation. Figure 1 shows sequential ultrasonic irradiation (20 kHz → 500 kHz → 1.6 MHz → 2.4 MHz) steps for acoustic emulsification of a water insoluble monomer methylmethacrylate (MMA) in an aqueous medium. Polymerization happened by the addition of initiator [ammonium peroxydisulfate (APS)] and to stop the polymerization, the reaction vessel was cooled to 25 °C. PMMA

samples which were synthesized from emulsion (a) showed average particle size of 241 nm. Ultrasonication with 2.4 MHz after 20 kHz, 500 kHz, and 1.6 MHz produced particles with size of 23 nm. Higher frequency of ultrasonication could break up the larger droplets to create smaller droplets.

Recently, Mallakpour and coworkers [24] reported in detail the use of MW irradiation for the polycondensation of diacids containing different amino acids such as phenylalanine, leucine, isoleucine, valine and alanine with aromatic diamine. Step-growth polymerization reactions were carried out in molten tetra-n-butylammonium bromide salt (TBAB) and IL/triphenyl phosphite (TPP) under MW irradiation. Under this conditions, poly(amide-imide) (PAI) nanostructures were obtained. According to field emission scanning electron microscopy (FE-SEM) micrographs, the PAI was obtained with the particle size of smaller than 45 nm in more cases. Then, the effect of ultrasonic irradiation on the size and shape of PAI NPs was investigated. FE-SEM micrographs showed that after sonication process, the size of PAI particles was decreased and reached to 28–38 nm (Figure 2).

The influence of sonication and MW irradiations on the morphology and shape of different poly(ester-imide)s (PEI)s and PAIs containing natural amino acids was investigated and novel PNPs obtained by our group. Due to the presence of amino acids in their backbones, these polymers are expected to be biodegradable and hence could be categorized under environmental benign materials [25–32]. In 2013, the synthesis of several chiral nanostructure PAIs was performed under conventional heating and MW irradiation in IL media by Mallakpour and Dinari [33] to highlight the effect of MW heating. To provide the optimum reaction conditions, the influence of MW power levels and duration of heating was inspected and the results were summarized in Table 1. The best inherent viscosity and yield were obtained after 3 min at 90% (810 W) of MW power level according to this Table. The inherent viscosities of the resulting polymers under oil bath conditions (conventional heating) were in the range of 0.41–0.58 dL·g⁻¹ and the yields were 83–94%. The FE-SEM images of the resultant PAIs prepared by MW irradiation showed nanostructure morphology of PAI with size smaller than 60 nm while the size of PAI synthesized under conventional heating was smaller than 70 nm.

Figure 1. Photographic observations of tandem acoustic emulsification of MMA in aqueous solution. Photograph (a) represents the original MMA in aqueous solution mixture. Emulsification conditions were (b) 20 kHz, 8 min; (c) 20 kHz, 8 min → 500 kHz, 10 min; (d) 20 kHz, 8 min → 500 kHz, 10 min → 1.6 MHz, 10 min; and (e) 20 kHz, 8 min → 500 kHz, 10 min → 1.6 MHz, 10 min → 2.4 MHz, 10 min [22].

Figure 2. FE-SEM micrographs of (a and b) PAI-5a, (c and d) PAI-5b, and (e and f) PAI-5c after sonication process [24]

Table 1. Optimization of reaction conditions for the preparation of PAI1a using MW irradiation in molten TBAB [33].

Polymer	Microwave power	Reaction time [s]	Yield [%]	η_{inh}^a [dL/g]	$[\alpha]_D^{25\ a}$
PAI1a	100	60	67	0.32	-46.64
PAI1a	100	120	62	0.32	-47.02
PAI1a	100	180	58	0.31	-47.00
PAI1a	100	240 ^b	—	—	—
PAI1a	90	60	74	0.32	-50.80
PAI1a	90	120	78	0.38	-52.41
PAI1a	90	180	92	0.47	-52.43
PAI1a	90	240 ^b	—	—	—
PAI1a	80	60	50	0.30	-49.47
PAI1a	80	120	57	0.31	-50.52
PAI1a	80	180	59	0.34	-50.14
PAI1a	80	210	63	0.35	-49.87

