REVIEW ARTICLE

Nanoparticles based on PLGA and its co-polymer: An overview

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Poly (D, L-lactide-co-glycolide) (PLGA) is approved by the Food and Drug Administration for drug delivery use. The polymeric nanoparticles based on PLGA and its co-polymer are designed for controlled and targeted drug delivery. Also, PLGA and its co-polymer are important in designing nanoparticles with desired characteristics such as biocompatibility, biodegradation, particle size, surface properties, drug release and targetability. This review focuses on the polymer literature, methods for preparation of nanoparticles and recent studies on the nanoparticles based on PLGA and its co-polymer for the conventional and targeted delivery of drugs by various routes.

Key words: *Poly (D, L-lactide-co-glycolide), polymer literature, poly (D, L-lactide-co-glycolide) nanoparticles, targeted drug delivery*

INTRODUCTION

Recent developments in nanotechnology have allowed new research strategies to flourish in the field of drug delivery. There has been considerable interest in developing nanoparticles as effective drug delivery carriers.[1]

For pharmaceutical purposes, nanoparticles are defined as "solid colloidal particles ranging in size from 10 to 1000 nm (1 μm). They consist of macromolecular materials in which the active principle (drug or biologically active material) is dissolved, entrapped, encapsulated and/or to which the active principle is adsorbed or attached."[2]

In the recent years, a promising class of carriers that has been developed for drug delivery applications is liposomes. These vesicles, prepared from lipids, have been used as potential drug carriers because of the protection they can offer for various drugs contained in their core. However, liposomes have shown a low encapsulation efficiency, poor storage stability and rapid leakage of water-soluble drugs in the blood. As such, their ability to control the release of many drugs may not be good.[3] Therefore, polymeric nanoparticles from biodegradable and biocompatible polymers have been extensively studied as particulate carriers in the pharmaceutical and medical fields.[4]

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The biodegradable polymeric nanoparticles have shown their advantage over liposomes by their increased stability and the unique ability to create an extended release. Polymeric nanoparticles are advantageous in a number of ways over microparticles. They possess high drug-loading capacities, thereby increasing intracellular delivery of the drug and are better suited for intravenous delivery.[5]

Owing to their excellent biocompatibility, the biodegradable polyester called poly (D, L-lactide-co-glycolide) (PLGA) is the most frequently used biomaterial and is already commercialized for a variety of drug delivery systems (blends, films, matrices, microspheres, nanoparticles, pellets, etc.).[4] Polymeric nanoparticles of this polymer are used for the delivery of various drugs (antipsychotics, anesthetics, antibiotics, antiparasites, antitumorals, hormones, proteins, etc.).[6] Drug-loaded PLGA nanoparticles [Figure 1a] are investigated for targeted and non-targeted drug delivery. These nanoparticles have been investigated especially in drug delivery systems for drug targeting because of their particle size (ranging from 10 to 1000 nm) and long circulation in blood. Thus, if the carrier size is under 1 μm, an intravenous (i.v.) injection (the diameter of the smallest blood capillaries is 4 μm) is enabled, minimizing any possible embolism.[7] The reticuloendothelial system (RES), mainly the liver and spleen, is a major obstacle to active targeting because of its ability to recognize these systems, remove them from systemic circulation and, consequently, avoid effective delivery of the nanoparticles to organs other than those of the RES. The preparation of surface-modified polymeric nanoparticulate systems (stealth nanoparticles) with hydrophilic polymer (i.e. polyethylene glycol [PEG]) is

the most common way to control the opsonization process during passive targeting after i.v. administration. PLGA in combination with PEG (PLGA co-polymer or PLGA-PEG) is mainly used for the preparation of stealth polymeric nanoparticles [Figure 1b]. Depending on their composition and intended use, these polymeric nanoparticles can be administered orally, parenterally or locally.[6,8,9]

This review, therefore, was conducted with the view to summarize the PLGA literature and the recent developments in the area of polymeric nanoparticles developed based on PLGA and its co-polymer.

