International Journal of Pharmaceutics 415 (2011) 102–109

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Near-infrared spectroscopy (NIRS) and chemometric analysis of Malaysian and UK paracetamol tablets: A spectral database study

Mazlina M. Said[a,b], Simon Gibbons[a], Anthony C. Moffat[a], Mire Zloh[a,*]

[a] The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK
[b] Faculty of Pharmacy, National University of Malaysia, 43600 UKM, Bangi Selangor, Malaysia

ARTICLE INFO

Article history:
Received 1 March 2011
Received in revised form 20 May 2011
Accepted 21 May 2011
Available online 27 May 2011

Keywords:
NIRS
Spectral database
Paracetamol
Malaysia
Counterfeit medicines
SIMCA
PCA
Qualitative study
Chemometrics

ABSTRACT

The influx of medicines from different sources into healthcare systems of developing countries presents a challenge to monitor their origin and quality. The absence of a repository of reference samples or spectra prevents the analysis of tablets by direct comparison. A set of paracetamol tablets purchased in Malaysian pharmacies were compared to a similar set of sample purchased in the UK using near-infrared spectroscopy (NIRS). Additional samples of products containing ibuprofen or paracetamol in combination with other actives were added to the study as negative controls. NIR spectra of the samples were acquired and compared by using multivariate modeling and classification algorithms (PCA/SIMCA) and stored in a spectral database. All analysed paracetamol samples contained the purported active ingredient with only 1 out of 20 batches excluded from the 95% confidence interval, while the negative controls were clearly classified as outliers of the set. Although the substandard products were not detected in the purchased sample set, our results indicated variability in the quality of the Malaysian tablets. A database of spectra was created and search methods were evaluated for correct identification of tablets. The approach presented here can be further developed as a method for identifying substandard pharmaceutical products.

1. Introduction

Challenges faced by the pharmaceutical enforcement bodies in healthcare systems of developing countries includes an influx of unregistered products, adulterated products, adulteration in registered products, adulteration in food and food-supplements, and counterfeit materials. Problems faced by regulatory agencies are results of smuggling, illegal entry, parallel importation, diversion, tampering, repackaging, relabeling and the use of fake hologram meditag (Bate, 2008; Ismail, 2009; Wertheimer, 2008).

Among these challenges, the issues of counterfeit medicines and adulteration in pharmaceutical formulations are escalating throughout the globe. The Malaysian pharmaceutical industry is an example of problems that a developing country may experience. For example, a recent search on the Malaysian Drug Control Authority (DCA) website (DCA, 2010) showed that there are more than 250 registered products containing paracetamol as the main or one of the main active pharmaceutical ingredients (APIs) available on the market. The main efforts of the government agency are to ensure the quality of these products on the market and to establish the presence of counterfeit medicine in Malaysia. The first survey was conducted in 1997 on cough and cold medication which revealed that 5% of such medicines on the market were counterfeit (Cruez, 2006). Another survey conducted by the Pharmaceutical Association of Malaysia (PhAMA) between 1998 and 2002 showed that 14 out of 289 samples (nearly 5%) of three prescription medicines purchased from a total of 196 pharmacies and clinics in 6 states were found to be counterfeit (PAM, 2006). Additionally in 2008, 5.28% of over-the-counter products were identified as fake (Bernama). These percentages indicate that the prevalence of counterfeit drugs were consistent throughout almost a decade in this country.

In addition to this consistent problem, adulteration of herbal medicines appeared to be on the increase. From 2006 to 2008, 17 products indicated for men's health, 6 products for weight loss, 5 cough medicines and 4 products for joint pain were found to be adulterated with synthetic drugs in order to increase their pharmacological effects (ASEAN, 2007). This is potentially an exceptionally dangerous problem as herbal products are highly complex and conventional single chemical entity-herbal drug combination pharmacology is poorly understood.

Near-infrared (NIR) spectroscopy has gained wide acceptance within the industry for various pharmaceutical applications (Blanco et al., 1998; Luypaert et al., 2007), particularly for the identification and detection of counterfeit and substandard medicines through the comparison of suspected tablets with the spectra of authentic tablets (Assi et al., 2008, 2009; Moffat et al., 2010; O'Neil et al.,

* Corresponding author. Tel.: +44 20 7753 5879; fax: +44 20 7753 5964.
E-mail address: mire.zloh@pharmacy.ac.uk (M. Zloh).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.05.057

2008). An alternative approach for drug identification by NIR is to determine the APIs (Khan et al., 1997) or the source of the tablets (Yoon et al., 2004). Drug analysis has become easier and faster as sample preparation is not required. The ability to analyse samples intact is another advantage of the technique whereby samples can be retained for further analysis or as evidence for forensic purposes.

Previous studies have discussed NIR analysis by quantitative assay of intact tablets as the most obvious way to detect substandard preparations (Eustaquio et al., 1999; Trafford et al., 1999). These methods are based on developing calibration curves of active ingredient (Blanco and Peguero, 2010). In all these studies, the information about the tablets analysed were available and the analyses were designed based on this knowledge. However, one of the real problems occurring in developing countries is a consequence of medicines being sold or dispensed without original packaging; tablets are either wrapped in a piece of paper, or given in an envelope or a plastic bag, where the information about the tablets may be given verbally or just hand written on the container (Goodman et al., 2007). In this scenario, the questions to be answered by analytical methods are more complex: is the correct medicine dispensed, what is the composition of the dispensed formulation and is the dispensed medicine counterfeit?