^aMeasured at a concentration of 0.5 g/dL in DMF at 25 °C,

^bDecomposition occurred at higher power or extended irradiation time

Mallakpour and coworkers [34, 35] prepared the optically active and biodegradable polymers containing S-valine and L-leucine amino acids under MW irradiations. The obtained PAIs showed relatively spherical morphology with particle size smaller than 50 nm in more cases. The results showed that the diacids and aforesaid polymers were all nontoxic to fungal growth and all samples were colonized by fungal mycelia. The resulting samples showed weight loss due to fungal degradation while no weight loss could be detected in bisphenol-A (BPA) as control. Figure 3a demonstrates that BPA completely inhibited wheat seedling growth compared to grown seedling in control soil and lastly killed the plantlet because of its toxicity for plant growth. On the other hand, wheat seedling growth in soil containing the monomers and PAIs proposed that polymeric products have not substantial inhibition influence on normal plant growth (Figures 3b–e).

Figure 3. Effect of (b) PAI2, (c) diacid 7b, (d) diacid 7a and (e) PAI1 compared with (a) BPA on survival and growth of wheat seedlings [35]

The facile preparation of diverse and functional NPs with negatively and positively charged functionalities derived from a CO₂-based triblock amphiphilic polycarbonate system from a sequential copolymerization and chemical transformation strategy was reported by Wang *et al.* in 2015 (Figure 4) [36].

The results indicated that polymer **5** have not formed shell–core structure. In contrast, the dynamic light scattering (DLS) studies of anionic block polymer **4** and cationic polymer **6** presented that they underwent gathering to form NPs with high uniformity, giving a similar intensity-averaged hydrodynamic diameters of 26±15 nm. Both displayed a similar critical micelle concentration (CMC) of 66 mg·mL⁻¹ in DI water. They expressed that these CO₂-based

polycarbonates could afford a powerful platform for biomedical applications.

In 2015, Crucho and Barros [37] reported preparation of PNPs from the chemical modification of poly (D,L-lactide-co-glycolide) (PLGA) with sucrose and a cholic acid moieties (abbreviated as Suc-PLGA-Chol). They expressed that altering the polymer backbone not only can improve the physicochemical features of the PNPs but also their safety in biomedical applications. The synthesis of Suc-PLGA-Chol polymer conjugates was done through esterification. Virtually perfect spheres of lyophilized Suc-PLGA-Chol PNPs with a mean particle size of 260±50 nm were observed in SEM image. Several experimental parameters such as polymer concentration, organic solvent and evaporation rate were examined too. To evaluate dependence of the size of PNPs on the solubility parameters, acetone, acetonitrile, tetrahydrofuran as organic solvents were used for the preparation of Suc-PLGA-Chol PNPs. Using the most water miscible solvent (acetone) smaller particles were obtained. It could be ascribed to a more effectual solvent diffusion and faster polymer dispersion into water. The mean particle size of PNPs increased with increasing polymer concentration which is attributed to the slower solvent diffusion and formation of larger droplets during phase mixing. In 2015, Kumar's group reported an effective and simple technique for synthesizing highly fluorescent, protein-based NPs [38]. Figure 5 shows current approach of the synthesis of Prodots which made from bovine serum albumin (nBSA), glucose oxidase (nGO), horseradish perox-

Figure 4. Synthesis of amphiphilic block polycarbonates with different charges. Boc = tert-butoxycarbonyl [36]

Figure 5. Prodote synthesis by FITC labeling followed by EDC cross-linking of the resulting protein clusters [38]

idase (nHRP), catalase (nCatalase), and lipase (nLipase). The amino groups of the lysine residues of proteins were coupled with fluorescein isothiocyanate (FITC) followed by controlled aggregation of proteins. Then, cross-linking the protein units was done by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). In this study, FITC labeling of proteins was accomplished to cross-link these clusters and form stable particles.

Transmission electron microscopy (TEM) micrographs showed nGO particles with size ~ 10 nm, while nHRP had a diameter of ~ 20 nm and nLipase a diameter of ~ 15 nm. Prodots showed enhanced thermal stabilities and improved half-life besides to conserved biological activity, and these unique properties may facilitate their usage in imaging. Their aim of producing stable, fluorescent, functional, biocompatible Prodots of controllable size was testing the potential of the Prodots for cellular imaging. The results showed enhanced thermal stabilities and improved half-life besides to conserved biological activity of Prodots, and these unique properties may facilitate their usage in imaging.

