PLGA Based Nanoparticles for Targeted Drug Delivery – A Review

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ABSTRACT

Many scientists developed poly (lactic co-glycolic acid) (PLGA) nanoparticles, which are recognized as an enabling technology in the field of nanomedicine. This article reviews the current advancements in the design, characterization, and use of PLGA nanoparticles as a drug-delivery tool. It highlights the shift from batch fabrication to microfluidics for the preparation of nanoparticles, since it enhances the dimensional size and monodispersity of nanoparticles. This article also highlights crucial advancements in interfacial science, i.e., Stealth PEGylation, mucus-penetrating, and platelet membrane cloak technologies. Moreover, it explores the range of different applications, including the use of nanoparticles to convey highCRISPR-Cas9 plasmids, anti-cancer therapeutic applications to induce necroptosis, anti-chronic inflammatory respiratory disease, and many other usages. It mentions some issues, such as the phenomenon of the protein corona, the need to use standardized in vitro models, and the necessity to develop new standardized in vitro models, yet it concludes that PLGA nanoparticles are still an enabling design technology, since, through "design-by-intent" methodology, it can accommodate the need to develop novel targeted therapies.

KEYWORDS: PLGA nanoparticles, Targeted drug delivery, Microfluidics, Bio-interfacial engineering, Gene therapy, Bio-degradable polymers

INTRODUCTION

Polymeric nanoparticles (NPs) composed of poly (lactic-co-glycolic acid), commonly referred to as PLGA NPs, have proven to be a revolutionizing agent in the nanomedicine application area. PLGA is well established for its uses, approved as a biocompatible drug-delivery system and acceptable for use in the body due to its degradation times, making it an apt candidate for the encapsulation of a variety of drugs such as small molecules, nucleic acids, and proteins. PLGA is a biodegradable substance that degrades in the body into lactic and glycolic acid monomers that are metabolized with low toxicity [1].

These nanocarriers have immense advantages over conventional drug delivery systems by displaying improved bioavailability and the ability to protect sensitive drug molecules from degradation. Importantly, the PLGA-NPs promote targeted drug delivery and sustained release of the drug, thereby allowing the administration of low doses and less frequent administration that can reduce severe side effects. For example, the nanoparticles have the ability to cross intestinal barriers for transcellular and paracellular routes and are therefore useful for the treatment of intracellular infections [2].

Despite the advantages associated with the nanoprecipitation process, control over the size and polydispersity of the nanoparticles remains a limiting issue associated with large-scale production. Although the conventional methods of nanoprecipitation and double emulsion are the most commonly adopted for nanoparticle synthesis, they have limitations that lead to nonhomogeneous mixing. Microfluidic technologies are currently offering control over the flow and are helping create rapid nucleation that enables the synthesis of safe PLGA nanoparticles [3].

EMERGING FABRICATION AND CHARACTERISATION PHILOSOPHIES

In the preparation of PLGA nanoparticles for targeting drug delivery, the move from traditional batch preparation to the evolving microfluidic philosophy is a major improvement in preparation accuracy. Traditional batch methods, such as nanoprecipitation, involve the spontaneous precipitation of polymers when an organic phase is added to an aqueous phase. Even though these methods are useful in preparing particles in a 100-200 nm size range that are spherical in shape, which are ideal for cancer treatment, these particles are often preparatively dependent on factors such as the concentration of the polymers, the solvent used, and the temperature conditions of the preparation. For instance, size is determined by the diffusion coefficient (Dpw) of the solvent in water; a greater Dpw leads to a smaller particle size [1].

MICROFLUIDICS VS. BATCH METHODS

The conventional nanoprecipitation in a batch process is also used due to its ease of operation, low cost, and simplicity in equipment requirements [1]. Nevertheless, the scalability of the process is usually limited due to the micromixing dynamic issues. To some extent, these issues have become a serious concern, and as such, methodologies such as the Design of Experiments (DoE) have been used to optimize a key variable, such as the concentration of the polymer, as identified in the particle formation process, which is a major variable in the determining of particle size [4].

