QUANTITATIVE MULTIVARIATE ANALYSIS (PLS AND PCR) OF CARBAMAZEPINE POLYMORPHIC MIXTURES USING RAMAN SPECTROSCOPY

C.J. Strachan1*, J.A. Zeitler1, D. Pratiwi1, K.C. Gordon2 and T. Rades1

1School of Pharmacy, University of Otago, Dunedin, New Zealand; Email: thomas.rades@stonebow.otago.ac.nz
2Department of Chemistry, University of Otago, Dunedin, New Zealand; Email: kgordon@alkali.otago.ac.nz

Keywords: partial least squares (PLS), principal components regression (PCR), carbamazepine, polymorphism, quantitative analysis

Abstract: The ability of Raman spectroscopy combined with multivariate analysis (PLS and PCR) to quantify binary mixtures of polymorphic forms of carbamazepine was investigated. Accurate quantitative models were generated with limits of detection of less than 1%.

The polymorphic behaviour of drugs is a major concern of the pharmaceutical industry as it may have considerable formulation, therapeutic, legal and commercial implications [1]. Different polymorphic forms of drugs usually exhibit different dissolution rates and solubilities. The stable polymorph will usually have the lowest dissolution rate, and as these drugs usually display dissolution rate-limited absorption, different polymorphs are likely to exhibit different absorption profiles and bioavailabilities. For such drugs, methods to achieve higher aqueous dissolution include the use of the active compound in an amorphous rather than in a crystalline form, or use of a metastable polymorphic form. However, these forms might crystallise into the stable form at any stage during manufacturing, packaging, distribution and storage. In addition, some polymorphs or amorphous forms are not easily formulated into solid dosage forms, owing to differences in their chemical stability, flow behaviour, compressibility, etc [2]. The aim of the present study was to investigate the application of Raman spectroscopy and different approaches of multivariate analysis [PLS and PCR], to the quantitative analysis of polymorphic mixtures of carbamazepine (CBZ) forms III and I, based on two wavenumber ranges of the Raman spectrum.

Raman spectra were obtained of pure polymorphic forms I and III of CBZ and of binary geometric mixtures. Binary mixtures (approx. 10 mg) were prepared in triplicates with an interval of 1% (0–10% of CBZ form I in form III). A Bruker IFS 55 FT-Raman interferometer fitted with a Bruker FRA 106 S FT-Raman accessory was used. Spectra were collected for a total of 196 scans at a resolution of 4 cm⁻¹. Spectral analysis was performed using Galactic Grams/AI 7.01 after converting from OPUS data. Raman intensities over defined wavenumber ranges were used. The wavenumber ranges chosen were 2950–3100 cm⁻¹ (region I), and 2950–3100 cm⁻¹ and 225–1710 cm⁻¹ (region II). Multivariate analysis on the spectra was performed using the PLSplus IQ module of the Grams/AI software. For both PLS (PLS-1) and PCR different preprocessing parameters (mean centering, multiplicative scatter correction (MSC) and 1st derivative) were used and applied to regions I and II. The models were cross-validated leaving out one spectrum at each step. To ensure the models generated were neither under- nor over-fitted, prediction residual error sum of squares (PRESS) combined with F-test probability determinations were used to optimize the number of factors used in the models. Linear regression of actual versus predicted concentration data provided 95% confidence intervals (CI) and prediction intervals (PI). The limit of detection (LD) and limit of quantitation (LQ) of polymorphs in binary mixtures were calculated from the standard deviation (S.D.) at the lowest concentration studied (0 %) and the slope of the linear regression of the actual versus predicted concentration plot using LD = 3.3 S.D./slope and LQ = 10 S.D./slope.
Figure 1. FT-Raman spectra of CBZ form I and form III and form I - form III.

Figure 2. Actual versus predicted concentration (PLS and PCR) of form I in form III for low levels of form I (1–10%) for regions I and II using various preprocessing techniques.

This study demonstrated that PLS and PCR of Raman spectroscopic data provides a sensitive method for the quantitative analysis of polymorphic forms, with a LD of frequently <1%. There is however, no specific advantage in using either PLS-1 or PCR. Using MSC generally improves the $R^2$-value. Surprisingly, there appears to be no advantage in using region II over the much smaller region I.

Acknowledgements:
The study has been supported by a grant from the University of Otago Research Foundation.

References: