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POLYMER (PLGA, PLA) BASED NANOCONSTRUCTS AND THEIR IMPLICATION IN CANCER TREATMENT

Harish Kumar Chandrawanshi*, Neelesh Chaubey

College of Pharmacy, Sri Satya Sai University of Technology and Medical Sciences, SH-18, Bhopal-Indore Road, Sehore-466002, M. P., India

*Corresponding author's Email ID: hchandrawanshi@gmail.com

Abstract

Nanoconstructs can be used for a variety of cancer therapies including tumor-targeted drug delivery, hyperthermia, and photodynamic therapy etc. Poly (lactic-co-glycolic acid) (PLGA)-based materials are frequently used in such setups. This review article gives an overview of the properties of previously reported PLGA nanoparticles (NPs), their behavior in biological systems, and their use for cancer therapy. Strategies are emphasized to target PLGA NPs to the tumor site passively and actively. Furthermore, combination therapies are introduced that enhance the accumulation of NPs and, thereby, their therapeutic efficacy. In this context, the huge number of reports on PLGA NPs used as drug delivery systems in cancer treatment highlights the potential of PLGA NPs as drug carriers for cancer therapeutics and encourages further translational research.

Keywords: PLGA, nanoparticles, drug delivery, cancer treatment, combination therapy

INTRODUCTION

The field of nanomedicine, which refers to the application of nanotechnology in medicine, offers valuable tools for the diagnosis and treatment of diseases. In this regard, a wide range of submicron materials has been designed and engineered, especially for defeating cancer. Its applications expedite the development of contrast agents, therapeutics, drug delivery vehicles and theranostics. Nanoparticles (NPs) for drug delivery applications have been composed of biodegradable and biocompatible polymers based on natural and/or synthetic materials. Synthetic polymers can be produced with high purities in a precise and well-controlled production process, as compared to natural products (Lai et al.,2014).

In this review article, we will address the displayed aspects of this cube for PLGA-based NPs and we will discuss how they can be tailored by synthesis methods as well as strategies for drug delivery with PLGA to improve cancer treatment.

PLGA PROPERTIES

Poly (lactic-co-glycolic acid) is one of the best characterized biodegradable copolymers that decompose to non-toxic products (H_2O and CO_2) that are eliminated from the body. Its polymeric NP degrades *in vivo* through hydrolysis of the ester bonds to its monomeric anions (lactate and glycolate). While D-Lactate is not further metabolized before excretion, L-lactate is converted into CO_2, which is excreted through the lungs and it is converted to pyruvate, which enters the Krebs cycle. Glycolate on the other hand is either directly excreted through the renal system or it can be oxidized to glyoxylate, which is afterward further converted into glycine, serine, and pyruvate. The latter can again enter the Krebs cycle and is metabolized into CO_2 and H_2O. (Danhier et al., 2012; Silva et al., 2015). Typically, PLGA is produced by a catalyzed ring-opening copolymerization of LA and GA. PGA is a crystalline hydrophilic polymer with low water solubility and fast degradation rate under physiological conditions. On the contrary, PLA is a stiff and hydrophobic polymer with low mechanical strength. As a copolymer of both, PLGA inherits the intrinsic properties of its constitutional monomers where the polymeric content, based on LA/GA ratio and Mw, strongly affect its degradation rate. For example, with an increase in the LA/GA ratio, the overall PLGA hydrophobicity increases, which leads to lower degradation

and thus slower drug release rate (Engineer et al., 2011)? Furthermore, the final Mw of the polymer also influences the degradation and drug release kinetics of the resulting formulations; i.e., with a decrease in the Mw, degradation as well as drug release rates both increase (Xu et al., 2017). Next, degradation, release kinetics, and the Mw also correlate with the size of the resulting NPs formulate. These are crucial factors for the therapeutic performance of PLGA NPs. Despite the higher drug loading potential of larger sized formulations, achieving a lower nano-size range is essentially important for the ability of the NPs to overcome biological barriers and to reach the disease site. In this context, a study pointed to the impact of the Mw of four 1:1 (LA:GA) PLGA copolymers with different Mw of 14.5, 45, 85, and 213 kDa on polymeric degradation and release rate (Mittal et al.,2007).