POLYMER LITERATURE

PLGA in drug delivery systems

Devices based on polymers of lactic and glycolic acids are widely used in a number of biomedical and pharmaceutical applications.[10] Co-polymers of lactide and glycolide, referred to as PLGA, have generated tremendous interest because of their excellent biocompatibility, biodegradability and mechanical strength. The discovery and the synthetic work on low molecular weight (M.W.) oligomeric forms of lactide and/or glycolide polymers was first carried out several decades ago. The methods to synthesize high M.W.s of these polymers were first reported during the late 1960s and early 1970s. A number of groups have published pioneering work on the utility of these polymers to make sutures/fibers. Various polymeric devices like microspheres, microcapsules, nanoparticles, pellets, implants and films have been fabricated using these polymers. They are also easy to formulate into various delivery systems for carrying a variety of drug classes, such as vaccines, peptides, proteins and micromolecules, which have been approved by the Food and Drug Administration for drug delivery use.[11-13]

Physicochemical properties of PLGA

PLGA prepared from L-poly lactide (L-PLA) and poly glycolide (PGA) are crystalline co-polymers while those from D,L-PLA and PGA are amorphous in nature [Figure 2]. It has been found that PLGAs containing >70% glycolide are amorphous in nature. The degree of crystallinity and the melting point of the polymers are directly related to the M.W. of the polymer.[14]

Physical properties such as the M.W. affect the mechanical strength of the polymer and its ability to be formulated as a drug delivery device. Also, these properties may control the polymer biodegradation rate and hydrolysis. Commercially available PLGA polymers are usually characterized in terms of intrinsic viscosity, which is directly related to their M.W.s.[14]

The mechanical strength, swelling behavior, capacity to undergo hydrolysis and, subsequently, the biodegradation rate are directly influenced by the crystallinity of the PLGA polymer. The resultant crystallinity of the PLGA co-polymer is dependent on the type and the molar ratio of the individual monomer components (lactide and glycolide) in the copolymer chain. PLGA polymers containing a 50:50 ratio of lactic and glycolic acids are hydrolyzed much faster than those containing a higher proportion of either of the two monomers.[11,14]

PGA is highly crystalline because it lacks the methyl side groups of the PLA. Lactic acid is more hydrophobic than glycolic acid and, therefore, lactide-rich PLGA co-polymers are less hydrophilic, absorb less water and, subsequently, degrade more slowly.[15-18]

It has a glass transition temperature (Tg) of 45°C and an inherent viscosity of 0.5-0.8 mPa. The Tgs of the PLGA co-polymers are above the physiological temperature of 37°C and hence they are normally glassy in nature. Thus, they have a fairly rigid chain structure, which gives them significant mechanical strength to be formulated as a degradable device. It has been reported that the Tgs of PLGA decrease with the decrease of lactide content in the co-polymer composition with decreasing M.W.[11,14]

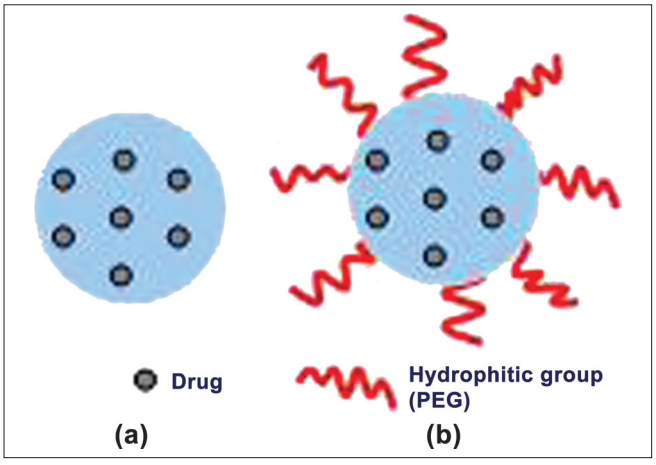

Figure 1: Polymeric nanoparticles (a) prepared with poly (D, L-lactide-co-glycolide) (PLGA) and (b) prepared with poly (D, L-lactide-co-glycolide) co-polymer

