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Mini Review

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# Recent advancement in pgla nano polymer synthesis and its applications

## Abstract

Poly lactic-glycol acid (PLGA) plays vital role in pharma industry especially as encapsulation material. Considering importance of polymeric material especially PLGA. In the PubMed searched we found total 937 articles were reported in the year of 2015 (01-01-2015 to 31-12-2015).In these articles we focused on reviewing advancement of PLGA nanoparticle synthesis method, characterization and applications of PLGA mediated Nano polymer ranging from drug delivery to in vivo imaging arena. The review ends with a concluding outlook on the possibilities and future challenges presented to PLGA polymer-based nanotechnologies in healthcare.

**Keywords:** PLGA, Synthesis, Characterization, Application, Healthcare, Nano-micro technology, Biodegradability, Biocompatibility, Ultra-sonication, PLGA-Cellulose particles, Nanoparticles

Volume 4 Issue 1 - 2016

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**Received:** March 13, 2016 | **Published:** July 21, 2016

**Abbreviations:** PLGA, Poly Lactic-Co-Glycolic Acid; PEG, Polyethylene Glycol; FDA, Food and Drug Administration; Alg-PLGANP, Alginate-PLGA Nanoparticle; PDI, Polydispersity Index; TRF, Tocotrienol Rich Fraction; FA, Folic Acid; α, Alpha; ZP, Zeta Potential; SEM, Scanning Electron Microscopy; PXRD, Powder X ray Diffraction; DSC, Differential Scanning Calorimetry; FTIR, Fourier Transform Infrared Spectroscopy; nm, Nanometer; ESI-ms/MS, Electro spray Ionization Mass Spectrometry

## Introduction

Form last decade, researchers have worked towards biocompatibility, and controlled drug release to improve methodology of treatment of diseases. With improvement in Nano-micro technology, researchers have developed dual functional implantable devices which work as drug reservoir and release machine.[1-2] on other hand, diffusion based drug release systems have got special attention because of its cost effective and simple synthesis methodology. Among various biocompatible polymers, PLGA poly (lactic-co-glycolic acid) is attracted noteworthy attention due to its attractive properties:

i. Biodegradability and biocompatibility;
ii. FDA and European Medicine Agency approval in drug delivery systems;
iii. Possibility of sustained release;
iv. Possibility to modify surface properties to provide stealthness and/or better interaction with biological materials.[1-3]

PLGA [poly (lactic-co-glycolic acid)] is synthesized by means of ring-opening co-polymerization of two different monomers, the cyclic dimers (1,4-dioxane-2,5-diones) of glycolic acid and lactic acid. Polymers can be synthesized as either random or block copolymers thereby imparting additional polymer properties. During polymerization, successive monomeric units (of glycolic or lactic acid) are linked together in PLGA(Figure 1) X: number of units of lactic acid; y: number of units of glycolic acid. Lactic acid: glycolic acid composition of PLGA alters properties of PLGA and its applicability by ester linkages, thus yielding linear, aliphatic polyester as a product.[2-3]

As of now research fraternity had focused on formulating spherical PLGA nanoparticle. Considering the dire need of more controlled release, one can expects research in tuning size and shape of the PLGA nanoparticles for drug delivery applications. On other hand we can expect application of PLGA in theranostic material based therapy where PLGA or related materials linked biocompatible fluorescent material or fluorescent Nanomaterial for Imaging-Guided chemo or photo thermal combinatorial therapy. Considering the future potential application of PLGA materials, in this article we have reviewed advancement of PLGA research in the year 2015. In PubMed, we searched number of articles published form 01/01/2015 to 31/12/2015 on PLGA, and we found 937 articles. Researchers have demonstrated a patrol of applications ranging from drug delivery to in vivo imaging system, which indicates the direction of future research and its current progress .