On the other hand, microfluidics presents a paradigm shift which is marked by quick and homogeneous mixing, as well as highly controlled flow conditions. Unlike other batch techniques, microfluidic devices employ unique channel configurations, namely staggered herringbone mixers, which incorporate chaotic advection and therefore enhance rapid interactions and controlled nucleation between the reactants. Such controlled conditions pose an intrinsic advantage in producing nanoparticles which are not only small and monodisperse, but also highly stable. Additionally, unique inlet configurations, namely three-inlet junctions, have been reported to offer a better alternative compared to improved Y-junction designs by providing greater flow and concentration homogeneity, establishing the significance of device design in enabling the synthesis of nanomedicines capable of addressing clinical needs [4].

Table 1: Comparative Analysis of Fabrication Strategies for PLGA Nanocarriers.

FABRICATION STRATEGY	BRIEF DESCRIPTION	KEY ADVANTAGES	KEY LIMITATIONS	REFERENCES
Single Emulsion (O/W)	PLGA and hydrophobic drug dissolved in organic solvent, emulsified in aqueous phase, followed by solvent evaporation.	Widely used for hydrophobic drugs; relatively simple process.	Less suitable for hydrophilic drugs; potential for broad size distribution and residual solvent.	31
Double Emulsion (W/O/W)	Aqueous solution of hydrophilic cargo emulsified in organic PLGA solution, then re-emulsified in aqueous phase.	Better suited for hydrophilic biomolecules (e.g., proteins, nucleic acids).	More complex process; potential instability or loss of cargo; higher Polydispersity Index (PDI).	32
Nanoprecipitation	PLGA and drug in water-miscible organic solvent are rapidly mixed into aqueous phase causing polymer precipitation.	Simple process; good for hydrophobic drugs; potential for relatively small particles.	Control of mixing is critical; batch-to-batch reproducibility can suffer; less suitable for large biomolecules.	33
Microfluidics-Assisted	Use of microfluidic mixers to precisely control mixing of polymer/drug and aqueous phases.	Excellent control of size and PDI; better reproducibility; scalable potential.	Requires specialized equipment; scaling up may require parallelization; higher initial cost.	34

CHALLENGING THE "HARD PELLET" DOGMA: AUGMENTED COLLECTION METHODS

Conventional approaches for nanoparticle collection are mainly dependent on fast centrifugation for the separation of the synthesized carrier from the free substrates. Nevertheless, the "hard pellet" rule faces many hurdles, as it generally produces a dense, compacted pellet with minimal resuspendability characteristics. Moreover, resuspending such pellets through sonication may have adverse effects on nanoparticle integrity, such as changes in size, shape, and polydispersity indices, as well as compromising the stability of the entrapped therapeutic compounds [5].

Toward resolving such issues, modern augmented harvesting techniques tend to make use of molecular weight (MW)-dependent centrifugal filters. Thus, a protocol using tabletop centrifuges and low-g forces, specifically 200-300 mg, is effective for harvesting nanoparticles. The improvised harvesting techniques circumvent high shear forces, thereby retaining the monodisperse nanoscale size and spherical morphology of the PLGA nanoparticles, leading to higher yields and better results in the targeted delivery system [6].

SOLUBILISATION AND GREEN SOLVENTS

The choice of solvents is a critical factor in the fabrication of PLGA nanoparticles, particularly when encapsulating sensitive therapeutic cargo [7]. Traditional methods often utilize toxic organic solvents such as dichloromethane (DCM) or acetonitrile that can pose residual systemic toxicity risks and denature structure-sensitive proteins. Moreover, harsh surfactants and high-shear agitation associated with conventional protocols can result in further compromise to the integrity of hydrophilic payloads [8].

Such limitations have recently been addressed with the use of "green" or non-toxic solvents, such as glycofurol and isosorbide, in these phase-separation techniques. These alternatives enable the generation of stable nanoparticles in the absence of toxic surfactants. The use of copolymers, such as PLGA-PEG, enhances the solubilization of hydrophilic proteins and imparts "stealth" properties to the carrier. Such a trend toward biocompatible solvent systems ensures that clinically viable nanomedicines are produced with high drug bioactivity and minimal off-target effects [8].

ENGINEERING THE BIO-INTERFACE: TARGETING AND STEALTH

OVERCOMING THE MUCUS BARRIER: MPP VS. MAP

The airway mucus layer provides a profound barrier against the inhalation of PLGA nanoparticles via “size filtration” by the mucin meshworks or “interaction filtration” by adhesive interactions. Conventional mucoadhesive particles (MAPs) are designed to interact with mucins by binding to their cationic or thiolated surface domains; however, they are generally plagued by aggregation phenomena and short physiological residence times [9].

