Journal of Pharmaceutical and Biomedical Analysis 131 (2016) 87–93

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

Chemometric aided NIR portable instrument for rapid assessment of medicine quality

Y.V. Zontov[a,*], K.S. Balyklova[b], A.V. Titova[c], O.Ye. Rodionova[d], A.L. Pomerantsev[d]

[a] National Research University Higher School of Economics (HSE), Myasnitskaya Str. 20, 101000 Moscow, Russia
[b] I.M. Sechenov First Moscow State Medical University, Trubetskaya Str. 8. b.2, 119991 Moscow, Russia
[c] Pirogov Russian National Research Medical University, Ostrovityanova Str. 1, 117997 Moscow, Russia
[d] N.N. Semenov Institute of Chemical Physics RAS, Kosygin 4, 119991 Moscow, Russia

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form 5 August 2016
Accepted 6 August 2016
Available online 7 August 2016

Keywords:
Counterfeit drug detection
Handheld near-infrared spectrometer
Data driven soft independent modeling of class analogy

ABSTRACT

The progress in instrumentation technology has led to miniaturization of NIR instruments. Fast systems that contain no moving parts were developed to be used in the field, warehouses, drugstores, etc. At the same time, in general these portable/handheld spectrometers have a lower spectral resolution and a narrower spectral region than stationary ones. Vendors of portable instruments supply their equipment with special software for spectra processing, which aims at simplifying the analyst's work to the highest degree possible. Often such software is not fully capable of solving complex problems. In application to a real-world problem of counterfeit drug detection we demonstrate that even impaired spectral data do carry information sufficient for drug authentication. The chemometrics aided approach helps to extract this information and thus to extend the applicability of miniaturized NIR instruments. MicroPhazir-RX NIR spectrometer is used as an example of a portable instrument. The data driven soft independent modeling of class analogy (DD-SIMCA) method is employed for data processing. A representative set of tablets of a calcium channel blocker from 6 different manufacturers is used to illustrate the proposed approach. It is shown that the DD-SIMCA approach yields a better result than the basic method provided by the instrument vendor.

1. Introduction

More and more counterfeit and substandard drugs are revealed all over the world. The variety of such products is so wide that the World Health Organization (WHO) has introduced a special term 'SSFFC Medical product' that combines spurious, substandard, falsified, falsely labeled and counterfeit drugs [1]. A huge effort in combating SSFFC medicines is made by the national health regulators and law enforcement agencies from different countries together with international organizations such as the WHO, the European Agency for the Evaluation of Medicinal Products, INTERPOL, etc. These activities are of different types. The first kinds of activities are wide international operations such as PANGEA. More than 100 countries and over 200 national agencies were involved in this operation in 2015, resulting in 20.7 million fake and illicit medicines being seized [2]. Another type of activity is everyday monitoring of medicine quality by the national health regulators. Various detection technologies are applied to reveal SSFFC products. A review of these methods can be found elsewhere [3,4]. One promising and widely used technique is near infrared spectroscopy (NIR) [5] which is a rapid and non-destructive method that enables preliminary monitoring of a wide range of tablets, capsules, and substances directly in warehouses, drugstores, and hospitals without special sampling and violation of the integrity of the packaging. The NIR-based approach for counterfeit drug detection is described in literature [6–8] and widely applied by health authorities for regular monitoring of medicine quality in China and Russia using mobile laboratories. A distinct feature of the screening approach utilized in China and in Russia is analyzing a remedy as a whole object, without singling out API, special excipients, coating quality, etc. This helps to reveal suspicious products of different types, as well as various violations in product manufacturing. The final decision is made after thorough testing in a laboratory. However, this approach has a high cost associated with it, as one needs a specialized laboratory, equipped with an expensive FT-NIR instrument mounted inside a dedicated vehicle.

The progress in instrumentation technology has led to miniaturization of various devices. New NIR instruments with fast, no

* Corresponding author.
E-mail address: yury.zontov@gmail.com (Y.V. Zontov).

http://dx.doi.org/10.1016/j.jpba.2016.08.008
0731-7085/

Table 1
Specifications of NIR instruments.

