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# Application of near-infrared spectroscopy to the determination of the sites of manufacture of proprietary products

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**Abstract**

Reflectance near-infrared (NIR) spectroscopy has been investigated as a method to distinguish between the sites of manufacture of a number of proprietary tablets. As test samples, parallel imports which are pharmaceutically equivalent products manufactured at different sites have been used. Three products: Aremis/Besitran®, Renitec® and Voltarol Retard® originating from two or more sites and Adalat® from a single site were examined. The principal component analysis (PCA) score plots showed that spectra of tablets originating from different sites of manufacture often gave rise to statistically different populations. PCA loadings indicated that the differences were related to moisture content and excipients. Spectra were used to construct a library for the classification of tablets to predict the site of manufacture based on the method of residual variance of the principal components. Where a large data set was available (Aremis/Besitran® tablets) prediction rates for the successful identification of the two sites of manufacture, Madrid and Barcelona, were 95.7 and 98.1%, respectively for the validation set with all errors encountered of Type I.


*Keywords:* Near-infrared spectroscopy; Pharmaceutical tablets; Principal component analysis; Sites of manufacture

## 1. Introduction

Reflectance near-infrared (NIR) spectroscopy is a rapid and non-destructive technique that is sensitive to both the chemical and physical properties of the sample. In combination with various chemometric procedures (e.g. principal components analysis, Euclidean distance, polar qualification system, correlation coefficient, soft independent modelling class analogy) [1–3] it has been used to classify raw materials [4–6], clinical samples [7,8] solvents [9]and herbal products [10]. This paper examines the feasibility of using the technique to identify and/or authenticate the source of manufacture of tablets produced at different sites.

While the NIR literature contains examples of applications of the technique to trace the origins of materials, very few are for finished pharmaceutical products. Woo et al. [11] demonstrated that the

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geographical origins of herbal medicines could be traced based on the differences in constituents which arise from differing soil and climatic conditions. Van der Vlies and coworkers [12] have shown that the technique was capable of identifying the source of raw materials based on differences in particle size. Scafi and Pasquini [13] used near-infrared spectroscopy as an aid to the identification of counterfeit drugs. Classification of proprietary tablets originating from various sites of production has not been previously reported and is more challenging because such pharmaceutical products are generally manufactured using the same formulation and according to tight specifications in order to comply with the Good Manufacturing Practice Guidelines [14]. Any variation between products from different sites will be small and arise from slight variations in the materials used, tablet process conditions (e.g. force of compaction), ambient conditions (e.g. humidity, temperature etc.) and any combination of these factors. Conventional methods such as HPLC are unlikely to be able to detect such subtle differences and are also sample destructive in nature. In comparison, NIR spectroscopy allows for a rapid and non destructive analysis of intact tablets which in combination with suitable chemometric procedures should enable such differences to be detected.

Parallel imports are proprietary medicinal products imported into the UK from a member state of the European Economic Area (EEA) with a valid marketing authorization (MA) in that member state. They will have been made by, or under licence to, the same company or a member of the same group of companies, as the holder of the MA for the UK product. They must be therapeutically equivalent to the product covered by the UK MA. When importing such products into the UK the wholesaler is required to obtain what is called a parallel import product licence. As a result of price differentials of medicines between countries, parallel importing has been deemed as one of the methods to control drug costs [15]. For the year 2001, parallel imports in the UK have been estimated at 13% of the total market [16]. Pharmaceutically equivalent products, manufactured at different sites, will provide a good test of the effectiveness of NIR to discriminate between minor differences in tablet composition. The identification of the site of manufacture may be of value to manufactures, customers and the industry regulators, ensuring consistency of quality of all medicines, whether parallel imports or not. For example it might help in identifying and preventing counterfeit or diverted products.

## 2. Experimental

### 2.1. Materials

Packets of tablets (generic names in parentheses) of: Adalat® 20 mg (nifedipine), Aremis/Besitran® 50 mg (sertraline hydrochloride, UK generic name is Lustral®), Renitec® 5 mg (enalapril maleate) and Voltarol Retard® 100 mg (diclofenac sodium), were supplied by the Medicines and Healthcare products Regulatory Agency. All tablets were supplied in their original unopened packaging. For all products the actual tablets were encased in blister packs in the boxes.

### 2.2. Instrumentation

Reflectance NIR spectra were measured using a FOSS NIRSystems 6500 spectrophotometer fitted with a Rapid Content Analyser (Silver Springs, MD, USA). The instrument was controlled by Vision software (FOSS NIRSystems, version 2.20). Tablets were placed centrally on the sample stage and measured on both sides. Each recorded spectrum was the average of 32 scans and measured over the wavelength range 1100–2498 nm. All reflectance ($R$) measurements were made relative to the instrument's ceramic reference. Tablet hardness was measured using a Schieuniger Tablet Hardness Tester, model 2E/205 (Dr. K Schieuniger & Co., Zurich, Switzerland).

### 2.3. Data processing and analysis

Standard normal variate (SNV) normalisation was performed according to Eq. (1):

$$z_i = \frac{(x_i - \bar{x})}{s} \quad (1)$$

where $z_i$ is the normalised value, $x_i$ is the ordinate value at wavelength $i$, $s$ and $\bar{x}$ are the standard deviation and mean of the ordinate values calculated over the wavelength range being normalised, respectively.

Second-derivative spectra were calculated by means of a Savitsky-Golay [17,18] filter using 11 data points

and a second-order polynomial. Principal component analysis (PCA), PCA scores and loadings were all calculated using The Unscrambler (version 7.6) software (CAMO Ltd., Unit 11, Studlands Park Ave., Newmarket, Suffolk, CB8 7EA, UK). Population means for multivariate data sets were compared using Hotelling's $T^2$ test [19]. An in-house computer program written in C was used for this test. Classification using the residual variance method of the principal components was performed using the Vision software (FOSS NIRSystems, version 2.20).