This research intended to propose a way forward to solve some of these problems. We have designed a strategy that can be used for product identification, screening and classification using a database of NIR spectra. The spectroscopic data reflecting chemical fingerprints of the products stored in a database will enable direct comparison between different products without the use of reference samples provided by manufacturers.

Qualitative analysis of the most common type of analgesic, namely paracetamol tablets purchased in pharmacies and supermarkets, was used as an example in this work. Different brands of Malaysian paracetamol products were analysed by NIR and compared to a similar set produced in the UK. NIR spectra were imported into the database and validation searches were conducted using two test sets, a set of paracetamol samples acquired at the same time as the training set and a new set of paracetamol samples acquired a year later. Chemometric analysis was used to observe the distribution of samples in the score plot and its correlation to the database search outcome.

2. Materials and methods

2.1. Drug samples

A sample set used in this study consisted of 16 and 6 batches of paracetamol 500 mg tablets (except for one batch with 650 mg) purchased in Malaysia and the UK, respectively. Each batch was represented by 20 tablets with paracetamol as the only active ingredient. Three additional products, that contained additional active ingredients to paracetamol or did not have paracetamol at all, were included into the test set as negative controls. After a year, a new set of tablets consisting of three new batches of the brands available in the database and one additional batch of paracetamol from a different manufacturer were purchased from the Malaysian market and their NIR spectra were recorded. The additional spectra were added to the database for identification purposes as test sets. Details of the samples are listed in Table 1.

All samples were obtained by purchasing samples in pharmacies and supermarkets since attempts to obtain the samples directly from the manufacturers had either been ignored or rejected (for Malaysian samples). The Malaysian samples were supplied either in original blister packaging or as repacked products. All UK samples were dispensed in blister packs. Samples consist of uncoated tablets of different shapes and colours.

2.2. NIR analysis

The NIR diffuse reflectance analyses were carried out using a NIRSystems 6500 spectrophotometer, equipped with a Rapid Content Analyzer (FOSS NIRSystems, Silver Springs, USA). Intact tablets were placed centrally on the sample stage over the light beam in the NIR instrument. Each side of the tablet was analysed four times while rotating them at 90° each time. Eight accumulations of 32 scans, data spacing every 2 nm of the reflectance spectra were recorded over the wavelength between 1100 and 2500 nm to give a mean spectrum for each sample. The experiment was conducted under a monitored humidity and ambient temperature.

2.3. Software

The NIR instrument was controlled by Vision Spectral Analysis Software for Windows (FOSS NIRSystems, version 2.11) for data acquisition. Chemometric analysis was conducted by taking the original averaged NIR spectra, exported in ASCII format and then converted to JCAM-DX files using an in-house programme. The spectral files were then imported into the Unscrambler v9.7 software, CAMO (Oslo). The spectral database was created using SPECTAL ID v9.0 database module implemented in the GRAMS ID (Gram Suite Software; Thermofisher).

2.4. Chemometric methods

2.4.1. Principal component analysis (PCA)

PCA treatment of spectra decomposed them into scores and loadings for variables called principal components (PC). The main purpose of PCA was to reduce the number of variables to represent a multivariate data table in a low dimensional space (Esbensen, 2005). PC models were constructed individually for each batch of the samples. After the first run, the presence of outliers, groups, clusters and trends were determined based on the observation of the score plots. At this stage, the outliers detected belonged to the same population but they were poorly described by the model.

Table 1
Details on the samples used for product assessment, database development and validation discussed in this work. A set of 20 tablets were analysed for each batch.

Purposes	Active pharmaceutical ingredients (APIs)	Amount (batch/es)	Source	Sample label
Calibration samples	Paracetamol 500	15	Malaysia	BG_A, BG_B, BG_C, FP, IF, MIL_A, MIL_B, OR, PC, PG, PR, PM, PT, UP_A, UP_B
		6	UK	UK_bts, UK_lidl, UK_mrs, UK_vh, UK_wtr, UK_ gsl
PCM 650	Paracetamol 650 mg	1	Malaysia	UP_C
Negative control	Paracetamol 500 mg, dihydrocodeine tartrate 7.46 mg	1	UK	NC1 (paramol)
	Paracetamol 200 mg, aspirin 300 mg, caffeine 45 mg	1	UK	NC2 (epr)
	Ibuprofen 200 mg	1	UK	NC3 (ibu)
Internal validation	Paracetamol 500 mg (internal)	3	Malaysia	IF, PM, UP_A
External validation	Paracetamol 650 mg (external 1)	3	Malaysia	IF, PM, UP_A
Unknown	Paracetamol unknown (external 2)	1	Malaysia	pcm_unknown

The optimum number of PCs was determined based on the total explained variance plot. PCA was conducted on the data with leverage correction as the validation method and the scaling factor was set as 1.

