EDITORIAL

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Recent Developments in the Application of Polymeric Nanoparticles as Drug Carriers

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Nanotechnology is an interdisciplinary field of science offering interesting solutions for many branches of human life. Nanomaterials, defined as structures with at least one dimension below 100 nm, are the focus of increasing research attention as versatile tools for nanomedicine. Among the various nanostructures recently described in the literature, polymeric nanoparticles, characterized by satisfying biocompatibility, have aroused great interest as the carriers for various biologically active substances such as drugs, proteins and nucleic acids. These nanoparticles have already been reported as efficient vehicles for therapeutic agents in many disease entities. They can be delivered to the body *via* different administration routes. This review addresses recent advances in the usage of polymeric nanoparticles as drug carriers described in the years 2013 and 2014. The advantages of polymeric nanocarriers for medical application are highlighted, including their low toxicity, evaluated *in vitro* and *in vivo*. Moreover, the classification of polymeric nanoparticles is presented as well as various protocols of their synthesis (**Adv Clin Exp Med 2015, 24, 5, 749–758**).

Key words: biocompatibility, polymeric nanoparticles, drug carrier, nanomedicine.

The enormous progress recently observed in the field of nanotechnology provides many interesting tools for medical sciences. Nanomaterials are structures with at least one dimension below 100 nm [1]. These materials possess unique features such as large surface-to-volume ratio resulting from their small dimensions. The specific characteristics of nanostructures make them extremely attractive as valuable devices for nanomedicine. Among the various nanomaterials, quantum dots [2], graphene [3], carbon nanotubes [4], metallic and metal oxide nanoparticles [5] and polymeric nanoparticles [6] have already been reported as promising candidates for medical applications. Particularly the latter have recently been investigated as carriers for biologically active substances and widely used for the potential treatment of many disease entities.

Polymeric nanoparticles may provide targeted drug delivery, especially desirable for cancer therapy, markedly decreasing the systemic side effects of highly toxic anticancer drugs [7]. Moreover, the polymer-based nanocarriers may enhance the bioavailability of poorly water-soluble drugs and provide their sustained release [8, 9]. The numerous advantages offered by polymeric nanoparticles as drug delivery systems (DDSs) also include the extension of drug circulation time in the body [10], increased stability of acid-labile drugs [11], uniform drug distribution in the targeted site e.g. alveoli [12], high drug encapsulation efficiency [13] and stimuli-responsiveness e.g. to oxidative stress [14] or hypoxia [15]. Furthermore, polymer-based nanocarriers provide high thermodynamic stability to the system [15] and can easily permeate through various biological barriers [16]. It deserves to be emphasized that surface modification of polymeric nanoparticles can markedly increase the interaction of active substance with the biological target [17]. Intriguingly, the encapsulation or dispersion of drugs with a polymeric matrix might protect the drug molecules from

premature release and degradation before reaching the targeted site [18]. Polymer-based nanoparticles can be used as the carrier for numerous biologically active molecules including drugs [18], proteins [7], monoclonal antibodies [13], nucleic acids [19, 20], biological extracts [16, 21] and others [22]. This review will be especially concerned with the application of polymer-based nanoparticles for the treatment of various disease entities including bacterial [23, 24], fungal [25] and parasitic [26] infections, ulcers [11], hypertension [12], angina [8], glaucoma [9], uveitis [27], asthma [22], cancer [15, 28], neurodegenerative disease [29] and many others [30, 31]. It deserves to be emphasized that several polymers are characterized by satisfying biocompatibility and predictable biodegradability [9, 22] while others are non-degradable or undergo slow degradation [22, 32]. Remarkably, polymer–based nanoparticles can be administered orally [20, 23], intravenously [18], percutaneously [30], ophthalmically [27], pulmonarily [12, 25], transmucosally to nose and lungs [33] or delivered to the brain via inner ear administration [16]. It is noteworthy that selected polymers are approved by the Food and Drug Administration (FDA) to be used for therapeutic applications [27].