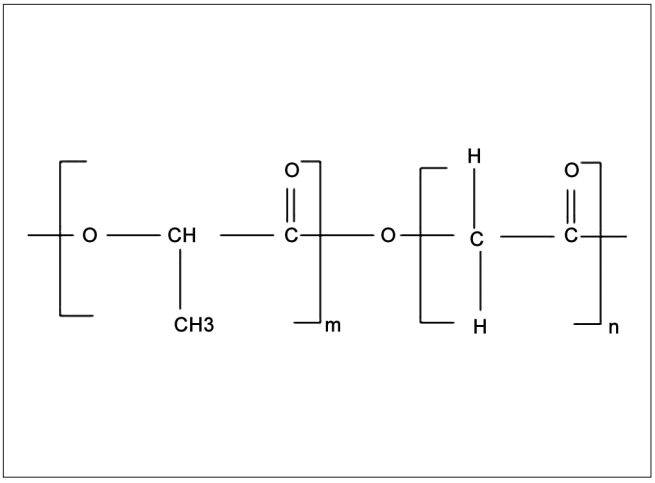

Figure 2: Structural formula of poly (D, L-lactide-co-glycolide)

The PLGA polymers chosen should also have considerable mechanical strength. Different factors like the M.W., co-polymer composition (lactide/glycolide ratio), crystallinity and geometric regularity of individual chains significantly affect the mechanical strength of the particular polymer.[14]

Biodegradation of PLGA

In both *in vitro* and *in vivo,* the PLGA co-polymer undergoes degradation in an aqueous environment (hydrolytic degradation or biodegradation) through cleavage of its backbone ester linkages. The polymer chains undergo bulk degradation and the degradation generally occurs at a uniform rate throughout the PLGA matrix. It has been recorded that the PLGA biodegradation occurs through random hydrolytic chain scissions of the swollen polymer. The carboxylic end groups present in the PLGA chains increase in number during the biodegradation process as the individual polymer chains are cleaved. These are known to catalyze the biodegradation process. It has also been reported that large fragments are degraded faster internally and amorphous regions degrade faster than crystalline regions. The biodegradation rates of the PLGA co-polymers are dependent on the molar ratio of the lactic and glycolic acids in the polymer chain, M.W. of the polymer, the degree of crystallinity and the Tg of the polymer.[10,19]

A three-phase mechanism for PLGA biodegradation has been proposed:

1. Random chain scission process. The M.W. of the polymer decreases significantly, but no appreciable weight loss and no soluble monomer products are formed.
2. In the middle phase, a decrease in M.W. accompanied by a rapid loss of mass and soluble oligomeric and monomer products are formed.
3. Soluble monomer products formed from soluble oligomeric fragments. This phase is that of complete polymer solubilization.[19]

The role of enzymes in any PLGA biodegradation is unclear. Most of the literature indicates that the PLGA biodegradation does not involve any enzymatic activity and is purely through hydrolysis. However, some findings have suggested an enzymatic role in PLGA breakdown based on the difference in the *in vitro* and *in vivo* degradation rates. It has also been found that motion and buffers may affect their rate differences. However, it is known that PLGA biodegrades into lactic and glycolic acids. Lactic acid enters the tricarboxylic acid cycle and is metabolized and subsequently eliminated from the body as carbon dioxide and water. Glycolic acid is either excreted unchanged in the kidney or it enters the tricarboxylic acid cycle and is eventually eliminated as carbon dioxide and water.[11,13]

Biocompatibility of PLGA

The PLGA polymer had several advantages like good mechanical properties, low immunogenicity and toxicity, excellent biocompatibility and predictable biodegradation kinetics. The wide acceptance of the lactide/glycolide polymers as suture materials made them attractive candidates for biomedical applications like ligament reconstruction, tracheal replacement, surgical dressings, vascular grafts and nerve, dental and fracture repairs.[10,20]

PLGA microspheres (average size 30 μm) induced a mild foreign body reaction and were reported to be biocompatible.[20] The volume of microspheres injected into the tissue may be considered as an open porous implant, which induces an inflammatory response characterized by the infiltration of macrophages, neutrophils, fibroblasts and some lymphocytes and by the formation of fibrin, giant cells and new blood vessels.[21-23] Tissue reaction to the PLGA microsphere injection site after Week 1 showed heavy macrophage infiltration around the muscle due to a systemic rise in the level of activated macrophages, which release cytokines, growth factors and other bioactive agents to modulate the function of other cell types in the inflammatory milieu.[24,25]