## 3. Results and discussion

Tablets of four proprietary products; Adalat® 20 mg, Aremis/Besitran® 50 mg, Renitec® 5 mg and Voltarol Retard® 100 mg were examined in this study. Packets of tablets with different batch numbers manufactured at one or more sites were used. The expiry dates on the packs indicated that for each product the batches available had been manufactured randomly throughout the year. For each of the individual products; Adalat®, Aremis/Besitran® and Voltarol® the physical dimensions, nominal mass and colour of the tablets were the same irrespective of the site of manufacture. The only differences were in the tablet markings.

For Renitec® tablets the physical size and shape varied with the site of manufacture. Tablets from Greece and Italy were cylindrical (9 mm diameter × 3 mm and 8 mm diameter × 3.5 mm, respectively) while those from France and Spain were oblong (8.13 mm length × 7.19 mm maximum width × 4.22 mm maximum thickness). All these tablets were of the same nominal mass irrespective of the source of manufacture and shape and consequently differed in density. There were also differences in hardness (France 7.4 kPa, Greece 6.63 kPa, Italy 6.38 kPa and Spain 8.31 kPa; each value the mean of six measurements).

According to the Patient Information Leaflet (PIL) enclosed in the packaging all tablets for a given product contained the same chemical components. The site of manufacture was ascertained from the PIL. Colour and markings of the outer packaging varied for each product according to the site of manufacture. Table 1, lists for each product the sites of manufacture, number

Table 1
Details of proprietry tablets

| Product | Description (colour, shape, markings) | Number of batches | Number of tablets |
|---|---|---|---|
| Aremis/Besitran® 50 mg (sertraline hydrochloride) | | | |
| Dr. Esteve SA, San Martin, s/n Poligono Industrial, 08100 Martorelles, Barcelona, Spain | White, capsule-shaped, 'Are/mis', '50' | 6 | 270 |
| Pfizer S.A., San Sebastian De Los Reyes, Madrid, Spain | White capsule-shaped, 'Pfizer', 'ZLT/50' | 4 | 117 |
| Renitec® 5 mg (enalapril maleate) | | | |
| Laboratoire Merck Sharp & Dohme-Chibret, Route de Marsat, BP 88, Riom, 63203, France | White, oval/flat ended, 'RENITEC', breakline | 9 | 96 |
| Merck Sharp & Dohme de Espana, S. A., C/ Josefa Valcarcel, 38 28027, Madrid, Spain | White, oval/flat ended, 'RENITEC', breakline | 6 | 83 |
| Merck Sharp & Dohme Italia S.p.a e Neopharmed S.p.a via Emilia 21 Pavia | White, round, '712', breakline | 2 | 23 |
| Vianex SA, Lab, 15302 Pallini, Attikis, Greece | White, round, uncoded, breakline | 2 | 18 |
| Voltarol Retard® 100 mg (diclofenac) | | | |
| Ciba Geigy Hellas S.A., Anthoussa, Greece | Pale red, round, no markings | 1 | 10 |
| Ciba-Geigy Gmbh. Geigy Pharma, 79662 Wehr, Germany | Pale red, round, 'CG', 'CGC' | 5 | 49 |
| Novartis Pharmaceutticals UK Limited Wimblehurst Road, Horsham, West Sussex, UK | Pale red, round. 'Voltarol R', 'Geigy' | 1 | 12 |
| Adalat® 20 mg (nifedipine) | | | |
| Bayer AG, Leverkusen, Germany | Pink grey lacquered, 'IU', Bayer logo | 19 | 221 |

Table 2
Formulation of products

| Product | Contents |
|---|---|
| Renitec® 5 mg | Enalapril maleate, lactose, magnesium stearate, maize starch and pregelatinised starch |
| Aremis/Besitran® 50 mg | Sertraline hydrochloride, calcium hydrogen phosphate, hydroxypropylmethyl cellulose, magnesium stearate, microcrystaline cellulose, polyethylene glycol, polysorbate-80, sodium starch glycollate, titanium dioxide and hydroxy-propylcellulose |
| Voltarol Retard® 100 mg | Diclofenac sodium, colloidal silicon dioxide, cetyl alcohol, povidone, sucrose, magnesium stearate, hypromellose, ploysorbate-80, purified talc, polyethylene glycol, titanium dioxide and iron oxide |
| Adalat® 20 mg | Lactose, maize starch, microcrystalline cellulose, polysorbate-80, magnesium stearate, hydroxypropylmethyl cellulose, polyethylene glycol 4000, titanium dioxide and iron oxide |

of batches available, number of tablets used for the study along with the tablet markings. A list of the chemical components for each product are given in Table 2.

### 3.1. NIR spectra

Original absorbance ($-\log_{10} R$) spectra for tablets of Aremis/Besitran® and Renitec® are shown in Fig. 1a and b, respectively. Each spectrum represents one tablet, the side of the tablet measured being selected at random. Throughout this study the different tablet markings on each side of a tablet were not found to make any notable difference. For Aremis/Besitran® there were no obvious spectral differences between tablets originating from the different sites of manufacture while for Renitec® (the Italian tablets which present a larger surface area to the NIR spectrophotometer) clearly formed a separate group. There was no other visual indication that differences in tablet hardness, density or shape affected the spectra. For all products, multiplicative baseline shifts caused by changes in orientation and specular reflection from the tablet surface dominated the spectral variation. To minimise these effects, spectra were SNV normalised and/or converted to second-derivative spectra. Fig. 1c and d show the SNV normalised spectra for Aremis/Besitran® and Renitec® tablets respectively, clearly showing the removal of most of the spectral variation. SNV normalised spectra for tablets of Voltarol Retard® from Greece and Germany were clearly differentiated from one another by the water peak at 1940 nm, Fig. 1e. The SNV normalised spectra for 19 batches of Adalat® tablets all from a single manufacturing site are shown in Fig. 1f.

