Project 7: ***Crystal Transformations and Methodologies*** Date: **20/08/2010**	Author: **Marcus O'Mahony** Strand: **Particle Engineering** Institute: **University of Limerick**

Title: Determination of the solubility of F(III) carbamazepine in six solvents and the solution mediated transformation of F(I) carbamazepine in ethanol.

Principal Focus: To measure the solubility of the most stable polymorphic form of carbamazepine, F(III), in a range of solvents and to examine the transformation of a less stable polymorphic form, F(I), in contact with an ethanol solution. The aim of the experiment was to monitor the transformation in this manner such that precise mechanisms governing such a solution mediated polymorphic transformation may be revealed.

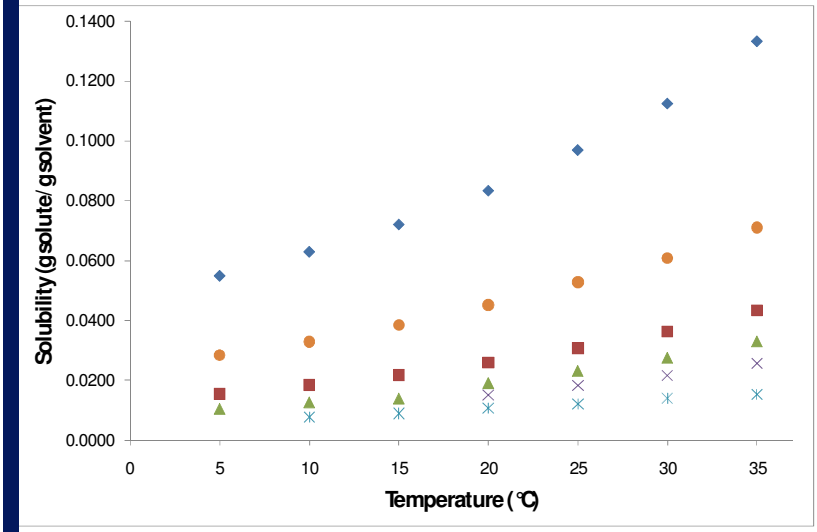

Figure 1. Solubility of F(III) carbamazepine from 5 to 35°C in methanol - ♦, ethanol - ■, 1-propanol - ▲, 1-butanol -x, ethyl acetate - ж and acetonitrile - ●.

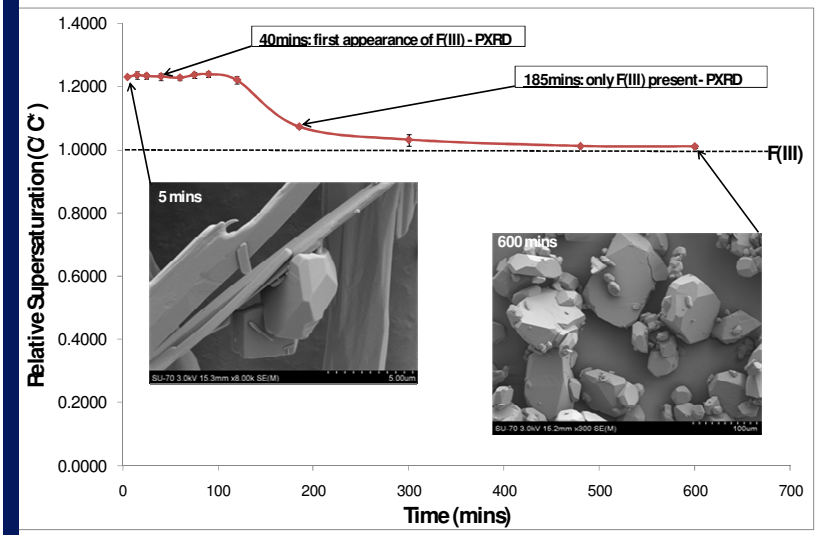

Figure 2. Concentration time profile for the transformation of F(I) to F(III) carbamazepine in ethanol. The dashed black line represents the solubility of F(III) carbamazepine.

Solubility measurements: The solubility of F(III) carbamazepine (CBZ) in methanol, ethanol, 1-propanol, 1-butanol, ethyl acetate and acetonitrile was measured gravimetrically from 5-35°C. F(III) CBZ was suspended in contact with each solvent and allowed to reach equilibrium. Filtered solution samples at each temperature were weighed before, and after complete evaporation of the solvent to determine the amount solute present in the solution. In this way the solubility could be expressed as g_{CBZ} / $g_{solvent}$ (see figure 1). The solid form present at the time of sampling was verified to be F(III) by powder X-ray diffraction (PXRD)

Transformation of F(I) in Ethanol: Pure F(I) was produced - confirmed by PXRD and differential scanning calorimetry (DSC). F(I) was then added to a pre-saturated solution of carbamazepine and ethanol held at a constant temperature. The concentration in solution was monitored over time using gravimetric methods. Solid samples filtered at the same time as solution sampling were analysed by PXRD and scanning electron microscopy (SEM). Results are displayed in figure 2.

Discussion: The gravimetric solubility measurements obtained for this work agrees well with the solubility measurements made via the synthetic method by Liu and co-workers (Liu et al. 2008). Determination of solubility data in ethyl acetate and acetonitrile has also been achieved in this work, contributing new solubility data to the literature (O'Mahony et al. 2010). F(I) is known to be a metastable polymorph (Grzesiak et al. 2003). Addition of pure F(I) to a pre-saturated solution of CBZ and ethanol resulted in the dissolution of F(I) - supersaturating the solution with respect to F(III) - followed by the surface nucleation of F(III) on F(I), see inset SEM image of solid after 5mins in figure 2. It is not yet known whether this nucleation is epitaxial in nature. Once nucleated, F(III) continues to grow until all the supersaturation is consumed and the solubility of F(III) is reached. **Future Work:** Further examine the transformation of F(I) in other solvents and at other temperatures.

References:

Grzesiak, A. L., Lang, M., Kim, K. and Matzger, A. J. (2003) '*Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I*', Journal of Pharmaceutical Sciences, **92**(11): p. 2260-2271.

Liu, W., Dang, L., Black, S. and Wei, H. (2008) '*Solubility of Carbamazepine (Form III) in Different Solvents from (275 to 343) K*', Journal of Chemical & Engineering Data, **53**(9): p.2204-2206.

O'Mahony, M., Croker, D., Rasmuson, A. and Hodnett, K. (2010) '*Gravimetric measurements of Solubility of Carbamazepine F(III) in six Solvents* ', Publication pending.