2.4.2. Soft Independent Modeling of Class Analogy (SIMCA)

SIMCA was applied in the original method (Candolfi et al., 1999). Classification was carried out on all of the PC models against one sample as a class model with the significance level set at 95%. Evaluation was made by using the distance versus leverage plot.

2.5. Database creation and search

2.5.1. Database development

Raw NIR spectra were imported directly into Spectral ID database using NSAS format. The database has a smart-convert functions which automatically converted the NSAS file to .SPC files. Other information computed together with the spectra was the brand and proprietary name, batch number, expiry date, manufacturer name and address, sample origin, other excipients (where available) and sample description.

2.5.2. Database search

Before every search, the unknown spectra and other spectra in the database were set to be baseline corrected to reduce the scattering effect that highly contaminate NIR spectra. This was achieved using the auto baseline correction algorithm which removes linear baseline error of positive going peak data (Grams).

A database search was conducted on the whole spectrum based on a correlation algorithm; whereby the least squares dot products of the unknown spectra were compared with the spectra in the database after being centralised to their respective means. A hit list of the top matches was provided together with hit quality index (HQI) values. Low HQI values measured between the unknown spectra with the spectra in the library indicating a good match.

3. Results and discussions

The first part of this work was focussed on obtaining spectral fingerprints of each set of samples and observing the product variations in NIR raw spectra and PCA. This information was correlated to the search outcomes in the database.

3.1. NIR analysis

All of the tablets contained 75–90% mass fraction paracetamol relative to the tablet weight and hence it was expected to that the most of the peaks NIR spectrum are coming from the paracetamol. NIR raw spectral analyses indicated that all of the samples produced a similar spectroscopic fingerprint of paracetamol (Fig. 1A) while being different compared to the negative control samples (Fig. 1B). The main difference among the spectra was the absorbance shift concerning the whole spectral range which corresponded to scattering effects and physical properties (e.g. particle size, shape or surface structure) of the samples. Moreover, a clear difference of absorbance over the whole range of wavelengths could be observed with one of the Malaysian samples, PM. One of the negative control samples NC1 had some degree of similarity with the other paracetamol spectra due to similar main active composition.

3.2. Principal component analysis (PCA)

PCA was employed to validate spectral interpretations and provide more information on the chemical differences between batches. These results indicated that the type of ingredients but not the amount of active ingredient influence classifications. One batch from the Malaysian samples, identified as sample PM, was not included in the 95% confidence interval set, indicating significantly different properties of the tablets in that batch, which may indicate different excipients or manufacturing process (Fig. 2). The PCA score plot in Fig. 3 showed that all of the negative control samples were well excluded while the 650 mg sample was well clustered with the other samples.

The confidence ellipse has expanded to accommodate new samples and two negative controls samples were clustered apart from the samples. However NC1, which had 500 mg of paracetamol as the main active ingredient in addition to other active ingredients was included in the 95% ellipse together with the paracetamol sample. However, its cluster was separated from the rest of the group.

3.3. SIMCA classifications

All the PC models were projected into the PC space based on their distance towards the sample PM as class model. PM was selected to be the model class due its distinct character in NIR analysis and PCA. Using the distance versus leverage plot in Fig. 4, a clear distinction of variability between the Malaysian and UK samples was observed. All Malaysian samples clustered well within batches but scattered from 0 to 120 leverage ranges while the UK samples clustered together within only 15 to 35 leverage ranges. Additionally, the 650 mg batch was also well separated from the other batches.

Candolfi et al., have demonstrated that the number of PCs included in classification models is an important factor for SIMCA and that using pre-processed data decreases the within-class variance and increases the between-class variance [20]. Taking the first factor into consideration, we have used the raw NIR spectra, as all of the data was sufficiently described by only one and two PC. Despite compromising the second factor, our results did not appear to be affected.

3.4. Database construction

3.4.1. Database library

All spectra were imported into a paracetamol database to consider its usage and reliability for classification. In the database, all of the *X*-axes of the spectra represented the spectral wavelength in nanometers between the range 1100 and 2500 and the *Y*-axes were the spectral absorbance values. For each brand of paracetamol, 20 averaged spectral profiles with 700 individual points in each were combined as a multi-file to enhance the accuracy of the spectral search. The spectra were saved in 32-bit resolution.

3.4.2. Database search

Spectral searches of several paracetamol tablets were conducted to compare seven different algorithms; euclidian distance, absolute value, first derivative absolute value, least square, first derivative least square, correlation and first derivative correlation. The correlation algorithm proved to be the most reliable in the spectral classification (supplementary material Figure S1).

Furthermore, the NIR spectra of examined tablets were used to interrogate the spectral database by comparison of spectra. The option used was the “spectrum search” method, where a whole spectrum of an unknown sample was compared to the spectra in the database using correlation algorithms. The outcome of a search was presented as a database hit list and a correlation value between the spectra given as a hit quality index (HQI) value. The lower the HQI value, the higher similarity between spectra would be observed. A perfect match gave an HQI value of 0.