The higher the GA content, the faster the resulting degradation rate (Xu et al., 2017). *Vice versa* the drug release is prolonged with an increase in LA content. Hence, these polymeric characteristics, as well as their size, are important to tailor hydrophobicity, drug loading efficacy, and the pharmacokinetic profile of PLGA formulations.

Furthermore, cylindrical docetaxel (DTX)-loaded PLGA NPs accumulated less in liver, spleen, and lung in comparison with the free drug and DTX-loaded spherical NPs (Chu et al., 2013). Likewise, the shape of PLGA copolymer structure can influence the efficiency of drug encapsulation.

Next to the intrinsic properties of PLGA NPs, their surface modification plays an important role with respect to targeting strategy, biocompatibility, and blood half-life. The latter can particularly be increased when PLGA is combined with other polymers such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), and d-α-tocopheryl PEG 1000 succinate (TPGS).

Surface modification with, e.g., PEG (PEGylation) increases the hydrophilicity of the formulation yielding a stealth particle with enhanced blood circulation time and improved pharmacokinetics by preventing opsonization, and uptake by the mononuclear phagocyte system (Turecek et al.,2016).

However, due to the same reasons, the cellular uptake by target cells (which might be mandatory depending on the treatment) might as well be decreased and the targeting capabilities of those particles are strongly dependent on the exact chemical

composition of the surface. For instance, Khalil et al. synthesized curcumin (CUR)-loaded PLGA NPs with and without PEGylation via single emulsion solvent-evaporation technique and compared both formulations with the free drug, showing that PEGylation could improve the pharmacokinetic properties of the drug and the PLGA particle. The CUR biological half-life after per os administration was also increased for PEGylated PLGA NP formulations compared to non-PEGylated ones and the bioavailability of the loaded CUR could be increased by 55.4 times. However, despite improved pharmacokinetics, the stealth PEG-PLGA NP showed a slightly faster release of the drug as the PLGA NPs. Another study by Bertrand et al. (2017) investigated the impact of the PEG density on blood circulation times for various NPs sizes (55, 90, and 120 nm) with varying PEG density on the PLGA surface. Interestingly, results have shown that above a certain threshold of repeating units and Mw of the PEG chain (20 PEG chains (5 kDa) per 100 nm^2) the circulation times of the $PEG_{5\ kDa}$- PLGA NPs were dependent on the PEG density rather than the size of the PLGA NP. This effect might be attributed to the shielding properties of the densed PEG surface and the resulting hydration of the PLGA NP. However, a further increase of the PEG density did not show an additional benefit, thus indicating that surface modification can solely alter the biodistribution to a certain extent. On the contrary, PEGylation can promote PLGA NPs degradation and consequently accelerates the loaded drug release. This phenomenon is attributed to the hydrophilic nature of PEG chains that absorb water and stimulate the decomposition of PLGA chains (Rafiei and Haddadi, 2017). Thus, PLGA properties can be further tuned by the introduction of "third party" components as shown for surface modification with stealth polymers. With respect to active targeting approaches, the attachment efficacy of targeting ligands to the NPs and their targeting specificity may vary. Besides the requirement of multiple production steps, their therapeutic effect is often less fruitful than expected. For instance, a previous study performed with prostate-specific membrane antigen (PSMA)- targeted PLA/PLGA-NPs containing DTX showed that the effect of active targeting was not as high as expected. This could be explained by, e.g., PEGylation. Backfilling of the targeted NP with hydrophilic polymers can cover and hide the targeting ligand, and by thus hindering it's binding. Furthermore, incorporation of a targeting moiety might cause size enlargement in NPs and thus,

may reduce its ability to cross biological barriers (such as the vascular wall and the extravascular stroma) and/or simultaneously increase the uptake by MPS.

PLGA-BASED NPS PREPARATION METHODS

The production techniques of NPs play an important role in their final features such as the shape, size, size distribution, and stability. A wide range of techniques have been used for PLGA-based NPs synthesis such as (single- or double-) emulsification, nanoprecipitation, dialysis, and spray drying. Herein, we highlight the most frequently used approaches (**Figure 2**) in the production of PLGA-based drug delivery nano- sized systems. For detailed information on rather sophisticated techniques, the reader can refer to previous publications (Ding and Zhu, 2018).

