Application of a Polar Qualification System in the near infrared identification and qualification of raw pharmaceutical excipients

Weng L. Yoon,[a] Nigel C. North,[b] Roger D. Jee[a] and Anthony C Moffat[a]

[a]*Centre for Pharmaceutical Analysis, The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, UK.*

[b]*SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex, CM19 5AW, UK.*

Introduction

The routine identification and qualification of pharmaceutical excipients is a demanding analytical task which is subjected to regulatory requirement.[1] To comply with pharmacopoeial standards, a variety of tests must be carried out to check the identity and quality of samples, for example, infrared spectrum, limit tests, bulk density is necessary to verify the identity and quality of compounds. The near infrared reflectance spectra contains both chemical and physical information and, consequently, of checking the identity and quality of a sample in a single measurement. The success of such an approach would offer tremendous savings in time and resource for the pharmaceutical industry.

Pharmaceutical excipients often exist in various grades which differ in terms of particle size (for example, Avicel PH101 and Avicel PH102), degree of polymerisation (for example, Povidone 12, 15 etc .) and water content (lactose monohydrate and anhydrous lactose) etc. It is, therefore, necessary to develop a method of NIR spectral analysis which is sensitive to such differences, but robust enough to stand the variations observed in spectra caused by sample packing and batch to batch differences between samples. Ideally the procedure should also be transferable between different instrumental setups.

Complex chemometric pattern recognition methods, such as soft independent model for class analogy (SIMCA) and Mahalanobis Distance for the classificaiton of raw materials, have previously been reported.[2,3] Unfortunately, the heavy reliance on such methods has been viewed skeptically by some regulatory authorities.[4]

The use of Polar Qualification System (PQS) in the pharmaceutical industry was first reported by Van der Vlies *et al*.[5] and offers a simple method for comparing spectra which also gives a simple visual representation. In this procedure, a spectrum is transformed to a single point on a plane. PQS involves two basic steps : (1) transformation of spectra to polar coordinates and (2) calculation of the centre of gravity of the resulting polar plot. When repeat measurements or a range of values from different batches of material are available, confidence ellipse enclosing specified properties of the population may be calculated.

In this work, the ability of PQS to classify ten commonly used excipients is investigated along with the effects of sources of variation, such as powder repack and differences between instrumentation.

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Experimental

Materials

All excipients used were of pharmaceutical grade and had been shown to meet the British Pharmacopoeia and/or United States Pharmacopoeia specifications. The excipients investigated were : microcrystalline cellulose (Avicel PH102, Honeywill & Stein, Surrey, UK), dicalcium phosphate dihydrate (Emcompress, Edward Mendell Co. Inc., Surrey, UK), sodium starch glycollate (Explotab, Edward Mendell Co. Inc., Surrey, UK), lactose monohydrate(DMV International, Veghel, Netherlands), hydroxypropyl methylcellulose (Methocel, Colorcon, Orpington, UK), Opadry White YS-1-7003 (Colorcon, Orpington, UK), povidone (Kollidon 30, BASF Plc, Cheshire, UK), methyl-, propyl- and butyl- hydroxybenzoate (Nipa Laboratories Ltd, Mid Glamorgan, UK), magnesium stearate (Akros Chemicals, Manchester, UK) and talc (Luzenac Europe, Toulouse, France).

Opadry White YS-1-7003 is a proprietary mixture of hydroxymethyl propyl cellulose, pigment and plasticiser.

Apparatus

Three different instrumental set-ups were used. Instruments I and II were based on the FOSS NIRSystems (Silver Springs, MD, USA), using the 6500 spectrophotometer fitted with a Rapid Content Analyzer (RCA). Instrument III was a Bran+Luebbe Infraprover II Fourier Transform Polarisation Spectrophotometer (GmbH, Norderstedt, Germany) fitted with a Sample Presentation Accessory (SPA).

Measurement of spectra

All spectra were measured by reflectance. The powders were filled into clear, neutral glass vials (C/N : BDH/Merck/215/0074/23) to a depth of about 10 mm. Twelve replicates of each sample were measured to average out spectral variation arising from sample packing.

Each recorded spectrum measured on the FOSS NIRSystems instruments was an average of 32 scans, measured over the range 1100 to 2498 nm (2 nm intervals, 700 datapoints). Spectra were measured relative a reference ceramic standard.

For the Bran+Luebbe instrument, spectra were measured over the range 4000 to 9996 cm^{-1} (12 cm^{-1} intervals, 500 datapoints) and each recorded spectrum was an average of six scans. Spectra were measured relative to a Spectralon® standard.

Data treatment

Derivative spectra were calculated by simple difference procedures using an in-house written program. Equal size blocks of data points before and after the data point at which the derivative is to be calculated were averaged and the derivative taken as the simple difference in means. The process was repeated across the whole spectrum a number of times until the required derivative was obtained. To normalise spectra, they were scaled so that the absolute maximum absorbance or second derivative absorbance was equal to 1.