### 3.2. Principal component analysis (PCA)

As simple visual inspection of spectra did not generally permit different batches or sites of manufacture to be differentiated, principal component analysis was applied to the spectra. SNV normalised or second-derivative spectra were found to give the best results.

### 3.3. Moisture exchange with the atmosphere

Tablets of all the products were found to rapidly exchange moisture with the atmosphere. To investigate this a single tablet was placed on the measurement stage and twelve spectra measured in rapid succession followed by a further 12 rapidly measured spectra after a period of 1 h. To minimise spectral variations due to sample positioning the tablet was not moved during these measurements. As an example, the spectra obtained for a Aremis/Besitran® tablet, Fig. 2a, shows a very small decrease ($\Delta A \approx -0.006$) in the water peak at 1940 nm (atmospheric conditions used: 25 °C and 50% RH). Though the effect is very small, it can be clearly seen in the PCA score plot, Fig. 2b, with the spectra falling into two distinct groups. Both the first and second PCA *x*-loading plots, Fig. 2c and d, are characteristic of water. Applying a multiplicative scatter correction to the spectra reduces the second principal component *x*-loading to little more than noise suggesting that the exchange of moisture with the atmosphere might

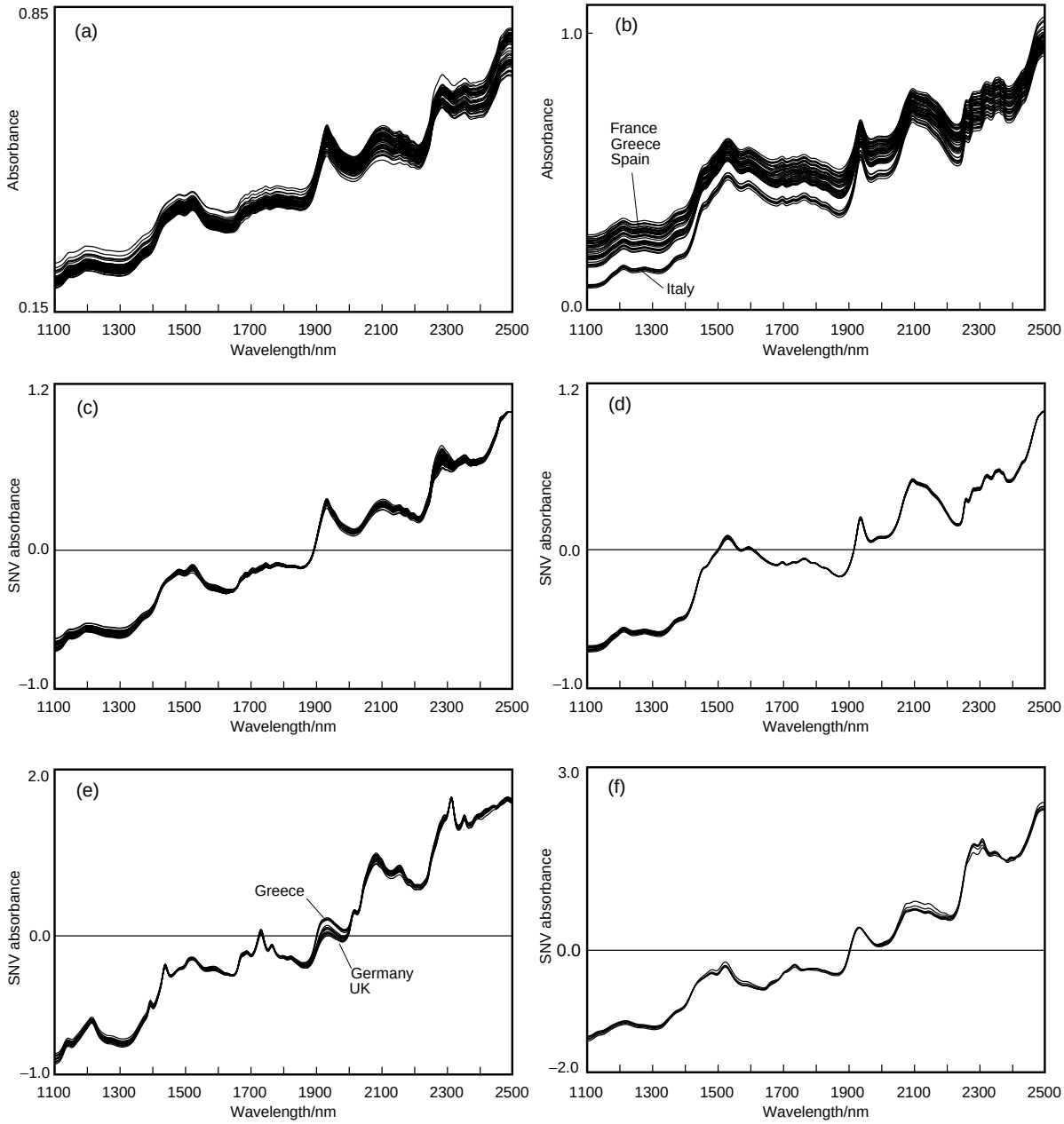


Fig. 1. Absorbance ($-\log_{10} R$) spectra of tablets for the different products and sites of manufacture: (a) Aremis/Besitran® (Barcelona and Madrid); (b) Renitec® (France, Greece, Spain and Italy); (c) as (a) but SNV normalised spectra; (d) as (b) but SNV normalised spectra; (e) SNV normalised spectra for Voltarol Retard® (Greece, Germany and UK); and (f) SNV normalised spectra for Adalat® (Germany).

involve changes in particle size at the tablet surface.