EMULSIFICATION-EVAPORATION METHOD

Emulsification is the most commonly used method for PLGA NPs production, where the drug dissolved in a volatile organic solvent is added to an aqueous phase containing surfactants under continuous stir. Subsequently, evaporation is applied to achieve the oil/water (O/W) emulsion form (**Figure 2A**). This procedure can be further followed by adding the resulting (O/W) emulsion to another aqueous solution to form a water/oil/water (W/O/W). Alternative types of advanced emulsion techniques used for

PLGA-based microparticle production based on $W/O_1/O_2$ or solid/oil/water (S/O/W). For hydrophilic drugs the encapsulation efficiency is lower than in single emulsion compared to double- or multiple-emulsion techniques. The polymer concentration and evaporating step determine the NPs size. The higher the concentration of polymer in the discontinuous phase, the larger the size of the resulting particles. This method aims at the incorporation of a wide range of drugs, as well as, contrast agents (i.e., iron oxides) or the co-encapsulation of both substances in one formulation. Despite the relatively poor loading of temozolomide in PLGA NPs, the single emulsion method performed best with respect to encapsulation efficiency compared with other preparation methods. The pitfall of this commonly used method is the presence of surfactant residues on the NPs surface even after several washing steps (Ananta et al., 2016).

SALTING OUT METHOD

In the salting-out method, a solution consists of polymer, drug, and a water-miscible organic solvent, which is added to an aqueous phase where salt and stabilizer are dissolved and stirred to form an emulsion (**Figure 2B**). The sudden introduction of water content causes the organic solvent to diffuse into the water and leads to NP formation. The method is favorable for high concentrations of the polymer and also applicable to heat-sensitive drugs/agents since heat is not required during the process (Mir et al., 2017). However, it is not suitable for lipophilic drugs and its purification procedure is time-consuming since it requires several washing steps to remove stabilizers.

NANOPRECIPITATION METHOD

If a solution that consists of polymer, drug, and water- miscible organic solvent is added drop wise to an aqueous solution, the resulting precipitation process results in NPs (**Figure 2C**). This method is a straightforward single-step process with high reproducibility and was initially applied for hydrophobic drugs. Its advantages are scalability and low energy requirement where the NPs properties depend on polymer content and Mw, the nature of the solvents, and the ratios accompanied by mixing rate. PLGA NPs (with various surface modifications such as PEGylation) and targeted PLGA NPs were prepared with this method and used to deliver anticancer drugs to the tumor site (Almoustafa et al.,2017).

MICROFLUIDICS-ASSISTED METHOD

In microfluidic systems, small volumes (micro- or nano-liter) of liquids are processed in microchannels to achieve better results in comparison with the conventional bulk system. Depending on the type of reagents flow, microfluidic systems can be classified into two general types, (1) continuous-phase flow, and (2) segmented/droplet-phase flow microfluidic systems. The continuous phase flow microfluidics can be used to produce PLGA particles in the nanoscale while particles produced by segmented flow are typically in the micron size range. To produce PLGA nano-scale particles by continuous phase flow, an organic mixture of polymer and drug is assisted by a flow of aqueous phase solution on both sites along the microchannel, and the precipitation takes place in the organic phase

(**Figure 2D**). PLGA NPs produced by microfluidic systems have several advantages; narrow size distribution, well-controlled NP synthesis by controlled reaction time and temperature, improved heat and mass transfer, expedited synthesis, and an overall high reproducibility rate from batch-to-batch (Jiang, 2018). Moreover, microfluidically produced NPs have a compact morphology, which can hinder initial burst release. There are reports on microfluidic systems for the synthesis of various PLGA NPs (e.g., PEGylated, lipid coated and targeted NPs) for anticancer drug loading ranging from simple two dimensional to more complex 3D and also origami designs (Sun et al.,2013).

