

Impact of the formulation pathway on the generation of nanoprecipitated polycaprolactone particles

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Polymer self-assembly is a ubiquitous and well-known physico-chemical process although not fully understood yet especially in terms of thermodynamics and kinetics. [1] Indeed, it can lead to thermodynamic equilibrium or be kinetically driven. In the latter case, the formulation initial conditions like the polymer concentration, the mixing rate and order of addition can strongly affect the final assembled state. [2]. Even though such dependence is relatively known, it has not been studied in a comprehensive manner yet. In this work, we have undertaken an *in-depth* study of the nanoprecipitation of polymer chains, a widespread method to generate polymer nanoparticles (NPs) (or encapsulate drugs for biomedical applications) to put forward the link between formulation pathway, final morphologies and thermodynamics. Polycaprolactone (PCL, M_w 45kDa) chains were dissolved in THF, a non-selective good solvent, into which miscible water was added in a second step to change the solvent polarity and trigger the assembly. Two common mixing routes encounter in many labs have been put under scrutiny: the fast (FA) and drop-by-drop (DD) addition of water into THF. PCL is a semi-crystalline polymer with a melting point (T_m) around 60°C. Depending on the route, the generated PCL NPs have a semi-crystalline or amorphous core as revealed by a different μ DSC signature (**Fig. 1**). NPs made by DD at low THF/H₂O (10/90 or 20/80) ratio did not show any evident thermal transition in line with an amorphous core. On the contrary, FA led to NPs with distinct melting points depending on the THF/H₂O ratio. While a THF/H₂O ratio of 30/70 gave a similar thermal behavior for both routes. When the THF content is low, the formulation pathway does indeed matter. FA likely generates “kinetically frozen” aggregates into which the solvent has no time to diffuse entirely throughout the NPs. In the DD route however, both the polymers and the solvent have time to rearrange in a more stable configuration. The final solvent content inside FA or DD aggregates can then really differ together with their final crystallinity rate; an important feature especially for biomedical applications where it is crucial to know the amount of trapped solvent. Some other parameters such as the PCL concentration and M_w as well as other characterization techniques (DLS, NMR, SANS) will be discussed in order to get a full control **through the formulation route** over various key features of the NPs like their stability, morphology, crystallinity and solvent content.

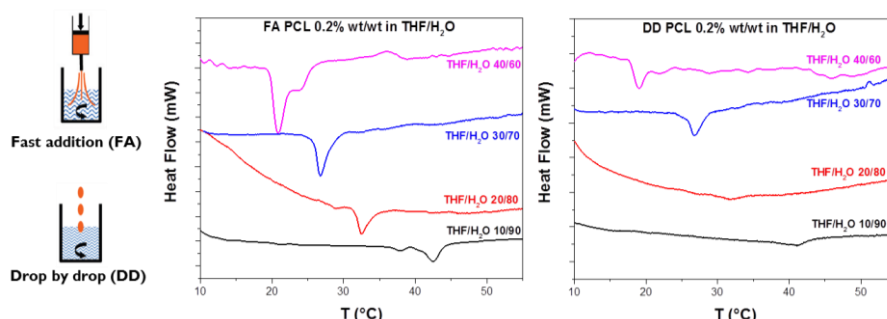


Figure 1. μ DSC of PCL (45 kDa) NPs 0.2% wt/wt made by FA and DD mixing routes at THF/H₂O = 10/90 (black), 20/80 (red), 30/70 (blue), 40/60 (magenta). The thermograms refer to a heating scan from 5 to 60°C at 1°C/min.

[1] Y. Wang, J. He, C. Liu, W. Chong and H. Chen, *Angew. Chem. Int. Ed.*, 2015, **54**, 2022.

[2] L. Qi, J. Fresnais, J.-F. Berret, J.-C. Castaing, I. Grillo and J.-P. Chapel, *J. Phys. Chem. C*, 2010, **114**, 12870.