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REVIEW

# Recent advances in PLGA particulate systems for drug delivery

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**Abstract** PLGA is a FDA-approved biocompatible and biodegradable polymer that is widely used in biomedical fields including drug delivery. Micro and nanoparticles based on PLGA have been extensively studied as drug delivery systems. Numerous studies proved that PLGA particulate systems are highly promising drug carriers for tumor targeting as well as pulmonary, oral, ophthalmic and vaginal delivery. PLGA particles can load a variety of classes of drugs including peptides, proteins and siRNA, protect unstable drugs in the body and have an ability to adapt versatile surface functionalities. PLGA particle systems have evolved with advancement of nano and biotechnology in the past decade. This review focuses on novel and innovative PLGA-based particulate drug delivery carriers in recent years.

**Keywords** PLGA · Nanoparticles · Microparticles · Drug delivery · Biocompatible drug carrier

Several problems associated with free drugs such as low solubility, poor stability and unwanted side effects, had led to developing novel drug delivery systems (Yoo et al. 2011b). Although various innovative delivery systems have been introduced, there still remains need for further improvement of the issues. Past few decades particle-based delivery systems have been enormously investigated to resolve the problems. The particulate systems have unique advantages over convention formulations, such as protection of unstable drugs, controlled release and targeting ability. Among an array of particulate systems, e.g., polymeric particles, liposomes, micelles, inorganic nanoparticles, PLGA-based micro and nanoparticles are one of the most frequently studied delivery carriers.

Poly(D,L-lactide-co-glycolide), PLGA, is a copolymer composed of lactic acid and glycolic acid (Fig. 1). PLGA is one of a few polymers approved by the US FDA for medical purposes due to biodegradability and nontoxicity (Di Toro et al. 2004). PLGA in the body degrades by hydrolysis into endogenous monomers, lactic acid and glycolic acid, which subsequently degrade to water and carbon dioxide, resulting in ignorable toxicity (Wu 1995). By properly choosing molecular weights, the degradation time of PLGA can be modulated from a week to several months, thus enabling drug release in a controlled or sustained manner. Lupron Depot that releases human growth hormone for a month is the first FDA-approved PLGA microparticles implant system. Several other implantable PLGA microparticles have been developed for controlled release of various drugs, some of which obtained the FDA approval. PLGA microparticles have also been widely studied for controlled drug release of oral and pulmonary formulations (Aguiar et al. 2004; Bhavane et al. 2003; Carino et al. 2000; des Rieux et al. 2006; Dong and Feng 2005; Evora et al. 1998). Nano-sized particles prepared with PLGA are an attractive delivery carrier. A majority of PLGA nanoparticle have been utilized as a tumor-targeting carrier. The small size (less than ~200 nm) and drug loading capacity of PLGA nanoparticles enable targeted delivery to tumors via the enhanced permeability and retention (EPR) effects (Acharya and Sahoo 2011). Surface

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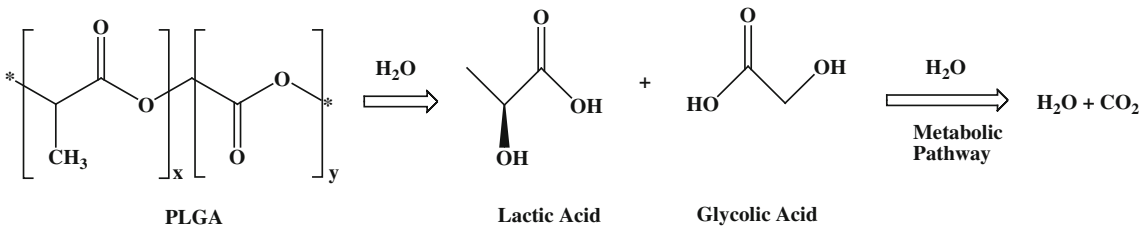


**Fig. 1** Chemical structure of PLGA and its biodegradation by hydrolysis in the body PLGA

modification with polyethylene glycol (PEG) make the nanoparticle evade immune responses and reside in the blood circulation for longer time (Gref et al. 1994), thus enhancing the EPR effects. Non-spherically shaped PLGA particles would also increase the circulation time by avoiding phagocytosis by macrophages (Champion et al. 2007; Yoo and Mitragotri 2010). Moreover, PLGA nanoparticles are known to enter cells via endocytosis and are able to escape from endosome to release drugs into cytoplasm (Panyam et al. 2002).

