Cerium–catalyzed synthesis of PLGA and PLGA–PEG copolymers for advanced nanoparticle engineering

Cristina Casadidio[1†], Dario Gentili[2†], Saniya Salathia[1§], Giacomo Di Giambattista[1,2§], Gabriele Lupidi[2], Genny Pastore[2], Francesca Stella[2], Maria Giovanna Sabbieti[3], Dimitrios Agas[3], Enrico Marcantoni[2], Serena Gabrielli[2], and Roberta Censi[1]

[1]School of Pharmacy, Drug Delivery Division, University of Camerino, 62032 Camerino (MC), Italy
[2]School of Science and Technology, Organic Chemistry Division, University of Camerino, 62032 Camerino (MC), Italy
[3]School of Biosciences and Veterinary Medicine, University of Camerino, 62032 Camerino (MC), Italy

Introduction

Background:

- Conventional poly(lactic-co-glycolic) acid (PLGA) catalysts for ring opening polymerization (ROP) lead to metal toxicity, and regulatory challenges[1, 2]
- Widely used PLGA nanoparticles (NPs) require batch homogeneity and application-specific tunability

Objective:

- Developing cerium (Ce)-based eco/bio-friendly sustainable catalysts for ROP for PLGA synthesis.
- A flow-focused controllable and scalable PLGA-based NPs synthesis protocol with microfluidics

Cerium(III)laurate ($Ce(Lau)_3$) employed as a catalyst for synthesizing:
- **PLGA- $Ce(Lau)_3$**
- Copolymers of PLGA and poly(ethylene glycol) (PEG) with PEG molecular weights of 2000 Da **(PLGA-PEG2000)** and 550 Da **(PLGA-PEG550)**

The formulations of NPs compared with a commercial PLGA **(PLGA-comm)** (17000 Da, PURASORB PDLG5002A)

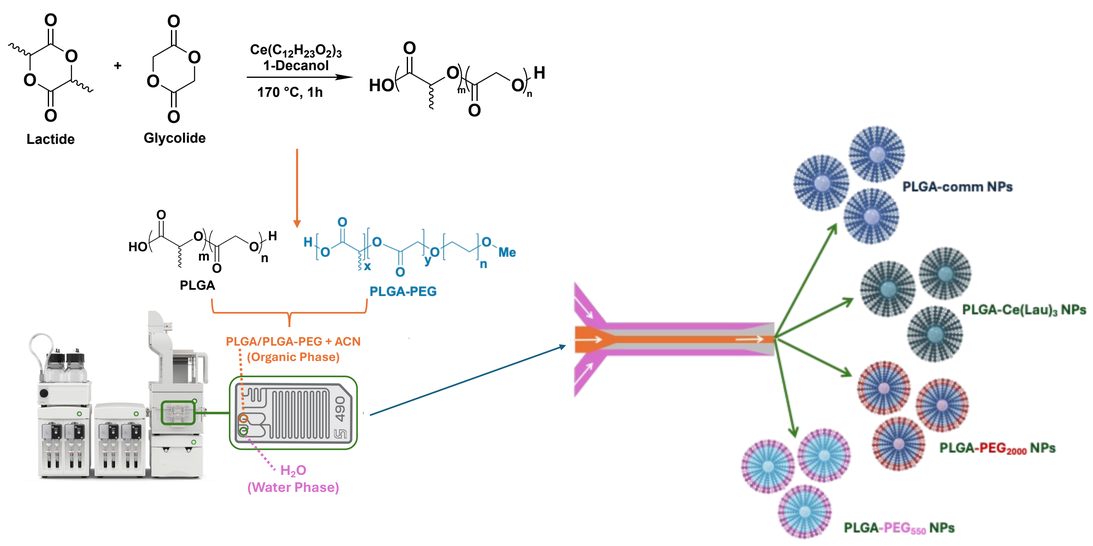


Figure 1: Schematic representation of the microfluidic preparation of PLGA-based NPs using the hydrodynamic flow-focusing system.

Polymer Synthesis and Characterization

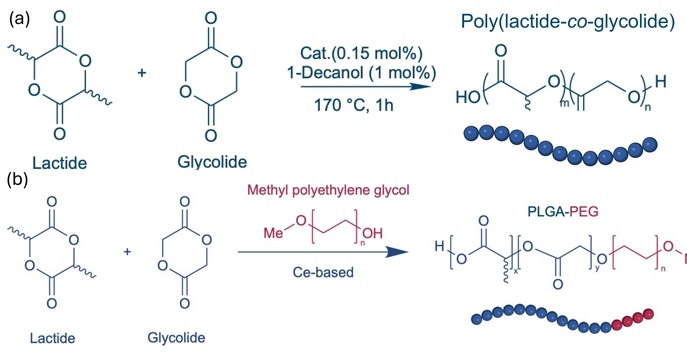


Figure 2: ROP Synthesis routes for polymers. **(a)** PLGA synthesis after the screening with different catalysts. **(b)** cerium(III) laurate catalyst for the preparation of PLGA–PEG from methoxy-PEG

Table 1: Ce(Lau)3 resulted in the closest target (18kDa) PLGA MW of 17,600 Da, compared to 20,160 Da achieved by conventional catalyst dibutyltin dilaurate (PLGA-DBTDL).