The release of octreotide acetate from PLGA microspheres has been tested in rabbits and humans. Similar release patterns from rabbits and humans were observed.[26]

Methods for the preparation of PLGA and its co-polymer-based nanoparticles

Three well-developed methods exist for the preparation of nanoparticles using PLGA and its co-polymer.[5] These include emulsification solvent diffusion/evaporation,[27,28] salting out[29] and nanoprecipitation.[30]

Emulsification solvent evaporation/diffusion method

Emulsification solvent diffusion/evaporation method involves two steps. The first step is emulsification of the polymer (PLGA or PLGA-PEG) solution into a non-solvent. In the second step, the polymer solvent is diffused, inducing polymer precipitation as nanoparticles. A polymeric organic solution containing the dissolved drug is dispersed into nanodroplets using a dispersing agent and high-energy force (e.g., ultrasonication), in a non-solvent such as chloroform, ethyl acetate etc. The polymer precipitates in the form of nanoparticles in which the drug is finely loaded in the polymeric matrix. The solvent is subsequently evaporated/diffused by increasing the temperature under reduced pressure for evaporation or by dilution for diffusion.[27,28]

Salting-out method

Polymer (PLGA or PLGA-PEG) and drug are initially dissolved in a solvent such as acetone, which is subsequently emulsified into an aqueous gel containing the salting-out agent (electrolytes, such as magnesium chloride, calcium chloride etc.) using a colloidal stabilizer such as polyvinyl pyrrolidone. This oil/water emulsion is then diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus, inducing the formation of nanoparticles.[29]

Nanoprecipitation method

In this method, polymer (PLGA or PLGA-PEG) is dissolved in acetone and then the drug is added and dissolved. This organic solution is injected into distilled water containing stabilizer under magnetic stirring. Acetone and some proportion of water are eliminated under reduced pressure and the final volume of the suspension is adjusted to the required volume.[30]

In these methods, three major strategies were employed during the preparation methods: (1) covalent attachment of the drug to the particle surface or to the polymer before preparation, (2) adsorption of the drug to a polymeric carrier system and (3) incorporation of the drug into the polymeric matrix during particle preparation.[31,32]

PLGA and its co-polymer-based nanoparticles

Triclosan

Pinon-Segundo *et al*.[33] prepared and characterized triclosan-loaded nanoparticles by the emulsification-diffusion process to obtain a novel delivery system for the treatment of periodontal disease. The nanoparticles were prepared using PLGA, PLA and cellulose acetate phthalate. Polyvinyl alcohol (PVA) was used as a stabilizer. Batches were prepared with different amounts of triclosan in order to evaluate the influence of the drug on nanoparticle properties. Solid nanoparticles of $<$ 500 nm in diameter were obtained. Entrapment efficiencies were higher than 63.8%. The characterization by scanning electron microscopy and light scattering indicated that high concentrations of triclosan seemingly caused the increase in the mean size of the nanoparticles. A decrease in the PLGA glass transition temperature was observed by differential scanning calorimetry. This could indicate that triclosan in PLGA nanoparticles behaves as a non-conventional plasticizer. A fast release of triclosan from nanoparticles was detected. A preliminary *in vivo* study in dogs with induced periodontal defects suggested that triclosan-loaded nanoparticles penetrate through the junctional epithelium.

Paclitaxel

Dong and Feng[34] developed a novel bioadhesive drug delivery system, PLGA/montmorillonite nanoparticles, for oral delivery of paclitaxel. Paclitaxel-loaded PLGA/montmorillonite nanoparticles were prepared by the emulsion/solvent evaporation method. Montmorillonite was incorporated in the formulation as a matrix material component, which also plays the role of a co-emulsifier in the nanoparticle preparation process. Paclitaxel-loaded PLGA/montmorillonite nanoparticles were found to be of spherical shape with a mean size of around 310 nm and polydispersity of $<$ 0.150. Adding the montmorillonite component to the matrix material appears to have little influence on the particle size and the drug encapsulation efficiency. The drug release pattern was found to be biphasic with an initial burst followed by a slow, sustained release, which was not remarkably affected by the montmorillonite component. Cellular uptake of the fluorescent coumarin 6-loaded PLGA/montmorillonite nanoparticles showed that montmorillonite enhanced the cellular uptake efficiency of the pure PLGA nanoparticles by 57-177% for Caco-2 cells and 11-55% for HT-29 cells, which was dependent on the amount of montmorillonite and the particle concentration in incubation. Such a novel formulation is expected to possess extended residence time in the gastrointestinal tract, which promotes oral delivery of paclitaxel.