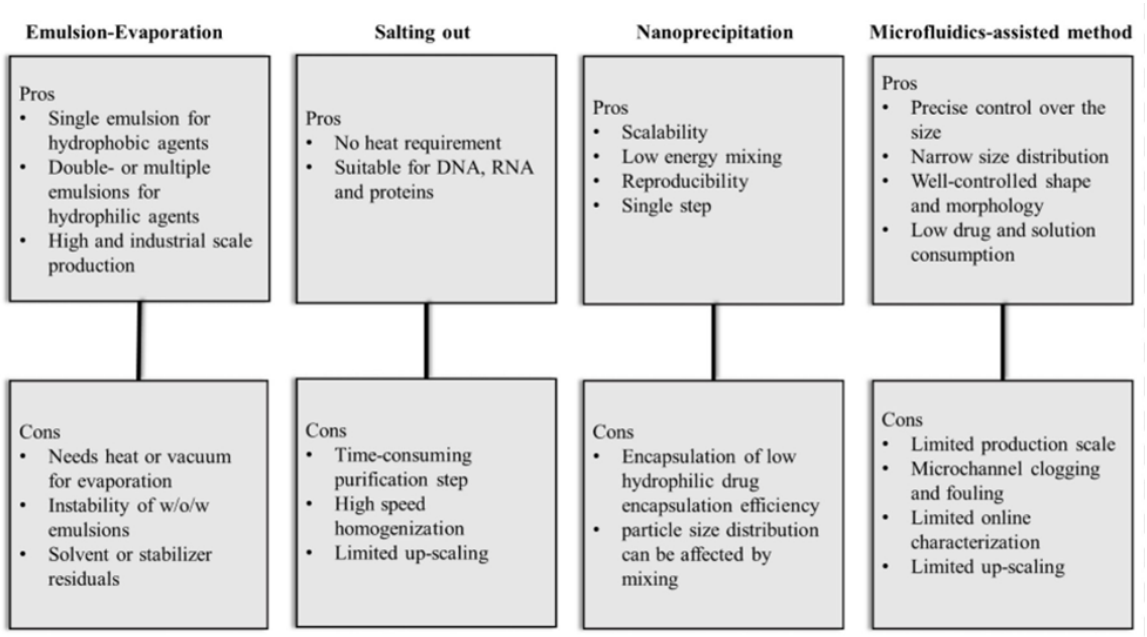

FIGURE 2 | Illustration of PLGA NPs production methods: Pros and Cons (i) emulsification-evaporation, (ii) salting-out,

(iii) nanoprecipitation, (iv) microfluidic-assisted method.

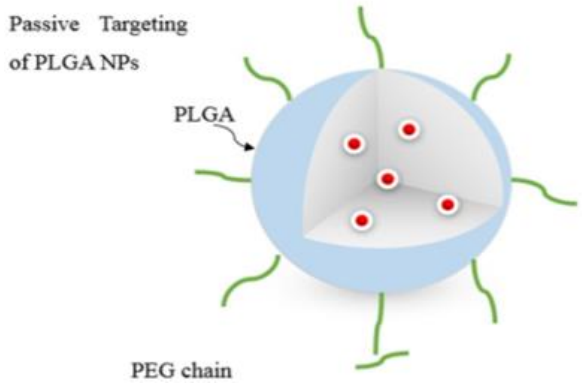

FIGURE 3 | Passively targeted drug-loaded PLGA NPs

DRUG TARGETING

Typically, cancer therapies involve the systemic administration of drugs into the body or its oral uptake, both of which can damage healthy tissues by significant off-target accumulation and thus, generate serious side effects. Off-target accumulation limits the dosage that can be administered. To overcome this limitation, various targeting strategies are being investigated.

PASSIVE TARGETING

PLGA NPs characteristics such as high stability and tunable prolonged blood circulation time are ideal to use this so-called passive targeting approach. This passive targeting strategy has been applied for PLGA- based NPs encapsulating chemotherapeutics (**Figure 3A**) such as doxorubicin (DOX), PTX (**Figure 3B**), cisplatin and CUR to enhance antitumor activity, prolong circulation time and improve stability of the drug by protecting it from the blood components. For instance, CUR-loaded PEGylated PLGA nanocapsules with castor oil core exhibited increased blood circulation time to overcome CUR's short half-life in the biological environment (Klippstein et al.,2015).

ACTIVE TARGETING

To increase the specificity of NPs for the target site and to promote cellular uptake, specific ligands can be attached to the surface of NPs (**Figure 4A**) that bind to receptors or antigens on tumor cells, the tumor microenvironment or the tumor vasculature. The application of the magnetic field in combination with transferrin receptor targeting also resulted in an increase in the overall survival rate of the animals and a higher therapeutic efficacy as compared to control groups treated with either magnetic or active targeting alone. Infact maintaining the high magnetic gradient strength needed for clinical translation remains challenging and costly (Tay et al., 2018).