Classification and Properties of Polymeric Nanoparticles

Recent advances in nanotechnology provide us with a wide range of polymers able to be formulated into nanoparticulate carriers for various active substances. Numerous synthetic and natural polymeric materials, including biodegradable, biocompatible and non-biodegradable substances, have already been used for nanoparticle preparation. Among the synthetic biodegradable polymeric matrices, poly(lactide-co-glycolide) (PLGA) [26, 28, 34] and poly(D, L-lactide) (PLA) [35] are the most common. Polymeric materials such as poly(methylmethacrylate) (PMMA) [36] and poly(ethylene-co-vinyl acetate) (PEVA) [12] are characterized by satisfying biocompatibility. On the other hand, poly(ethylene glycol) (PEG) [15] and Eudragits® [10, 31] belong to the group of non-biodegradable synthetic polymeric materials. The -biodegradable natural polymers already used for the preparation of nanoparticulate DDSs include poly(L-glutamic acid) (PGA) produced by *Bacillus subtilis* [37], pullulan produced from starch by the fungus *Aureobasidium pullulans* [33], gelatin [6], alginate [9, 33], chitosan [15] and its derivatives including N-palmitoyl chitosan [14] or mannose-modified trimethyl chitosan-cysteine (MTC) conjugate [20] and many others [19].

Intriguingly, the widespread application of PLGA results from its relatively inert composition, stable rate of degradation and known degradation products [22], namely lactic acid and glycolic acid [23]. PLGA-based nanoparticles are characterized by good mechanical stability and narrow size distribution [38]. This polymer, used as a matrix during nanoparticulate carrier preparation, can protect the drugs from enzymatic degradation [27] after oral administration [23]. More relevantly, it has been reported that the drug release rate can be controlled by the PLGA molecular weight as well as by the glycolide to lactide ratio [23]. Polymer-based nanoparticles are also promising candidates for non-invasive transdermal delivery without removing the stratum corneum [30]. In this view, especially biocompatible and biodegradable chitosan possessing mucoadhesive properties can significantly enhance penetration into the deeper skin layers [30]. Furthermore, similarly to PLGA, it has the approval of the FDA for biomedical usage [15, 22]. Remarkably, PEG can be used as a stabilizer during polymeric nanoparticle preparation [15] or applied as a linker for conjugation of targeting ligands to the surface of the nanoparticles [17]. Additionally, the modification of drug carriers with water-soluble PEG can contribute to a significant increase of the circulation half-life *in vivo* of as-prepared nanovehicles [18].

Biologically active substances can be encapsulated in polymeric nanoparticles and consist of a so-called core-shell system [34]. In such a case, an active agent is protected from degradation by a polymeric coat able to be functionalized to specifically recognize the targeted site [28]. Other strategies consist of dispersion of the active substance in the polymeric matrix [24]. Recently, the polymeric form of a prodrug containing the molecules of the active substance coupled with the polymeric backbone has been demonstrated to release the therapeutic agent upon hydrolytic degradation [39]. Curiously, drug-loaded polymeric nanoparticles incorporated into other matrices (e.g. synthetic polymers) can consist of a component of materials designed for biomedical applications [35].

Synthesis of Polymeric Nanoparticles

Polymeric nanoparticles can be fabricated using various synthesis techniques. Nanoprecipitation, emulsion/solvent evaporation, emulsification, desolvation and polyelectrolyte complexation can be listed among the numerous synthesis approaches, and will be exemplified below. It is worth mentioning that the most common methods of

polymer-based nanoparticle preparation are nanoprecipitation, emulsion/solvent evaporation and its modifications. These approaches of polymeric nanoparticle synthesis are schematically presented in Fig. 1. In the next paragraph, the strategies most recently described demonstrating fabrication of polymeric nanoparticles will be presented. Some examples are reviewed in the main text while others are summarized in Table 1.

Zhao and Feng [13] have described the preparation of nanoparticles composed of poly(lactide)--D-α-tocopheryl polyethylene glycol 1000 succinate copolymer (PLA-TPGS) and carboxyl group-terminated TPGS (TPGS-COOH) using the nanoprecipitation method. The previously synthesized polymers, PLA-TPGS and TPGS-COOH, and the drug were dissolved in acetone and dropwise added to water to form nanoparticles. The as-prepared carrier was loaded with docetaxel and chemically conjugated with a humanized monoclonal antibody *via* a carboxyl terminal group present in the prepared polymeric matrix [13]. A curious instance of carvedilol-loaded nanoparticles composed of poly(ethylene-co-vinyl acetate) (PEVA) prepared *via* the emulsion/solvent evaporation method has been described by Varshosaz et al. [12]. In this work, the solution of the polymer in carbon tetrachloride was mixed with a solution of the drug and PEG400 in dichloromethane. The as-prepared mixture was dispersed in the aqueous phase containing Tween 20 and agitated until complete evaporation of the organic phase [12]. Interesting studies have been also conducted by Alai and Lin [11] who have prepared lansoprazole-loaded polymeric nanoparticles composed of PLGA. The nanoparticles were prepared using a double water-in-oil-in-water (W/O/W) emulsion/solvent evaporation method. The drug and polymer dissolved in a mixture of dichloromethane and acetone were emulsified with an aqueous solution of $NaHCO_3$. The as-prepared primary emulsion was added to the aqueous solution of PVA and emulsified. After stirring, the emulsion was evaporated and the nanoparticles were collected after centrifugation [11]. It is also worth mentioning that the group of Hazra et al. [36] have used an oil-in-water (O/W) modified atomized emulsification process to fabricate core/shell poly(methyl methacrylate) (PMMA)/biosurfactant nanoparticles. The nanoparticles were loaded with ibuprofen, anthraquinone and curcumin. As biosurfactants, rhamnolipid, surfactin and trehalose lipid have been