Polymer	Catalyst	Mn (Da)[a]	MW (Da)[a]	PDI[a]	Lactide/Glycolide L/G[b]	DP[a]
PLGA–$Ce(Lau)_3$	$Ce(C_{12}H_{23}O_2)_3$	10,900	17,600	1.6	45/55	169
PLGA–DBTDL	DBTDL	12,200	20,160	1.7	47/53	190

Fourier–Transform Infrared Attenuated Total Reflectance spectroscopy — FTIR
Nuclear Magnetic Resonance Spectroscopy — 1H-NMR
Thermogravimetric analysis — TGA
Differential scanning calorimetry — DSC

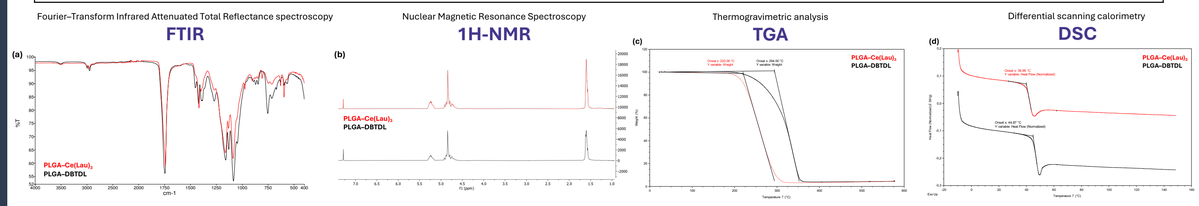


Figure 3: Physicochemical characterization of PLGA–$Ce(Lau)_3$ and PLGA–DBTDL show that polymers synthesized with cerium(III) laurate display physicochemical properties comparable to those obtained using DBTDL.

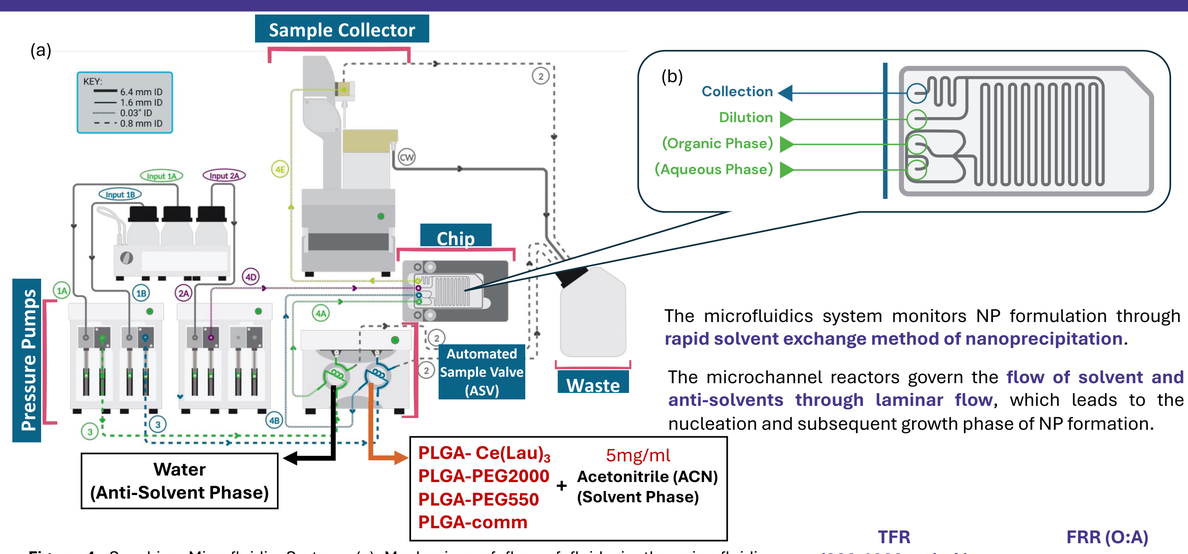
Table 2: Chemical characterization of PLGA–PEG polymers

Polymer	Mn (Da)[a]	MW (Da)[a]	PDI[a]	L/G[b]	End cap	DP[a]
PLGA–PEG_{2000}	5,600	10,000	1.8	42/58	Ester	87
PLGA–PEG_{550}	10,000	17,000	1.7	45/55	Ester	155