All spectra in the rest of this study were measured on tablets immediately after removal from their blister packs and any differences in water content can be considered to have originated at the site of manufacture. Because of the very strong NIR absorption for water it can be expected that differences in humidity from

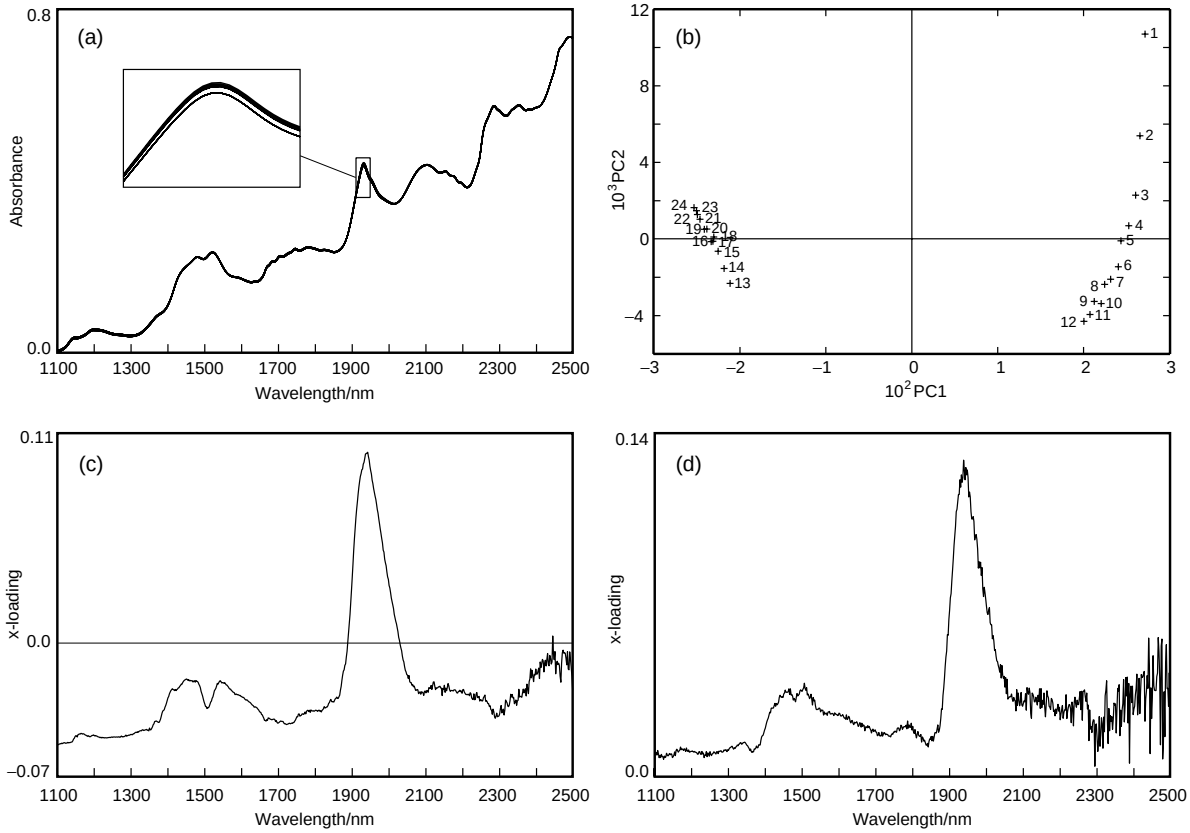


Fig. 2. Loss of moisture to the atmosphere (25 °C and 50% RH) for a single Aremis/Besitran® tablet. (a) Absorbance spectra with insert showing the main water peak; twelve scans in rapid succession (upper traces in insert) followed by a further 12 scans (lower single line in insert) after a period of 1 h; (b) PCA score plot; (c) first principal component *x*-loading; and (d) second principal component *x*-loading.

one site of manufacture to another will play a very important part in distinguishing manufacturing sites.

### 3.4. Batch and pack variation

Fig. 3 shows a PCA score plot for 19 batches of Adalat® tablets based on the first three principal components obtained from their second-derivative spectra. Although some of the packs had been re-packed and relabelled in different countries, all the NIR spectra of all the 19 batches formed a single global cluster on the PCA score plot, implying that they originated from a single manufacturing site. This is consistent with there being only one known site of manufacture for these tablets within Europe. Within the single global cluster representing all the batches it is clearly observed that the individual batches are not randomly distributed and there is considerable batch to batch variation. Using Hotelling's $T^2$ test for the difference between two population means of multivariate data (first three principal components in this case) it could be shown that many of the batches represented statistically ($P < 0.05$) different populations. For a number of batches more than one pack of tablets with the same batch number were available and the clusters of points associated with these tablets were generally much closer together, though not necessarily statistically equivalent ($P > 0.05$), than the clusters from different batches. This is not unexpected as tablets from a given batch might well have been produced on more than one tablet press, also differences can be expected between the start and end of a production run. Removing the wavelength region 1850–2010 nm (main water region) was also found to enhance the differences