On the other hand, mucus-penetrating particles (MPP) are produced with “muco-inert” surfaces, commonly realized via high-density PEGylation or lipids, to circumvent adhesive-trap confinement. In addition,

studies confirm that MPP with a size below 300 nm demonstrate more homogeneous dispersal in airways and show longer lung residency times than MAPs with a similar size [10].

Most importantly, the manufacturing of the pulmonary delivery system should take into consideration the compatibility of the device; for example, vibrating mesh nebulizers are effective in nebulizing nanoparticles smaller than 200 nm compared to those larger than 500 nm that can clog the micron-size pores. Hence, both size and chemistry play important roles for the effective delivery of the targeted drug through the mucus barrier [11].

TABLE 2: Characteristics of PLGA Nanospheres For Macrophage-Specific Targeting. (SD – Standard Deviation, PDI – Polydispersity Index)

POLYMER	PREPARATION METHOD	SIZE (nm)	PDI	ZETA POTENTIAL (mV)	REFERENCES
PLGA (Lactide: Glycolide) 50:50	Nanoprecipitation (NPM)	157.5	0.06	-27	33
PLGA (Lactide: Glycolide) 50:50	Emulsification Solvent Evaporation (ESE)	91.1	0.09	-22	35
PLGA (Lactide: Glycolide) 75:25	Nanoprecipitation (NPM)	138.0	0.07	-28	36
Branched PLGA	Nanoprecipitation (NPM)	131	0.08	-32	37
Branched PLGA	Emulsification Solvent Evaporation (ESE)	97.7	0.10	-27	38
Purasorb® 5002	Nanoprecipitation (NPM)	145.3 ± 0.8	0.1 ± 0.01	-24 ± 3	39

(SD – Standard Deviation, PDI – Polydispersity Index)

TARGETED BIO-INTERFACING

Actively targeting PLGA nanoparticles involves modifications of the PLGA nanoparticles' surfaces that rely on specific biological interactions for the purpose of promoting cellular uptake.

Functionalization of PLGA nanospheres with targeting ligands makes it possible to specifically target drug delivery to macrophages, taking advantage of their high phagocytic uptake [12]. It has been found that surface modification of the nanoparticle with multifunctional poly(zwitterions)-mannose brush conjugates can enhance multivalent affinity to mannose receptors. This brush architecture shows four times greater

uptake by macrophages compared to the non-brush mannose surface-functionalized nanoparticles. In addition, "stealth" functionality can be provided by surface conjugation of zwitterions, which is equal in functionality to PEGylation in inhibiting blood plasma aggregation [13].

An elegant biomimetic strategy would be the "cloaking" of PLGA cores with biological platelet membranes. The platelet membrane bio interface of these particles enables them to resist immune system-mediated uptake while selectively targeting dysfunctional vasculature and binding specifically to platelet-associated pathogens such as MRSA [14]. The engineered bio-interfaces mentioned above have collectively converted PLGA carriers into highly selective, long-circulating therapeutic systems [12-14].

TABLE 3: Efficacy of Targeted PLGA Nanoparticles on Specific Cancer Cell Lines.

CELL LINE (CANCER TYPE)	TARGETING LIGAND	ACTIVE COMPOUND	PARTICLE SIZE (nm)	CYTOTOXICITY (IC_{50}) / OUTCOME	REFERENCES
U87 (Brain)	Transferrin	Doxorubicin and Paclitaxel	150	0.13 µg mL^{-1} (96 h); Time-dependent effect.	40
SKBR-3 (Breast)	Transferrin	Aromatase inhibitor (7a-APTADD)	170.3	0.00031 to 0.00049 µg mL^{-1} (24 h).	41
H1975 (Lung)	RGD peptide	Paclitaxel	217	0.0017 µg mL^{-1}; Enhanced uptake due to integrin $\alpha_v\beta_3$ targeting.	42
HT-29 (Colon)	Wheat germ agglutinin (WGA)	Paclitaxel	330	0.028 µg mL^{-1}; WGA binds to N-acetyl-D-glucosamine on cell membrane.	43
HepG2 (Liver)	LFC131 peptide	Epirubicin	138	0.78 µg mL^{-1} (24 h); 0.38 µg mL^{-1} (48 h).	44