As nano- and biotechnology grow rapidly, PLGA particle systems have evolved for more efficient delivery function. In this review, we summarize the recent drug delivery approaches based on PLGA particle systems in tumor targeting and various administration routes. Although there are countless publications involving PLGA particle systems, here we focus on novel and innovative studies which have not been attempted before.

## Tumor targeting

Despite better understanding of tumor biology and advancement in diagnostic technologies and treatments, a majority of current cancer therapies still involve aggressive processes including surgery, radiation and chemotherapy, which destroy tumor as well as healthy cells, causing unwanted side effects to patients. It would be therefore desirable to develop effective treatments that have an ability to precisely target and kill the cancer cells while leaving healthy cells unaffected. Efforts have been made to develop nanoparticles that allow chemotherapeutics to accumulate exclusively in cancer cells either passively or actively (Brigger et al. 2002). Nano systems can offer various advantages over free drugs in anticancer drug delivery (Peer et al. 2007); (1) protection of the drug from premature degradation, (2) enhancement of drug deposition into target tumors, (3) control of the PK/PD profile, and (4) improvement of intracellular penetration. Among various polymers and inorganic materials that have been used for tumor-targeting systems, PLGA have long been employed to target tumor cells and delivery antitumor agents in a controlled manner. In recent years, a number of innovative and novel tumor-targeting approaches using PLGA particles have been developed to enhance tumor targeting ability, thus improving therapeutic effects.

Active targeting can be achieved by tethering targeting ligands on the particle surface, which recognizes a cell-surface target, followed by uptake of the particles into tumor cells via endocytosis. Traditionally, transferrin and folic acid have been used for PLGA nanoparticles as tumor-targeting ligands (Patil et al. 2009b; Sahoo and Labhasetwar 2005). Several new targeting ligands have been recently introduced and evaluated.

Antibodies that specifically interact with the receptors can be good candidates for an active tumor-targeting ligand. Fas receptor is a member of the tumor necrosis factor (TNF) super family, which expresses on the plasma membrane of various tumor cells (Arruebo et al. 2009; Balamurugan et al. 2008). McCarron et al. (2008) incorporated camptothecin into PLGA nanoparticles and functionalized the surface with anti-Fas antibody. The anti-Fas-functionalized PLGA nanoparticles were internalized into human colorectal cells more effectively than plain counterparts. $IC_{50}$ value was also significantly decreases with antibody-PLGA nanoparticles as compared to a camptothecin solution and non-coated nanoparticles, indicating anti-Fas antibody is a good tumor-targeting ligand. Epidermal growth factor receptor (EGFR) was used as a target receptor for targeted PLGA nanoparticles. EGFR is highly expressed on a variety of tumors including breast cancer and ovarian cancer (Rogers et al. 2005). Acharya et al. (2009) conjugated anti-EGFR antibody on rapamycin-loaded PLGA nanoparticles. The antibody-coated PLGA nanoparticles showed greater antiproliferation activity by arresting a cell-cycle at G1 phase and more apoptosis as well as necrosis in MCF-7 cells in comparison to non-targeted nanoparticles.