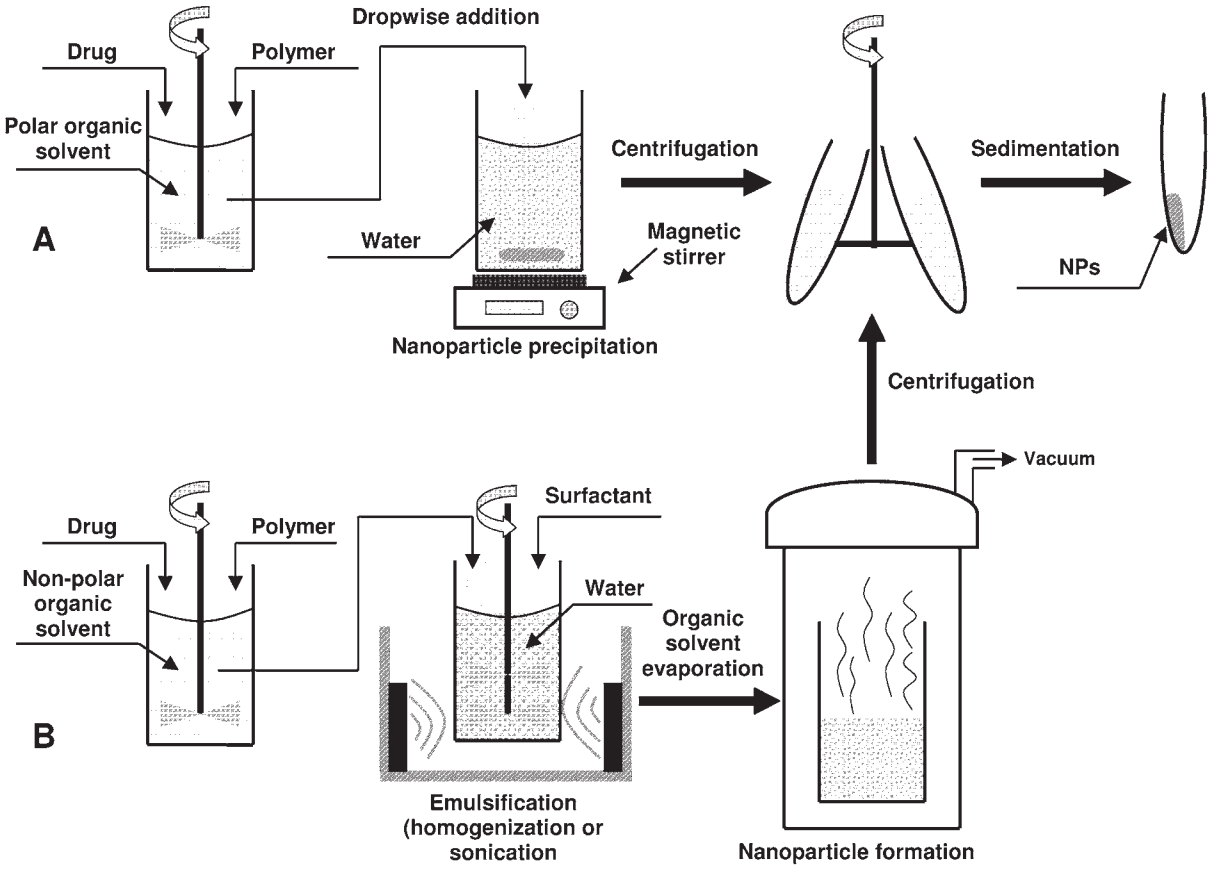

Fig. 1. Two approaches of polymeric nanoparticle preparation: (A) precipitation, (B) emulsification and solvent evaporation