Klymchenko's group [39] investigated the effect of one to two charged groups per polymer chain to obtain ultrasmall PNPs as nanocarriers. Positively charged trimethylammonium groups or negatively charged carboxylate and sulfonate were introduced into the PLGA, PMMA, and polycaprolactone (PCL). They concluded that the existence of charged groups per polymer chain can strongly decrease the size of PNPs made by nanoprecipitation (NPP). As it could be observed from TEM images, the size of particles made from uncharged chains was largest for all three

polymers (above 100 nm). The TEM images of uncharged and carboxy PMMA particles represented a strong affinity of aggregation. Trimethylammonium and sulfonate-bearing polymers obtained the smallest particles (below 25 nm). They further exhibited that small NPs of 15 nm size preserve the capacity to encapsulate capably large quantities of ionic dyes with bulky counterions which creates PNPs 10-fold brighter than quantum dots of the same size.

Kausar and coworkers [40] synthesized polystyrene (PS) NPs through modified nanoprecipitation cosolvent evaporation technique (NcoSE) and two widely used strategies, i.e., solvent evaporation and NPP to examine the scope of the novel technique. The usage of modified NcoSE method improved several material properties such as the simplicity of fabrication, effectiveness, homogeneous and uniform morphology, narrow size distribution, and suitability for the composite fabrication compared to other extensively used techniques. FE-SEM image showed the spherical morphology, uniform size distribution and ordered nanostructures for obtained PSNPs/SiNPs by NcoSE method while the rough and unclear surface topology of grafted NPs were observed for PSNPs/SiNPs synthesized through NPP and solvent evaporation methods. Silica NPs and graphite were incorporated into the obtained PS NPs to study the scope of this novel method. The results revealed the improved conductivity and thermal properties of PS and Si NP-grafted graphite CNs.

In 2015, polyamic acid (PAA) formation was attained using precipitation with a compressed fluid antisolvent technique [41]. The particle size of obtained PAA was decreased with decreased PAA con-

centration, decreased temperature and increased pressure. Subsequently, the polyimide NPs synthesized by thermal imidization treatment of PAA.

4. Application of PNPs

Due to the attendance of characteristic properties presented by PNPs, these materials exhibit important roles in several applications including NCs preparation, optoelectronic and drug delivery. In this section, the design, morphology examination as well as application of two classes of PNPs are reviewed in detail: conducting polymers including polypyrrole, polyaniline (PANI), polyacetylene, poly(p-phenylene-vinylene) and polythiophene which have been a popular subject of exploration [42] and biosafe PNPs that are another important class of polymers and have many advantages such as biocompatibility and biodegradability. They are easily removed from the body by the normal metabolic path or they can have susceptibility to fungal enzymatic degradation [43–45].

4.1. Application of conductive nanostructure polymers

Conducting micro-/nano-structure polymers received increasing attention due to their specific electronic properties and potential applications in rechargeable batteries, electrochromic displays [46], corrosion inhibition and camouflage [47]. Conductive polymers are polymers with highly unpaired (π) conjugated polymeric chains. In comparison to their bulk forms nanostructured conductive polymers, provide several advantageous features, such as large surface areas, improved mechanical properties for strain housing and shortened paths for charge/mass/ion transport [48]. Among the conducting polymers, polypyrrole (PPy), is one of the most widely studied electronic materials which have potential applications in drug delivery, sensors and corrosion protection [49, 50]. Samanta *et al.* [51] synthesized PPy NPs without the use of dopants. They loaded these PPy NPs with fluorescein sodium salt, a negatively charged model drug, and rhodamine 6G, a positively charged model drug. PPy was used because it is an electrically conducting polymer which is both nontoxic and biocompatible. The obtained NPs exhibited good drug loading capacity. They showed that PPy NPs can be adjusted to release drugs at both acidic and basic pH by vary-

ing the pH. In other work, Chen *et al.* [52] synthesized PPy NPs with size of 50 nm as a metal-free ultraviolet (UV)/

near-infrared (NIR) shielding material and mixed them with polyacrylic acid (PAA) resin for the preparation of PPy–PAA full-polymer films. Their results showed that PPy–PAA films have great potential as novel coating in the application of cost-efficient energy-saving windows without potential pollution.