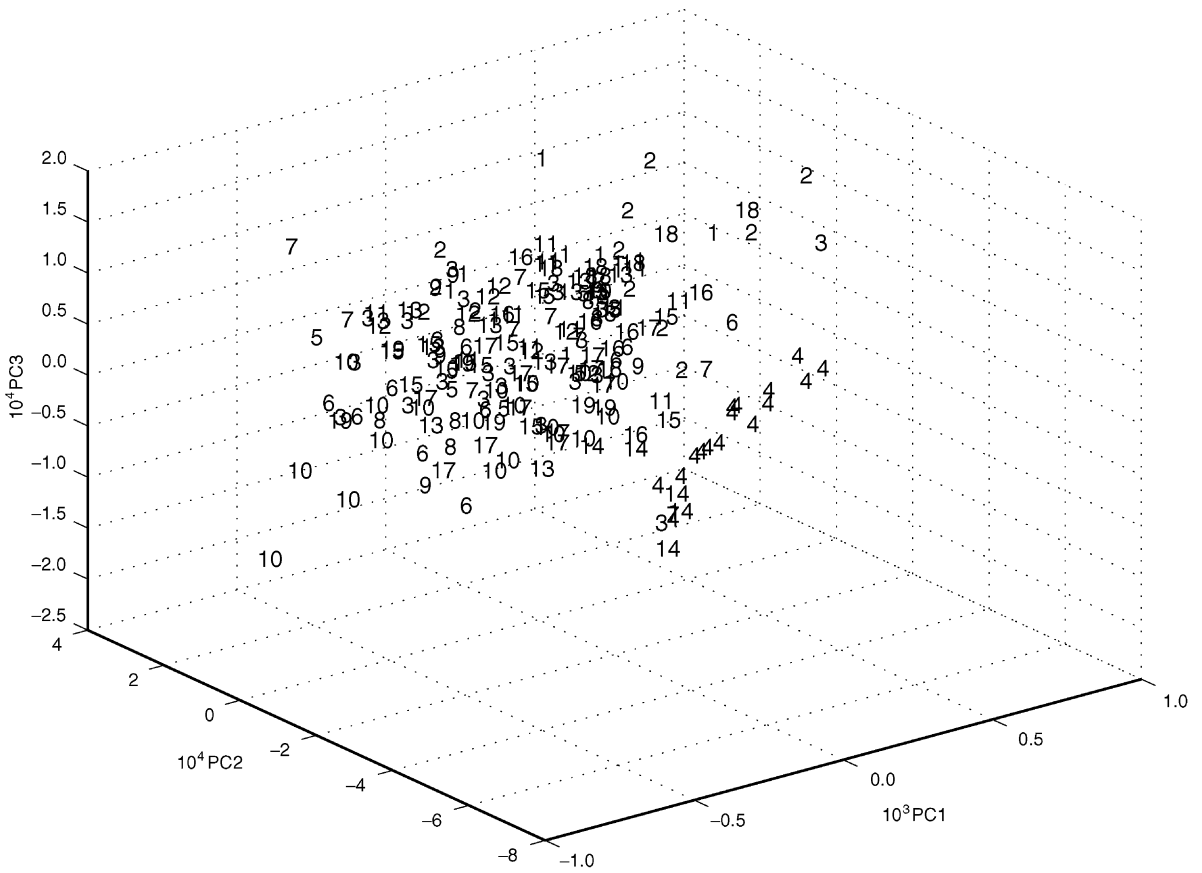


Fig. 3. PCA score plot (first three principal components) for 19 batches of Adalat® tablets calculated from the second-derivative spectra. Numbers represents different batches. All batches from one site of manufacture.

between some of the batches on the PCA score plot. While reasons for differences are not always obvious it is clear that a large number of different batches of a product will be required to adequately define the population from a given site of manufacture.

### 3.5. Variation between manufacturing sites

The PCA score plot, Fig. 4a, Aremis/Besitran® tablets manufactured at two sites in Spain, Barcelona (six batches) and Madrid (four batches) gave a number of separate clusters. Batches from Barcelona formed a single cluster, though as with the Adalat® tablets, different batches formed statistically different (Hotelling's $T^2$ test, $P < 0.05$) sub-clusters within the main grouping. The first three principal components account for about 94% (82, 8 and 4%, respectively) of the variability of the data and examination of the loadings for the first and second principal components suggests that water is one important cause of the difference between the sites of manufacture. Fig. 4b and c shows these loadings and from it can be seen that a prominent peak at 1940 nm, characteristic of water occurs. Removing the main water spectral region (1850–2010 nm) before PCA does not, however, prevent the separate clusters forming indicating that differences besides moisture content exist. The tablets manufactured at the Madrid site formed two separate non-overlapping clusters consisting of two batches each. With more batches it is quite possible that these would merge into one large cluster, however, PCA on the original absorbance spectra for just these samples reveals some interesting results. The two sub-clusters (batches 1, 2 and 3, 4) separate along the second