Aptamers are oligonucleic acid or peptide molecules that bind to a target molecule with high affinity and selectivity (Levy-Nissenbaum et al. 2008). Since aptamers can be produced by chemical synthesis, they are a good alternative to antibodies which requires intensive works and high cost for production. Dhar et al. (2008) prepared the aptamers-labeled PLGA nanoparticles containing anticancer drug, cisplatin, for the treatment of prostate cancer. The aptamers was used to target the prostate-specific membrane antigen which is

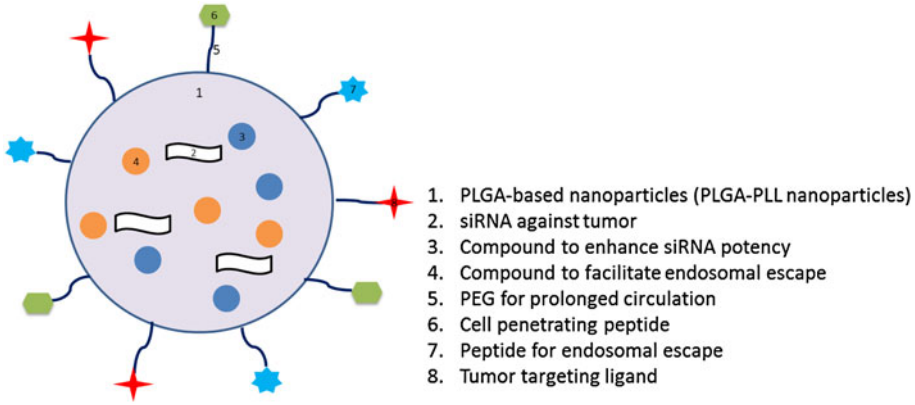


**Fig. 2** Multifunctional PLGA-based nanoparticles for tumor targeting [modified from Zhou et al. (2012)]

overexpressed in prostate cancer. The aptamers–cisplatin–PLGA nanoparticles showed increased cellular uptake of cisplatin and even higher toxicity as compared to free cisplatin or nanoparticles without aptamers. In another study, paclitaxel-loaded PLGA nanoparticles were surface-functionalized with anti-nucleolin aptamers (Aravind et al. 2012). The presence of aptamers substantially promoted cellular uptake of the nanoparticles and enhanced apoptotic activities.

Peptides have also been utilized as tumor-targeting ligands. RGD, a tripeptide arginine–glycine–aspartic acid specifically bind to the $\alpha_v\beta_3$ integrin which are highly expressed only tumor endothelial cells (Brooks et al. 1994). RGD-coated PEGylated PLGA nanoparticles were developed to delivery paclitaxel to tumors (Danhier et al. 2009). In vivo study in mice demonstrated that anti-cancer activity of PLGA nanoparticles are considerably enhanced in the presence of RGD in comparison to non-targeted ones. Luo et al. (2010) investigated whether LyP-1, a 9-amino acid cyclic peptide, which was identified by an in vivo phage display technology has a targeting ability to lymphatic tumors. LyP-1-functionalized PLGA-PEG nanoparticles were fourfold more effectively internalized into tumor cells in vitro and eightfold more effectively accumulated in lymphatic metastatic tumors in vivo.

PLGA nanoparticles have been used for delivery of small interfering RNA (siRNA) for targeted gene silencing because they can protect the rapid degradation of siRNA in plasma and cytoplasm by various RNase and facilitate cellular uptake (Zhang et al. 2007). Zhou et al. (2012) developed multifunctional PLGA nanoparticles that are suitable for siRNA delivery. The multifunctional nanoparticles, so called octa-functional nanoparticles, were fabricated with PLGA-PLL-PEG-iRGD and loaded with siRNA against PLK1 for modulating tumor growth. The octa-functional nanoparticles showed siRNA stabilization, controlled release of siRNA, endosomal escape, tumor targeting, cell penetration and prolonged knockdown of PLK1, proving the true multifunctional ability (Fig. 2). Gene silencing by siRNA was also employed to knockdown the drug efflux transporter to overcome tumor drug resistance. Patil et al. (2010) prepared paclitaxel-loaded PLGA nanoparticles along with siRNA against P-glycoprotein (P-gp) and functionalized the nanoparticles with biotin for active targeting. In vitro study showed that cell cytotoxicity was significantly increased when siRNA against P-gp was co-encapsulated with paclitaxel as compared to when only paclitaxel was loaded. In vivo study demonstrated that siRNA efficiently inhibit P-gp expression, resulting in significantly improved inhibition of tumor growth. Although PLGA nanoparticles have potential to delivery siRNA, one should be aware of the fact that a low loading efficiency of siRNA in PLGA nanoparticles are still a barrier for PLGA nanoparticle-based siRNA delivery systems.