Alizadeh *et al.* [53] synthesized two types of potentiometric sensors, based on the nano-sized molecularly imprinted polymer (MIP) for high selective determination of promethazine. Two different methods containing microemulsion polymerization and suspension polymerization in silicon oil were applied to prepare nano-MIP(1) and nano-MIP(2), respectively. SEM images of the obtained polymers showed very small and spherically shaped particles. The results of the rebinding experiments represented that the binding sites of the nano-MIP(2) obtained by suspension polymerization in silicon oil had more affinity to target molecules, comparison to those of the nano-MIP(1). The results of the rebinding experiments for both MIPs in aqueous phase are shown in Table 2. It can be observed that in the case of promethazine, the adsorption ability of the nano-MIP(2) is more than that of the nano-MIP(1). In addition, it is clear that the difference between the adsorption capability of the chlorpromethazine and promethazine on the MIP(1) is more than that of nano-MIP(2), demonstrating higher selectivity of nano-MIP(2), compared to nano-MIP(1). Also, the nano-MIP(2) based sensor, displayed higher selectivity and sensitivity, compared to the nano-MIP(1) based electrode. Vaitkuviene *et al.* [54] synthesized pure polypyrrole (Ppy NPs) by one-step oxidative polymerization and in order to study about biocompatibility of Ppy, their cyto-compatibility was assessed. The effect of different concentration of Ppy NPs on primary mouse

Table 2. Adsorption capabilities of promethazine and chlorpromethazine to the nano-MIP(1) and nano-MIP(2) and their relevant NIPs [53]

Polymer type	Adsorption amount [mmol/g]	
	Promethazine	Chlorpromethazine
nano-MIP(1)	0.51	0.36
nano-MIP(1)	0.47	0.23
nano-MIP(2)	0.85	0.47
nano-MIP(2)	0.37	0.26

embryonic fibroblasts (MEF), mouse hepatoma cell line (MH-22A), and human T lymphocyte Jurkat cell line was examined. Achieved results exhibited that Ppy NPs at low concentrations are biocompatible, whereas at high concentrations they got cytotoxic for MEF, Jurkat and MH-22A cells, and it was concluded that cytotoxic effect is dose-dependent.

Polyaniline (PANi) is one of the oldest known and the most widely studied conducting polymer due to unique doping mechanism, its relative ease in preparation, low specific mass, good environmental stability and controllable conductivity [55–57]. It has numerous applications in rechargeable batteries, anti-corrosion coatings, energy storage, photovoltaic devices, catalyst, electrochromic displays and electronic switches [58, 59]. Berti *et al.* [60] developed and characterized conductive PANi nanostructures for applications in electrochemical biosensing. PANi nanotubes were arranged in an ordered structure directly on an electrode surface using nanoporous alumina membranes as nano-mould. Then, grafting of PANi was done with a MIP receptor to create a model sensor for catechol detection. Actually, PANi nanostructures as conductive nanowire system allowed direct electrical connection between the synthetic receptor (MIP) and the electrode. A significantly lower detection limit for catechol attained, thus representing that the nanostructures are capable of improving the analytical performance of the sensor. A simple chemical route for synthesizing highly crystalline PANi NPs was proposed by Mahato *et al.* [61]. It was carried out by an *in-situ* polymerization of aniline monomers in a hot and dilute aqueous acidic solution. The particles with diameter ranging

from 15 to 30 nm appeared as circular disk like structures in TEM image (Figure 6). The polymer exhibited good thermal stability. The PANi NPs were utilized for preparing composite with graphene NPs (2wt% loading). It was tested as a coating material for protection of mild steel from corrosion in 0.1 N HCl. Still surface with composite coating (thickness of ~0.5 mm) showed good corrosion protection to mild steel surface in acidic environment.

Recently, Hong *et al.* [62] demonstrated an acidic environmental sensing technique based on PANi NPs. In this regards, PNs were immobilized to an aminated glass substrate to sense environmental pH conditions. The fabricated PANi NPs showed outstanding capabilities to sense acidic environments at the single NP level. In 2016, Luo *et al.* [63] reported the design and production of a novel MIP conductive PANi NPs using polymeric micelle as nanoreactor for enhanced paracetamol (PCM) detection. The obtained PANi sensor showed high selectivity toward PCM. It also revealed a wider linear range over PCM concentration which was attributed to numerous effective recognition sites among the PANi matrix and it was due to the large specific surface area of PANi NPs. Considerably lower detection limit was obtained compared to previously reported PCM electrochemical sensors that should be attributed to the electrical conductivity of PANi.