Subsequent searches for several paracetamol samples from different manufacturers and different batches (5 brands) were carried out against the spectral database that in addition of paracetamol spectra had NIR spectra of other pharmaceutical formulations;

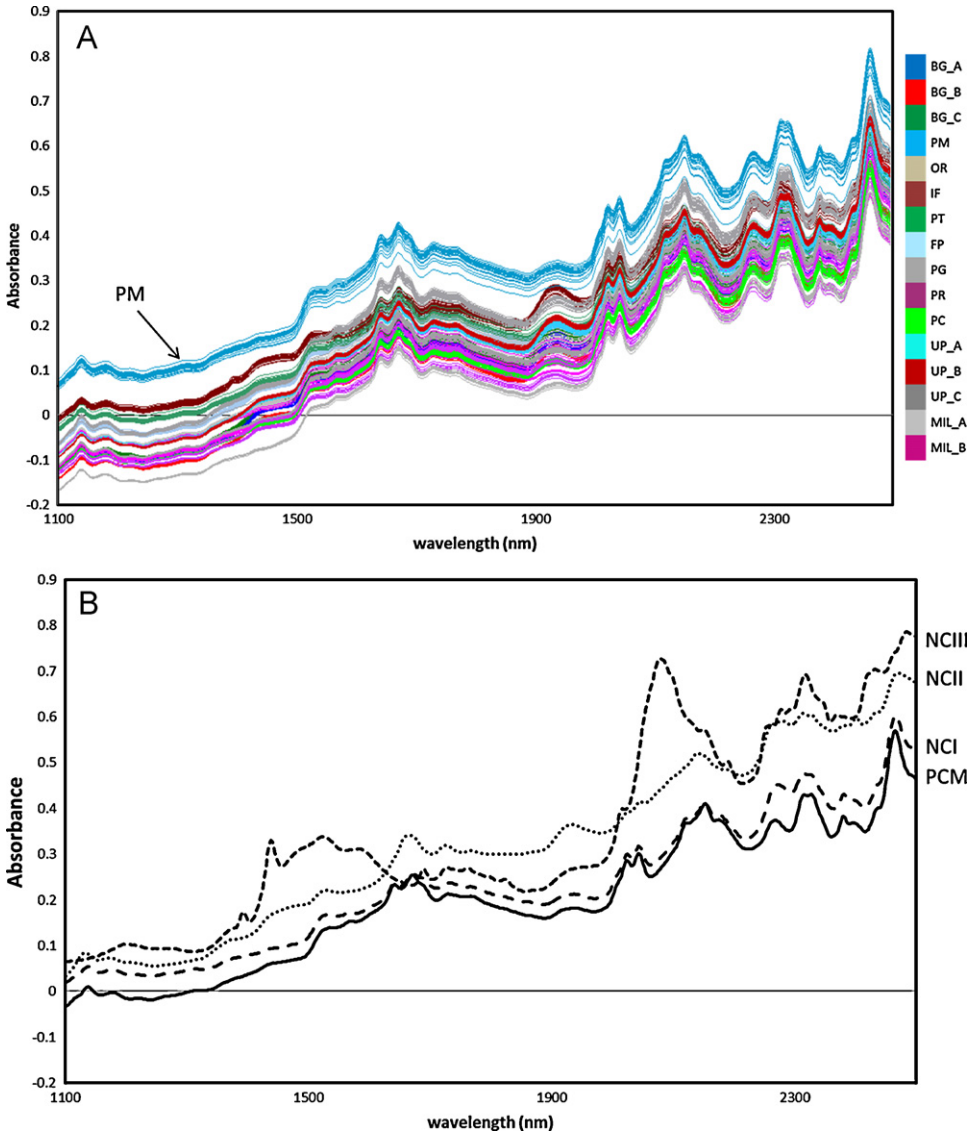

Fig. 1. Mean NIR spectra in reflectance mode of (A) 22 batches of paracetamol samples and (B) representative paracetamol spectrum compared to the negative control spectra (NC1, NC2 and NC3).

amoxicillin (4 brands), mefenamic acid (2 brands), *Ginkgo biloba* (3 brands), *Eurycoma longifolia* (3 brands) and Chinese herbal mixtures (2 brands). This confirmed that it was possible to identify the correct type of medicines and furthermore to suggest a manufacturer of the examined samples (if the similar product was present in the database (supplementary material Figure S1 and Table 1).

These results were used to propose the cut-off values for the classification of the analysed sample into four types (Table 2).

The values in Table 2 are suitable to be used as a reference for other products with a similar composition of samples (where more than 75% of the tablet mass is the active pharmaceutical ingredient)

Table 2
Proposed cut-off points for pharmaceutical formulation classification based on the degree of similarities and differences between unknown spectrum and spectra in the database.

Classification type	Search outcomes	Cut-off values (HQI)
I	Match (same batch)	<0.0001
II	Similar brands/source	<0.0100
III	Similar class medicines	<0.1000
IV	Different product	>0.2000

when using a spectrum search method on single or multi-file averaged spectra input. For other types of products, for example potent drugs, or a complex mixture like herbal medicines, new cut-off values would need to be determined. These values however, should be used as a guide, and may be overlapped, especially for typical samples.