Another strategy to avoid multidrug resistance is the co-encapsulation of P-gp modulators with anticancer drugs. Song et al. (2009) loaded vincristine into PLGA nanoparticles along with a P-gp inhibitor, verapamil. Patil et al. (2009a) fabricated PLGA nanoparticles which encapsulated with paclitaxel and third generation of P-gp inhibitor, tariquidar. Both studies demonstrated that addition of P-gp modulators to anticancer drug-loaded PLGA nanoparticles is able to reverse the multidrug resistance and synergistically enhance cytotoxicity in drug-resistance tumor cells.

## Pulmonary delivery

Since the lung is an organ that is directly connected from the outside, pulmonary drug delivery is an attractive way for the treatment of local lung diseases such as lung cancer, cystic fibrosis and tuberculosis. The lung has ~300 million alveoli providing extremely high surface area with a well-developed capillary network and low enzymatic activities, which makes efficient absorption of drugs and macromolecules for systemic delivery (Sung et al. 2007). Lack of targeted deposition and rapid elimination of drugs

are, however, barriers for effective pulmonary delivery (Beck-Broichsitter et al. 2012). Particulate systems containing therapeutic agents have been extensively investigated to circumvent the problems for effective treatments of various lung diseases. Due to non-toxicity for lung tissue and lung macrophages (Coowanitwong et al. 2008; De Stefano et al. 2011; Hara et al. 2008), PLGA micro and nanoparticles have been widely used for pulmonary particulate delivery systems.

Inhalable PLGA particles have been used for the treatment of lung. Susarez et al. (2001) developed and evaluated PLGA microparticles loaded with rifampicin. The PLGA particles were intended to target alveolar macrophages to reduce systemic toxicity. Rifampicin-PLGA particles were administered by nebulization and insufflation methods, showing 10-fold-reduced lung bacterial burden as compared to rifampicin alone. Very recently, PLGA nanoparticles systems embedded in a microcarrier, called nano-embedded micro-particles (NEM) have been developed for lung delivery of antibiotics (Ungaro et al. 2012). In this study, lactose was used as an inert microcarrier to ameliorate flow and aerosolization properties and tobramycin, which is a first line drug for cystic fibrosis treatment, was used as an antibiotics. On the surface of PLGA nanoparticles, various helper polymers such as alginate and chitosan were used for optimization of particle properties. The results showed that the dry powder of NEM formulation provided a good flow and deposition to lung, while unique features of PLGA nanoparticles were preserved.

Pulmonary gene delivery is a promising strategy for treating lung diseases. DNA vaccine, which uses DNA encoding tuberculosis antigen to induce immunogenicity, is an attractive strategy for tuberculosis control. For pulmonary DNA delivery, PLGA nanoparticles were fabricated in the presence of a cationic polymer, polyethyleneimine (PEI) (Bivas-Benita et al. 2004). The PLGA–PEI nanoparticle showed a cellular uptake by human bronchial epithelial cells, resulting in protein expression. The same nanoparticles also showed effective in vivo proliferation of T cells and interferon-$\alpha$ production by aerosol inhalation in mice whereas intramuscular administration of the same DNA vaccine was not as effective (Bivas-Benita et al. 2009). siRNA has also been encapsulated in PLGA nanoparticles for pulmonary delivery. Jensen et al. (2012) prepared siRNA-loaded PLGA nanoparticles using a cationic lipid to improve the gene silencing activity. The nanoparticles were then spray dried with a sugar excipient to an inhalable dry microparticle powder, which is similar to NEM approach as mentioned above. The final dry powder containing PLGA-siRNA nanoparticles had good aerodynamic properties while preserving gene silencing activity of siRNA. This study suggested that spray-dried powders composed of PLGA-siRNA nanoparticles have potential for pulmonary siRNA delivery.