ADVANCED THERAPEUTIC APPLICATIONS AND MECHANISMS

ONCOLOGY: BEYOND APOPTOSIS TO NECROPTOSIS

PLGA NPs have been increasingly applied to overcome the drawbacks of conventional chemotherapy due to their disadvantages in poor solubility and systemic toxicity [15, 16]. PLGA NPs successfully encapsulate capecitabine in the treatment of prostate cancer with a controlled release profile, maintaining the therapeutic drug level and reducing the off-target effects [16]. For breast cancer therapy, γ-oryzanol-loaded PLGA NPs

enhance drug delivery via improving cellular uptake and inducing significant sub-G1 phase cell cycle arrest in the tumor cells [17]. Apart from the induction of traditional apoptosis, a necroptotic process as a form of programmed inflammatory cell death has recently been shown to be induced by docetaxel-loaded PLGA NPs in lung cancer models. The necroptotic process is based on intracellular calcium ion increase and excessive ROS generation within the tumor microenvironment. The resulting mitochondrial dysfunction with membrane rupture not only destroys primary tumor cells but also releases DAMPs. These DAMPs initiate an immunomodulatory response and could potentially induce a conversion of "cold" tumors to "hot," through the migration of immune cells to this site [15]. Thus, PLGA nanoparticle delivery systems present a dual strategy in treating cancer: through targeted cytotoxicity on cells via necroptosis and the activation of anti-tumour immunostimulatory responses [15, 17].

GENE DELIVERY: LARGE PLASMIDS AND CRISPR-CAS9

The problem of transferring large molecular weight genetic material has been a great challenge when it comes to gene therapy, hence requiring effective carriers such as PLGA nanoparticles (NPs) [18]. PLGA systems are most useful when used to encapsulate large plasmids containing CRISPR-Cas9, effectively shielding them from degradation by DNase – mediated degradation [18, 19].

The use of amine-ended PLGA allows for a high encapsulation efficiency of up to 80%, achieving a loading capacity of up to 1.6 wt% for large DNA molecules. These engineered nanoparticles, averaging a size of 160 nm, can successfully transfect primary bone marrow-derived macrophages, which are typically refractory to transfection [18]. Analysis by double emulsion-solvent evaporation methods has been used to indicate the importance of having a homogenous distribution of size for reproducible transgene expression [19]. The results have also confirmed a controlled release of DNA as the PLGA degrades [18].

Additionally, the encapsulation of plasmids carrying human IFN-λ1/IL-29 genes shows that PLGA NPs maintain the bioactivity of their genetic cargo in immunomodulation approaches [19]. The availability of a secure microenvironment translates to a flexible nanotechnology that can facilitate the application of advanced genome editing and gene expression in a clinical setting [18, 19].

PULMONARY AND VASCULAR THERAPY

PLGA nanoparticles (NPs) provide a smart platform for pulmonary delivery that enables both controlled release and targeted treatment for chronic respiratory disorders [20, 21].

For PAH treatment, tadalafil-loaded PLGA NPs in dry powder inhalers show improved aero dynamic properties for optimal deep lung deposition and drug activity persistence in the lungs [21]. For pulmonary fibrosis treatment, surface-functionalized PLGA NPs using citrus pectin (CP), a targeting ligand, acts by specifically inhibiting the galectin-3 protein involved in pulmonary fibrosis and its subsequent upregulation by enhancing inhibitory activity and preventing systemic cytotoxicity [20].

Moreover, PLGA encapsulation has a pivotal role in countering lung injuries caused by drugs, for instance, the severe pulmonary toxicity commonly observed during amiodarone treatment. By protecting the lung tissue from a high local dose of drugs, these carriers effectively hinder inflammation factors like TNF-α

and IL-1β, thus making these therapeutic drugs much safer to administer [22]. Apart from conventional medicinal drugs, PLGA NPs have been developed to act as biological signalling carriers in the form of extracellular vesicles referred to as Exos originating from mesenchymal stem cells [23].