Table 1. Various strategies of polymeric nanoparticle fabrication

Technique	Polymeric matrix	Active agent	Reference
Nanoprecipitation	PLGA, TPGS	docetaxel	[17]
	PLGA	cefixime	[24]
	PLGA	felodipine	[8]
Emulsification	POX	hydroxybenzyl alcohol	[22]
Emulsification and solvent evaporation	PLGA	cinnamon bark extract	[21]
	PLGA	curcumin	[28]
	PLGA	salvianolic acid B, tanshinone IIA, panax notoginsenoside	[16]
	PLGA	vancomycin	[23]
Emulsification or nanoprecipitation	gelatin, PLA	doxorubicin	[6]
Multiple emulsification	PLGA	voriconazole	[25]
Free radical emulsion polymerization	PMMA	TO-PRO3	[38]
Ionic cross-linking	chitosan	hydrocortisone, hydroxytyrosol	[30]
Electrospraying	Eudragit® L100-55, Eudragit® RS PO	aspirin	[31]

CA – cholic acid; PEG – poly(ethylene glycol); PLA – poly(lactide); PLGA – poly(lactide-co-glycolide); PMMA – poly(methyl methacrylate); POX – polyoxalate; TPGS D-α-tocopheryl polyethylene glycol 1000 succinate.

used. At the outset, the tenside was dissolved in water. Then, an aqueous solution of ammonium persulfate was added to the as-prepared solution to initiate the formation of free radicals. The monomer was sprayed over the surface of the biosurfactant solution to form nanoparticles [36]. As has been demonstrated by Katiyar et al. [9], the gelation method can be also employed for the preparation of polymeric nanoparticles. In this study, chitosan nanoparticles loaded with dorzolamide were formed by the dropwise addition of tripolyphosphate to a dorzolamide-containing chitosan solution. Finally, the sedimented nanoparticles were suspended in a sodium alginate solution to obtain an *in situ* gel [9]. A curious instance has been described by Narayanan et al. [18] who have used the desolvation method for preparation of poly(ethylene glycol)-modified gelatin nanoparticles loaded with ibuprofen. High molecular weight aggregates of gelatin dispersed in water were mixed with a solution of ibuprofen in ethanol. The dropwise addition of acetone resulted in precipitation of the ibuprofen-loaded nanoparticles which were subsequently cross-linked by adding calcium chloride [18]. Another group has prepared pullulan-based nanoparticles using the polyelectrolyte complexation method [33]. The negatively-charged sulfated and positively-charged aminated derivatives of the polymer were firstly synthesized by sulfonation and alkylation of the original polysaccharide, respectively. The interactions of sulfated pullulan-chitosan and aminated pullulan-carrageenan resulted in the formation of nanoparticles. The as-obtained nanocarriers were able to associate with the model protein, bovine serum albumin (BSA), demonstrating the potential of the as-prepared system for protein delivery [33].

The group of Kwon et al. [39] has conducted compelling studies on the preparation of nanoparticles based on a polymeric prodrug of vanillin. In this work, the polymeric material was composed of poly(vanillin oxalate) (PVO) covalently coupled vanillin in its backbone. The as-synthesized PVO dissolved in dichloromethane was added to the solution of poly(vinyl alcohol) (PVA) to form oil-in-water (O/W) emulsion. The nanoparticles were obtained by the evaporation of the solvent. The vanillin was released from the as-prepared nano-carrier upon its hydrolytic degradation [39].

Toxicity and Bio-compatibility Concerns

The biocompatibility of polymeric nanoparticles used as a drug carrier is of crucial importance for development of drug delivery systems based on polymeric materials [33]. Hence, polymer-based

nanoparticles should be examined through various *in vitro* and *in vivo* assays including cell viability, hemocompatibility and histological analysis [18]. One of the most common methods used to examine the *in vitro* cytotoxicity of polymeric nanoparticles is the MTT test [13]. In the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay, the metabolic activity of cells is assessed relying on the evaluation of cellular enzyme activity [33]. In this test, the formation of blue formazan dye is related to mitochondrial dehydrogenase activity. High cell viability is ascribed to a high concentration of formazan dye, mirroring the high amount of metabolically active cells [33].