4.2. Application of biodegradable nanostructure polymers

Biodegradable polymers can be classified as artificial or natural. Polysaccharides, nucleic acids and proteins are the illustrative natural biodegradable

Figure 6. (a) TEM image and (b) selected area diffraction pattern of the PANi NPs [51]

polymers. Polyesters and polyamides are typical examples for the artificial polymers [64]. Due to their biodegradability, good biocompatibility and minimal side effects, usage of biodegradable polymers for biomedical applications has increased in recent decades. The biodegradable polymeric NPs provide controlled release of bioactive compounds, and improve properties such as stability and bioavailability [65]. Nano-particulate delivery system can effectively control particle size, surface character; it enhances permeation, solubility, flexibility, and release therapeutically active agents to reach the target and attain specific activity at a predetermined rate and time [66, 67]. PLGA is one of the most successfully applied biodegradable nanosystem for the development of nanomedicines because it is a copolymer and can hydrolyze in the body to produce the biodegradable metabolite monomers, lactide and glycolide that are finally removed from the body by the citric acid cycle [68]. Poly(lactic acid) (PLA) is one of the most popular members of biodegradable polymers that can be naturally degraded in compost or soil by enzymes or fungi [69]. Surface grafting copolymerization of glycidyl methacrylate (GMA) on PLA NPs was accomplished through emulsion/evaporation procedure as a novel method by Li *et al.* [70]. Rhodamine B (RhB) initially interacts with sodium dodecyl sulfate (SDS) through electrostatic interaction to generate hydrophobic complex of SDS-RhB. According to the high-affinity of SDS-RhB with GMA, hydrophilic RhB can be successfully joined into PLA NPs. The obtained results indicated that the PLA with particle size smaller than 200 nm can prevent the macrophage uptake. On the other hand, the bigger PLA particles with polyethylene glycol (PEG) surface modification showed the lowest internalization by macrophage comparison to those with poly(ethylene oxide-propylene oxide) copolymer or poly(vinyl alcohol) (PVA) surface. Yoo's group reported synthesis of PLGA NPs with well-defined sizes of ~70 nm (NP70), ~100 nm (NP100), ~200 nm (NP200), ~400 nm (NP400), ~600 nm (NP600) and ~1000 nm (NP1000) [71]. The NPs showed high yield with a narrow size distribution. Uniform size distribution and mean size of 103.7 nm for NP100, 204.6 nm for NP200, 421.1 nm for NP400, 604.8 nm for NP600 and 990.0 nm for NP1000 were obtained. The obtained results showed as particle size becomes

Figure 7. Quantification of the cellular uptake by KB carcinoma cells (closed circle) and RAW264.7 cells (open triangle). Data were expressed as mean $\pm$ SD ($n = 6$) [71]

smaller, cellular uptake and toxicities increased in tumor cells and decreased in macrophages (Figure 7). They also found that paclitaxel (PTX)-loaded NPs showed a size-dependent inhibition of tumor cell growth and the size-dependency was influenced by cellular uptake and PTX release.

Reinforcement of biomolecules within biodegradable NPs and further insertion of such carriers into tissue-engineered scaffolds will provide a controlled-release drug delivery system. With this in mind, Nazemi *et al.* [72] investigated the influence of adding PLGA NPs on a chitosan-bioactive glass (CH–BG) scaffold. They prepared two groups of scaffolds (with and without NPs) and studied drug release. The SEM micrographs showed nearly spherical morphologies of the PLGA NPs which were uniformly distributed on the scaffolds pore walls. According to these images, the PLGA NPs loading into the CH–BG scaffolds did not considerably affect the microarchitecture of the scaffolds. It was reported that the incorporation of these NPs slightly decreased the swelling behavior of the scaffolds whereas increased the mechanical strength. In addition, it was mentioned that the obtained scaffolds containing PLGA NPs could be used as bioactive bone tissue engineering scaffolds with the potential of localized delivery of biological molecules (Figure 8).