COMBINATION TREATMENTS WITH PLGA NPS

Chemotherapeutic PLGA formulations with varying properties (i.e., shape, carrier, size, etc.) are currently available and FDA- approved for several types of cancer treatments. However, the study failed in phase II due to low response rates and the company was

sold with substantially all of BIND's assets to Pfizer in 2016.

With respect to drug development, researchers often need to take a step back to the fundamental research to continue improving anticancer drug delivery such as enhancing hydrophilicity, reducing uptake by the MPS, increase tumor to background ratios and tumor-targeted specificity to achieve a higher response rate.

The synergism of those standard combination treatments might be increased by the use of nanoformulations and researchers are evaluating their potential *in vitro* and in pre- clinical *in vivo* studies. The NPs offer a platform to co- encapsulate various pairs of drugs with varying hydrophobicity and pharmacokinetic profiles ensuring simultaneous long term distribution to the target site.

MAGNETIC HYPERTHERMIA

In hyperthermia the body temperature is increased to damage and kill tumor cells. Hyperthermia can be applied to the whole-body or regionally. The techniques used to induce local hyperthermia are radiofrequency, (high intensity focused) ultrasound, microwave, and laser irradiation as well as alternating magnetic fields. Regarding the latter, PLGA is considered as a suitable carrier to load and deliver magnetic NPs and (chemo-) therapeutics (**Figure 5A**). It has also been indicated that PLGA encapsulation can improve SPIONs stability without changing or affecting the photothermal ability of the nanocomposites (Sivakumar et al.,2017).

In general, promising therapeutic efficacy could exclusively be achieved via combination treatments; neither the sole delivery of chemotherapy nor the local magnetic hyperthermia could outperform the proposed and presented combination treatments. This can be due to synergistic effects and/or due to an increased drug accumulation following the hyperthermia-related enhancement of the EPR effect. However, despite those promising pre-clinical results (and as already discussed for magnetic targeting) the challenges for successful clinical translation remain unchanged. Importantly, even with MPI-guided induction of hyperthermia, the main challenge is to meet the clinical SPION dose limits and still achieve a therapeutically relevant heating in the region of interest (Tay et al.,2018).

PHOTODYNAMIC AND PHOTOTHERMAL THERAPY

In photodynamic treatments a photosensitizing agent (PS) is applied to generate highly ROS via photoexcitation. Most of the PS agents are hydrophobic, show a rapid decomposition under laser irradiation, do not accumulate well in the tumor and cannot be efficiently excited in the near infrared range (which is prerequisite for reaching deeper tissues). Nanocarriers like PLGA-NPs can be used to overcome some of these drawbacks. In line with this, the most commonly used PS agents that have been loaded into nanocarriers like PLGA NPs are poly(anilin) and indocyanine green (ICG) (Chang,2017).

GENE THERAPY

Next to standard chemotherapeutic treatments and immunotherapies, gene delivery and gene silencing are emerging approaches in the anticancer field. Here, a double-stranded DNA (dsDNA) or a single-stranded DNA (ssDNA) is used for replacing (or completing) a gene while short interfering RNA (siRNA) is typically used for silencing a gene. When cancer is initiated by cellular mutation, siRNAs can inhibit genes responsible for multidrug-resistance and in combination with, e.g., targeted chemotherapeutics; the self-defense mechanism can be inhibited. The major obstacle in gene therapy is the delivery of the large, negatively charged and very fragile nucleic acids into the cell cytoplasm, respectively, the cell nucleus. PLGA has been used as a carrier to protect and deliver nucleic acids (Xiao et al., 2017)

CANCER IMMUNOTHERAPY

Cancer immunotherapy can be performed via cancer vaccines, cytokine therapy, checkpoint-blockade therapy and adoptive T-cell transfer. Here, PLGA-based NPs can not only protect the sensitive cargos (e.g., antigens, adjuvants, etc.) from degradation but can also promote passive accumulation by the EPR effect and can facilitate additional active targeting strategies via surface modification. However, the stimulation of the immune system, which enables the recognition and attack of malignant cells, does not solely rely on tumor accumulation, but might as well be achieved or enhanced by targeting of immune cells, e.g., in liver, spleen, and lymph nodes. Thus, high affinity of many NPs to cells of the mononuclear phagocyte system as well as macrophage uptake might even be used to promote the desired immune

response.

