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PLGA Nanoparticles Loaded with 1,10-epoxyparthenolide for Potential Applications in Tuberculosis Therapies

Karol Yesenia Hernández-Giottonini[1], Cindy Alejandra Gutiérrez-Valenzuela[1], Rosalva Josefina Rodríguez-Córdova[1], Adriana Garibay-Escobar[2], Paul Zavala-Rivera[3], Armando Lucero-Acuña[3]

[1] Nanotechnology Graduate Program, Department of Physics, University of Sonora, Hermosillo, Mexico
[2] Department of Chemical Biological Sciences, University of Sonora, Hermosillo, Mexico
[3] Department of Chemical and Metallurgical Engineering, University of Sonora, Hermosillo, Mexico

The encapsulation of 1,10-epoxyparthenolide (EP) in polymeric nanoparticles could contribute to the development of novel treatments for tuberculosis (TB). TB caused by *Mycobacterium tuberculosis*, is one of the most devastating bacterial diseases to affect humans [1]. Although an effective therapeutic regimen is available, patient non-compliance results in treatment failure as well as the emergence of drug resistance [2]. Due to the appearance of resistant strains, new alternatives have been sought for the treatment of this disease, in this context, new compounds from plants with antimicrobial potential have been investigated. EP is a compound isolated from the plant *Ambrosia confertiflora*, which is responsible for the antimycobacterial activity of this plant [3]. PLGA nanoparticles loaded with EP (EP-PNP) were prepared by using a single emulsification technique followed by solvent evaporation [4]. Briefly, 50 mg of PLGA and 2.5 mg of EP were dissolved in 5 mL of dichloromethane (DCM). Next, 25 mL of aqueous solution of 3% w/v poly(vinyl alcohol) was added to the organic phase. The mixture was emulsified at 75% of amplitude for 1 minute. The organic solvent was evaporated at room temperature (25°C), under magnetic stirring. Then, the solution was washed by three centrifugation cycles. After washing, particles were characterized, freeze-dried and stored for further use.

Nanoparticles were analyzed for their size distribution and zeta potentials by dynamic light scattering (DLS) and laser Doppler electrophoresis, respectively. The average particle size for blank nanoparticles (PNP) was 137.5±2.6 nm and the polydispersity index (PDI) was 0.073±0.02. EP-PNP size increased proportionally to the initial amount of EP used in the preparation or the theoretical drug loading (TDL), this effect was reported by Rajan and Raj, who also report an increment in the size of the nanoparticles [5]. The diameters of nanoparticles were 208.6±10.21 nm, 223.4±0.72 nm, and 250.9±11.70 nm for TDL of 2%, 5%, and 8%, correspondingly (Figure 1). PDI and zeta potentials (ζ) do not show statistically significant differences in the range of TDL studied. PDI values for all the particles obtained were below of 0.095±0.03, indicating homogeneity of particle size. ζ values were -24.2±3.40 mV, -21.0±2.31 mV, and -19.1±3.71 mV for TDL of 2%, 5%, and 8%, correspondingly; showing a fair stability of particles.

No proportionalities between drug loadings (DL) and TDL were found in the range evaluated, with values of 1.37±0.02%, 1.43±0.05%, and 1.30±0.03% for TDL of 2%, 5%, and 8%, respectively; pointing that the system reaches saturation. The encapsulation efficiency (EE) resulted in values of 68.72±0.09%, 28.54±0.96%, and 16.27±0.33% for TDL of 2%, 5%, and 8%, correspondingly (Figure 2). PNP resulted in smooth spherical particles, as analyzed with a field emission scanning electron microscope (JSM-7800F, JEOL) (Figure 3). PNP size obtained from the histogram of Figure 3 using software Image J was 110.8±41.6 nm. This size is in accordance to the results obtained by DLS.

The experimental release of EP was evaluated under physiological conditions. Similar EP release profiles were obtained with particles prepared at different TDL. An initial burst phase was observed in the first days, followed by a slow release stage until the entire drug was released (around 20 days) (Figure 4), Tripathi *et al* report a release profile with an initial burst release (7.266%) on day 1 of the study, which they attribute to the associated drug on the surface of the nanoparticles that is released quickly upon contact with the dissolution medium[6]. This nanoparticle system has potential applications for the extended drug administration of EP in treatments against TB.

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[7] The authors acknowledge funding from projects UNISON-USO316003420 and SAGARPA-CONACYT No 2017-02-29131.

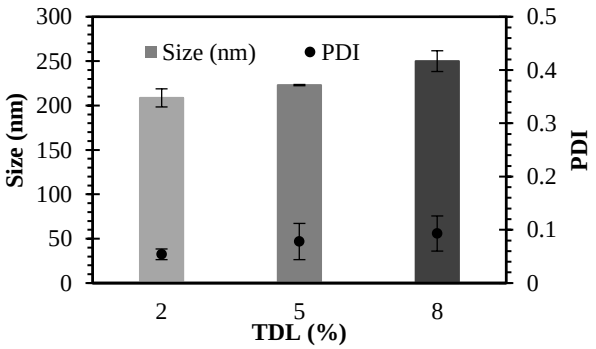

Figure 1. Size and PDI of EP-PNP. Data represent mean ± SD (n = 9).

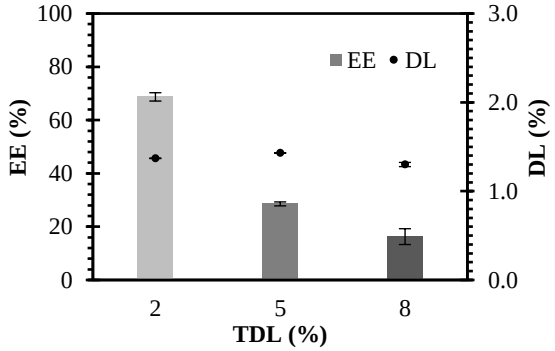

Figure 2. Percentages of EE and DL of polymeric nanoparticles as a function of TDL. Data represent mean ± SD (n = 3).

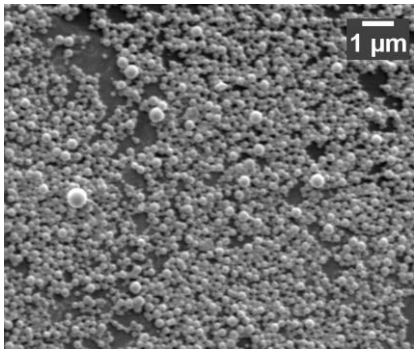

Figure 3. SEM of PNP.

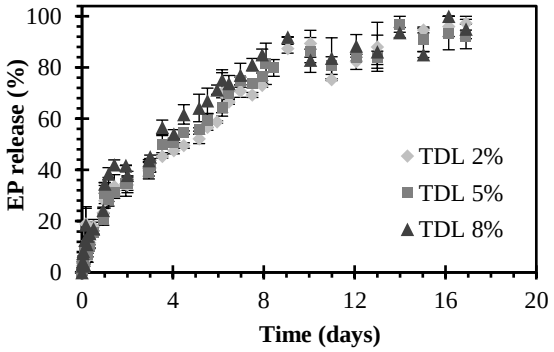

Figure 4. EP release profiles from EP-PNP. Data represent mean ± SD (n = 3).

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