Folic acid (FA)-conjugated chitosan (CS)-functionalized PLGA nanocarriers for treatment of prostate cancer were designed by Dhas *et al.* [43]. PLGA NPs were coated using FA–CS conjugates for binding with folate receptors. A cell toxicity assay verified that functionalized PLGA NPs were more effective than un-functionalized ones according to modified

Figure 8. (a) The Swelling behavior in PBS solution, (b) the mechanical behavior of the scaffolds from compression tests, and (c) the *in vitro* release profile of DEX from either free NPs or NPs incorporated within the scaffolds [72]

surface, which can improve the efficiency of NPs by increasing cell targeting and/or tissue targeting and/or site-specific delivery PLGA NPs.

Mallakpour *et al.* [73] designed chiral bioactive PEIs containing L-phenylalanine and L-leucine amino acids with nanoscale size and good thermal stability. *In vitro* toxicity studies and soil biodegradation test confirmed that synthesized polymers could be decomposed by soil microorganisms hence they were biodegradable. They applied the obtained PEI containing L-leucine amino acid as matrix to prepare multi-walled carbon nanotubes (MWCNT)s bionanocomposites (BNC)s [74]. Thermal analysis showed improvement in thermal stability of the composites compared to the neat PEI by the addition of the CNTs.

Abdolmaleki and coworkers synthesized optically active and potentially biodegradable poly(ester-amide)s (PEAs) based on tyrosine amino acid [75]. Nano spherical-shaped spheres of PEAs with average mean diameter as low as 79 up to 500 nm were obtained in this study. Higher number of colonies was counted from water extracts of soil containing diol and PEA than control treatments (Figure 9). In fact, soil burial test and dehydrogenase activity assay confirmed biodegradability of PEA NPs due to the presence of amino acid in the polymer backbone.

Afterward in 2014, they used from mentioned PEA for the fabrication of PEA/ZnO BNCs. They expressed that the synthesized NCs are expected to categorize as biologically active materials due to using

Figure 9. Fungal and bacterial colonies grown from soil water extract, 6 days after inoculation on PDA Petri plates: (a) PEA, (b) diol, and (c) control [75]

polymer based on biodegradable amino acid [76]. Hu *et al.* [77] studied assembled PNPs from gallic acid (GA) grafted chitosan (CS, GA-g-CS for GA grafted CS) and caseinophosphopeptides (CPP) to deliver (–)-epigallocatechin-3-gallate (EGCG) as novel functional foods. GA is a naturally occurring phenolic acid with high antioxidant activity. The GA-g-CS conjugates, compared with CS, exhibited much higher solubility under alkaline and neutral environments. Strong antioxidant activity and cytotoxicity against Caco-2 colon cancer cells were obtained by the GA-g-CS-CPP NPs. Paclitaxel is one of the most effective chemotherapeutic agents but it has poor water solubility and low therapeutic index so it needs an urgent solution to increase therapeutic efficacy of paclitaxel. According to this subject, in 2015, Thu *et al.* [78] designed synthesis of folate decorated paclitaxel loaded PLA-tocopheryl polyethylene glycol 1000 succinate (Fol/PTX/PLA–TPGS) NPs by a modified emulsification/solvent evaporation method. Targeting effect of the samples was evaluated by *in vivo* on tumor bearing mouse and *in vitro* on cancer cells. Research work showed that the cellular uptake

of drug into cancer cells are improved by folate decorated NPs [79]. In this study, PTX loaded NPs induced better targeting influence than free PTX, and also the best operative targeting was related to Fol/PTX/PLA NPs. For examination of *in vivo* targeting effect of NPs, PTX in different constructions (free PTX, PTX/PLA–TPGS NPs and Fol/PTX/PLA–TPGS NPs) was intravenously administrated into mouse. The Fol/PTX/PLA–TPGS NPs demonstrated the best tumor growth inhibition after 42 days of treatment (Figure 10).

Barba group synthesized new nanovectors based on copolymer of α , β -poly(N-2-hydroxyethyl)-D,L-aspartamide (PHEA) and PLA to control release of lipophilic drugs [80]. The drug release happened in shorter times in comparison to PLA corresponding to the presence of hydrophilic PHEA, so the produced NPs could be introduced for semi-long term release drug delivery systems. Xu *et al.* [81] introduced novel PEG–PLA–polycaprolactone (PEG–PLA–PCL) NPs/DNA complex as a valid gene vesicle. This complex was even better choice for transfecting rabbit bone marrow stromal cells than con-

Figure 10. Tumor images of mouse after 42 days of treatment: (a) control, (b) free PTX, (c) PTX/PLA–TPGS NPs and (d) Fol/PTX/PLA–TPGS NPs [79]

ventional liposomes. The synthesized PLA/PCL particles as vehicles through supercritical fluid technology were applied by Moraes group [82]. The use of low PCL fractions (up to 20%) obtained suitable release of 17 α -methyltestosterone hormone.