Cubic spline interpolation was used to convert spectra measured in wavenumbers to equally spaced data points in terms of wavelength. The wavenumber v. reflectance spectra were first converted to absorbance (- log R) spectra and then the absorbance values at 2 nm intervals over the range 1100 to 2498 nm calculated to give 700 values. Out of range (> 2200 nm) values were set to 0. Cubic spline interpolation was preformed using an in-house computer written program based on the functions *spline* and *splint*.[6]

Transformation of spectrum to polar coordinates and calculation of centre of gravity were carried out using an in-house programme.

Results and discussion

The feasibility of using PQS to distinguish between the different excipients was initially investigated. One batch of each excipient was measured twelve times using instrument I. The sample bottle was shaken in between each measurement. Second derivative spectra were calculated and then using the full spectral range (1100–2498 nm) transformed to polar plots. A 95% confidence ellipse was finally constructed for the centre of gravity points for each excipient. The centre of gravity plot, Figure 1, shows that apart from the three celluloses (Avicel, Methocel and Opadry White YS-1-003), the excipients may be clearly differentiated from one another. Powder repack caused considerable spectral variation for the celluloses resulting in overlap between the confidence ellipses. Normalisation of the spectra reduced this variation and confidence ellipses for the celluloses could be separated, Figure 2.

To investigate the effects of inter-batch and instrumental differences, five different batches of methyl and propyl para hydroxybenzoate and six different batches of butyl para hydroxybenzoate were measured using instruments I, II and III. Differentiation between the three groups of excipients

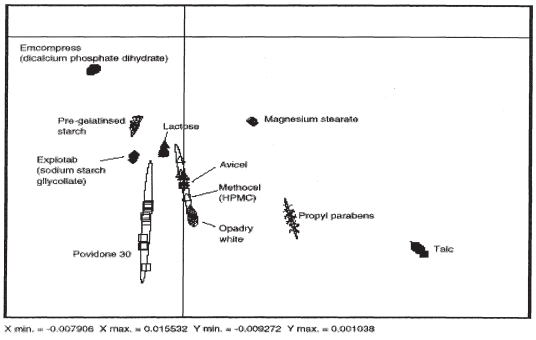

Figure 1. Centre of gravity plots for ten different excipients when measured on instrument I, based upon the full spectral range (1100–2498 nm) of the second derivative absorbance spectra.

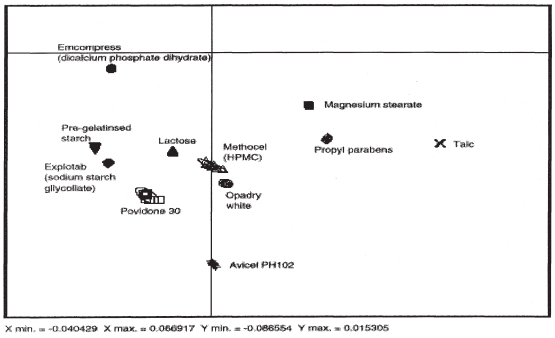

Figure 2. Centre of gravity plots for ten different excipients when measured on instrument I, based upon the full spectral range (1100–2498 nm) of the normalised second derivative spectra.

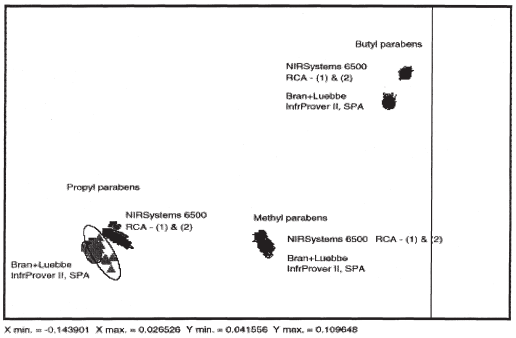

Figure 3. Centre of gravity plots for different batches of methyl, propyl and butyl para hydroxybenzoate when measured on instrument I, II and III, based upon a selected spectral range (1500–1900 nm) of the normalised second derivative spectra.

were still possible, provided that the spectral range was limited to 1500 to 1900 nm, Figure 3. The exclusion of the lower wavelength region was necessary to remove a spectral anomaly arising with instrument II due to the failure to correctly set the gain on instrument II. For propyl and butyl para hydroxybenzoates, the measurements made using instrument III were slightly separated from those using instruments I and II, however, not sufficient to cause any problems with identification. This difference is not surprising, considering that the spectra from instrument III had to be transformed from a wavenumber to wavelength basis and different reference standards were used.

Conclusion

PQS offers a sensitive and robust method for the identification and qualification of pharmaceutical excipients with the optimisation of parameters such as data pretreatment and spectral range.

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