Table 3: TGA and DSC analysis of PLGA, PLGA–PEG2000, and PLGA–PEG550 polymers

Compound	Co–initiator	T 5% (°C) [a]	T 10% (°C) [a]	T max (°C) [a]	T_g (°C) [b]
PLGA–PEG_{2000}	$mPEG_{2000}$	227.1	241.0	291.2	32.4
PLGA–PEG_{550}	$mPEG_{550}$	228.1	238.1	286.3	39.8
PLGA–$Ce(Lau)_3$	1–Decanol	231.3	248.4	306.2	36.0

Flow Focused Nanoparticle Synthesis with Microfluidics

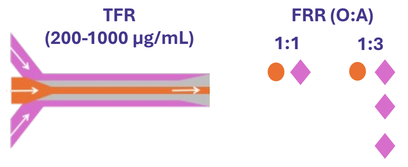


The microfluidics system monitors NP formulation through **rapid solvent exchange method of nanoprecipitation**.

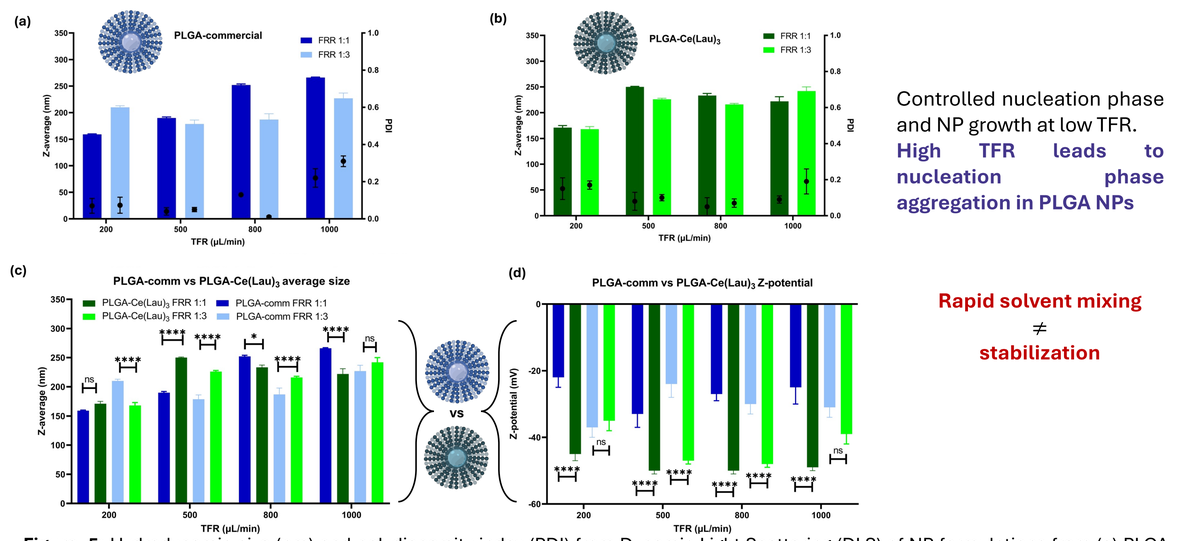
The microchannel reactors govern the **flow of solvent and anti-solvents through laminar flow**, which leads to the nucleation and subsequent growth phase of NP formation.

Figure 4: Sunshine Microfluidic System. (a) Mechanism of flow of fluids in the microfluidic capillaries for NP production. (b) Laminar flow controlled 490T microchannel chip.

NP formulation is tested based on **solvent:anti-solvent (O:A) Flow Rate Ratio (FRR)** and the **rate of flow of solvents (TFR; µg/mL)**