The whole spectra search method and correlation algorithm was used to analyse NIR spectra of two paracetamol samples; namely BG_B and UP_B. These samples were produced by manufacturers which were previously added to the database, but having different batch numbers. The results of the search are presented in the hit-list form in Table 3.

Using the database, both unknown spectra were identified similar to their similar production members. However, the HQI values were different due to product variations. Batch to batch variation was a more prominent source of variability compared to other factors such as like sample positioning or time of analysis (Candolfi et al., 1997). While this type of variability can be controlled by including spectra from different batches into the database to 'normalise' sample variability, it also gives an advantage of identifying samples and their manufacturer.

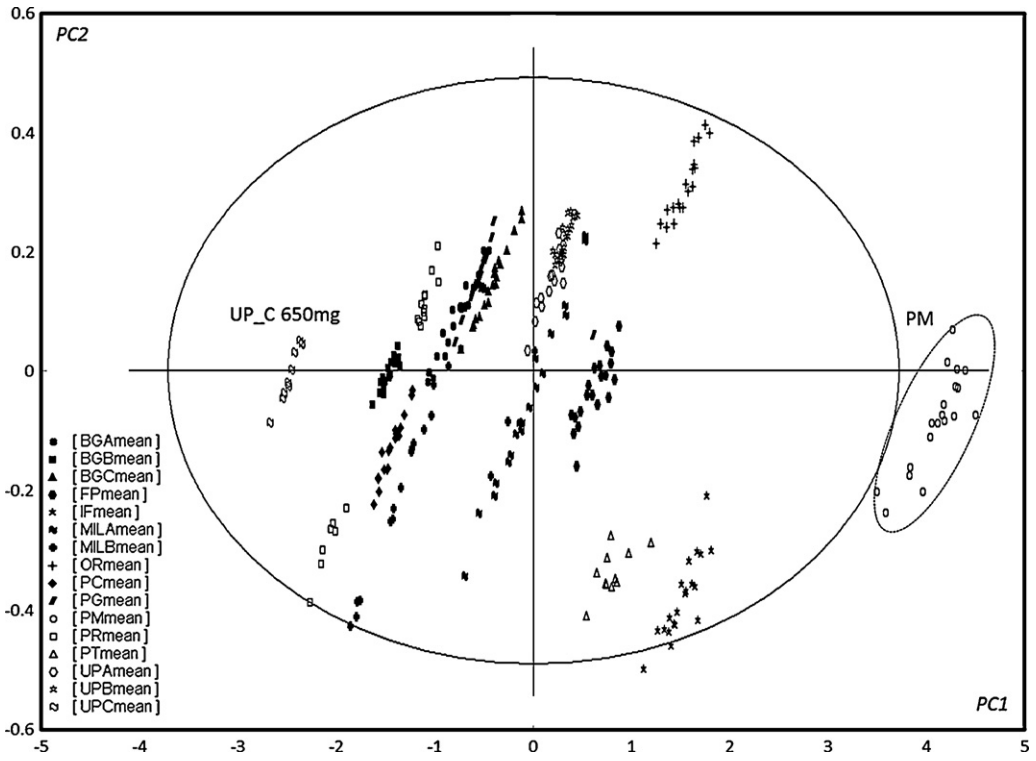

Fig. 2. PCA overview of raw NIR reflectance spectra of 16 Malaysian paracetamol samples. The ellipse represents 95% confidence interval for the two PCs (PC1 = 97%, PC2 = 2%).

The UP_B samples were classified (type II) to one of its co-batch product in the database UP_A and type III to another batch UP_C (hit #13). This was because this set of sample had a different dosage (650 mg). This showed that the database was capable of identifying products of different dose.

The HQI value for products of hit #20 in both hit lists were classified in ambiguity between the similar or different class of medicines from the rest of the samples. This corresponded well with the PCA observation whereby samples PM in Table 3A was excluded in the 95% confidence interval ellipses in PCA and sam-

