SSPC

Project 1: **The Effect of Processing on the Solid-State form of Selected Sulphonamides and their Sodium Salts, alone and as Drug-Excipient Composites**

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Author: **Christine Grossjohann**
Strand: **The API/Formulation Interface**
Institute: **Trinity College Dublin**

Title:

Co-crystal engineering of sulfadimidine/4-aminosalicylic acid by co-grinding in the solid state

Principal Focus: Co-crystallisation of active pharmaceutical ingredients (APIs) with suitable co-formers offers the possibility of influencing their physical and chemical properties in order to favourably alter biopharmaceutical parameters. The focus of this work is to compare the effectiveness of grinding methods, in the form of dry grinding and solvent drop grinding, in order to produce co-crystals of sulfadimidine and to investigate the physicochemical and dissolution characteristics of the co-crystals produced.

Experimental: Sulfadimidine (SD) and 4-aminosalicylic acid (4-ASA) were mixed in different molar ratios (1:2, 1:1, 2:1) and subjected to milling for 15, 30 and 45 minutes in a planetary ball mill. In the case of solvent drop grinding, a few drops of ethanol were added prior to the milling process. The products were analysed by Differential Scanning Calorimetry (DSC), Thermogravimetric analysis (TGA), Powder X-ray Diffraction (PXRD) and Fourier Transform Infrared Spectroscopy (FTIR).

Discussion: XRD results revealed that products obtained by dry grinding displayed diffraction peaks superimposable with those of the pure compounds. In contrast, the solvent drop ground products showed patterns with characteristic diffraction peaks, which differed from those of the starting components (Fig. 2). FTIR spectra of the dry ground material did not show evidence of significant intermolecular interactions, while solvent drop grinding revealed hydrogen bond formation between the two compounds.

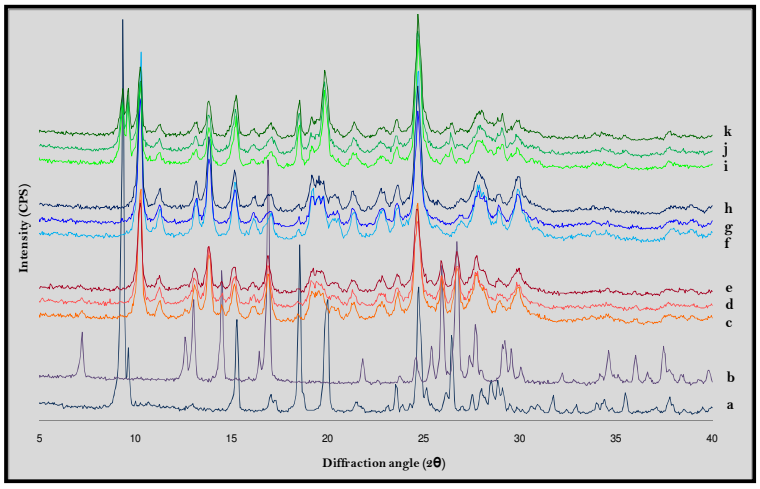

Fig. 2: PXRD patterns of (a) pure sulfadimidine; (b) pure 4-ASA and solvent drop ground composites: SD/4-ASA (1/2) EtOH (c) milled 15min, (d) milled 30min, (e) milled 45min; SD/4-ASA (1/1) EtOH (f) milled 15min, (g) milled 30min, (h) milled 45min; SD/4-ASA (2/1) EtOH (i) milled 15min, (j) milled 30min, (k) milled 45min.

Dissolution studies revealed significantly higher intrinsic dissolution rates for SD and 4-ASA from the co-crystal when compared with the equivalent physical mixture (Fig. 2, Table 1).

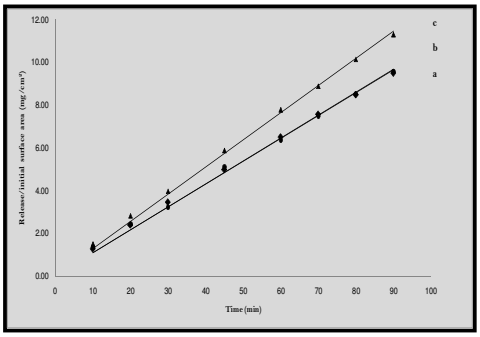

Fig. 2: Dissolution profiles of SD from (a) pure material, (b) SD/4-ASA (1/1) physical mixture and (c) SD/4-ASA (1/1) co-crystal prepared by solvent drop grinding

Table 1: Intrinsic dissolution rates of SDM

Substance	Description	IDR (mg/min/cm²) [± StDev]	t-test	Significance (α = 0.05)
SDM	Pure material	0.107 [± 0.004]		
SDM/4-ASA	Physical mixture	0.108 [± 0.005]	x	Statistically significant
SDM/4-ASA	Co-crystal	0.127 [± 0.020]	x	

Future Work: Studies currently being undertaken concern the production and characterisation of amorphous composites and co-crystals of SD/4-ASA prepared by co-spray drying. Future studies will also investigate the formation of co-crystals of sulfa compounds with other co-formers.