Nanoparticle Characterization and Cell Viability

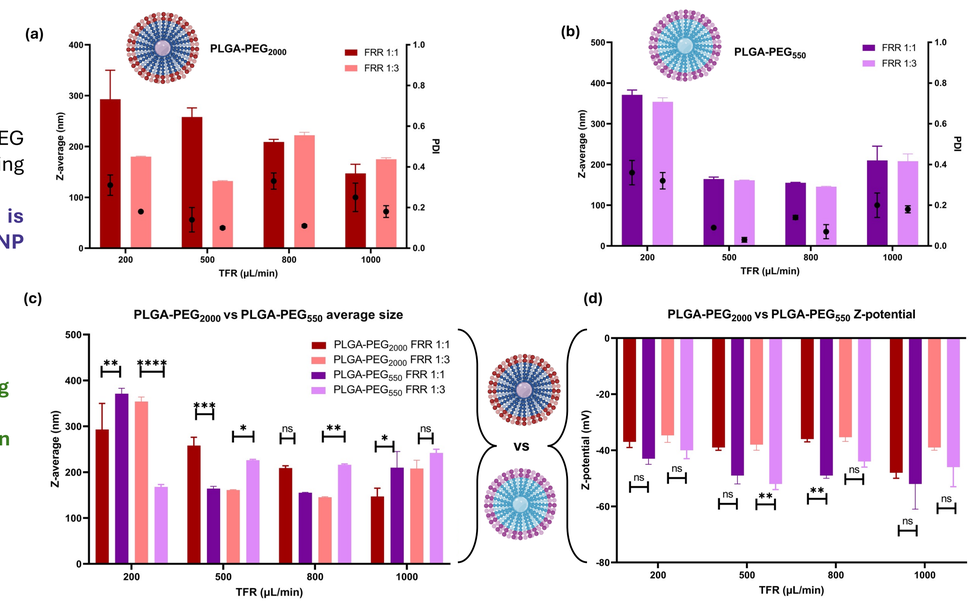


Controlled nucleation phase and NP growth at low TFR.
High TFR leads to nucleation phase aggregation in PLGA NPs

Rapid solvent mixing ≠ stabilization

Figure 5: Hydrodynamic size (nm) and polydispersity index (PDI) from Dynamic Light Scattering (DLS) of NP formulations from (a) PLGA-comm; (b) PLGA-Ce ($Lau)_3$; and (c) their comparison. (d) Zeta (Z)-potential of PLGA-comm and PLGA-Ce ($Lau)_3$ NPs. Data represents results from FRR 1:1 and 1:3 and TFRs from 200-1000 µL/min

Hydrophilic PEG provides a shielding effect at high TFR
Nucleation is followed by stable NP growth phase



Rapid solvent mixing = Reduced aggregation

Figure 6: Hydrodynamic size (nm) and PDI from DLS of NP formulations from (a) PLGA-PEG_{2000}; (b) PLGA-PEG_{550}; and (c) their comparison. (d) Z-potential of PLGA-PEG_{2000} and PLGA-PEG_{550} NPs. Data represents results from FRR 1:1 and 1:3 and TFRs from 200-1000 µL/min

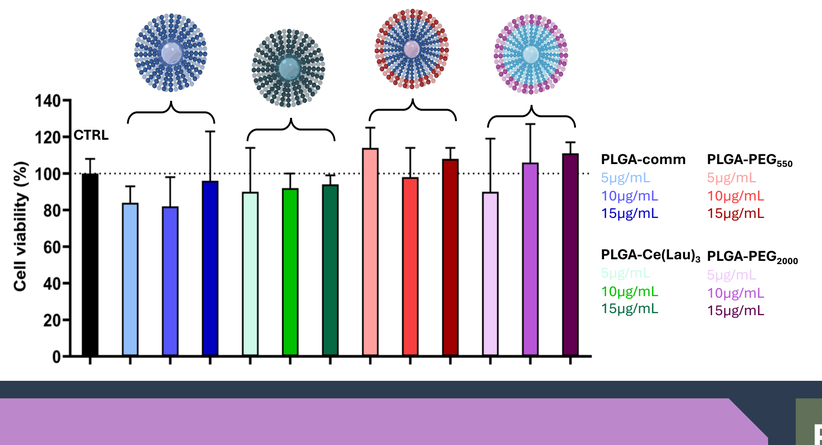


Figure 7: In vitro cytocompatibility tests of all PLGA-based NP formulations in NCTC L-929 mouse fibroblasts assessed by MTT assay after 48h NP exposure. PLGA-comm and PLGA-$Ce(Lau)_3$ NP formulations were prepared with FRR 1:1 and TFR 200µL/min and PLGA-PEG_{2000} and PLGA-PEG_{550} NPs were synthesized with FRR 1:1 and TFR 1000µL/min. (mean±SD; n=3)

Conclusion – Key Findings

Cerium (III) laurate as a catalyst
- Cost-effective
- Sustainable
- Comparable to conventional catalysts

Control over ROP with Polymer
- Molecular Weight
- Polydispersity
- Physicochemical and thermal properties

Systematic copolymerization of PLGA with PEG
- With increased NP stability
- Enhanced cytocompatibility

Flow Focused Microfluidics for NPs

Without PEG:
- High TFR leads to nucleation-phase aggregation in PLGA
- Rapid mixing = less stabilization time

With PEG:
- Hydrophilic shell for added stabilization during nucleation
- Reduced aggregation

References

1. Yan, J., *et al. Polym. Chem*. 2023.
2. Gao, Y., *et al. ACS Appl. Polym. Mater.* 2020.

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Appendix

†contributed equally as first authors

§contributed equally as second authors