Project 1: **The Effect of Processing on the Solid-State form of Selected Sulphonamides and their Sodium Salts, alone and as Drug-Excipient Composites** Date: **19/08/10**	Author: **Evelyn O' Shea** Strand: **The API/Formulation Interface** Institute: **Trinity College Dublin**

Title:

Investigation of the effect of milling time on the solid-state properties of sulfadimidine and its sodium salt

Principal Focus: To evaluate the effect of ball milling on the induced amorphous content of API and the crystal structure in terms of crystallite size and total lattice strain.

Experimental: Ball milling was carried out using a Retsch PM100 Planetary mill at a constant speed of 400 rpm. Milling times of 5, 30, 60, 120 minutes and 5, 10, 15 and 20 hours were used at room temperature. Crystallite size and lattice strain were calculated from PXRD data using PDXL software which utilised the Williamson-Hall equation[1]. Amorphous content was calculated from DSC data using the equation given by Desprez and Descamps[2].

Results and discussion: Distinct Bragg peaks were observed for all milled sulfadimidine (SD) samples regardless of milling time, indicating that the material remains predominantly crystalline. PXRD studies on ball milled sulfadimidine powders processed at both temperatures showed that the diffraction peaks decreased and broadened after processing (Fig. 1). The reduction of crystallite size and introduction of defects (microstrain) due to milling is confirmed by the reduced peak area of the (0 4 0) Bragg peak after 20 h of milling compared to the un-milled powder (Fig. 1). Increased milling time resulted in decreased peak area as outlined in Table 1. Milling for 300 minutes resulted in the largest degree of amorphisation induced by milling but as milling time increased the amorphous content appeared to recrystallise.

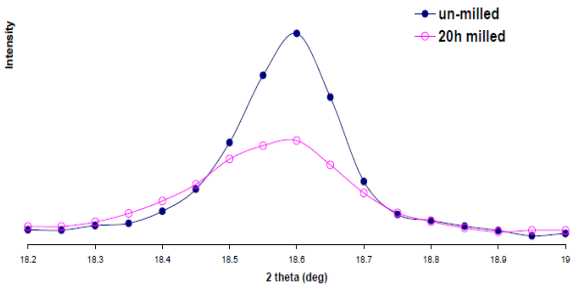

Figure 1: The (0 4 0) Bragg peak for un-milled SD and for SD milled for 20 h at 400 rpm at RT.

Table 1: The effect of mechanical activation of SD milled at RT.

Time (min)	Peak area (%)		Crystallite size (ang)		Lattice strain (%)		Amorphous content by DSC (%)	
0	100	(0.00)	392.17	(8.83)	0.14	(0.00)	0.00	(0.00)
5	70.80	(6.25)	326.68	(32.58)	0.51	(0.02)	0.00	(0.00)
30	74.95	(11.03)	209.33	(77.53)	0.48	(0.04)	1.45	(0.37)
60	70.92	(8.55)	310.34	(26.11)	0.54	(0.10)	0.92	(0.93)
120	68.72	(10.75)	298.62	(13.96)	0.55	(0.00)	1.18	(0.66)
300	66.73	(7.84)	276.96	(71.22)	0.46	(0.35)	1.95	(1.43)
600	55.75	(13.61)	301.15	(3.09)	0.53	(0.01)	1.27	(0.90)
900	71.17	(10.82)	286.67	(21.02)	0.48	(0.18)	1.45	(0.63)
1200	64.07	(7.66)	273.33	(44.94)	0.47	(0.01)	0.99	(0.52)

Note: Standard deviation in parenthesis

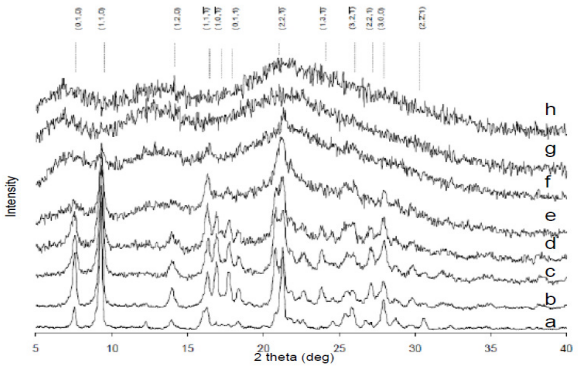

Figure 2: PXRD diffractograms of (from bottom to top) SD sodium un-milled and milled at 400 rpm, RT for 5, 30, 60, 120, 300, 600 and 900 minutes.

Table 2: The effect of mechanical activation of SD sodium at RT.

Time (min)	Peak area (%)		Crystallite size (ang)		Lattice strain (%)		Amorphous content by DSC(%)	
0	100.00	(0.00)	267.57	(14.14)	20.04	(0.40)	0.00	(0.00)
5	115.73	(46.49)	129.47	(43.00)	23.24	(0.07)	0.00	(0.00)
30	60.72	(20.94)	139.94	(54.49)	12.71	(0.83)	50.37	(7.13)
60	36.76	(10.05)	166.08	(64.81)	8.27	(0.14)	64.11	(2.18)
120	21.77	(3.66)	170.19	(42.76)	5.63	(1.03)	90.64	(0.77)
300	6.87	(1.00)	10.78	(1.77)	3.41	(0.27)	100.00	(0.00)
600	4.25	(1.94)	10.17	(0.69)	2.36	(0.00)	100.00	(0.00)
900	3.24	(2.57)	7.67	(4.78)	0.00	(0.00)	100.00	(0.00)

Note: Standard deviation in parenthesis

Figure 2 displays the PXRD patterns of ball milled sulfadimidine sodium milled at room temperature. Upon milling for 5 minutes the crystallite size was significantly reduced (~50 %) as shown in Table 2 and confirmed by the PXRD pattern (2b), characterised by more distinct Bragg peaks and increased peak area. No amorphous content was detected for this milling time. Beyond 5 minutes, the amorphous content increased proportionally with milling time. Complete amorphisation, as detected by DSC was achieved after 300 minutes (Table 2) but PXRD illustrates a partial crystal structure remains within this sample. This shows there is some discrepancy between the measurements. In contrast to SD, increased milling times (up to 900 minutes) did not result in recrystallisation.

Future Work: To investigate the effects of observed solid-state changes on the flowability of the materials and to explore the effect of ball milling on other sulfa compounds.

1. Williamson G.K.and Hall W. H. , *Acta Metall.*, **1**, (1953), 22-31.
2. Desprez S.and Descamps M. , *J. Non-Crys. Solids*, **352**, (2006), 4480-4485.