Project 6: Molecular Design and Dynamics of Pharmaceutical Solids Date: **19/08/2010**	Author: **Lorna Lennon** Strand : **2** Institute: **University College Cork**

Title: Crystallisation and process issues; glucuronide case study**.**
Principal Focus: Examines issues of solvent choice, reaction conditions, stereochemistry and impurities on the crystallization of API-like compounds: the glucuronides.

Glucuronides[1] are bio-active compounds which demonstate many of the challenges facing pharmaceutical crystallization: poor crystallinity, poor physical stability, solvate formation, residual impurities, process variability. We have examined crystallization of glucuronides obtained from the β-tetraacetate intermediate and by direct oxidation of the correspoding glucosides (Figure 1).

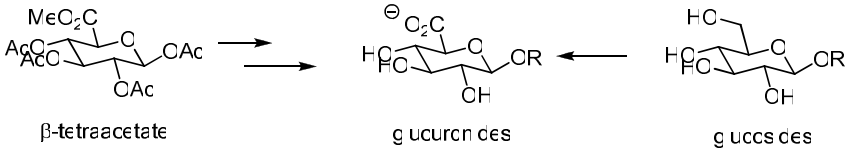

Figure 1:

Discussion: Crystallization of the β-tetraacetate intermediate itself is problematic as crytallization times are very variable. We have shown that the α-isomer also forms and have examined the effect of this impurity on β-tetraacetate crystallization. For the first time the crystal structures of both isomers has been determined (Figure 2). We have studied the effect of solvent and cooling profile on crystal morphology and size distribution. Morphologies were determined on individual crystal using the Bruker APEX II diffractometer (Figure 2), allowing us to relate crystal growth directions to the crystal structure packing.

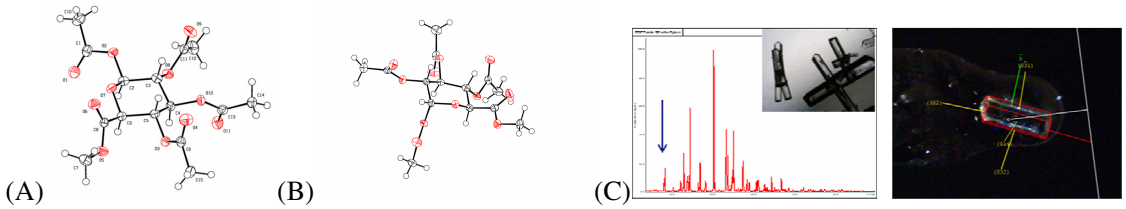

Figure 2: (A) Crystal Structure of methyl tetra-*O*-acetyl-β-D-glucopyranuronate **2β** (B) Crystal Structure of methyl tetra-*O*-acetyl-α-D-glucopyranuronate **2α** (C) PXRD patterns and morphology of methyl tetra-*O*-acetyl-α-D-glucopyranuronate **2α**

More recently we have examined the glucoside oxidation route and have crystallized and obtained structures of a number of acetate intermediates of these compounds (Figure 3).

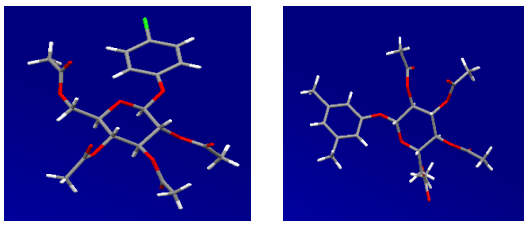

Figure 3

The glycoside and glucuronide derivatives of these compounds have been prepared. They are very challenging compounds to crystallize with a strong tendency to form oils or amorphous materials (typical 'real-world' issues). Solvent screening and salt selection are being used to address this challenge.

Future Work: This project is only in its first year, so the above are early findings. Future work will build on this to obtain methodology for obtaining stable crystal forms of glucuronides.

References:

(1) Stachulski A.V.; Jenkins G., *The Synthesis of O-Glucuronides, Nat. Prod. Rep.* ***1998***, 15, 173-186.