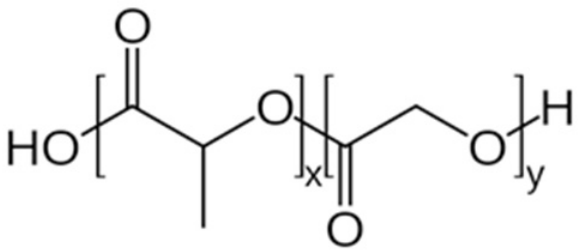


**Figure 1** Representative structure of poly (lactic-co-glycolic acid).

## Synthesis and Application

From last decade, researchers have synthesized PLGA poly (lactic-co-glycolic) acid nanoparticles using solvent displacement, emulsification-solvent evaporation, and nano precipitation methods for various applications summarized in Table 1. Apart from traditional solvent evaporation method some of research groups have used shearing based technologies such as high pressure homogenization, ultra-sonication. From last few years, PLGA with other polymeric nanoparticles were synthesized for various applications. To put in site on PLGA based bi-polymer nanoparticle synthesis, Rescignano N et al.,[4] studied synthesis of poly (DL-Lactide-co-Glycolide) copolymer based bi-polymer nanoparticles. The research group adopted a double emulsion (water/oil/water) method and compared the effect of alginate, chitosan and nanostructured cellulose crystals as natural emulsion stabilizers on the morphological, thermal, chemical, and rheological

properties of the synthesized nanoparticles.[4] The author reported that alginate-PLGA nanoparticles (Alg-PLGANPs) have wiled Polydispersity Index (PDI) ranging with particles size 2µm to 250nm. On other hand PLGA-chitosan and PLGA-Cellulose particles have narrow Polydispersity Index (PDI) with average size of 400nm and 560nm respectively. The study indicates that for pharma applications, PLGA-chitosan is a good material where as more iteration has to be studied for making smaller PLGA-bioPolymeric nanoparticles. In order to address the Polydispersity issue and to synthesize bi-polymeric nanoparticles, Alqahtani S et al.[5] used double emulsion (water/oil/water) method followed by high pressure homogenization. Here the research group studied synthesis of Chitosan-PLGA and formulation of α-Tocopherol (α-T) and Tocotrienol-Rich Fraction (TRF) entrapped in PLGA. The author reported that all synthesized nanoparticles measured were in the range 120-170 nm, with a PDI smaller than 0.2. In further studies, Alqahtani S et al. [5] evaluated cellular uptake, antioxidant and anti-proliferative activity of the formulated PLGA nanoparticles, and they inferred that PLGA and PLGA-Chi nanoparticles displayed a great enhancement in the cellular uptake of α-T and TRF without causing toxicity to the cells. This enhancement in the cellular uptake results in much improvement in the anti-proliferative activity of Tocotrienol. In addition, entrapment of α-T in PLGA and PLGA-Chi lead to more antioxidant activity.[5] Dhaset N et al. [6] investigated the use of Folic Acid (FA)-Conjugated Chitosan (CS) functionalized PLGA nano formulation for the treatment of prostate cancer in order to study effect of target molecule conjugated PLGA nano formulation on cancer cells. The research group formulated a folic acid-chitosan conjugate to coat Nanoparticles (NPs) and Bicalutamide (BCL)-loaded nanoparticles using the nano precipitation method and characterized through Dynamic light scattering, Zeta Potential, Scanning Electron Microscopy, Powder X-Ray Diffraction, *In Vitro* release, *In vitro* cytotoxicity, protein adsorption, hemolysis, and stability studies. The author inferred that as compared to non-functionalized PLGA NPs, folic acid-chitosan conjugate PLGA NPs were safe to use for prostate cancer drug delivery.[6]

The major hurdle, faced by drug delivery research fraternity, the scalability of developed formulation. To address this issue Schiller S et al.[7] used a novel method, in which author used focused Ultra-sounding an emulsion solvent diffusion method for formulation of protein loaded PLGA nanoparticles. To probe the scalability of the method Schiller S et al.[7] performed the formulation of Protein-PLGA nano particles for various scale batches and evaluate mean size, protein loading, and yield parameters; and found promising results.[7] In another study on PLGA modified with bi-target molecule and copolymerized for formulation of drug delivery system, He Z et al.[8] synthesized folic acid modified PEG-PLGA amphiphilic copolymers. They formulated Core-shell-corona particles by encapsulating Cisplatin and paclitaxel with an emulsion evaporation method.[8] The research suggested that the dual-drug-loaded particles had diameter of ~170 nm and zeta potential of about -25mV with spherical, uniform in size, and smooth-surfaced. In further studies author evaluated cytotoxicity against non-small-cell lung cancer cells; results implies that the co-delivery of Cisplatin and paclitaxel by FA-PEG-PLGA nanoparticles results in more effective antitumor effects than the combination of free-drugs or single-drug-loaded nanoparticles. These results implied that FA-PEG-PLGA nanoparticles can be used as effective carriers of dual drug.[8]