	Handheld		
	MicroNIR [12]	microPHAZIR-RX [13]	FT-NIR Matrix [14]
Weight	0.06 kg	1.8 kg	24 kg
Dimension	diameter 45 × 42 mm	254 × 292 × 152 mm	320 × 420 × 240 mm
Spectral region	950–1650 nm (10526–6060 cm^{-1})	1600–2400 nm (6250–4170 cm^{-1})	800–2500 nm (12500–4000 cm^{-1})
Resolution	less than 12.5 nm	12 nm	0.25 nm round 1000 nm, 0.48 nm round 1600 nm, 2.4 nm round 2400 nm

moving parts systems were developed to be used in the field, warehouses, drugstores, etc. [9–11]. These spectrometers are low-weight and do not demand any specialized vehicle to mount them onto. At the same time, these portable/handheld spectrometers have a lower spectral resolution and a narrower spectral region. To illustrate this progress, Table 1 presents specifications of three kinds of spectrometers. The stationary FT-NIR Matrix has the resolution of 2 cm^{-1}, which corresponds to several intervals if expressed in nanometers.

Obviously, the handheld instruments are much more mobile. The inevitable cost of miniaturization is weaker performance, as illustrated in Fig. 1 by the spectra of the NIST traceable standard MCR-1920x [15] acquired using the above mentioned devices.

Such characteristics as spectral resolution and range are important in counterfeit drug detection. It is often hard to guess how a forgery will manifest itself. It can be a drug without an active pharmaceutical ingredient (API), a medicine with a lower API concentration, a medicine with an addition of a wrong API, a medicine with wrong composition of ingredients, or it can possess many other kinds of deviations from the genuine product. For this reason, we cannot foresee the spectral region where these deviations will be found, or the spectral resolution, which will be necessary to reveal a SSFFC medicine.

Vendors of portable instruments supply their equipment with special software for spectra processing, which aims to simplify an analyst's work as much as possible. Often such software is not completely suitable for solving complex problems of counterfeit drug detection.

The goal of the study is to demonstrate that an enhanced chemometric technique can compensate for the shortcomings of a miniaturized NIR instrument and that this combination is able to make the assessment of the quality of tablets and capsules more accessible and reliable. The MicroPhazir-RX NIR spectrometer is used as an example of a portable instrument, the data driven soft independent modeling of class analogy (DD-SIMCA) method is employed for the data processing.

The proposed approach is illustrated by a representative set of tablets, which is selected with the goal to test the ability to recognize the 'high quality' fakes. However, it is hard to find a representative set of such counterfeits. To imitate the 'high quality' fakes of a drug, we suggested [16] using legitimate analogues of the drug that are manufactured by various producers. Such drugs should contain identical API and similar composition of excipients.

2. Methods

A number of studies devoted to counterfeit drug detection, solve this problem only partly. The problem is that these methods only aim to reveal whether a specific medicine contains a proper API, or to conduct a quantitative assessment of the API content [17,18]. It should be noted that the identification and/or potency of the API in a suspect dosage form is not sufficient to confirm the authenticity of a suspect product. Another frequently used approach is discrimination of two or several classes of objects, such as 'genuine objects' against 'falsified objects' [19,20]. This is also only a partial solution of the problem, because discriminant analysis can be utilized only if all classes are known, a priori, and each new object is attributed to one of these classes. At the same time, counterfeit objects can be very different and the discrimination of a single type of an SSFFC product against one or several genuine classes does not guarantee the success of appropriate classification of a new fake object. It is worth noting that in the frame of regular monitoring of the drugstores, hospitals, or warehouses, an operator inspects a medicine which package bears full information regarding this item. Thus, in these circumstances, for an appropriate detection of the SSFFC medicine it is necessary to solve an authentication problem, i.e. to answer the question whether the product is what it is declared to be [21]. From a chemometric point of view, we should develop a one-class classifier model, which is also referred to as a class-modeling approach. To achieve this goal, we have to collect a representative set of samples of the specific target remedy. This set should be selected accounting for a natural variation both inside each batch and between the batches, and provide a possibility to train and validate a one-class classifier. An ultimate outcome of this classifier is the decision rule that answers the key question – whether a new sample belongs to the target class, or not. The decision rule may take the form of an acceptance area and/or a threshold. The quality of the decision rule is characterized by the type I error α, that is the rate of wrong rejections of the target class samples. A similar characteristic, which is often used, is *sensitivity* [22] that is the share of the correctly accepted samples of the target class. It is clear that there is a simple relation between these features

