Influence of Mixing Strategy and Surfactant Presence on the Ouzo Boundary-Stability Limit in Polymeric Nanoparticle Nanoprecipitation

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Control over the characteristics of polymeric nanoparticles, particularly size, formed via nanoprecipitation is critical for their application in biomedicine[1]. Although nanoparticle formation by nanoprecipitation has been extensively studied, the influence of mixing strategy and surfactant presence on governing the Ouzo boundary and stability limits is not well understood. In this study, we systematically examine how batch and semi-batch mixing, with and without surfactants, affect the Ouzo boundary and the resulting nanoparticle characteristics.

Ouzo region and stability boundary/limit (onset of formation of gels and flakes along with the nano/micro particles often described as the system enters spinodal decomposition[2]) were mapped by varying solvent mass fraction (f_s) and polymer mass fraction (f_{PLGA}), indicating distinct compositional regimes with specific physico-chemical properties of particles formed.

At low solvent mass fraction ($f_s \approx 0.2$), these boundaries are dependent on both mixing conditions and surfactant presence in batch and semi-batch processes. A similar trend is observed for surfactant effects: pronounced influence at low f_s, followed by convergence of boundary locations up to $f_s \approx 0.5$. From a polymer concentration perspective, above a threshold (f_{PLGA} ~0.01), neither mixing nor surfactant plays a dominant role in determining the stability boundary. Dynamic light scattering (DLS) measurements show that increasing f_{PLGA} leads to increased polydispersity with volume – based hydrodynamic sizes (H_d) transitioning from monomodal to proximate and distant bimodal, marked by the appearance and growth of a secondary peak. H_d increases with f_{PLGA} only in the absence of surfactants and within the Ouzo region (reported from the literature) particles are formed across a wide size range (48-191 nm). At the stability limit, two types of populations (nanoparticles and gels/flakes) can be found which highlight the role of mixing kinetics.

These results indicate how composition, mixing strategy, and interfacial stabilization collectively shape nanoparticle formation within metastable regions, offering mechanistic insight for the design and the control of nanoprecipitation processes.

Keywords:

Polymeric nanoparticles, Ouzo effect, Stability limit, Mixing strategy, Surfactant

References:

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