And Project 9: ***Crystal Morphology Prediction*** Date: **19/08/10**	Author: **Nicole Walshe** Strand: **Particle Engineering, API/Formulation Interface** Institute: **NUI, Galway**

Title: Crystal Morphology Prediction

Principal Focus: This project aims to develop methods to predict the morphology of crystals grown from solution. Attachment and added slice energy calculations will be used to predict the relative growth rates of crystal faces. Crystal face analysis will also be used.

Experimental: The crystal morphologies of several systems have been studied. The program HABIT[1] is used to calculate lattice and attachment energies. HABIT uses Lennard-Jones 6-12 type potentials to calculate the attractive and repulsive contributions and a coulombic term to calculate the electrostatic contribution as shown below:

$$\textit{Equation 1:} \quad V = A/r^{12} - B/r^{6} + qiqj/r$$

Lifson-Hagler parameters[2] are used for C, H, N and O and parameters for all other elements have been computed to give a dip at a distance which is in agreement with the van der Waals radii values obtained from the CSD[3]. Atom charges, which are part of the Lifson-Hagler model, are calculated using DFT methods. Probe based crystal face analysis is included in the RITNOS program. This provides an understanding of the factors which control crystal growth directions and solvent effects through the measurement of the density of available named atoms on crystal faces. A probe of adjustable radius moves on a grid towards the surface of the crystal until the van der Waals sphere of an atom is entered. The atom can be tested for membership of two lists. These lists can be H-bond donors, acceptors or other atom types.

The morphology of Piracetam form II has been examined. Crystals of piracetam form II were grown in solution from 1,4-Dioxane. These crystals display a needle like habit which is extended in the a* direction.

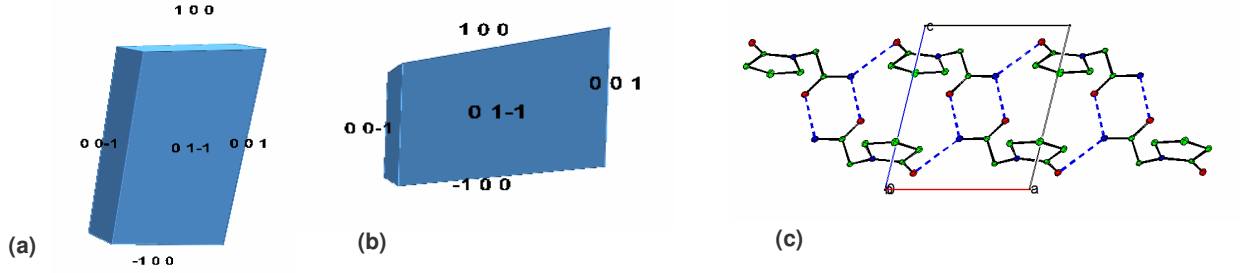

Figure 1. Observed morphology of piracetam form II (crystal cut at the {100} face. **(b)** Predicted morphology of piracetam form II. **(c)** H-bonding network in piracetam form II (H atoms omitted for clarity).

Discussion: The ASE predicted morphology does not show the observed elongation in the a direction (Fig 1). Crystal face analysis shows that all of the H-bond donors are on the {100} face. Analysis of the hydrogen bonding network shows that a 1-D, ribbon like H-bond propagates in the a direction (Fig 1(c)). It is widely observed that systems which have a ribbon like H-bond pattern extending in one direction tend to form needles which extend in that direction.

Future Work: A series of systems with identical 1-D H-bond motifs but with a range of morphologies are being modelled and the nature of species in solution is being examined.

References:

1. Clydesdale, G.; Docherty, R.; Roberts, K. J., HABIT - a program for predicting the morphology of molecular crystals. *Computer Physics Communications* **1991,** 64, (2), 311-328.
2. Lifson, S.; Hagler, A. T.; Dauber, P., Consistent Force-Field Studies of Inter-Molecular Forces in Hydrogen-Bonded Crystals .1. Carboxylic-Acids, Amides, and the C=O...H- Hydrogen-Bonds. *Journal of the American Chemical Society* **1979,** 101, (18), 5111-5121.
3. Table of covalent and vdW radii. http://www.ccdc.cam.ac.uk/products/csd/radii/