The group of Dionísio et al. [33] has examined the *in vitro* cytotoxicity of pullulan-based nanoparticles using MTT assay. The experiment was performed on respiratory Calu-3 cells, which is an immortalized cell line derived from lung adenocarcinoma. It has been found that upon 24 h exposure to the polymeric nanoparticle formulation, cell viability was in the range from 74 to 94% independently of polymer modification, concentration or incubation time. Such results indicate the biologically acceptable viability of Calu-3 cells without disturbing their metabolic functions when in contact with pullulan-based nanoparticles [33]. The MTT assay was also employed for the evaluation the cytotoxicity of poly(vanillin oxalate) (PVO) nanoparticles [39]. The test, performed on RAW 264.7 cells, revealed dose-dependent cytotoxicity after 24 h of incubation with PVO nanoparticles. Interestingly, no or a negligible cytotoxic effect was observed at nanoparticle doses less than 500 μg/mL, indicating a satisfying biocompatibility of the prepared nanocarrier. Furthermore, tissue compatibility was examined using Balb/c mice intramuscularly injected with 100 μL of nanoparticles (1 mg/mL) suspended in phosphate buffer saline (PBS). The histological analysis of the mice, sacrificed at 7 days after injection, revealed minimal inflammatory response as demonstrated by the very little formation of immune and inflammatory cells [39]. Another group [36] has examined the *in vitro* cytotoxicity of core/shell poly(methyl methacrylate)/biosurfactant nanoparticles upon incubation with peripheral blood mononuclear cells using MTT assay. Moreover, the nanoparticle samples were exposed to anticoagulated human blood to assess the antihemolytic activity. The results of the MTT test revealed that cell survival decreased with increasing concentrations of the nanoparticles. Meanwhile, a hemolysis assay showed that nanoparticles coated with surfactin are less toxic than those surrounded by rhamnolipid and trehalose lipid biosurfactants [36]. Interestingly, Papa and co-workers [38] used a CellTiter96® Aqueous Non-Radioactive Cell Proliferation Assay (3-(4,5-dimethylthiazol-2-yl)-5-(3--carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt, MTS) to determine the cell viability of microglial cells treated with poly(methyl methacrylate) nanoparticles. Upon incubation with polymeric nanoparticles up to 6 days, the cellular viability was not affected [38].

As will be argued below, a wide range of other methods exist which are suitable for the evaluation of polymeric nanoparticles biocompatibility. To take one example, Yoo et al. [22] have studied lung biocompatibility after injection of a hydroxybenzyl alcohol-incorporated polyoxalate nanoparticle suspension to the trachea of Balb/c mice. Histological analysis of the lung revealed minimal inflammatory response and no changes of airway structure [22]. To take another example, Katiyar and co-workers [9] have shown the non-irritant properties of dorzolamide-loaded chitosan nanoparticles designed for the potential treatment of glaucoma. For this purpose, the ocular tolerance assay was employed, relying on the observation of adverse changes (e.g. hemorrhage, hyperemia and coagulation) that occur in the chorioallantoic membrane of the egg after exposure to the test material [9]. A curious instance has also been described by Narayanan et al. [18] who have examined the hemocompatibility of ibuprofen-loaded gelatin nanoparticles with or without modification with poly(ethylene glycol) (PEG). Interestingly, both kinds of nanoparticles did not induce any hemolysis up to 1 mg/mL and did not prolong coagulation times for particles in the concentration range from 0.1 to 1 mg/mL. Moreover, *in vitro* experiments revealed that, upon exposure of peripheral blood mononuclear cells to nanoparticles, an insignificant immune response expressed by cytokine induction level, lymphocyte proliferation and suppression and lymphocyte toxicity was observed. The authors [18] have also examined *in vivo* toxicity after intravenous injection of nanoparticulate samples to Sprague Dawley rats. Pharmacokinetic studies revealed a prolonged drug release from the nanogelatin matrix and confirmed increased drug bioavailability from PEGylated vehicles. The improved bioavailability is ascribed to the hydrophilic nature of PEG molecules, providing a steric barrier able to decrease the adsorption of protein and enhance the circulation time in the body. The inflammatory response after a nanoparticle administration dose of 2.5 mg/kg revealed insignificant activation of the pro-inflammatory (INF-γ and TNF-α) and anti-inflammatory (IL-10, IL-4) cytokines. Histopathological analysis showed no apparent damage of tissue sections from the liver and kidney [18].