Ellagic acid

Bala *et al*.[35] developed ellagic acid-loaded PLGA nanoparticles for oral administration. PLGA nanoparticles were prepared by a method based on the concept of emulsion-diffusion-evaporation using PEG 400 as a co-solvent for solubilizing the drug. While developing this method, didodecyldimethylammomium bromide (DMAB) and PVA, alone and in combination with chitosan (CS) were employed. DMAB-stabilized particles were the smallest of all the formulations, with a particle size of 148.5 nm. PVA alone gave particles of 269.7 nm but a blend with CS (80:20) resulted in an increase in particle size (359.6 $\pm$ 23.6 nm). Initial release of ellagic acid from nanoparticles in pH 7.4 phosphate buffer was rapid, followed by a slower sustained release. Release rates followed the order PVA $>$ PVA-CS $>$ DMAB. Release rate from the PLGA-DMAB particles was slowest, which is attributed to the higher hydrophobicity of DMAB as compared with PVA, preventing diffusion of the drug out of the polymeric matrix. Insolubility of CS at alkaline pH could have retarded the release in case of the PVA-CS system. An *in situ* intestinal permeability study of pure drug and the drug encapsulated in nanoparticles prepared using PVA, PVA-CS blend and DMAB as stabilizer in rats showed 66, 75, 73 and 87% permeation, respectively. Ellagic acid showed a good free-radical scavenging effect in a yeast cell culture model as well as in a cell-free system.

Streptomycin

Pandey and Khuller[36] have developed an oral drug delivery system for an injectable antibiotic, streptomycin. PLGA nanoparticles encapsulating streptomycin were prepared by the multiple emulsion technique and administered orally to mice for biodistribution and chemotherapeutic studies. The mean particle size was 153.12 nm with 32.12 $\pm$ 4.08% drug encapsulation and 14.28 $\pm$ 2.83% drug loading. Streptomycin levels were maintained for 4 days in the plasma and for 7 days in the organs following a single oral administration of PLGA nanoparticles. There was a 21-fold increase in the relative bioavailability of PLGA-encapsulated streptomycin compared with intramuscular free drug. In *Mycobacterium tuberculosis* H (37)Rv-infected mice, eight doses of the oral streptomycin formulation administered weekly were comparable to 24 intramuscular injections of free streptomycin. Further, the nanoparticle formulation did not result in nephrotoxicity as assessed on a biochemical basis. These results suggest that nanoencapsulation might be useful for developing a suitable

oral dosage form for streptomycin and perhaps for other antibiotics that are otherwise injectable.

Estradiol

Mittal *et al*.[37] investigated estradiol-loaded PLGA nano particulate formulations in the size range between 90 and 143 nm for improving oral bioavailability and to sustain the release of estradiol by varying the M.W. and co-polymer composition of PLGA. Nanoparticles were prepared following the emulsion-diffusion-evaporation method employing DMAB as a stabilizer. The effect of polymer M.W. and co-polymer composition on particle properties and release behavior (*in vitro* and *in vivo*) has been reported. Drug release *in vitro* decreased with increase in M.W. and lactide content of PLGA. Zero order release was obtained with low M.W. (14,500 and 45,000 Da) PLGA, while high M.W. (85,000 and 213,000 Da) and different co-polymer compositions followed square root of time (Higuchi's pattern)-dependent release. The bioavailability of estradiol from nanoparticles was assessed in male Sprague Dawley rats at a dose of 1 mg estradiol/rat. The *in vivo* performance of the nanoparticles was found to be dependent on the particle size, polymer M.W. and copolymer composition. The $C_{(max)}$ of drug in the plasma was dependent on the polymer M.W. and composition while particle size was found to influence the duration of release, suggesting that smaller is better. The histopathological examination revealed absence of any inflammatory response with the formulations prepared of low/high M.W. or high lactide content polymers for the studied period. Together, these results indicate that nanoparticulate formulations are ideal carriers for oral administration of estradiol, having a great potential to address the dose-related issues of estradiol.