In vascular and bone pathologies, such "PLGA-Exos" hybrids enable the slow release of regenerative factors to effectively impede the generation of ROS and prevent periprosthetic osteolysis. In vivo imaging confirms that PLGA-based delivery maintains therapeutic concentrations of these vesicles longer than their free administration, promoting osteogenic differentiation and tissue repair [23]. Collectively, these recent advances illustrate the versatility of PLGA NPs in surmounting biological barriers and affording targeted, sustained intervention not only in pulmonary but also in vascular therapeutic scenarios [20-23].

TABLE 4: Inhalable PLGA-Based Nano-Powders for Respiratory Therapy.

DRUG / AGENT	DRUG CLASS	TARGET CONDITION	FORMULATION	REFERENCES
Vancomycin	Antibiotic	Infection	Dry Powder Inhaler (DPI)	45
Clarithromycin	Antibiotic	Infection	Dry Powder Inhaler (DPI)	46
Tacrolimus & Cyclosporine A	Immunosuppressant	Lung transplant rejection prevention	Dry Powder Inhaler (DPI)	47
Budesonide	Glucocorticoid	Asthma and COPD	Dry Powder Inhaler (DPI)	48
Ciprofloxacin	Antibiotic	Cystic Fibrosis	Dry Powder Inhaler (DPI)	49
Paclitaxel	Microtubule inhibitor	Lung Cancer	Dry Powder Inhaler (DPI)	50
Rifampicin	Antibiotic	Tuberculosis	Dry Powder Inhaler (DPI)	51
Doxorubicin	Anticancer agent	Lung Cancer	Dry Powder Inhaler (DPI)	52

STABILITY, SAFETY, AND THE PROTEIN CORONA

The clinical efficacy of PLGA nanoparticles (NPs) relies to a large extent on their stability in physiological systems. Once exposed to biological fluids, PLGA nanoparticles are rapidly covered by a "protein corona," a layer of adsorbed protein that plays a critical role in immunological and metabolic systems. The protein corona may affect the stability of nanoparticles and could cause them to aggregate or trigger leakage if not controlled properly. For neuro-therapeutic targets, localized drug delivery through gelatin-coated nerve implant devices has been explored to improve the stability of minocycline-loaded PLGA nanoparticles. This method relies on a non-cross-linked matrix composed of gelatin to retain nanoparticles in a protective system, which evades systemic elimination. These systems mitigate acute brain tissue responses and microglial activation in mice, through the local and sustained administration of therapeutics. Moreover, PLGA is highly biocompatible, since this polymer degrades into non-toxic lactic and glycolic acid

monomers. This degradation profile is critical for maintaining the integrity of the neural interface and preventing long-term foreign body responses. Finally, understanding the interplay between the protein corona and the nanoparticle surface holds the key to engineering safe, stable, and predictable targeted delivery systems [24].

PERSPECTIVES FOR FUTURE RESEARCH

SELECTION OF PLGA ARCHITECTURE

The future of targeted drug delivery hinges on the careful design and engineering of PLGA architectures that could circumvent the natural hurdles presented by physiological barriers [25, 26]. Although conventional PLGA serves as a biodegradable and solid platform, it rapidly gets cleared from the body by the mononuclear phagocytic system, and therefore, the incorporation of hydrophilic blocks such as Polyethylene Glycol (PEG) is required. PEG-PLGA architectures create a "stealth" system that resists opsonization and greatly prolongs the blood circulation of the encapsulated hydrophobically- complexed ciprofloxacin [25].

The next level of architectural optimization would be the use of lipid-polymer hybrid nanoparticles, which consist of a PLGA core encapsulated in a lipid bilayer. Optimization of the lipid bilayer with a defined concentration of cholesterol can achieve sophisticated control over mechanical properties and drug delivery kinetics for vaccine/antigen delivery [26].

The choice of PLGA architecture further dictates the surface charge and metabolic fate; the use of stearylamine-modified PLGA, for example, enables the layer-by-layer assembly of therapeutic agents such as heparin and glutathione. These types of multifunctional architectures further allow for dual-purpose therapies, exhibiting antioxidant effects with anticoagulant activity in vascular disease models [27]. In addition, a movement toward naturally derived compounds such as curcumin within PLGA matrices illustrates the possibility of biocompatible architectures that are angiogenic and devoid of developmental toxicity.