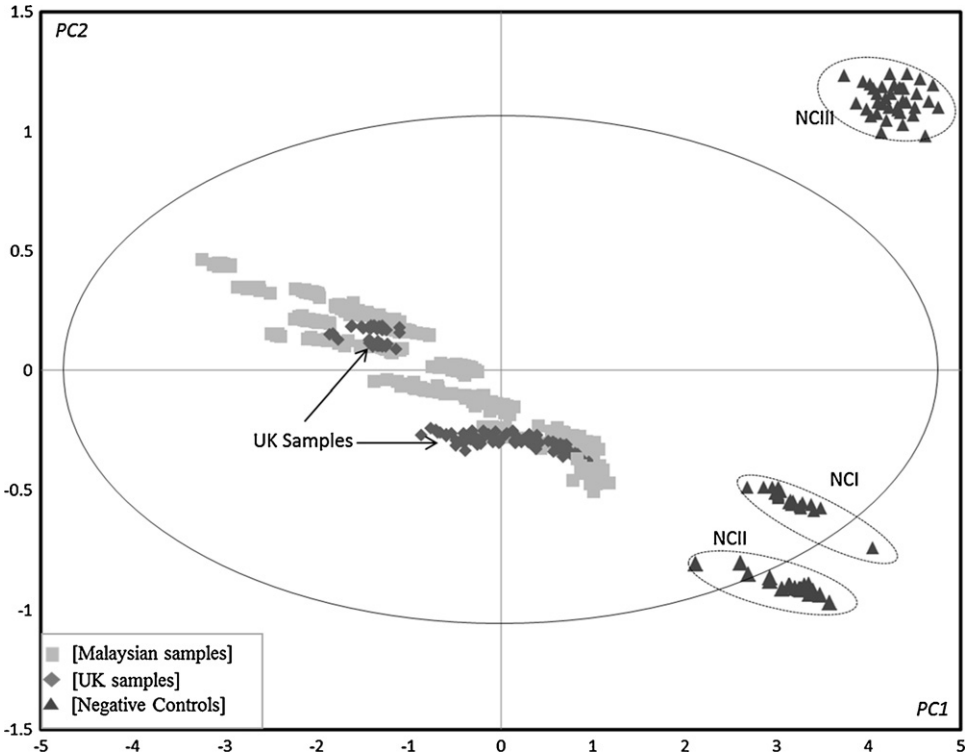

Fig. 3. PCA overview of NIR reflectance spectra of Malaysian and UK paracetamol samples, and the negative control samples. The ellipse represents 95% confidence interval for the two PCs (PC1 = 92%, PC2 = 5%).

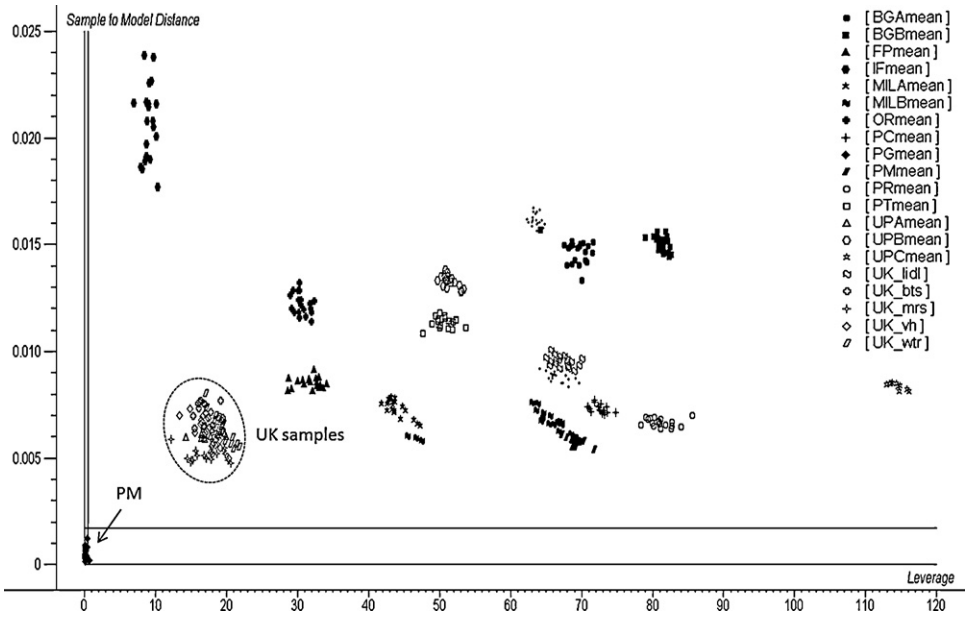

Fig. 4. The distance versus leverage plot showing the relative distance of the samples to sample PM (class model). All of the UK samples were clustered together in the region between 15 and 35 leverage scales.

ple distance plot (Figs. 2 and 4) while sample paramol in Table 3B was one of the negative control (NCI) samples, namely consisting of 500 mg paracetamol and 7.46 mg of dihydrocodeine tartrate.

3.5. Internal/external validation

Internal and external validations were conducted to show the reproducibility and reliability of the database search. Three sets of samples from the initial sample set were re-analysed (internal) after a year. Additionally, a set of three new samples of similar brand to the spectra in the database were obtained from the market (external 1). A set of new brand of paracetamol (pcm_unknown) was also subjected to the database search (external 2).

The spectra of all of the above samples were acquired and searched against the existing paracetamol database, 12 months after the database being created and the initial study being conducted. Between these periods, the NIR instrument had been serviced once and the processing software (VISION, Foss) has been upgraded to a newer version.

The PCA distribution of the validation spectra among the other spectra available in the database can be viewed in Fig. 5.

All of the validation samples fell within the 95% confidence interval in the distribution range of the available spectra. The new sample (pcm_unknown) was however excluded from the ellipse. This sample was actually paracetamol with a different dosage form as paracetamol granules in capsules.

Ideally, the internal validation should give a perfect match to the spectra in the database as similar samples were used to test the database. However, product degradation and instrument variations after servicing were maybe two of the important factors that caused spectra variations between these samples. External validation is also affected by product variation, instrument variation, and time of analysis. Despite these drawbacks, the database managed to identify all of the internal and external samples to their simi-

Table 3
The search outcome of samples (A) BG_B and (B) UP_B has classified the new spectra as samples of a similar brand/source to BG_C (HQI = 0); BG_A (HQI = 0.0038) and UP_A (HQI: 0.0009), respectively.