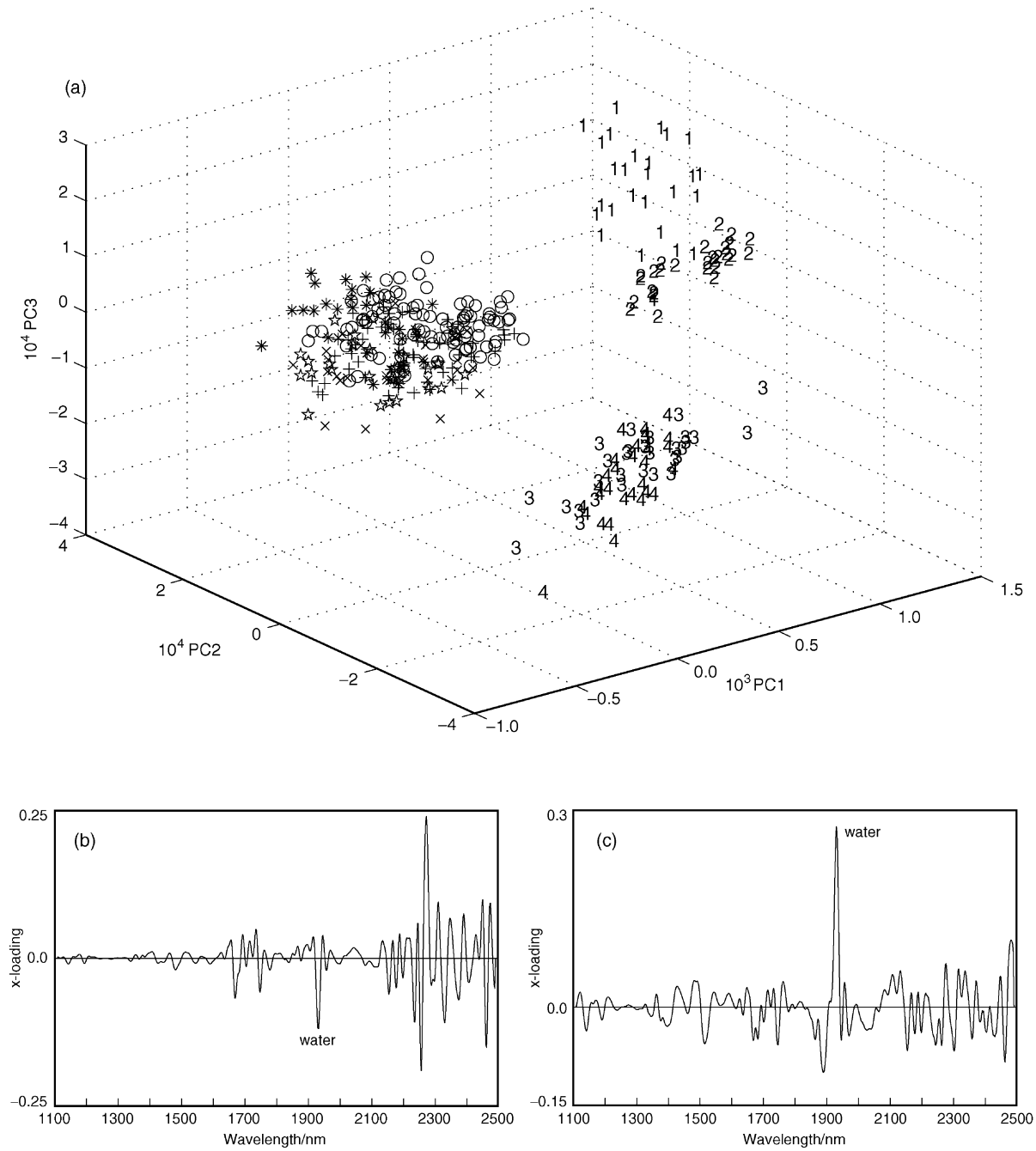


Fig. 4. PCA showing inter-site variation for Aremis/Besitran® tablets based on second-derivative spectra: (a) score plot (symbols indicate batches manufactured at Barcelona site, while numbers are for the Madrid site); (b) first principal component *x*-loading; and (c) second principal component *x*-loading.

principal component, Fig. 5a, and the corresponding loading, Fig. 5b, shows a striking resemblance to the spectrum of hydroxypropyl methylcellulose, Fig. 5c. Original absorbance spectra were used here rather than second-derivative spectra to aid easy visual comparison. Hydroxypropyl methylcellulose (HPMC) is one of the listed excipients in these tablets (Table 2) and it is possible that the two groupings arise due to a small difference in grade or quantity of this component. Gustafsson et al. [20] have shown using mid-infrared spectroscopy and multivariate analysis that HPMC originating from different suppliers can affect the quality of tablets.

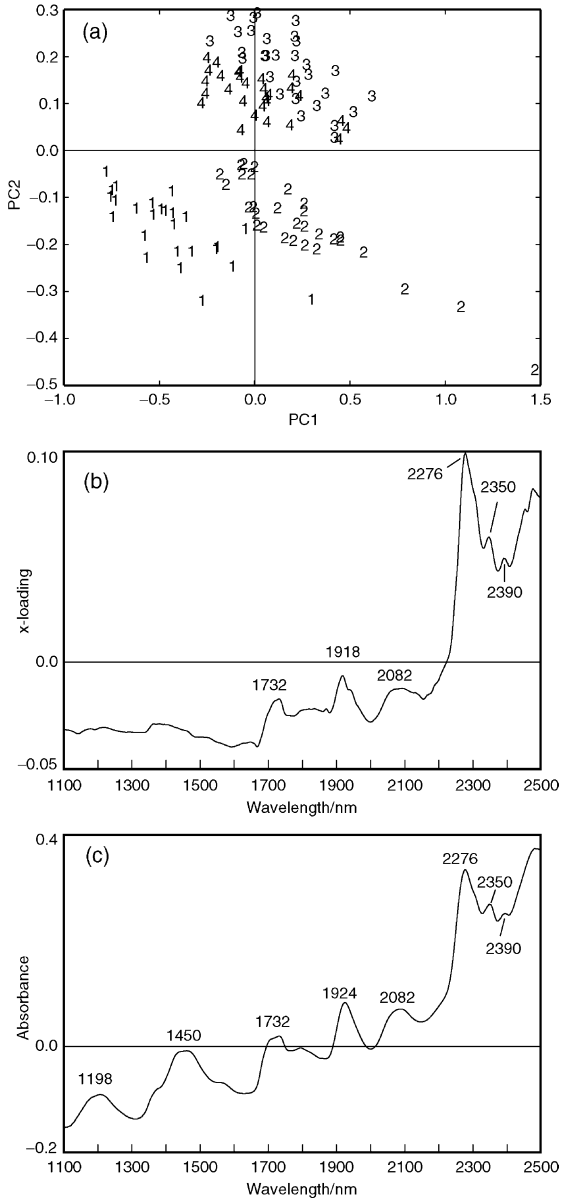


Fig. 5. PCA based on absorbance spectra showing intra-site variation for Aremis/Besitran® tablets manufactured at the Madrid site: (a) score plot; numbers represent different batches (same numbering as in Fig. 4a); (b) second principal component *x*-loading; and (c) absorbance spectrum for hydroxypropyl methylcellulose.

