Mesophase and Size Manipulation of Itraconazole Liquid Crystalline Nanoparticles Produced via Quasi Nano-Emulsion Precipitation

N. A. Mugheirbi, L. Tajber
Trinity College Dublin

Purpose
The fabrication of drug nanoparticles (NPs) with process-mediated tunable properties and performances has continued to grow rapidly during the last decades. This study investigates size and phase tuning of nanoparticulate itraconazole (ITR) mesophases using quasi nanoemulsion precipitation from acetone/water systems to seek out an alternative pathway to the nucleation-based NP formation.

Methods
The properties of the produced NPs, including size and mesophase, were tuned through controlling the quasi nano-emulsion precipitation process parameters. The impact of the solvent to antisolvent temperature difference (ΔTS:AS) and the solvent:antisolvent viscosity ratio (ρ) were examined. Poloxamer 407 (P407) was used as a stabilizer for nanodispersions. Each experiment was represented as Fx where x is 1, 2 ... to 6 and represents distinct conditions’ combination. The produced nanoparticles’ size and morphology were examined using dynamic light scattering (DLS), scanning electron microscopy (SEM) and transmission electron microscopy (TEM), while the solid state characterisation was achieved using wide angle and small angle powder X-ray diffraction (WAX and SAX), differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) spectroscopy.

Results
The mean particle size and the polydispersity indices (PDI) of NPs are displayed in Figure 1a. At a given temperature, the higher the solvent to antisolvent viscosity ratio, the smaller the NPs produced. The ΔTS:AS was found to affect the shell diameter (Figure 1). ITR nematic-smectic mesomorphism was also achieved via controlling ΔTS:AS. The use of ΔTS:AS =49.5 °C was associated with a nematic assembly, while intercalated smectic A layering was observed at ΔTS:AS =0 °C with the inclusion of P407 in the solvent phase (Figure 2), with both phases confined in the nanospheres’ shell at room temperature. FTIR data illustrated that, among the NPs, the greatest differences, in the triazole, mixed aromatic, C-N and C=O regions, were seen for sample F4 (TAS=50 °C, with P407) with band shapes resembling those of crystalline ITR. The presence of the –CH···π contact and the π···π; stacking, which fit the hydrophobic preference contours in the full interaction map generated using Mercury 3.5.1 software, is suggested to stabilise the liquid crystalline forms of ITR.

Conclusion
An investigation of the factors governing the quasi nanoemulsion precipitation of ITR revealed the ability to tune the properties of the produced NPs via controlling the fabrication conditions. The higher the ΔTS:AS, the thinner the particle shell thickness and the lower the molecular order with the nematic LC phase arrangement resulted. The highest periodically ordered intercalated smectic A was also observed. It should be highlighted that to date an LC phase of ITR has been only achieved via melting followed by cooling and here we demonstrate the use of a precipitation technique to accomplish this. This comprehensive study might help in the rational design of NPs made of other drugs.