In general, encapsulation of drug happens into the polymeric particle and it is released in a controlled way by diffusion and erosion of the polymeric matrix. However, it was found that the hydrophobic character of the PLGA causes the nonspecific adsorption of plasma proteins directing to the uptake of the particles by the mononuclear phagocyte system and therefore their fast clearance from the body. It is recognized that this problem can be prevented if the particles are surface modified by the adsorption or grafting of hydrophilic polymers such as polyethylene glycol (PEG) or poly(ethylene oxide) (PEO) to improve its surface biocompatibility [83, 84]. In 2016, Gyulai *et al.* [83] with the aim to increase the potential of targeted drug delivery synthesized the end group derivative of Pluronics a promising drug carrier systems. Then, Pluronic and Pluronic-amine stabilized PLGA NPs were prepared by nanoprecipitation. When the Pluronic-amine derivative was applied for the NPs stabilization, intracellular antibacterial effect and in vitro efficiency increased. Also, tuneable surface modification of PLGA NPs had been accomplished by Kiss *et al.* in 2013 [84]. Rhodamine-6G labelled PLGA NPs were prepared by a double emulsion solvent evaporation freeze-drying method by Nkabine *et al.* [85]. The obtained PLGA NPs were non-cytotoxic to three different mammalian cell lines, which confirmed their safe usage as drug carrier systems.

4.3. Application of other class of nanostructure polymers

Amphiphilic poly(dimethylsiloxane) (PDMS)-containing poly(ether amine) (PDMS-gPEA) were synthesized by Di *et al.* [86]. The prepared PDMS-gPEA could directly self-assemble into stable uniform-sized NPs in aqueous solution. Temperature, pH and ionic strength could control their aggregation. The responsive PDMS-gPEA NPs showed the unique selective encapsulation of water-soluble dye and great potential in smart separations. Kuruppuarachchi *et al.* [87] used from polyacrylamide NPs with potential of delivery for photodynamic agents in photody-

namic therapy for cancer. Dang *et al.* [88] investigated preparation of PS NPs with dendrimer-Ag shell and studied their application in catalytic reduction of 4-nitrophenol (4-NP). The presence of faintly thin outer layer of PS microsphere was related to the PAMAM dendrimer shell was observed in TEM images. The attached silver NPs onto the fourth PAMAM dendrimer shell were observed too. The synthesized PS@PAMAM-Ag NPs were packed into a column for reduction of 4-NP in the presence of NaBH₄ and showed adequate catalytic activity. Their results indicated that reactants could be catalyzed directly by the column system with stable flow rate and column pressure. They mentioned that this approach can decrease the loss of catalyst and prevent tedious and repeated separation using filtration or centrifugation for typical catalytic reactions. So, they concluded that it may also find application in other fields such as for antibacterial materials and in water treatment. Fritzen-Garcia, Creczynski-Pasa and coworkers [89] studied adsorption of peroxidase on PEGylated polyurethane (PU-PEG) NPs using a purified horseradish peroxidase (HRP). TEM image of the PEGylated PU NPs was shown in Figure 11a. Figure 11b displays incubated NPs by HRP with several little ‘bubbles’ around the NPs. As could be observed in Figure 11c, the localization of HRP molecules labeled with Au particles (dark spots with 10 nm size) is possible. Figure 11d representing the schematic of the TEM image of Figure 11c. This system was used as a modified carbon paste electrode for determination of dopamine in pharmaceutical products that showed improved detection limit and good performance in dopamine determination with less amount of enzyme adsorbed on PU-PEG NPs.