Principal component analysis of the second-derivative spectra for Renitec® 5 mg tablets from France, Spain, Italy and Germany gave the score plot shown in Fig. 6a. Some sites of manufacture are well separated from the others, however, there were also many overlapping groups. Tablets from Italy and Greece are distinguished from the others mainly along the first principal component axis. The loading for this principal component, Fig. 6b, shows a prominent peak at approximately 1940 nm, characteristic of water. Like Aremis/Besitran® tablets, the main cause of site to site variation therefore appears to be due to differing amounts of moisture. One Spanish batch (S1) showed a marked deviation along the second principal component, but again the loading would suggest that water is still an important factor for this difference, Fig. 6c.

The final product examined, Voltarol Retard® tablets, showed a separation into two clear groups corresponding to Greece and a combined group for the UK and Germany, Fig. 7a. Separation occurred along the second principal component rather than the first and again due to moisture content. Though the loadings, Fig. 7b and c, show peaks at approximately 1940 nm there are clearly other unknown factors besides water that are important.

### 3.6. Classification according to site of manufacture

The residual variance method of the principal components, available in the FOSS Vision software, was used to develop classification models for identifying sites of manufacture for single tablets using the SNV second-derivative spectral data. Three steps are involved; sample selection, finding the critical value of the test statistic and external validation. This process was carried out on all products, including Renitec® tablets for which good classification results are not to be expected based on the score plots obtained earlier.

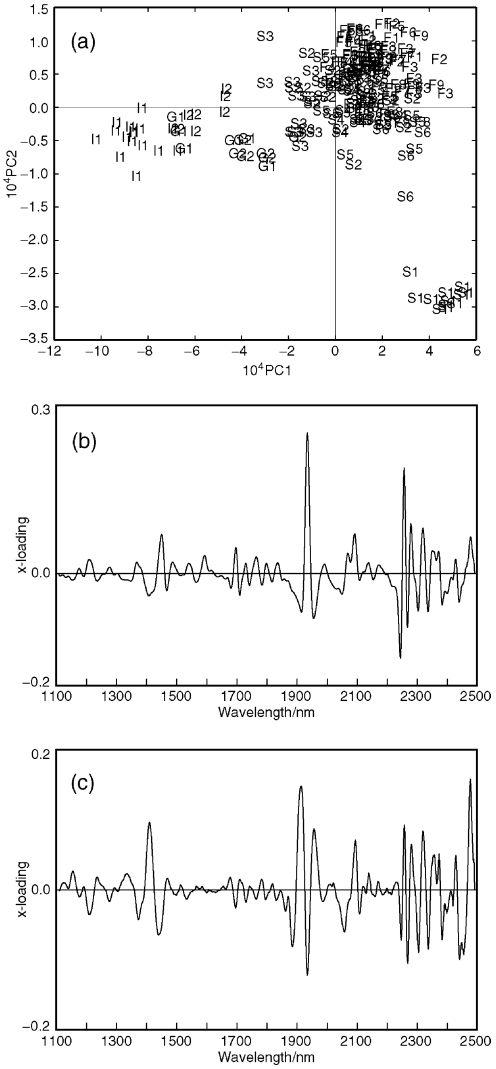


Fig. 6. PCA for Renitec® tablets based on second-derivative spectra: (a) score plot; (b) *x*-loading plot for first principal component; and (c) *x*-loading plot for second principal component. Tablet batches and site: F1-F9 (France), G1-G2 (Greece), I1-I2 (Italy) and S1-S6 (Spain).

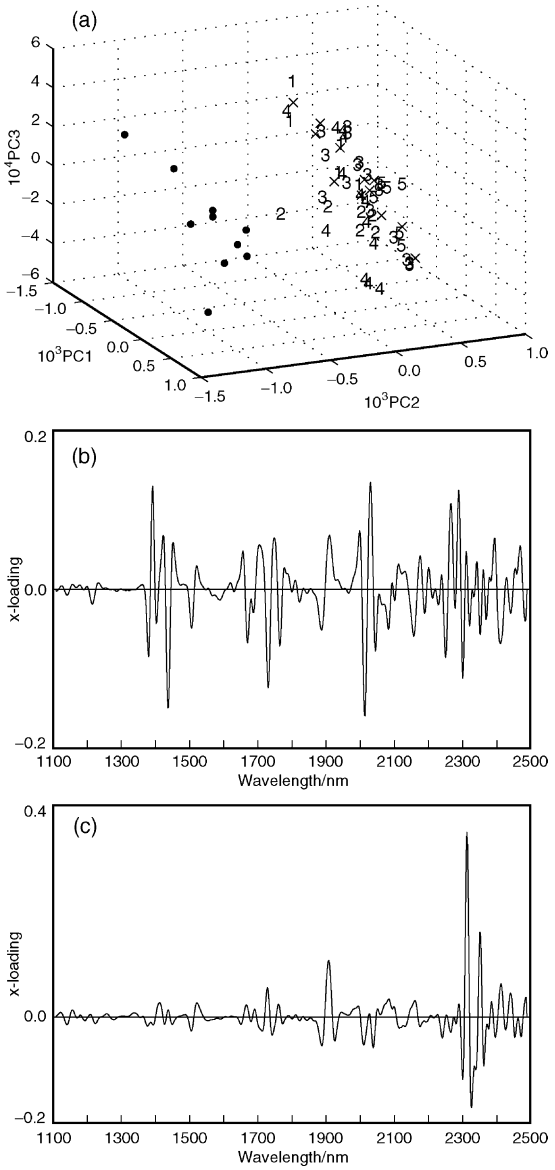


Fig. 7. PCA for Voltarol Retard® tablets based on second-derivative spectra: (a) score plot, (×) UK; (●) Greece and 1–5 German batches; (b) *x*-loading plot for first principal component; and (c) *x*-loading plot for second principal component.