The lung is an attractive delivery route of therapeutic proteins, which has a low oral bioavailability due to an enzymatic degradation and a poor absorption. Insulin is the most widely studied protein for pulmonary applications. PLGA particulate systems have been employed to improve therapeutic effects of insulin via lung. The PLGA-insulin PLGA particles were often suspended in an aqueous solution and administered by a nebulizer (Kawashima et al. 1999). While the nebulized PLGA-insulin particles prolonged a release profile and protected insulin from an enzymatic degradation, a severe burst release of insulin was observed. In order to avoid an aqueous formulation and provide a portability and convenience, dry powder systems have been attempted in recent years. Insulin-loaded PLGA microparticles fabricated by using an oil-in-oil method showed a minimized burst release and improved protein stability in vitro (Emami et al. 2009). The pulmonary absorption of the same PLGA-insulin microparticles was tested in a diabetic rat model (Hamishehkar et al. 2010). As compared to respirable insulin powder and subcutaneous injection of insulin, inhaled PLGA-insulin microparticles had a sustained release profile and a prolonged hypoglycemic activity, indicating of an effectiveness of the dry microparticle system. Large porous particles (LPP), which enables a deep lung deposition due to their good aerodynamic characteristic and avoidance of phagocytic clearance due to their large size (10–20 μm) (Edwards et al. 1998), also have been adapted for pulmonary insulin delivery. However, a use of salts to make porous PLGA particles may harm a stability of insulin (Pérez and Griebenow 2003). Ungaro et al. (2006) developed insulin-loaded PLGA LPP using hydroxypropyl-$\beta$-cyclodextrin (HP$\beta$CD). HP$\beta$CD is a good osmotic agent while not affecting insulin integrity. The following in vivo study demonstrated that the PLGA LPP administered by a dry powder inhaler reaches the alveoli region and significantly lowers blood glucose level as compared to the sprayed insulin solution of the same dose (Ungaro et al. 2009).

## Oral delivery

Oral is the most widely used route for drug delivery due to high absorptive surface area in the gastrointestinal track and high patient acceptance. Despite the obvious advantages, poor solubility and low stability by an enzymatic degradation, which result in poor bioavailability, limit the use of many drugs including peptides, proteins and chemotherapeutics. Recently, nanoparticle systems have emerged as an alternative formulation to overcome the problems because they have unique properties such as a protection of drugs, a targeted delivery and a controlled release (Ensign et al. 2012).

One of the most difficult drugs to deliver via the oral route is insulin (Damgé et al. 1990). High hydrophilicity, molecular weight and susceptibility to enzymes make insulin challenging to be absorbed from the gastrointestinal mucosa. To improve the bioavailability of insulin, PLGA nanoparticles encapsulated with insulin–sodium oleate (SO) complex was developed (Sun et al. 2010). Since insulin is too hydrophilic to obtain a sufficient loading amount in hydrophobic PLGA nanoparticles, SO, an anionic surfactant, was used to form a complex system with positively charged insulin, thus increasing hydrophobicity (Sun et al. 2008). The loading efficiency of insulin was approximately 90 %. In vivo study showed that oral administration of insulin–SO complex-loaded PLGA nanoparticles significantly enhanced bioavailability and reduced the blood glucose level for a prolonged period of time. In another study, dual-functional PLGA nanoparticles were designed to efficiently delivery insulin to the upper region of the small intestine (Wu et al. 2012). To enhance the penetration of insulin into mucosal layer, cationic polymer, Eudragit® RS, was incorporated with PLGA to prepare the cationic nanoparticles. Then the nanoparticles were placed in the enteric capsule coated with pH-sensitive hydroxypropyl methylcellulose phthalate (HP55) for preventing the premature release in the stomach. The insulin-loaded dual-functional PLGA nanoparticles reduced blood glucose levels in diabetic rat model for an extended period of time. The results of studies presented above imply that protein or peptide drugs including insulin might be orally delivered by PLGA nanoparticles with improved bioavailability.

