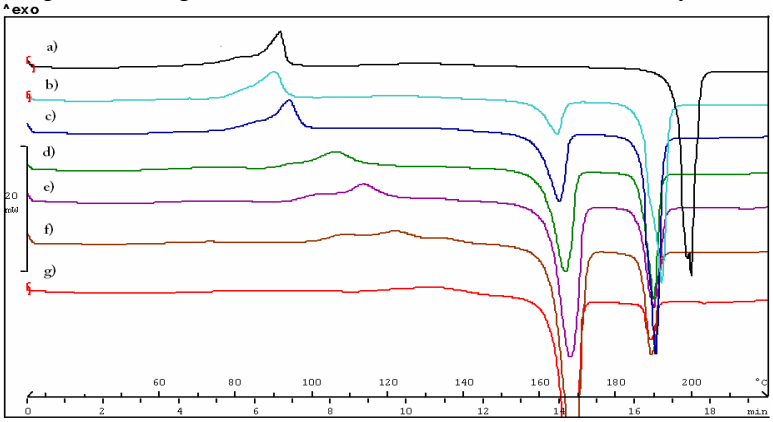
Project 2: **The Effect of Physical and Solid-State Form of Selected Sulphonamides and their Sodium Salts on Bulk Powder Flowability and Mixing** Date: **19/08/10**	Author: **Vincent Curtin** Strand: **The API/Formulation Interface** Institute: **Trinity College Dublin**

Title: The feasibility of co-processing sulfadimidine with low Tg excipients as a novel strategy for preventing process induced amorphisation.

Principal Focus: To stabilise the initial crystalline solid state of sulfadimidine following ball milling. The API was co-milled with two polyols (**mannitol** and xylitol), two dicarboxylic acids (**adipic acid** and succinic acid) and one hydroxylated dicarboxylic acid (malic acid). Importantly, all selected excipients have their glass transition temperatures (Tg) located below RT and retain their initial crystalline state when milled alone.



Experimental

- Retsch PM100 Planetary Ball Mill
- Milling jars of volume 50cm^3 with three stainless steel balls of diameter 20mm
- Ball to powder mass ratio of 40:1
- Co-milling performed for 10 hours at RT
- Different weight ratios (w/w) of excipient employed ($10 \leq X_{excipient} \leq 80$)
- Analysis by DSC, HyperDSC, MTDSC, pXRD, FTIR, helium pycnometry

Note: X_{MA} = Mannitol weight fraction
X_{AA} = Adipic acid weight fraction

Fig.1. DSC scans of sulfadimidine-mannitol milled composites: a) X_{MA} =0, b) X_{MA} =10, c) X_{MA} = 20, d) X_{MA} = 40, e) X_{MA} = 50, f) X_{MA} = 60, g) X_{MA} = 80

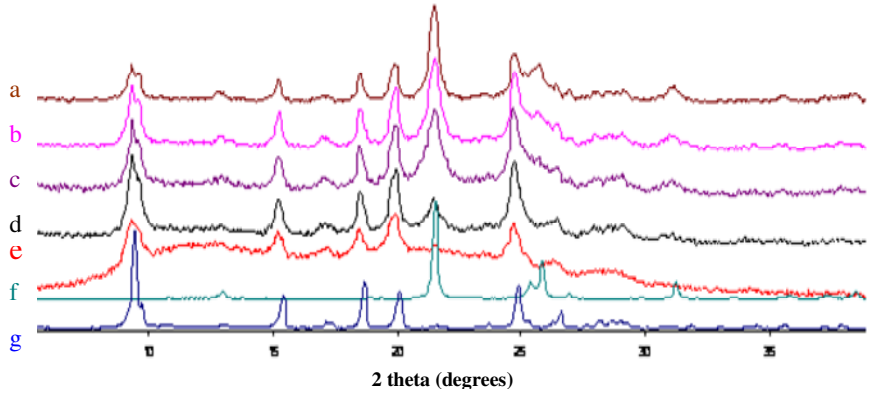


Fig. 2. pXRDs of sulfadimidine-adipic acid milled composites; a) X_{AA} = 60, b) X_{AA} = 50, c) X_{AA} = 40, d) X_{AA} = 20, e) X_{AA} = 0, f) milled AA, g) crystalline sulfadfimidine

Discussion: Mannitol had an unexpected antiplasticising effect on the API, appearing to stabilise the amorphous phase. As indicated in Fig. 1, the recrystallisation exotherm progressively shifted to higher temperature with increasing content of excipient, indicating a more thermostable amorphous phase. The composition dependence of Tg appeared to be monotonic. Comparison with the physical mixture confirmed co-milling induced amorphisation. Co-processing with another polyol, xylitol, yielded a similar result.

Adipic acid was capable of enhancing Bragg peak resolution of the API compared to mannitol, even at the lowest concentration of excipient employed. The pronounced halo at low angular 2 theta, as observed when sulfadimidine was milled alone, was reduced in all composite systems, and peaks characteristic of both API and excipient were observed (Fig. 2). Co-milling with succinic acid proved to be less successful in preventing amorphization, while malic acid resulted in binary amorphous dispersions with excipient compositions of <40%.

Future Work: To co-spray dry the aforementioned composites and to evaluate and compare their physiochemical properties with the results obtained for milled systems. Further investigations with other API-excipient combinations will be conducted in order to elucidate relationships between physical properties/chemical structure of the individual components and the final state of the resultant processed system.

Later, the effect of different levels of amorphization/crystallization on the flow and compaction properties of single component or composite systems will be investigated.