Project 8: ***Comprehensive Polymorph Analysis*** Date: **23/08/10**	Author: **Michelle Hennigan** Strand: **Particle Engineering and API/Formulation Interface** Institute: **NUI Galway**

Title: Quantifying APIs and polymorphs in the solid state using spectroscopic and chemometric methods.

Principal Focus: Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in their solid form by inclusion in tablets, capsules and spray dried powders. APIs can exist in various solid state forms including polymorphs, solvates, and hydrates. Accurate characterisation and quantification of the precise solid state form(s) present is of vital concern for safety and regulatory affairs. We have developed a model system which comprises of a model API, 5-methyl-2-[(2-nitrophenyl) amino] -3-thiophene carbonitrile (ROY), with several excipients (e.g. microcrystalline cellulose (MCC) and magnesium stearate (MgSt)). ROY exhibits extensive polymorphism with ten known polymorphs. For the initial studies powder mixtures containing 1 to 17.5 % by weight of the stable yellow polymorph of ROY were generated. From NIR data, quantitative calibration models were developed using a variety of pre-processing methods and the best model enabled the prediction of ROY content with an accuracy of ±0.3%.

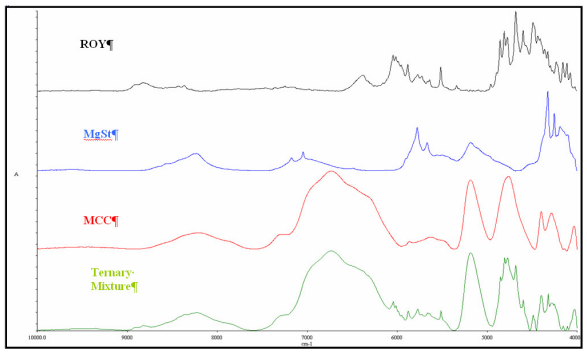

Figure 1 NIR spectrum of ROY, Magnesium Stearate, Microcrystalline Cellulose and a Ternary mixture spectrum of all three components.

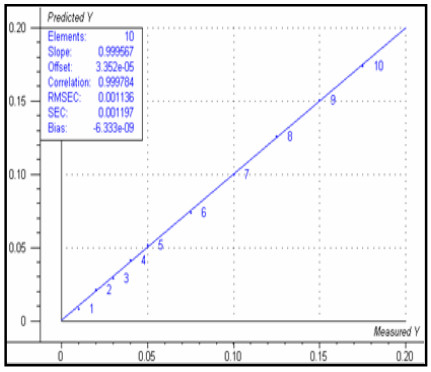

Figure 2 Calibration plot of MSC treated Roy 5515cm^{-1} spectral region.

NIR	cm^{-1}
Full spectrum	10000-4000
A and B	6200-4000
A	6200-4950
B	4950-4000
Roy 5515cm^{-1}	5560-5470

Table 1 Spectral subsets chosen for modelling.

Untreated Data	LV	Correlation	RMSEC	RMSEP
Full	3	1	0.17	0.34
A and B	2	0.999	0.19	0.43
A	3	1	0.11	0.22
B	2	0.998	0.34	0.5
Roy 5515cm^{-1}	2	0.999	0.18	0.25
Baseline Corrected Data	**LV**	**Correlation**	**RMSEC**	**RMSEP**
Full	2	1	0.26	0.41
A and B	2	0.999	0.21	0.16
A	2	0.997	0.41	0.62
B	2	0.999	0.24	0.27
Roy 5515cm^{-1}	2	1	0.14	0.22
MSC treated Data	**LV**	**Correlation**	**RMSEC**	**RMSEP**
Full	2	1	0.13	0.18
A and B	2	0.998	0.34	0.44
A	2	0.997	0.44	0.18
B	2	0.998	0.32	0.4
Roy 5515cm^{-1}	2	1	0.11	0.16

Table 2 PLS modelling results of NIR data

Discussion: For the chemometric analyses, the spectra were either used over the full range or as discrete regions of interest. To determine what were the best pre-processing methods, models were generated using the raw, baseline corrected, and MSC (Multiplicative Scatter Correction) treated data. MSC is designed to remove both additive baseline and multiplicative signal effects. The best model used MSC treated data from a narrow region of interest (ROY 5515 cm^{-1}). Chemometric analysis of the XRPD dataset generated using these powders gave poorer quantification and the best models using the full spectra were able to predict ROY concentrations to~±2.6%. Raman spectroscopy of these powders was poor due to fluorescence interference from both the ROY and the microcrystalline cellulose. Therefore, NIR seems to be the method of choice for ROY analysis.

Future Work: Raman, Fluorescence, FT-IR, and XRPD methods will be used to collect data from these powders and model tablets sample sets using ROY and other APIs. A variety of chemometric methods will then be employed to determine the optimal methods for quantifying APIs in solid forms and for identifying the presence of polymorph contamination.

References: *Yu, L et al, Thermochemistry and Conformational Polymorphism of a Hexamorphic Crystal System, J. Am. Chem. Soc.* ***2000****, 122, 585-591. Mitchell, C. A.; Yu, L.; Ward, M. D. Selective Nucleation and Discovery of Organic Polymorphs through Epitaxy with Single Crystal Substrates, J. Am. Chem. Soc.* ***2001****, 123, 10830-10839. Chen, S.; Guzei, I. A.; Yu, L. Cross-Nucleation between ROY Polymorphs, J. Am. Chem. Soc.y* ***2005****, 127, 9881-9885. Chen, S. et al, New Polymorphs of ROY and New Record for Coexisting Polymorphs of Solved Structures, J. Am. Chem. Soc.* ***2005****, 127, 17439-17444. McArdle, P.; Gilligan, K.; Cunningham, D.; Ryder, A. Determination of the polymorphic forms of bicifadine hydrochloride by DSC-TG, XRPD, ATR-IR, and ATR-NIR. Appl. Spectros.* ***2005****, 59, 1365-1371. Hu, Y.; Erxleben, A.; Ryder, A. G.; McArdle, P. Quantitative Analysis of Sulfathiazole Polymorphs in Ternary Mixtures by Attenuated Total Reflectance Infrared, Near-infrared and Raman Spectroscopy, Journal of Pharmaceutical and Biomedical Analysis,* ***2010****, 53, 412-420.*