$$\text{Sensitivity} = (1-\alpha)100\% \quad (1)$$

It is equally important to avoid misclassification of genuine samples and to recognize fakes. In practice, it is very hard to find counterfeited samples for each type of drug. In paper [16] it was demonstrated that similar medicines of various manufacturers can be used to assess the ability of a model to recognize 'high quality fakes'. The ability to properly recognize any kind of alien objects is accessed via *specificity* [22] that is the share of objects that do not belong to the target class, which are correctly identified as aliens. A similar feature is the type II error β, which is the rate of wrong acceptances of aliens as target objects. The relation between these characteristics is as follows

$$\text{Specificity} = (1-\beta)100\% \quad (2)$$

In case we have several alternative classes, we can consider both *total* and *partial* specificity values. The former is calculated for all known alien samples, while the latter is obtained using only samples from a specific alternative class. The Type I and the Type II errors characterize the quality of the developed model; they are employed for a science-based risk assessment.

2.1. Spectral matching

Spectral Matching (SM) is a part of software called Thermo Scientific Method Generator, which is provided by the vendor together with the NIR instrument. This software provides two methods for quality analysis, named 'identification' and 'verification'. Identification applies the K-nearest neighbors (KNN) [23] procedure to attribute a new unknown sample to one of the predefined classes.

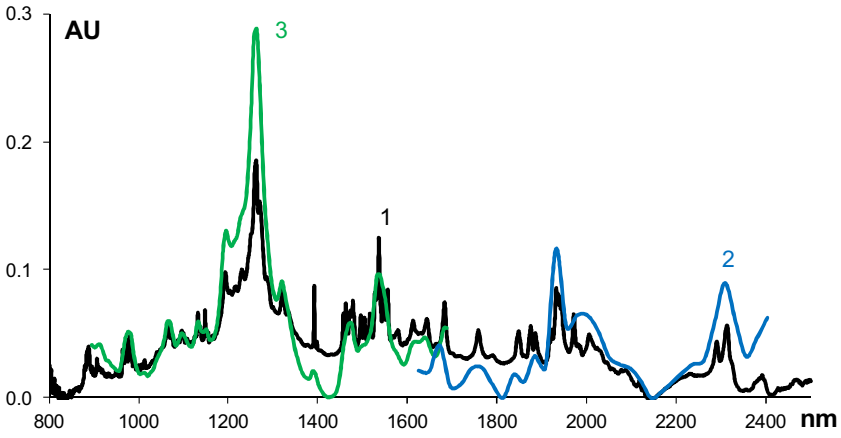

Fig. 1. Diffuse reflectance spectra of NIST traceable standard MCR-1920x acquired using Matrix (1); Phazir-RX (2); MicroNIR (3). See Table 1 for details.

KNN is a discriminant approach; therefore it does not serve our goal. For a class modeling approach, the software provides a special procedure called 'verification'. This procedure compares a new spectrum with each of the spectrum from the target 'library', by calculating the corresponding correlation coefficient (CC). In this case a new sample may be attributed to several libraries, or to no library at all. The decision rule is based on the threshold value of the CC that is suggested by the software. At the same time, the user may adjust this value arbitrarily or intentionally, for example, after analyzing such characteristics as sensitivity and specificity. The merit of the built-in software is the possibility to keep the libraries in the memory of the instrument. Moreover, for a routine test the result is presented directly on the display of the spectrometer and no additional computer is necessary.

2.2. DD-SIMCA

DD-SIMCA is an advanced method for class modeling [24,25], which allows to compute the misclassification errors theoretically. This technique is based on principal component analysis (PCA) that is applied to the target class training data matrix **X**. The following decomposition is obtained

$$\mathbf{X} = \mathbf{T}\mathbf{P}^{\mathrm{t}} + \mathbf{E} \tag{3}$$

where $\mathbf{T} = \{t_{ia}\}$ is the $(I \times A)$ scores matrix; $\mathbf{P} = \{p_{ja}\}$ is the $(J \times A)$ loadings matrix; $\mathbf{E} = \{e_{ij}\}$ is the $(I \times J)$ matrix of residuals; and A is the number of principal components (PC).