It is worth noting that in cancer therapy the toxicity driven by a nanoparticulate carrier has a desirable effect. For example, Kulhari and co-workers [7] employed the MTT test to assess the *in vitro* cytotoxicity of PLGA nanoparticles loaded with docetaxel and conjugated with bombesin peptide. The cellular toxicity studies using MDA-MB-231 breast cancer cells overexpressing gastrin releasing peptide (GRP) receptor revealed 12-fold higher toxicity of the as-prepared nanoparticles as compared to pure docetaxel and Taxotere. Interestingly, the toxicity of bombesin peptide-conjugated nanoparticles was significantly improved as compared to the docetaxel-loaded formulation in a dose-dependent manner from 6.25 to 100 ng/mL. The results demonstrated the potential of a nanocarrier in anticancer therapy especially for the targeted therapy of cancer cells overexpressing GRP receptor [7]. Important studies have been also conducted by Zhao and Feng [13] who have employed the MTT test for an examination of the *in vitro* cytotoxicity of Herceptin-functionalized nanoparticles composed of poly(lactide)-D-α-tocopheryl polyethylene glycol 1000 succinate copolymer (PLA-TPGS) and loaded with doxorubicin. The viability studies were conducted using SK-BR-3 breast cancer cells upon exposure to the drug-loaded nanocarrier with or without functionalization with herceptin. The experiment revealed dose-dependent toxicity and a reduction of cellular viability upon incubation with antibody-functionalized nanoparticles as compared to a non-conjugated polymeric carrier. This may result from the intrinsic toxicity of Herceptin [13].

Other examples of cytotoxicity assays performed on cells exposed to polymer-based nanoparticles are summarized in Table 2.

Table 2. *In vitro* methods for evaluation of polymeric nanoparticle cytotoxicity

Assay	Polymeric nanoparticles	Cell line	Comments	Reference
MTT	Eudragit® NPs loaded with aspirin	Caco-2	cell viability ca. 65% after 48 h of incubation	[31]
MTT	PLGA NPs loaded with silver NPs and ascorbic acid	HepG2	not affected cells viability after 24 h of incubation	[37]
MTT	Carboxymethyl dextran NPs loaded with doxorubicin	SCC7	higher cytotoxicity of DOX-loaded NPs to hypoxic than normoxic cells. Insignificant cytotoxicity of unloaded NPs	[15]
MTT	NPs composed of chitosan derivative loaded with curcumin	RAW 264.7	insignificant cytotoxicity for cells treated with parent and curcumin-loaded NPs	[14]
MTS	Polycationic NPs	HEK293T RAW 264.7	both cell lines demonstrated high viability at low NP concentration range	[19]
MTS	NPs composed of PMMA-b-PMAETMA block copolymer loaded with bemiparin	BaF32	encapsulated bemiparin revealed dose-dependent increase in cell proliferation	[10]
MTS	Elastin-based NPs loaded with rapamycin	MDA-MB-468 MDA-MB-231	MDA-MB-468 cells sensitive to rapamycin revealed more significant decrease in viability as compared to rapamycin-insensitive MDA-MB-231 cells	[40]
SRB	NPs composed of QPAMN, adipic and glutaric acid loaded with paclitaxel	T47D MDA-MB-231	both cell lines demonstrated high viability at low NP concentration range. Cell viability was not affected by unloaded NPs	[34]

MTS – (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt, MTS); MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NPs – nanoparticles; PLGA – poly(lactide-co-glycolide); PMMA-b-PMAETMA – poly(methyl methacrylate-b-trimethyl aminoethyl methacrylate); QPAMN – N-(1,3-dihydroxypropan-2-yl)-3-methyl-3-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl); SRB – sulforhodamine.

BaF32 – IL-3 dependent and HP sulphate proteoglycan deficient myeloid B cell line stably transfected with recombinant human fibroblast growth factor 2 (FGF) receptor 1c (FGFR-1c); Caco-2 – human colonic carcinoma cell line; HEK293T – human kidney lymphocyte-like cells; HepG2 – human hepatoma cell line; MDA-MB-231 – human breast cancer cells; MDA-MB-468 – human breast cancer cells; RAW 264.7 – mouse macrophage-like cells; SCC7 – squamous carcinoma cells; T47D – human breast cancer cells.