In addition to insulin, other classes of drugs have been loaded in orally applicable PLGA nanoparticles. Kalaria et al. (2009) designed PLGA nanoparticle systems for oral delivery of doxorubicin, which has low oral bioavailability due to the first-pass metabolism, and found that doxorubicin-loaded PLGA nanoparticles markedly increased the oral bioavailability for prolonged time, presumably because of the sustained release of doxorubicin for the nanoparticles. The same research group investigated PLGA nanoparticles for oral delivery of estradiol (Mittal et al. 2007) and amphotericin B (Italia et al. 2009), and demonstrated that bioavailability of both drugs can be significantly improved by PLGA nanoparticle systems. Curcumin was incorporated in PLGA nanoparticles by a similar method described above and its oral bioavailability was improved by ninefold as compared to an oral curcumin solution with absorption enhancers (Shaikh et al. 2009).

## Ophthalmic delivery

A rapid clearance by lacrimation, tear dilution and tear turnover, leads to a poor bioavailability of eye drops, which is the most commonly used eye formulation. Other ophthalmic formulations such as gels and ointments also have problems of blurred vision, sticking of the eye lid and low patient compliance (Ali and Lehmussaari 2006). The impediments of currently used formulations have accelerated research on novel ophthalmic delivery systems composed nanoparticles. Nanoparticles of biodegradable polymers can load various types of therapeutic cargoes, for examples, a poorly water-soluble drugs, proteins and genes and release them in a controlled or sustained manner. Since nanoparticles dispersed in a liquid vehicle have a similar viscosity of conventional eye drops, they would have a good patient acceptance (Nagarwal et al. 2009). Mucoadhesive property can be added for higher penetration and prolonged residence time. Recently, PLGA nanoparticles have been studied for efficient delivery of an array of drugs to eyes.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used drugs to manage ocular inflammations and prevent intra-operative miosis and cystoid macular edema, but their low ocular bioavailability limits the use of the drugs (Badawi et al. 2008). Vega et al. (2008) have developed PLGA nanoparticles containing flurbiprofen (FB) to improve the ocular bioavailability which is low with the commercially available eye drop formulations such as Oculflur®. FB was efficiently loaded into PLGA nanoparticles and the nanoparticles released the drug in a controlled manner. The ex vivo study revealed that the corneal permeability of FB was increased by twofold as compared to Oculflur® and by fourfold as compared to FB solution in a pH 7.4 phosphate buffer. Corneal hydration did not change after the application of FB-PLGA nanoparticles, indicating that nanoparticles have no damage to eye tissues. In a following study, it was found that the FB-loaded nanoparticles were physicochemically stable over 75 days and were not irritant to ocular tissues (Araújo et al. 2009). Diclofenac sodium, a poor water-soluble NSAID, was also formulated to nanoparticles using PLGA (Agnihotri and Vavia 2009). Diclofenac-loaded PLGA nanoparticles improved corneal adhesion and did not show any irritancy on cornea, iris and conjunctiva for up to 24 h.

A poorly water-soluble anti-bacterial drug, sparfloxacin, was formulated into PLGA nanoparticles. As compared to marketed eye drop formulations, a drug release profile, precorneal residence time and ocular penetration were improved with the PLGA nanoparticle system. The ocular tolerability study using hen's egg chorioallantoic membrane test demonstrated that the PLGA nanoparticles are not irritant (Gupta et al. 2010).

Chang et al. (2011), reported on doxycycline-loaded PLGA microparticles for protecting a corneal barrier disruption in dry eye. Instead of nanoparticles, microparticles were chosen for higher loading efficiency and prolonged drug release to overcome inconvenience of daily dose of

eye drops. The drug-loaded microparticles in a diameter of 4.6 μm were administered by subconjunctival injection into dry eyes in mice. The results showed that doxycycline-loaded PLGA microparticles had as efficacious as a daily administration of eye drops for 5 days.