At the second step, for each object $i = 1,\ldots, I$ from the training set, two distances are calculated. They are the score distance h_i, and the orthogonal distance v_i:

$$h_i = \mathbf{t}_i^{\mathrm{t}}(\mathbf{T}^{\mathrm{t}}\mathbf{T})^{-1}\mathbf{t}_i = \sum_{a=1}^{A}\frac{t_{ia}^2}{\lambda_a}, \qquad v_i = \sum_{j=1}^{J} e_{ij}^2 \tag{4}$$

In this formula elements $\lambda_a = \sum_{i=1}^{I} t_{ia}^2$ are the eigenvalues of matrix $\mathbf{X}^{\mathrm{t}}\mathbf{X}$ ranked in descending order. The score distance characterizes a sample position within the score space and orthogonal distance represents the distance of the sample to the score space. DD-SIMCA adds a possibility to estimate data-driven distribution parameters for the $\{h_i\}$ and $\{v_i\}$, and, thus, to develop an acceptance area/decision rule for a given value of type I error, α [25]. In case an alternative class is available, DD-SIMCA provides the possibility to calculate the type II β error [26]. Formulas for calculation of the acceptance area for the given α and β values are presented in the Supplementary materials to the article. The MATLAB code for DD-SIMCA can be downloaded from [27].

3. Materials and measurements

3.1. Data set

Except for one manufacturer, all samples used in this study are the same ones that were analyzed in [16] using an FT-NIR spectrometer. Since these data sets have already been studied rather minutely, we consider that such a real-world example is a good prove-out for a handheld instrument. The objects are uncoated intact tablets of a calcium channel blocker packed in blisters. All tablets contain 10 mg of the same API, but the quantity and composition of excipients slightly varies. Details are presented in Table 2.

Tablets are provided by six different manufacturers and comprise 6 subsets A1, A2, ..., A6. Each subset consists of 50 tablets collected from 5 different batches, 10 tablets per batch. 40 tablets from 4 batches form the training set and ten tablets obtained from the fifth batch are used for the test set. Tablets are supplied directly by the manufacturers, thus, there is no doubt about their genuine nature. All samples are packed in blisters covered with optically transparent one-layer polyvinyl chloride (PVC) films, which NIR spectra are similar for different subsets.

3.2. NIR measurements

NIR spectra are acquired in the range of 1600–2400 nm with 8.7 nm wavelength increment using handheld spectrometer PHAZIR-RX (ThermoScientific, USA). Measurements are carried out in the diffuse reflectance mode through a PVC blister. The spectrum of a PVC blister is presented as dotted line in Fig. 2a. It can be seen that except for two regions around 1700 and 2300 nm, the PVC blister is transparent for NIR radiation. As a result, the acquired spectrum is a combination of the signal from a tablet and from PVC. For analysis the entire spectral region is utilized, because it is difficult to foresee where alien objects will manifest deviations from the genuine sample.

Each time triplicate measurements are made to control reproducibility. Replicas are averaged before the data analysis. Examples of initial spectra for 6 different subsets are presented in Fig. 2a.

Raw spectra look rather similar. Baseline shifts are mainly caused by reflection from the blisters (Fig. 2a). To remove these artifacts, a pre-processing is necessary. Different methods and their combinations provided by the software of the instrument were tested. In our case, the most efficient is the second order Savitzky-Golay differentiation, using the third order polynomial within the

Table 2
Data sets description.

Name	Tablet mass, (mg)	Excipients	Marker
A1	300	lactose, microcrystalline cellulose, magnesium stearate	
A2	200	lactose, povidone, crosspovidone, calcium stearate	
A3	200	potato starch, lactose, microcrystalline cellulose, magnesium stearate, calcium stearate	
A4	180	corn starch, lactose, microcrystalline cellulose, magnesium stearate	
A5	150	potato starch, lactose, microcrystalline cellulose, magnesium stearate, calcium stearate	
A6	200	lactose, microcrystalline cellulose, magnesium stearate, croscarmellose sodium	