Cyclosporine

Italia *et al*.[38] prepared cyclosporine-loaded PLGA nanoparticles by the emulsion-diffusion-evaporation method, which were optimized for particle size and entrapment efficiency. The optimized particles were 143.3 $\pm$ 8.7 nm in size with narrow size distribution and 71.9 $\pm$ 1.7% entrapment efficiency at 20% w/w initial drug loading when prepared with 0.1% w/v of Didodecylmethylammonium bromide as stabilizer. These particulate carriers exhibited controlled *in vitro* release of cyclosporine for 23 days at a nearly constant rate and showed very good hemocompatibility *in vitro*. The nanoparticulate formulation showed significantly higher intestinal uptake as compared with the SIM-Neoral® and cyclosporine suspensions. The relative bioavailability of the nanoparticulate formulation was found to be 119.2% as compared with SIM-Neoral®. A marked difference in the pharmacokinetic profile between nanoparticulate and SIM-Neoral® formulations was observed. The nanoparticulate formulation showed controlled release of cyclosporine over 5 days. On the other hand, the marketed formulation showed a sharp C_{max} with a 3-day release profile. The nanoparticulate formulation exerted significantly lower nephrotoxicity in the rats as compared with SIM-Neoral®, which was evidenced by lower blood urea nitrogen, plasma creatinine and malondialdehyde levels in the plasma and kidney. The results were further supported by the histopathological changes in the kidneys. Together, these results indicate that PLGA nanoparticles have a greater potential for oral delivery of cyclosporine.

Gentamicin

Drug delivery systems containing gentamicin were studied as a treatment against experimental brucellosis in mice. Micro- and nanoparticles (with an average size of 310 nm) prepared using PLGA 502H and microparticles made of PLGA 75:25H were successfully delivered to the liver and the spleen, the target organs for *Brucella melitensis*. Both polymers have the same M.W. but different lactic acid/glycolic acid ratios. Microparticles of PLGA 502H and 75:25H released their contents in a sustained manner in contrast to PLGA 502H nanoparticles, which were degraded almost completely during the first week post-administration. The values of the pharmacokinetic parameters after administration of a single intravenous dose of 1.5 mg/kg of body weight of loaded gentamicin revealed higher areas under the curve (AUC) for the liver and the spleen and increased mean retention times (MRT) compared with those for the free drug, indicating the successful uptake by phagocytic cells in both organs and the controlled release of the antibiotic. Both gentamicin-loaded PLGA 502H and 75:25H microparticles presented similar pharmacokinetic parameter values for the liver, but those made of PLGA 75:25 H were more effective in targeting the antibiotic to the spleen (higher AUC and MRT). The administration of three doses of 1.5 mg/kg significantly reduced the load associated with the splenic *B. melitensis* infection. Thus, the formulation made with the 75:25H polymer was more effective than that made with 502H microspheres. Therefore, both pharmacokinetic and pharmacodynamic parameters showed the suitability of 75:25H microspheres to reduce the infection of experimentally infected mice with *B. melitensis*.[39]

Risperidone

Muthu *et al*.[40] developed extended-release PLGA nanoparticles of risperidone and a thermal-responsive *in situ* gel containing risperidone nanoparticles for parenteral (subcutaneous) delivery and to reduce the dose-dependent extrapyramidal side effects of risperidone. PLGA nanoparticles of risperidone were designed by the nanoprecipitation method using polymeric stabilizer (Poloxamer 407). The prepared nanoparticles were characterized for particle size by photon correlation spectroscopy and atomic force microscopy. Poloxamer 407-based *in situ* gel containing PLGA nanoparticles of risperidone was prepared by the modified cold method to control the initial rapid release from the nanoparticles. The *in vivo* efficacy (antipsychotic effect) of the prepared formulations (nanoparticles and *in situ* gel containing nanoparticles) was studied by administering them subcutaneously into mice. Extrapyramidal side effects

of the formulations were also studied. The particle size of the prepared nanoparticles ranged between 85 and 219 nm. About 89-95% drug encapsulation efficiency was achieved when risperidone was loaded at 1.7-8.3% by weight of the polymer. During *in vivo* studies, prepared risperidone formulations showed an antipsychotic effect that was significantly prolonged over that of risperidone solution for up to 72 h, with fewer extrapyramidal side effects. The prolonged effect of risperidone was obtained from the risperidone formulations administered subcutaneously, which may improve the treatment of psychotic disorders by dose reduction.