Ocular delivery of peptide drugs were attempted using PLGA microparticles. Gavini et al. (2004), fabricated PLGA microparticles encapsulated with a peptide anti-bacterial drug, vancomycin. To increase the drug loading efficiency, a novel fabrication method, an emulsification/spray-drying technique, was used instead of a double-emulsion method which is commonly used for protein or peptide encapsulation in PLGA particles. In a rabbit model, vancomycin concentration in the aqueous humor was increased for prolonged time as compared to vancomycin solution. Interestingly, authors added hydroxypropyl cellulose as a suspending agent to PLGA microparticles to improve the residence time and bioavailability; however, the ocular bioavailability did not change, implying that the size of PLGA microparticles can reside in the cul-de-sac and precorneal area, releasing the drug in a controlled manner.

The ocular residence time can be further prolonged with mucoadhesiveness. Jain et al. (2011), developed PLGA–chitosan nanoplexes for the purpose. Using a fluorescent dye, the residence time of the nanoplex system and a fluorescent solution were compared. The nanoplexes showed prolonged residence time and higher paracellular and transcellular uptake of the dye as compared to the dye solution, implying that chitosan opens tight junctions and enhances endocytosis processes.

## Vaginal drug delivery

A majority of vaginal drug delivery systems are intended for the treatment or the prevention of local vaginal abnormalities such as HIV infections, even though well-developed blood vessels under vaginal walls makes the vagina a promising route for a systemic delivery (Yoo et al. 2011a). Particulate systems are suitable to vaginal application due to their thixotropic properties and resistance from pH changes in vaginal mucosa (Lee et al. 2009). Nanoparticle delivery systems to the vagina have advantages of a once-a-day vaginal application which can improve patients' compliance. Since nanoparticles with a diameter of less than 300 nm are able to permeate mucosal membranes which have an average pore size of 340 nm (Lai et al. 2010), they can be evenly distributed in the vaginal cavity which are composed of the highly folded epithelial surfaces (Whaley et al. 2010). These benefits have accelerated development of novel vaginal delivery systems using micro and nanoparticles.

Vaginal applications of topical microbicides utilizing PLGA nanoparticles have been developed for the prevention and treatment of HIV-1 infection. Ham et al. (2009), prepared PLGA nanoparticles containing an analog of naturally occurring chemokine, PSC-RANTES, which modulate a fusion between virus membrane and the cell membrane. By incorporating the drug into PLGA nanoparticles, tissue uptake was increased by five times and tissue permeability was significantly enhanced as compared to the unformulated drug. Degradation of the PSC-RANTES can be also protected in the nanoparticles. A commercialize microbicide, tenofovir, was formulated by PLGA nano systems for a controlled release. Zhang et al. (2011) developed novel pH-sensitive tenofovir-loaded nanoparticles composed of PLGA and pH-sensitive polymer, Eudragit-S100. The release rate of tenofovir was controlled by changing a ratio of PLGA and Eudragit-S100. The nanoparticles did not induce any toxicity for 48 h in vaginal cells and *Lactobacillus crispatus*, suggesting that the novel pH-sensitive nano system is a promising strategy for anti-HIV microbicide delivery.

Blum et al. (2011), fabricated topical PLGA nanoparticles loaded with anticancer drug, camptothecin for the prevention of intravaginal tumor. To test the effectiveness of the nanoparticle system, a vaginal tumor model was established in mice. Camptothecin-loaded PLGA nanoparticles administered by intravaginal lavage completely prevent tumor growth, indicating that topical PLGA nanoparticles are an effective delivery system for the treatment of vaginal tumors.