Moreover, a combination of cancer immunotherapy with other modalities like PTT can provide a more effective treatment. In this context, multifunctional PLGA-PEG NPs co-loaded with ICG (photothermal and PS agent) and imiquimod (R837), an immune-adjuvant TLR-7 agonist, triggered vaccine-like immune responses. Additional combination of this NIR heater-loaded PLGA-based nanovaccine with an anti-cytotoxic T-lymphocyte antigen-4 checkpoint- blockade therapy synergistically inhibited the growth of metastasis and prevented recurrence of cancer. Furthermore, the use of cells as vaccines for generation of effective and adaptive immune responses is well established in cancer immunotherapy. Ahmed et al. coupled γ-irradiated non- vital prostate cancer cells with PLGA NPs. (Ahmed et al., 2017). The particle-cell hybrid was then additionally functionalized with the adjuvant CpG ODN, which selectively activates the toll-like receptor 9. This activation resulted in efficient cancer vaccination in a prostate cancer model. Interestingly, comparable results could not be achieved with a similar particle-melanoma cell hybrid.

CONCLUSION

In this review article, we summarize the physicochemical properties of polymers and NPs based on PLGA, and discuss their preparation methods, and applications for various drug delivery approaches. While several different PLGA-based therapeutics are already routinely used in the clinic, despite promising pre- clinical results, PLGA-NPs are neither listed nor approved and the only formulation that made it into clinical trials was based on PLA-PEG and failed in phase II due to non- responders.

As a consequence, researchers need to critically reflect the clinical feasibility of their approaches and develop NPs that better match the biomedical need (**Figure 6**). This not only relates to the optimization of size, drug loading and drug release, but also to biocompatibility, pharmaceutical upscaling and batch- to-batch reproducibility. In this context, it is advantageous if the experimental setup is from beginning on tailored to a concrete clinical problem. Especially in the case of PLGA NP synthesis batch-to-batch consistency (due to the heterogenous mixing conditions required for self-assembly), which directly relates to drug loading efficacy, and the challenge to obtain particle sizes below 100 nm in an up-scalable process are

remaining issues regarding PLGA-NP production. The lack in reproducibility and the need for additional purification steps impede manufacturing according to good manufacturing practices (GMP) that is mandatory for successful clinical translation. Furthermore, awareness of pharmacokinetics and pharmacodynamics of the NPs is mandatory to avoid off- target accumulation and potential side effects. The (often too large) sizes of NPs as well as their surface charge can result in severe off-target accumulation and can even prevent targeted NPs from binding to the target tissue/cell. Surface modifications, yielding, e.g., in a stealth NP, might avoid the recognition by the immune system but will simultaneously increase the size, may prevent penetration of the nanomedicine, hide targeting motifs, and reduce cellular uptake (which is mandatory for the therapeutic effect of many drugs). Any even minor chemical modification of a nanomedicine formulation can alter the physicochemical properties and thus the *in vitro* and *in vivo* performance as well as therapeutic efficacy. Furthermore, when combining nanomedicines with approaches like PDT/PTT or magnetic guidance, one needs to consider that these concepts of drug delivery will only be operant if the external stimulus (e.g., magnet) can be applied to the target region of the human body (which is often not the case for tumors located deeply below the skin).

Next to the influence of the NPs design and the challenges regarding the application of (external) stimuli-induced delivery and cancer treatment, it has been increasingly recognized that the high inter- and intra-individual heterogeneity of the EPR effect is an important reason for the moderate clinical translation of many nanomedicine formulations including PLGA-NPs. Thus, nanomedicine research will strongly take advantage from concepts that consider and address pathophysiological features that impact the EPR effect and affect the accumulation, penetration, distribution, retention and efficacy of NPs formulations.

In conclusion, for an efficient clinical translation a more rational design of PLGA-NPs, along with clinically relevant preclinical therapy settings, in which nanomedicines are tested are mandatory to close the currently huge gap between material research, preclinical experimentation and clinical reality.

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