Hit #	Hit quality	Samples ID.	Hit #	Hit quality	Samples ID.
A			B		
1		BG_C	1	0.0009	UP_A
2	0.0038	BG_A	2	0.0095	PT
3	0.0229	FP	3	0.0131	PC
4	0.0247	UP_A	4	0.0148	BG_A
5	0.0329	UK_lidl	5	0.0149	UK_bts
6	0.036	UK_bts	6	0.0156	UK_lidl
7	0.0385	PT	7	0.0157	PR
8	0.0471	PC	8	0.0209	UK_vh
9	0.0509	PR	9	0.0216	BG_C
10	0.0513	UK_vh	10	0.0255	FP
11	0.0514	UK_gsl	11	0.0267	UK_gsl
12	0.0538	UK_mrs	12	0.027	PG
13	0.0553	OR	13	0.0287	UP_C
14	0.0604	UP_C	14	0.0313	MIL_B
15	0.0633	UK_wtr	15	0.0324	UK_wtr
16	0.0643	MIL_A	16	0.0326	UK_mrs
17	0.0667	PG	17	0.035	MIL_A
18	0.0669	MIL_B	18	0.0392	IF
19	0.0781	IF	19	0.046	OR
20	0.161	PM	20	0.1783	Paramol (NCI)

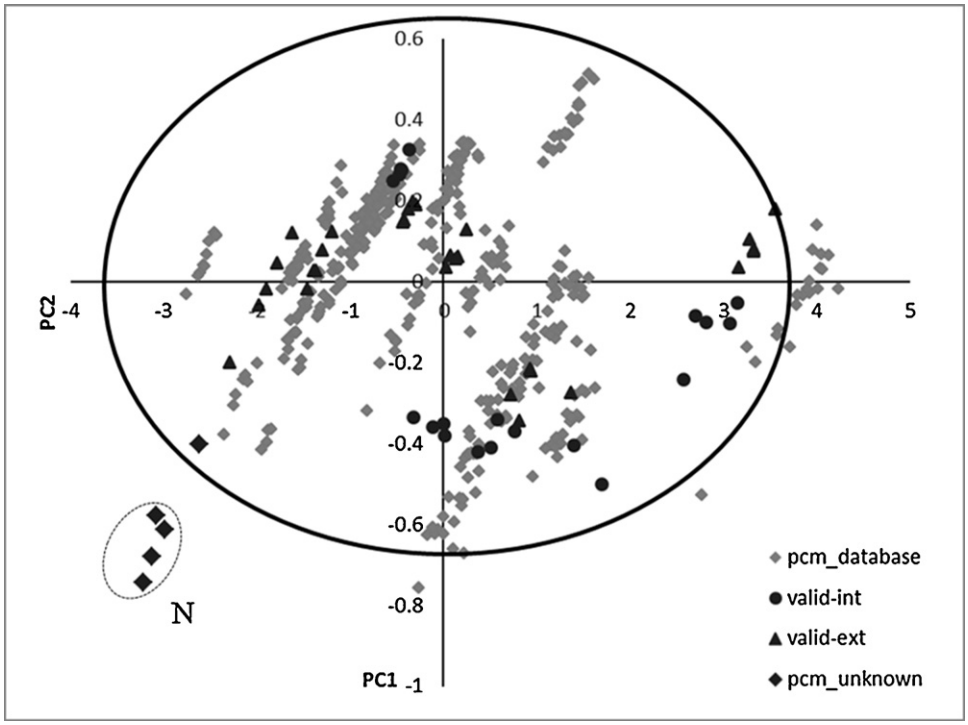

Fig. 5. PC score plot and 95% confidence interval ellipse to describe the distribution of NIR reflectance spectra of samples used to create library (pcm_database), internal (valid-int) and external (valid-ext) validation samples, and unknown sample (pcm_unknown).

Table 4
The hit-quality index (HQI) for internal and external validations of three brands of paracetamol available in the database. The analysis was conducted 12 months after the database had been created.

Samples	Internal validation (HQI)	External validation (HQI)
UPA	0.0023	0.0109
IF	0.0163	0.0336
PM	0.0008	0.0003

lar samples in the database and classified them as samples coming from the same source or of similar brand names (type 2). The HQI values are listed in Table 4.

4. Conclusion

In conclusion, the NIR spectral database of paracetamol has proven to be reliable for identification and for a quick product screening procedure. The database also managed to classify samples according to their type of dose, dosage forms and product variability. The internal and external validation conducted over 12 months proved that the database search was reproducible. PCA allowed observation of differences in intra-batch and inter-batch variability for different products. Although some degree of changes to the spectra were observed after a year, the database successfully classified the tablets accordingly using the pre-determined cut-off value. The possible ambiguity issues could be resolved by using either chemometric analysis or other analytical chemistry techniques.

Building a database of medicines on the market can be a tedious process, however once it has been established, drug spectral analysis will be a relatively simple task, less time consuming and a cost-effective procedure. Furthermore, the existence of a comprehensive spectral database will be of a benefit as a repository of data for further chemometric analysis and also for drug identification, drug quality surveillance and as a potential method of counterfeit and adulterated drug-screening, particularly in the case where the original samples are difficult to obtain from the manufacturers.