The confirmation that the physical architecture of the nanoparticle, including its mean diameter and encapsulation efficiency, are determining factor in achieving high bioavailability with low systemic toxicity comes from zebrafish embryo models [28]. The approach to future research should aim at the "design-by-intent" approach wherein the PLGA copolymer ratio and surface functionalization are uniquely designed for the target tissue's microenvironment [25-27]. Refinement of such architectures will bridge the gap between experimental nanomedicine and successful clinical translation in diverse fields of therapies [25, 28].

ION-PAIRING STRATEGIES

The incorporation of ion-pairing approaches is an important step while enhancing the surface properties as well as the loading capacity of PLGA NPs. With the incorporation of ion-pairing agents, it is possible to maximize the desired surface charge of the carriers, which leads to enhanced biological interactions and reduced toxicity. For example, during the preparation of NPs, the incorporation of charged

surfactants/polymers lead to changes in the zeta potential, reducing it from a strongly negative value to positive/neutral ones. Experiments conducted on Calu-3 bronchial epithelial cells showed that the magnitude and polarity (charge) of the zeta potential determines the rate of uptake as well as its intracellular localization [29].

While usually providing enhancements in membrane affinity and internalization, cationic modifications must be balanced so that not to compromise cell viability or induce inflammatory responses. Ion-pairing also facilitates stabilization of various therapeutic payloads, within the PLGA matrix through neutralization of drug-polymer repulsive forces or enhancement of hydrophobic interactions. Strategically choosing ion-pairing partners therefore remains a versatile tool in engineering "smart" PLGA-based delivery systems with improved safety profiles and targeted delivery capabilities [29].

STANDARDISATION OF IN VITRO MODELS

The need for the standardization of in vitro models arises from the requirement to assess the quality and efficacy of PLGA nanoparticles for targeted drug delivery.

- Physicochemical Characterization: Typically, physicochemical characterization of PLGA nanoparticles involves size and polydispersity index measurements using either Dynamic Light Scattering (DLS) or Nanoparticle Tracking Analysis (NTA). Surface charge (zeta potential) of the nanoparticles is also determined. High zeta potential values demonstrate favourable surface repulsion between nanoparticles.
- Morphological Assessment: The morphological analysis is done through imaging techniques such as Scanning Electron Microscopy or Transmission Electron Microscopy in order to confirm the spherical shape and smooth surface morphology of the formulations.
- Drug Content and Efficiency: The standard evaluation of drug loading and encapsulation efficiency involves assessing the amount of trapped drug compared to the initial weight, usually by high-performance liquid chromatography (HPLC) or enzyme-linked immunosorbent assays (ELISA).
- Release Kinetic Models: In vitro release testing is an important aspect, though there is a lack of universally standardized protocols for colloidal carriers. These generally include methods such as release tests using a dialysis membrane or centrifuged ultrafiltration tests to distinguish release characteristics based on pH differences designed to mimic target locations.
- Biological Models of Cellular Interaction: For the standardized testing of biological responses, there are particular epithelial cell lines (Caco-2 cells primarily for the intestine and HBE cells for the respiratory system) employed as models for cell uptake and barrier interaction. Dendritic cells (DCs) are also commonly employed as a model system to evaluate the efficiency of PLGA-NPs loaded with antigens in cross-priming immune responses.
- Stability Testing: Standardization comprises testing physicochemical stability under stress conditions such as changes in pH values, sonication processes, or freeze/thaw cycles to ensure that the payload is stable throughout formulation or storage processes [30].

CONCLUSION

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles have revolutionized the field of targeted delivery systems, filling the gap between polymer research and reality. The inherent biocompatibility and degradability offered by PLGA nanoparticles makes them the material of choice for encapsulating a wide range of molecules, from low-molecular-weight anti-cancer drugs to large CRISPR-Cas9 plasmids. As has been described in the course of this article, the future of PLGA nanoparticle preparation is for the better, from conventional batch preparation to microfluidics.

Furthermore, breakthroughs in the field of bio-interfacial engineering, such as “mucus-penetrating particles” or “platelet-membrane cloaking” have enabled these carriers to overcome major obstacles in the way of biologically active barriers. Despite notable hurdles relating to the "protein corona problem" and the standardization of in vitro testing, a "design-by-intent” strategy combined with "green chemistry" ensures a sustainable future for nanomedicines. Finally, PLGA-based carriers represent a well-rounded, highly developed platform ready to support the next generation of site-specific anticancer, pulmonological, and regenerative medicines.

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