PLGA's biocompatibility has attracted immunologist especially with vaccine delivery systems, Silva A et al.[9] used PLGA for analysis of effect of size of PLGA particles, on engulfment by Dendritic Cells (DC) affects the type and magnitude of the immune response in comparison to sustained release from a local depot. Author and team postulate that particle internalization is of crucial importance and therefore particulate vaccines should be formulated in the nano but not micro-size range to achieve efficient uptake, significant MHC class I cross-presentation and effective T and B cell responses.[9] In vaccine related study, Rodney A et al.[10] formulated a PLGA-NP based multi-compound particulate vaccine which target DC and deliver protein antigen and adjuvant via the cell-surface molecule CD40 with the aim to activate efficient cytotoxicity CD8+T cell responses. This study revealed an attractive method to improve the efficacy of protein based cancer vaccines.[10]

In another study related to drug delivery Joshi H et al.[1] first time demonstrated an efficient and effective delivery system to administrate letrozole for altering the sex to be interested in ornamental fish. They formulated PLGA nano encapsulated letrozole using solvent evaporation method. Author concluded that as compared to naked drug, PLGA nano encapsulated letrozole shows promising results effect on masculinization .[1]

**Table 1** Summary of methods used for PLGA nanoparticle synthesis and characterization

| Method Used | Analysis of PLGA NP | Reference |
|---|---|---|
| Solvent displacement technique, micro fluidization (3 pass, 30000psi) | TEM, DLS, Zeta potential | Alqahtani S et al.[5] |
| Nano precipitation method | SEM, DLS, Zeta potential | Dhas N et al. [6] |
| Emulsification-diffusion method | DLS, Zeta potential, SEM | Gossmanna R et al. [13] |
| Emulsification-evaporation method | DLS, Fluorescent microscopy, TEM, DSC, FTIR | Kumar S et al. [12] |
| Double emulsion-solvent evaporation | SEM, ATR-FTIR | Irmina Samb et al.[14] |
| Emulsification solvent evaporation technique | ESI-MS/MS | Pedram Rafiei et al. [15] |
| Focused ultrasound in an emulsion solvent diffusion method | DLS, Zeta potential | Schiller S et al. [7] |
| Double emulsion-solvent evaporation | DLS, Zeta potential, TEM | He Z et al.[8] |
| Solvent evaporation | DLS, Zeta potential, TEM, XRD, ICP-MS) | Ho IT et al. [11] |
| Double emulsion-solvent evaporation | DLS, Zeta potential, Raman-spectroscopy | Yan H et al. [16] |
| Nano precipitation | SEM, DLS, Zeta potential, FTIR | Esfandyari MM et al. [17] |

**Citation:** Mehta S, Jayeeta , Shastri V, et al. Recent advancement in pgla nano polymer synthesis and its applications. *J Nanomed Res.* 2016;4(1):1–6. DOI: 10.15406/jnmr.2016.04.00076

Bio-imaging is one of the key areas of healthcare research, in our observation we found that Ting Ho I et al.[11] synthesized porphyrinoid-containing nanoparticle. The author reported an emulsion based method for the synthesis of the complex nanoparticles. Research group also successfully demonstrated application for detection of uranium in ppm level and also for in vivo photo-acoustic imaging using nude female (nu/nu) mice (6-16 weeks old). The present study elucidates utility of the Macro cycle-based NPs for photo-acoustic molecular imaging in conjunction with B-mode to obtain anatomic information and also opens window for a real-time scavenging of various ions in vivo in addition to photo-acoustic imaging.[11]

Many reported methods have used solvent such as ethylene acetate; chloroform for dissolving PLGA.[4-8] Green approach has revolutionized the area of nanoparticles synthesis. Advancing this regards, the study proposes by Kumaret S et al. [12] was a solvent free method, for the preparation of PLGA-oil nanohybrids (G-PONHs) using Acrysol oil and encapsulation of resveratrol. Acrysol oil was used for dissolving PLGA and rest of the method was similar to emulsion based method.[12] This opens a new space to work on synthesis of PLGA nanoparticles using green approach.