Since vaginal delivery siRNA using liposomes cannot provide a controlled or sustained release, PLGA nanoparticles were investigated as an alternative to siRNA delivery system. Woodrow et al. first developed siRNA-loaded PLGA nanoparticles with a high siRNA loading efficiency. The PLGA nanoparticles showed a deep-penetration into vaginal epithelial tissues and induced effective and prolonged gene silencing activity, implying that various siRNA targeting HIV-1 and tumors can be used for vaginal delivery. In a following study, surface-modified PLGA nanoparticles with mucoadhesive avidin and PEG were prepared to find optimal in vivo distribution in a vaginal cavity (Cu et al. 2011). It was found that PEG-modified PLGA nanoparticles were more effectively penetrate mucus layers and entered vaginal epithelial cells than avidin-modified ones, implying that when designing particulate systems to deliver drug to vaginal cells, surface modification should be rationally considered.

A female sexual arousal disorder is caused by an insufficient vaginal blood flow. Nitric oxide (NO) is a naturally occurring strong vasodilator. However, very short half-life (a few second) of NO impeded the development of NO-delivery systems. Yoo et al. (2010b) developed a novel NO-releasing PLGA microparticles for virginal applications. DETA NONOate, a NO donor, was used since NO is a gas molecule and cannot be directly incorporated into the particles. It was found that oil-in-oil method protect DETA NONOate during the fabrication process, resulting in a high loading efficiency

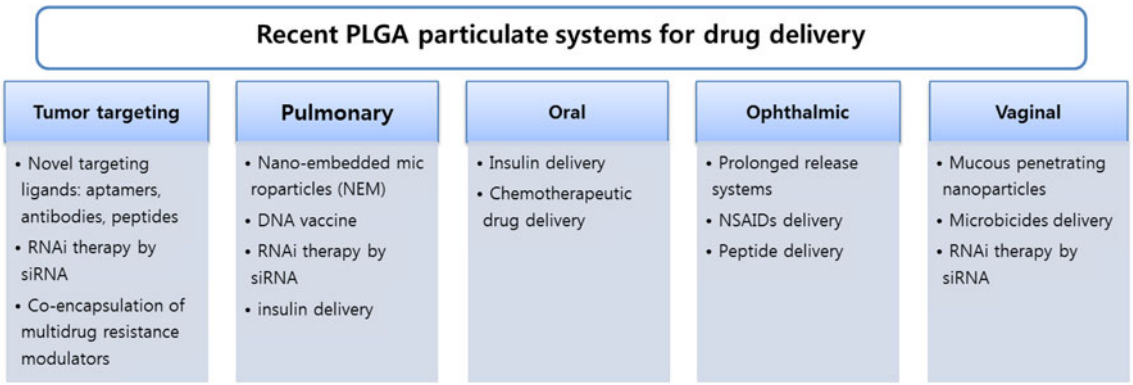


**Fig. 3** Summary of recent advances of PLGA particulate drug carriers

of the NO donor. The NO released from the microparticles was found to effectively penetrate a vaginal cell layer and increased the intracellular cGMP level. A following in vivo study in mice demonstrated that the NO-releasing PLGA microparticles are able to significantly increase the vaginal blood flow for the prolonged period of time, suggesting that NO-releasing PLGA microparticles are a promising treatment option for female sexual arousal disorder (Yoo et al. 2010a).

## Conclusion

PLGA micro- and nanoparticles have long been studied for a number of biomedical applications including drug delivery. A good biocompatibility and drug loading capacity as well as modifiable surface properties are key properties that made PLGA particle systems versatile. PLGA particles were used to encapsulate poorly soluble drugs as well as hydrophilic drug such as proteins, peptides, genes and siRNA. Novel fabrication methods such as pore-generating techniques enabled high loading efficiency of various hydrophilic drugs. To improve the performance, different types of materials including chitosan and PEG were mixed or chemically conjugated with PLGA to prepare the particles. Surface of the nanoparticles were functionalized for prolonged circulation time and active targeting. In this review, a variety of recently developed PLGA particles systems have been introduced (Fig. 3). This information would lead to more effective PLGA-based particulate drug delivery systems.

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