Current and future work will be the expansion of the database with other types (and dosage forms) of drugs including complex herbal mixtures. The database is also being enriched with other types of spectra such as data from NMR spectroscopy and mass spectrometry. Other applications of the database currently investigated are its use in drug quality control and the detection of adulterated and counterfeit products.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2011.05.057.

References

ASEAN, 2007. ASEAN Post-Marketing Alert (PMA) System – The Malaysian and Singapore Experience. Joint report by: National Pharmaceutical Control Bureau, Malaysia, and Health Sciences Authority, Singapore.
Assi, S., Watt, R.A., Moffat, A.C., 2008. Assay of ciprofloxacin in intact and powdered tablets by near-infrared spectroscopy. J. Pharm. Pharmacol. 60, 19.
Assi, S., Watt, R.A., Moffat, A.C., 2009. Identification of tablets through their blister packaging by near-infrared spectroscopy. J. Pharm. Pharmacol. 61, 41.
Bate, R., 2008. Making a Killing. The AEI Press, Washington, DC.
Bernama, V., 2008. New Bill to Help Curb Counterfeit Medicines. New Straits Time, Kuala Lumpur, 22 September.
Blanco, M., Coello, J., Iturriaga, H., Maspoch, S., de la Pezuela, C., 1998. Near-infrared spectroscopy in the pharmaceutical industry. Analyst 123, 135R–150R.
Blanco, M., Peguero, A., 2010. Analysis of pharmaceuticals by NIR spectroscopy without a reference method. Trends Anal. Chem. 29, 1127–1136.
Candolfi, A., De Maesschalck, R., Massart, D.L., Hailey, P.A., Harrington, A.C.E., 1999. Identification of pharmaceutical excipients using NIR spectroscopy and SIMCA. J. Pharm. Biomed. Anal. 19, 923–935.
Candolfi, A., Massart, D.L., Heuerding, S., 1997. Investigation of sources of variance which contribute to NIR-spectroscopic measurement of pharmaceutical formulations. Anal. Chim. Acta 345, 185–196.
Cruez, A.F., 2006. Viaga not Working? It may be Counterfeit. New Straits Time, Kuala Lumpur.

DCA, 2010. Ministry of Health Malaysia, Drug Control Authority, http://www.bpfk.gov.my/Search/Search_product.asp [online] (accessed 9.01.10).
Esbensen, K., 2005. Multivariate Data Analysis—In Practice, Fifth ed. CAMO Software AS, Norway.
Eustaquio, A., Blanco, M., Jee, R.D., Moffat, A.C., 1999. Determination of paracetamol in intact tablets by use of near infrared transmittance spectroscopy. Anal. Chim. Acta 383, 283–290.
Goodman, C., Kachur, S.P., Abdulla, S., Bloland, P., Mills, A., 2007. Drug shop regulation and malaria treatment in Tanzania why do shops break the rules, and does it matter. Health Policy Plann. 22, 393–403.
Grams, Grams ID User Guide. Grams Suite Help. ThermoScientific.
Ismail, M., 2009. Prevalence of counterfeit medicines in Malaysia, Pharmacy enforcement perspective (Presentation). http://portal.bpfk.gov.my/aeimages/File/Seminar../Chapter_12_Counterfeit.pdf [online] (accessed 25.10.10).
Khan, P.R., Jee, R.D., Watt, R.A., Moffat, A.C., 1997. The identification of active drugs in tablets using near infrared spectroscopy. Pharm. Sci. 3, 447–453.
Luypaert, J., Massart, D.L., Heyden, Y.V., 2007. Near-infrared spectroscopy applications in pharmaceutical analysis. Talanta 72, 865–883.
Moffat, A.C., Assi, S., Watt, R.A., 2010. Identifying counterfeit medicines using near infrared spectroscopy. J. Near Infrared Spectrosc. 18, 1–15.
O'Neil, A.J., Jee, R.D., Lee, G., Charvill, A., Moffat, A.C., 2008. Use of a portable near infrared spectrometer for the authentication of tablets and the detection of counterfeit versions. J. Near Infrared Spectrosc. 16, 327–333.
PAM, 2006. Counterfeit medicines: recommendation on measures to combat counterfeit medicines in Malaysia. Pharmaceutical Association Malaysia [online]. http://www.phama.org.my/pdf_document/CounterfeitMed_PositionPaper_vvfinal_March15_pdf.pdf (accessed 3.09.07).
Trafford, A.D., Jee, R.D., Moffat, A.C., Graham, P., 1999. A rapid quantitative assay of intact paracetamol tablets by reflectance near-infrared spectroscopy. Analyst 124, 163–167.
Wertheimer, A.I., 2008. Identifying and combating counterfeit drugs. Expert Rev. Clin. Pharmacol. 1, 333–336.
Yoon, W.L., Jee, R.D., Charvill, A., Lee, G., Moffat, A.C., 2004. Application of near-infrared spectroscopy to the determination of the sites of manufacture of proprietary products. J. Pharm. Biomed. Anal. 34, 933–944.