Most of the research advanced in 2015 was in line with synthesis and application of PLGA nanocomposites or bi-polymers, for drug delivery, vaccine carrier and in vivo imaging material. R. Gossmann et al.[13] performed comparative examination of adsorption of serum proteins on HSA and PLGA-based nanoparticles. The author had investigated influence of the nanoparticle starting material and the surface modification on the composition of the adsorbed serum proteins in a cell culture environment.[13]

Figure 2 illustrates a summary of the overall advancement of research with respect to PLGA in the year of 2015. Researchers have demonstrated a patrol of applications ranging from drug delivery to in vivo imaging system. Most of researchers have adopted an emulsion or solvent evaporation based method and synthesized material were characterized by SEM/TEM, and DLS for morphology and Polydispersity indexing; for Analytical study FTIR, MS, HPLC, and zeta potential have been used as well as UV Vis spectroscopy, micro Raman spectroscopy along with LCMS.[1-17] Research in 2015 have set the platform and challenge to find alternative methods for green synthesis of monodispersed PLGA particles.

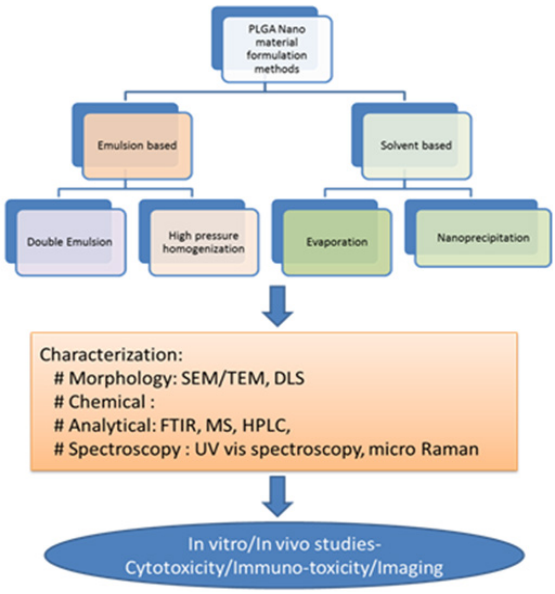


**Figure 2** Schematic of summary of PLGA related study and trends followed in 2015.

## Conclusion

Most of the research advanced in 2015 is in line with synthesis and application of PLGA nano composites or bi-polymers material, for drug delivery, vaccine carrier and in vivo imaging. In order to synthesize PLGA or composite nanoparticles most of the researchers have used environmentally hazardous organic solvent such as DCM (Dichloromethane), DMSO to dissolve API and PLGA for synthesis of nano materials. In order to address the issues with organic solvent, Kumar S et al.[12] proposed solvent free green synthesis method. This report opens window to research on finding new substances which may replace to organic solvents. Most of the research group focused on synthesizing known solvent /water emulsion, flash precipitation or solvent (such as ethylene acetate, DCM, chloroform) evaporation method. Most of the reported methods have major disadvantage that they are low yielding and non-amiable for large scale production, to address this issue Schiller S et al.[7] used a novel method, in which they used focused ultra-sounding an emulsion solvent diffusion method for formulation of protein loaded PLGA nanoparticles and author also studied the scalability of the method. Considering the industrial impact and demand of nano PLGA material, research should be focused on method development along with designing PLGA material in drug delivery systems.

PLGA nanomaterials have potential to be used drug carrier. In order to understand interaction of PLGA nanomaterials with blood components Gossmann R et al.[13] performed comparative examination of adsorption of serum proteins on HAS and PLGA-based nanoparticles. There is dire need to perform extensive studies for various polymorphs of PLGA and its components. Apart from drug delivery material PLGA can be used as carrier for various other material such protein, Antigens, and adjuvant. Ting Ho I et al.[12] synthesized porphyrinoid-containing PLGA nanoparticle for in vivo bio-imaging purpose. The studies presented in 2015 demonstrate the applicability and usability of PLGA in industries and its composition in various filed of health sciences and also underline importance of PLGA among the research fraternity.

As of now research fraternity has been focused on development and formulating spherical PLGA nanoparticles. Considering the dire need of more controlled release, one can expects research focused on tuning size and shape of the PLGA nanoparticles for drug delivery applications along with industrial amiable, green method development for synthesis of monodispersed PLGA nano materials. On other hand we can expect extension and advancement of PLGA application as theranostic material for biodegradable Imaging-Guided Chemo or photo thermal combinatorial therapy.

## Acknowledgments

None.

## Conflicts of interest

None.

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**Citation:** Mehta S, Jayeeta , Shastri V, et al. Recent advancement in pgla nano polymer synthesis and its applications. *J Nanomed Res.* 2016;4(1):1–6. DOI: 10.15406/jnmr.2016.04.00076