Polymeric Nanoparticles as Carriers for Therapeutic Agents

Polymer-based nanoparticles have been successfully used as carriers for antimicrobial agents. For instance, the group of de Carvalho et al. [26] has designed amphotericin-loaded polymeric nanocarriers decorated with maghemite nanoparticles to achieve a site-specific effect to treat cutaneous leishmaniasis. The antibiotic was encapsulated in poly(lactide-co-glycolide) (PLGA) and dimercaptosuccinic acid (DMSA) nanoparticles. The antimicrobial activity of the prepared system was evaluated on C57BL/G mice infected intradermally with promastigotes of *Leishmania amazonensis*. Remarkably, the controlled drug release from the prepared nanosystem was provided upon exposure to an AC magnetic field resulting in a magnetohyperthermia effect. The nanocarrier exhibited significantly greater reduction in *Leishmania amazonensis* number and cell viability as compared to a free form of the antibiotic. Moreover, it allowed an effective reduction of the dose frequency required to obtain the same therapeutic effect [26]. Intriguingly, Chaudhary and Kumar [24] have demonstrated the antibacterial activity of Cefixime-loaded PLGA nanoparticles against the intracellular multidrug resistance (MDR) of *Salmonella typhimurium*. The results revealed a sustained release of the antibiotic from the prepared formulation and its better permeation across rat intestines as compared to the free drug [24]. A curious instance has been explored by Hill and co-workers [21], who demonstrated that PLGA nanoparticles loaded with the natural antimicrobial cinnamon bark extract are effective inhibitors of *Salmonella typhimurium* and *Listeria monocytogenes*. The authors highlighted the potential of the as-prepared system for the food industry to help prevent foodborne diseases [21]. Interesting studies have been conducted by Phan and co-workers [35], who have examined the use of natamycin-loaded nanoparticles composed of dextran and poly(D, L-lactide) (Dex-b-PLA) for the surface modification of contact lenses fabricated from various polymeric materials. It has been found that extended drug release up to 12 h was observed for contact lens materials composed of *N, N*-dimethylacrylamide or [tris(trimethylsiloxy)silyl]-propyl methacrylate. The authors suggested that natamycin-loaded Dex-b-PLA nanoparticles incorporated into contact lens materials have the potential to be used for targeted drug delivery directly to the cornea for the treatment of fungal infections [35]. Another group [25] has prepared voriconazole-loaded PLGA nanoparticles for pulmonary drug delivery. After administration to mice using an inhalation chamber, the sustained drug release was observed for 15 days [25].

Polymeric nanoparticles have also been used successfully as carriers for antihypertensive drugs. As an example, pulmonary delivery of the antihypertensive drug carvedilol was the subject of studies performed by Varshosaz and co-workers [12]. The authors prepared drug-loaded poly(ethylene-co-vinyl acetate) (PEVA) nanoparticles coated with chitosan. The system revealed mucoadhesive properties and provided prolonged drug release up to 8 h. The drug delivery systems based on these nanoparticles spray-dried in the presence of mannitol revealed low density, satisfying flow ability, small aerodynamic diameter and fine powder fraction demonstrating potential as a suitable inhaler powder for the pulmonary delivery of carvedilol [12]. Another group [8] has observed the enhancement of felodipine bioavailability from a formulation based on PLGA nanoparticles. Furthermore, in an *ex vivo* experiment performed on isolated rat stomach and intestinal segments, the nanovehicles demonstrated sustained release of the antihypertensive drug [8].

Polymer-based nanoparticles have been examined as carriers for other biologically active substances. As an example, Tiwari et al. [29] has exploited the potential of curcumin loaded in PLGA nanoparticles for the induction of neural stem cell (NSC) proliferation in Alzheimer's disease. It has been found that nanoparticles are able to induce a generation of new neurons by internalization into the hippocampus and subventrical zone of adult rats. The authors demonstrated the potential of the prepared system to treat neurodegenerative diseases by enhancing a self-repair mechanism [29]. Polymeric nanoparticles have also been used in the treatment of various dermatoses. As a curious instance, Hussain and co-workers [30] have proposed chitosan nanoparticles co-loaded with hydrocortisone and hydroxytyrosol in the treatment of atopic dermatitis. In this study, hydroxytyrosol was used to decrease the adverse effects of hydrocortisone and provide additional anti-inflammatory and antioxidant properties. The experiment, performed on a NC/Nga mouse model, revealed higher epidermal and dermal accumulation of the as-prepared nanoformulation as compared to a commercial hydrocortisone formulation [30]. Interestingly, PLGA nanoparticles loaded with triamcinolone acetonide have been employed in the treatment of endotoxin-induced uveitis [27]. The authors have evaluated the inflammation mediator expression in a rabbit's eye after intravitreal injection of the endotoxin. The results indicated