Adriamycin

PLGA-PEG co-polymers were synthesized by ring opening polymerization of the D L-lactide and glycolide in the presence of PEG1000. The adriamycin-loaded nanoparticles were prepared using a precipitation-solvent evaporation technique. The physical characteristics and drug-loading efficiency of the PLGA-PEG nanoparticles were influenced by the composition of the PLGA-PEG co-polymers used to prepare the nanoparticles. Particle sizes were between 65 and 100 nm for different compositions of PLGA-PEG co-polymers. PLGA-PEG nanoparticles prepared from co-polymers having relatively high PLGA/PEG ratios were smaller. Entrapment efficiency was 25-33%. Adriamycin release from the nanoparticles at pH 7.4 showed an initial burst release and then sustained release phase. These results showed that PLGA-PEG nanoparticles could be an effective carrier for cancer therapy.[41]

Alendronate

Choi and Kim[42] developed PLGA nanoparticles in the size range of 42-57 nm by the dialysis method, modified with both alendronate and monomethoxy polyethylene glycol (mPEG) and evaluated the potency for bone-targeted drug delivery. Alendronate, a targeting moiety that has a strong affinity for bone, was conjugated to PLGA polymer via carbodiimide chemistry. mPEG-PLGA block co-polymers with different M.W.s of mPEG (M(n) 550, 750 and 2000) were synthesized and used for a hydrophilic layer on the surface of the nanoparticles to avoid RES. The surface-modified PLGA nanoparticles with various ratios of alendronate and mPEG densities on their surface were evaluated by adsorption study onto hydroxyapatite. It was confirmed that alendronate-modified nanoparticles had a strong and specific adsorption to hydroxyapatite. The amount of nanoparticles absorbed onto hydroxyapatite tended to be smaller when the content of alendronate was decreased and the large block length of mPEG was found to reduce the potency of alendronate.

Cisplatin

Cisplatin nanoparticles with an average size of 150-160 nm and approximately 2% w/w cisplatin content were prepared by a modified emulsification and solvent evaporation method. Normal BALB/c mice tolerated three weekly intravenous injections of a relatively high dose of blank PLGA-mPEG nanoparticles (500 mg/kg, equivalent to about 10 mg nanoparticles/mouse) and three weekly intravenous injections of a high dose of nanoparticle-entrapped cisplatin (10 mg/kg). Also, histopathology examination indicated that there were no differences in the kidneys or spleens from animals treated with cisplatin-loaded nanoparticles or blank nanoparticles compared with the untreated control group. A moderate granulation of protoplasm of hepatic cells was observed in the livers from mice treated with cisplatin-loaded nanoparticles and blank nanoparticles; however, both the hepatic lobe and the portal hepatis maintained their normal architecture. The cisplatin-loaded PLGA-mPEG nanoparticles appeared to be effective in delaying tumor growth in HT 29 tumor-bearing SCID mice. The group of mice treated with cisplatin-loaded nanoparticles exhibited a higher survival rate compared with the free cisplatin group.[43]

Also, nanoparticles based on PLGA and its co-polymer for the delivery of drugs by various routes, which are currently under progress, are listed in Table 1.

Poly (D, L-lactide-co-glycolide) and its co-polymer-based nanoparticles for targeted drug delivery

Magnetic nanoparticles

Magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) are the most commonly used magnetic materials for PLGA-based targeted

Table 1: Selected PLGA nanoparticle formulations studied at the pre-clinical level