PS NPs with particle size range of 29.4–52.7 nm were manufactured via emulsion polymerization by Kong *et al.* [90]. Due to the lowered water to cement ratio, the use of superplasticizers has drastically altered the properties of concrete including workability, durability, impermeability and strength. Adsorption of polycarboxylate (PCE) superplasticizers on the cement surface creates the steric hindrance and electrostatic repulsion force which leads to better dispersion of cement grains in water media. Obtained results represented that the synthetic PNPs can also provide plasticizing influence to cement mixtures like as the traditional superplasticizers such

Figure 11. TEM images of (a) PEGylated PU NPs; (b) in the presence of HRP and (c) HRP molecules labeled with Au particles; (d) scheme representing the image 11c [89]

as PCE. TEM image of obtained PS NPs are shown in Figure 12 and displayed narrow particle size distribution of PNPs.

According to their funding, adsorbed PS NPs on the surface of cement grains could improve the fluidity of the fresh cement pastes (fcps) effectively. The fluidity of fcps increased with increase in quantity of

PNPs. Also, the plasticizing effectiveness of PNPs was lower than that of PCE, which should be owing to their larger particle size and thicker adsorption layer on the surface of cement. Pu *et al.* [91] introduced semiconducting PNPs (SPNs) as near-infrared photoacoustic contrast agents for photoacoustic molecular imaging. They selected poly(cyclopentadithio-

Figure 12. TEM images of the synthesized PS NPs [90]

phene-alt-benzothiadiazole) and poly(acenaphthothienopyrazine-alt-benzodithiophene) for the preparation of SPNs. Results showed that these NPs not only can generate a stronger signal than the usually used gold nanorods and single-walled carbon nanotubes on a per mass basis but also they are an ideal nanoplatform for enhancing photoacoustic molecular probes. Mallakpour *et al.* [92] synthesized poly (amide-benzimidazole-imide) (PABI) nanostructure containing amino acid. FE-SEM images showed nano-patterns of PABI particles with homogenous spherical shape. Then, PABI/Ag BNC was fabricated through in situ procedure. TEM image of obtained PABI/Ag NC represented good dispersion of Ag NPs in the PABI matrix. Also, resulting PABI/Ag NC exhibited antibacterial behavior rather than the pure PABI. Pure PABI was biologically active and undergoes biodegradability in soil burial test due to the presence of amino acid and also nitrogen functional groups in polymer backbone. More antibacterial effectiveness of the BNC rather than the pure PABI was obtained by embedding Ag NPs into the polymer matrix.

Because PS does not decompose in the cellular environment and is biocompatible with cells, it can be used as new drug delivery systems [93]. PS as biocompatible NPs with particle size of 44 nm were used as a model by Arciello and coworkers to analyze the endocytosis and uptake paths in primary human renal cortical epithelial (HRCE) cells [94]. These cells play a key role in the clearance of drugs. Results showed that PS NPs didn't exhibit any toxic influence to renal cells, and they were not released overtime. Therefore, they concluded that NPs could be used at low doses and, could to deliver drugs to specific targets upon functionalization with particular biomolecules. Also, they indicated that PS NPs entered HRCE cells through multiple mechanisms, either energy-independent or energy-dependent (endocytosis).

5. Conclusions

The combination of nanotechnology and polymers will be extremely useful in various applications, producing materials with unique properties. The first section of this review has provided information about recent developments in synthesis of PNPs. The using of ultrasound and MW irradiations as fast and green

available methods was introduced for the preparation of PNPs too. Then, this review paper has focused on the properties and application of novel synthesized PNPs. The discussed nanostructured polymers have been applied as nanoreactors, coating materials, electrochemical biosensors, drug delivery, nanocarriers, catalysts and polymer composite fabrication. Due to main applications of PNPs in various fields, the demand for such materials is highly significant, and this is possibly one of the most important fields of research for the future. As could be observed in this review there has been a considerable research interest in the area of drug delivery using PNPs delivery systems as carriers for small and large molecules. The polymers used in delivery systems should be compatible with the body in the terms of adaptability (non-toxicity) and (non-antigenicity) and should be biodegradable and biocompatible. So, toxicity and environmental impact issues of these nanomaterials are of particular concern but are often ignored. Hence, the safety of PNPs, acute as well as long-term toxicity, should be addressed further, and special attention should be paid to off-target effects, demanding careful design and proper controls, as well as extreme caution in interpretation of data from *in vivo* studies. Another key issue about usage of PNPs is their potential effects on global economics, as well as speculation about various doomsday scenarios. These worries have accounted for a discussion among advocacy groups and governments on whether special statutory regulation of nanobiotechnology is warranted.

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