Project 14: ***Polymorphic Transformations in Piracetam*** Date: **19/08/10**	Author: **Anthony Maher** Strand: **Particle Engineering** Institute: University of Limerick

Title: Polymorphic Transformations in Piracetam

Principal Focus: The objective of this project is to better understand the phenomenon of polymorphism in drug systems, in this case piracetam. Initially the aim was to isolate and characterise the different polymorphs of piracetam and subsequently identify polymorphic transformations of the drug and establish the mechanism of the transformations.

Principal Outcomes to Date: All three polymorphs have been isolated and characterised by XRD and DSC analysis. Solubility data was obtained for FII(6.403) and FIII(6.525) in 6 solvents in the temperature range 5 – 50 °C (Fig 1). The solution – mediated polymorphic transformation from FII(6.403) to the stable FIII(6.525) was monitored using *ex-situ* XRD and SEM analysis as well as *in-situ* optical microscopy. The effect of solvent and temperature on the induction time of the transformation was also examined (Fig 2).

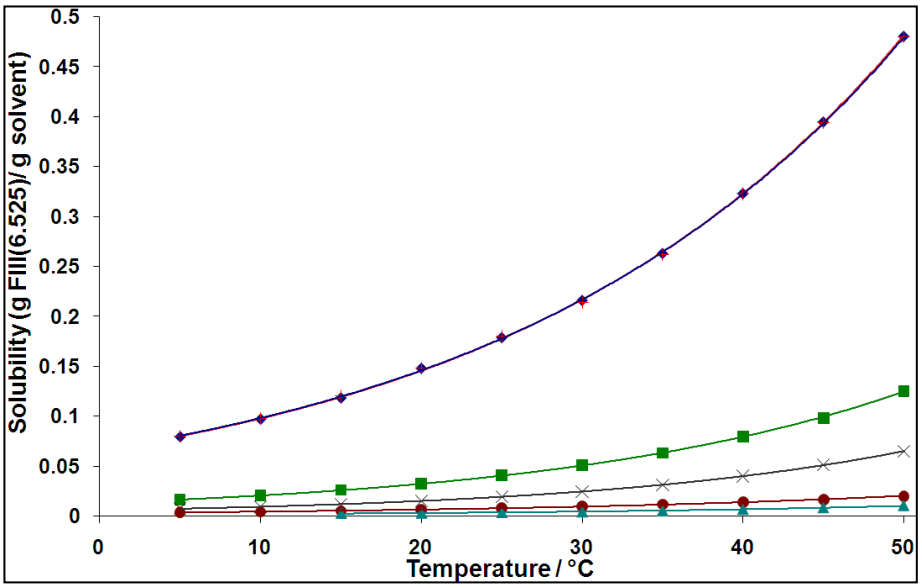

Figure 1: Solubility of FIII(6.525) versus temperature in a range of solvents from 5 – 50 °C; ♦ methanol; + methanol repeat; ■ ethanol; × 2-propanol; ● acetone; ▲ 1,4-dioxane[1]. (Solubility of FII(6.403) is 5-10 % higher than FIII(6.525))

Although very unstable at room temperature, FI(6.747) is the stable form at higher temperature. The solid – state polymorphic transformation from FII(6.403) and FIII(6.525) to FI(6.747) was examined using High Temperature XRD, DSC and Hot – Stage Optical Microscopy. There is some confusion in the literature about the order of this transformation but it was established that FII(6.403) transforms to FI(6.747) at a slightly lower temperature (112.5 °C) than FIII(6.525) (116.4 °C).

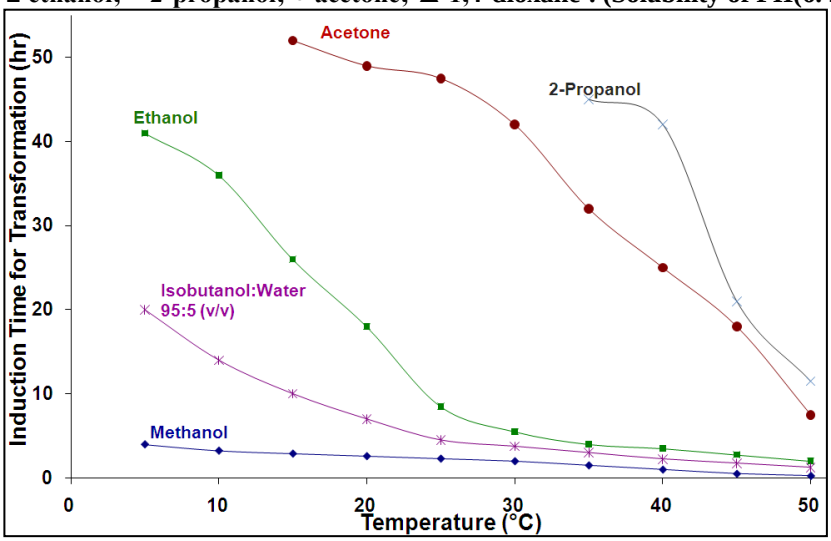

Figure 2: A graph showing induction times for the transformation (FII(6.403) → FIII(6.525) in five solvents over the range 5 – 50 °C[2].

Discussion: Solubility data gives information on the stability hierarchy of polymorphs in a system. There is no solubility data in the literature on any of the polymorphs of piracetam. The solubility data obtained correlated positively with solvent polar characteristics (Fig 1). As the number of carbons in the *n*-alcohols increases, the polarity of the solvent and its hydrogen donor ability decreases and so does the solubility of polymorphs in the solvent.

While polymorphic transformations have been mentioned in the literature, no characterisation study has been carried out for either solid – state or solution – mediated transformations.

XRD analysis of the crystals sampled from solution during the transformation showed the FII(6.403) peaks decreasing over time while the FIII(6.525) peaks increased. In all solvents the induction time of the transformation decreased with increasing temperature. A trend of decreasing induction time of the transformation (Fig 2) across the solvents correlated positively with the trend of decreasing solubility of piracetam across the solvents.

Future Work: Initial work has been carried out on the mechanism on the solid – state and solution – mediated transformations discussed above using different variations of optical microscopy. In the future an understanding of the mechanisms on a molecular level will be reached.

References:

1. Maher, A. Croker, D. Rasmuson, A. C. Hodnett, B. K. The solubility of Form III piracetam in a range of solvents, Journal of Chemical and Engineering Data, Article accepted for publicantion, 2010
2. Maher, A. Croker, D. Rasmuson, A. C. Hodnett, B. K. "Influence of Solvent on a Solution Mediated Polymorphic Transformation in Piracetam" CGOM Poster Presentation, Singapore 2010