Type of drug delivery system	Drug/polymer	Advantages	Reference
Nanoparticles via periodontal route	Triclosan/PLGA	Effective periodontal applications	[33]
Nanoparticles via oral route	Paclitaxel/PLGA	Enhanced cancer cell uptake	[34]
Nanoparticles via oral route	Ellagic acid/PLGA	More free radical scavenging activity	[35]
Nanoparticles via oral route	Streptomycin/PLGA	Formulation without nephrotoxicity	[36]
Nanoparticles via oral route	Estradiol/PLGA	Better oral bioavailability	[37]
Nanoparticles via oral route	Cyclosporine/PLGA	Potent carrier for oral administration	[38]
Nanoparticles via parenteral route	Gentamicin/PLGA	Effective in Brucellosis	[39]
Nanoparticles via parenteral route	Risperidone/PLGA	Antipsychotic effect with fewer adverse effects	[40]
Nanoparticles via parenteral route	Adriamycin/PLGA-PEG*	Effective carrier for cancer therapy	[41]
Nanoparticles via parenteral route	Alendronate/PLGA-PEG*	For potent bone targeting	[42]
Nanoparticles via parenteral route	Cisplatin/PLGA-PEG*	Effective in cancer therapy	[43]

*Stealth nanoparticles prepared with PLGA co-polymer; PEG = Polyethylene glycol

drug delivery due to their good chemical stability and biocompatibility.[44]

Novel applications of magnetic nanoparticles are expected in the field of cancer thermal treatment, magnetic targeting, imaging and remotely triggered targeted drug release.[2] Recently, magnetic material (nanoparticles)-loaded PLGA nanoparticles are developed to target the cancer site under the influence of external magnets. If cancer drugs are loaded into such PLGA nanoparticles, such a system will offer an increased therapeutic activity at lower doses with fewer toxic effects.[45]

Ngaboni Okassa *et al*.[45] developed biodegradable PLGA nanoparticles loaded with magnetite/maghemite nanoparticles for intravenous drug targeting. Magnetite-loaded PLGA particles were prepared by a modified double emulsion method (w/o/w) or by an emulsion-evaporation process (o/w). The influence of some experimental parameters, such as types of magnetite/maghemite nanoparticles, volume of magnetite suspension and amount of polymer were investigated. The morphology, size and zeta potential of the magnetite/PLGA nanoparticles were determined. The magnetite entrapment efficiency and magnetite content were assessed by dosing iron in the composite nanoparticles. Transmission electron microscopy photomicrographs showed that the composite nanoparticles were almost spherical in shape, with a rather monomodal distribution in size. All composite nanoparticle formulations were found to have the mean diameter within the range of 268-327 nm with a polydispersity index within the range of 0.02-0.15. Magnetite nanoparticles coated with oleic acid showed more efficient entrapment (60%) as compared with uncoated magnetite nanoparticles (48%).

Polymeric nanomicelles

Polymeric nanomicelles, self-assemblies of block copolymers, have a fairly narrow size distribution in the range of 10-100 nm and are characterized by their unique core-shell architecture, in which an inner core (PLGA) loaded with hydrophobic drug is surrounded by an outer shell of hydrophilic layer, such as PEG. The PLGA co-polymer-based polymeric nanomicelles are also used as a targeted drug delivery carrier for various therapies (e.g., cancer therapy).[46]

Yoo and Park[47] have synthesized PLGA-PEG (PLGA co-polymer)-based polymeric nanomicelles and the primary amino group of doxorubicin was then conjugated to the terminal hydroxyl group of PLGA, which had been pre-activated using p-nitrophenyl chloroformate. The polymeric nanomicelles (PLGA co-polymer-based passive-targeted drug delivery carrier) containing chemically conjugated doxorubicin exhibited a more sustained release profile than PLGA-PEG nanomicelles containing physically entrapped doxorubicin. The cytotoxic activity of the micelles against HepG2 cells was greater than free doxorubicin, suggesting that the nanomicelles containing conjugated doxorubicin were more effectively taken up cellularly by an endocytosis mechanism rather than by passive diffusion.

CONCLUSION

PLGA is a suitable biomaterial or polymer for the preparation of novel drug delivery systems due to its biodegradability and biocompatibility. The present review summarized the recent studies on PLGA and its co-polymer-based polymeric nanoparticles. PLGA-based polymeric nanoparticles loaded with different drugs showed effectiveness in their respective therapies. The stealth nanoparticles based on the PLGA co-polymer are developed to overcome the opsonization process during i.v. administration for an improved and targeted drug delivery.

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