For the purposes of the Vision software, samples from different sites were classified as separate products. The software checks not only the value of the residual variance, but also the product name to that in the library resulting in a classification as either PASS or FAIL. To PASS the product must fall within the threshold for the product as well as having the correct name. Three scenarios can result in a FAIL: (1) a sample falls outside the threshold of all products in the library including the correct product (Type I error), this gives a NO MATCH identification; (2) a sample falls within the threshold of a wrong product (Type II error); or (3) a sample falls within the threshold of two or more products (Type II error).

Table 3
Percentage error rates for site of manufacture classification

| | Threshold value/error type | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.85 | | 0.90[a] | | 0.95 | | 0.98 | |
| | I | II | I | II | I | II | I | II |
| Aremis/Besitran® 50 mg | | | | | | | | |
| Training set | | | | | | | | |
| Madrid ($n = 78$) | 3.9 | 0.0 | 2.2 | 0.0 | 0.4 | 0.0 | 0.0 | 0.0 |
| Barcelona ($n = 180$) | 4.2 | 0.0 | 1.7 | 0.4 | 0.0 | 8.1 | 0.0 | 19.3 |
| Validation set | | | | | | | | |
| Madrid ($n = 39$) | 7.7 | 0.0 | 4.3 | 0.0 | 0.9 | 0.0 | 0.0 | 0.0 |
| Barcelona ($n = 90$) | 5.2 | 0.0 | 1.9 | 0.0 | 0.0 | 7.4 | 0.0 | 34.7 |
| Voltarol Retard® 100 mg | | | | | | | | |
| Training set | | | | | | | | |
| Germany ($n = 32$) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 6.3 | 0.0 | 27.1 |
| Greece ($n = 6$) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| UK ($n = 8$) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 37.5 | 0.0 | 100 |
| Validation set | | | | | | | | |
| Germany ($n = 17$) | 11.7 | 0.0 | 5.9 | 0.0 | 3.9 | 2.0 | 0.0 | 27.5 |
| Greece ($n = 3$) | 66.7 | 0.0 | 55.6 | 0.0 | 33.3 | 0.0 | 0.0 | 0.0 |
| UK ($n = 4$) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 33.3 | 0.0 | 100 |
| | 0.6 | | 0.68 | | 0.70 | | 0.80 | |
| | I | II | I | II | I | II | I | II |
| Renitec® 5 mg | | | | | | | | |
| Training set | | | | | | | | |
| France ($n = 64$) | 57.8 | 0.5 | 17.2 | 10.9 | 11.5 | 16.1 | 0.0 | 61.5 |
| Spain ($n = 55$) | 60.0 | 0.0 | 26.9 | 0.0 | 19.4 | 0.6 | 4.8 | 20.6 |
| Italy ($n = 15$) | 11.1 | 0.0 | 2.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Greece ($n = 12$) | 7.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Validation set | | | | | | | | |
| France ($n = 32$) | 87.5 | 0.0 | 53.1 | 15.6 | 43.8 | 20.8 | 12.5 | 68.8 |
| Spain ($n = 28$) | 92.8 | 0.0 | 60.7 | 1.2 | 52.4 | 1.2 | 23.8 | 21.4 |
| Italy ($n = 8$) | 100 | 0.0 | 91.7 | 0.0 | 41.7 | 0.0 | 33.3 | 0.0 |
| Greece ($n = 6$) | 100 | 0.0 | 94.4 | 0.0 | 0.0 | 0.0 | 61.1 | 0.0 |

[a] Optimum value.

For each product, the tablet spectra were randomly assigned to either a training set (66% of spectra) or a validation set (34% of spectra) irrespective of batch number. Using just the training set, the effect of altering the threshold on the classification was investigated. The results were found to be sensitive to the original assignment of the data to the training and validation sets particularly for models with small training sets ($n < 10$) and consequently the whole process was repeated six times and the average results presented. Table 3, shows these combined results expressed as percentage rates for the occurrence of Type I and II errors. Critical values for the threshold value were selected to give the minimum Type I error combined with a zero Type II error wherever possible. Type II errors being considered more serious than a small Type I error rate. The results of applying these threshold values to the validation data set are also shown in Table 3.

With tablets which showed a good separation between the sites of manufacture on their PCA score plots (Aremis/Besitran® and Voltarol Retard®) it was relatively easy to select a threshold value which gave no or minimal errors of both Type I and II, Table 3. For Aremis/Besitran® tablets, as the threshold value

was increased above the optimum of 0.90, the number of Type II errors increased and were mainly associated with samples from Barcelona. The samples were matched to both sites of manufacture, but in all cases the best match was always the correct site. Good results were also obtained for Voltarol Retard® tablets from Germany and the UK using a threshold of 0.90. To correctly classify tablets from Greece, a threshold of 0.98 was required to minimise Type I errors. For Renitec® tablets it was not possible to discriminate between the French and Spanish sites of manufacture, however, they could be clearly distinguished from the Italian and Greek sites. Considering that of all the products examined the Renitec® tablets from different manufacturing sites exhibited the greatest differences in physical properties (size and hardness) the limited ability of NIR spectroscopy to differentiate between them is disappointing. It should be noted, however, that NIR spectroscopy is often quite sensitive to physical properties such as tablet hardness and porosity [21].

## 4. Conclusion

Reflectance NIR spectroscopy has been shown to be a powerful technique for differentiating between sites of manufacture for a number of proprietary tablets. The main cause of variation between sites was in all cases found to be related to differences in moisture content, though other excipient based differences were also detected. As tablets can quite rapidly take up moisture from the atmosphere it is important to measure samples immediately they have been removed from their packaging if reliable classification is to be achieved. This work suggests that NIR spectroscopy should be an ideal technique for the differentiation between tablets from different manufacturing sites even when the tablet components are the same. In this respect it would be an excellent analytical tool for the rapid detection of counterfeit and diverted medicines.

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