a better performance of triamcinolone-loaded nanoparticles as compared to microparticles of triamcinolone and prednisolone acetate. It has been found that polymeric nanoparticles can be used as an efficient triamcinolone carrier for topical treatment, providing better patient compliance [27]. Alai and Lin [11] have described the application of lansoprazole-loaded polymeric nanoparticles for the treatment of gastric ulcers. The drug encapsulated in Eudragit® RS 100 nanoparticles and PLGA nanoparticles revealed sustained release behavior *in vitro*. After oral administration of enteric-coated capsules containing the nanoparticles, the sustained release of lansoprazole up to 24 h was observed in ulcer-induced Wistar rats [11]. Another group [20] has described application of mannose-modified trimethyl chitosan-cysteine conjugate nanoparticles for oral delivery of therapeutic TNF-α siRNA to macrophages. The authors observed effective improvement of siRNA protection in the physiological environment and its enhanced permeation through intestinal epithelium. Furthermore, siRNA uptake by the macrophages was facilitated through clathrin-independent endocytosis. *In vitro* experiments revealed that orally delivered nanoparticles inhibited TNF-α secretion by macrophages, thus protecting mice with acute hepatic injury from inflammation-induced liver damage [20]. Enteric-coated polymeric nanoparticles have been the subject of studies performed by Hao and co-workers [31]. The authors synthesized core/shell Eudragit® L100-55/Eudragit® RS nanoparticles loaded with aspirin. The external polymer coat provided a pH-sensitive drug release while polymeric core material played the role of the skeleton allowing sustained aspirin release [31].

Other examples demonstrating the application of polymeric nanoparticles as a carrier for various therapeutic agents are listed in Table 3.

Conclusion

The usage of polymeric nanoparticles as drug carriers for the treatment of many disease entities opens encouraging possibilities in clinical application. The present-day progress achieved in adapting polymeric nanoparticles for drug delivery makes the future of these nanovehicles bright and exciting. Employed as drug carriers, polymer-based nanoparticles offer numerous attractive features such as targeted drug delivery, sustained

Table 3. Use of polymeric nanoparticles as drug vehicles

Nanoparticle components	Active substance	Functionalizing agent	Cell culture/ /animal model	Pharmacological effect	Reference
PLA-TPGS, TPGS-COOH	docetaxel	herceptin	SK-BR-3	targeted delivery of anticancer drugs	[13]
PLGA	docetaxel	bombesin peptide	MDA-MB-231	targeted delivery of anticancer drugs. Sustained drug release	[7]
Carboxymethyl dextran	DOX	2-nitrozoimidazole derivative	SCC7	hypoxia-responsive and sustained drug release	[15]
PMMA, biosurfactants (rhamnolipid, surfactin, trehalose)	ibuprofen, anthraquinone, curcumin	–	PMBCs	PH-responsive and sustained drug release; antibacterial activity against *Bacillus subtilis* and *Pseudomonas aeruginosa* by induction of oxidative stress	[36]
Chitosan	dorzolamide	–	Goat cornea, male albino rabbit	reduced frequency of administration in the treatment of glaucoma	[9]
POX	hydroxybenzyl alcohol	–	RAW 264.7/ Balb/c mice	simultaneous antioxidant and anti-inflammatory effect	[22]
PVO	–	–	RAW 264.7/ Balb/c mice	step-wise release of antioxidant and anti-inflammatory vanillin upon hydrolytic degradation of polymeric matrix	[39]

DOX – doxorubicin; PLA-TPGS – poly(lactide)-D-α-tocopheryl polyethylene glycol 1000 succinate copolymer; PLGA – poly(lactide-co-glycolide); PMMA – poly(methyl methacrylate); POX – polyoxalate; PVO – poly(vanillin oxalate); TPGS-COOH – carboxyl group-terminated D-α-tocopheryl polyethylene glycol 1000 succinate.

MDA-MB-231 – gastrin releasing peptide receptor positive breast cancer cells; PBMCs – peripheral blood mononuclear cells; RAW 264.7 – mouse macrophage-like cells; SCC7 – squamous carcinoma cells; SK-BR-3 – breast cancer cells.

release or prolonged circulation half-life. Polymeric nanoparticles can protect the drug from degradation in physiological conditions and improve its bioavailability. Polymeric nanoparticle-based drug delivery systems have been successfully employed as carriers for anticancer, anti-inflammatory and antihypertensive agents, antioxidants, and nucleic acids, among others. In spite of the scientific advances in the usage of polymeric nanoparticles as drug vehicles, many more efforts from scientists from a variety of disciplines are needed before they can be fully exploited for therapeutic applications.

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