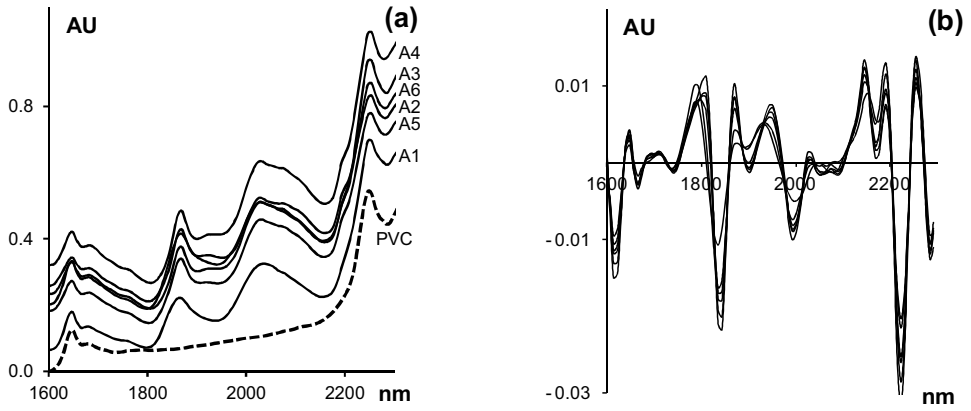

Fig. 2. (a) Raw spectra from 6 different manufacturers, solid lines; the spectrum of a PVC blister, dotted line; (b) pre-processed by the second order differentiation spectra from 6 different manufacturers.

7 point windows [23]. This pre-processing both removes baseline shifts and sharpens the spectral peaks (Fig. 2b). Afterwards the data are centered column-wise. All further calculations are conducted using the pre-processed data.

4. Results and discussion

4.1. Data overview

Principal component analysis (PCA) [23] applied to the pre-processed data shows that 3 PCs describe 95% of data variation.

The score plots presented in Fig. 3 demonstrate that some groups, i.e. A1 and A2, are well separated from the others in the plot depicting PC1-PC2. At the same time, other groups show substantial overlapping, i.e. A3, A4, A5 in the plot of PC1–PC2 scores, and A4 and A6 in the PC1–PC3 score plot.

Our goal is to extract information from the spectral data. We consider each class separately with the aim to delineate it from all other classes. Thus, we have six target classes and develop a separate model for every manufacturer. In each case, the test samples from the target class are used for external model validation. Test samples from the rest five classes are considered as aliens and are used for accessing the model specificity. All calculations are performed on the pre-processed data.

4.2. Spectral matching procedure

The spectra of 40 samples from each dataset, A1, A2,. . ., A6, are collected in the corresponding spectral libraries, which are used for training and sensitivity calculation. Additionally, 10 other spectra from each class are set aside for validation and assessment of specificity. We consider the results of verification for two threshold values of the CC, namely, CC = 0.95, automatically set by the software, and CC = 0.99, which is chosen based on the obtained figures of merit. All classes demonstrate excellent sensitivity of 100% for both threshold values. This means that all samples from the target classes are properly attributed to their own classes. This result looks very promising. At the same time, we have to verify whether the established models are able to recognize aliens. For each target class, we calculate a total specificity and five partial specificities, one for each alternative class. The results for all samples and six libraries/classes are collected in Table 3. Column 1 contains the target class names, the second and third columns show the total specificity for CC = 0.95 and CC = 0.99 respectively. The other six columns present the partial specificities, calculated separately for each alternative class. Mismatches (specificity is less than 90%) are marked in bold.

It can be seen that values of total specificity obtained for CC = 0.95 are unsatisfactory. Even the best case of class A1 is lower than 90%. This result means that, in the future, there will be a big chance of misclassification of the so-called 'high quality fakes'. When the threshold value is changed to CC = 0.99, the situation improves substantially. Now the models developed for the target classes A1, A2, A3 reliably distinguish between the target and the alien objects. However, the results for classes A4, A5, A6 are not so good. To understand the reason, we calculate the values of partial specificity for each alien class separately. Considering, for example, class A6 as the target, we see that its verification model cannot recognize the aliens from classes A4 and A5, but it properly classifies objects from classes A1, A2, and A3. Similar problems are observed for the verification models developed for the target classes A4 and A5.

Therefore, it can be concluded that the selection of a pertinent cut-off value for the CC can greatly influence the results of classifi-

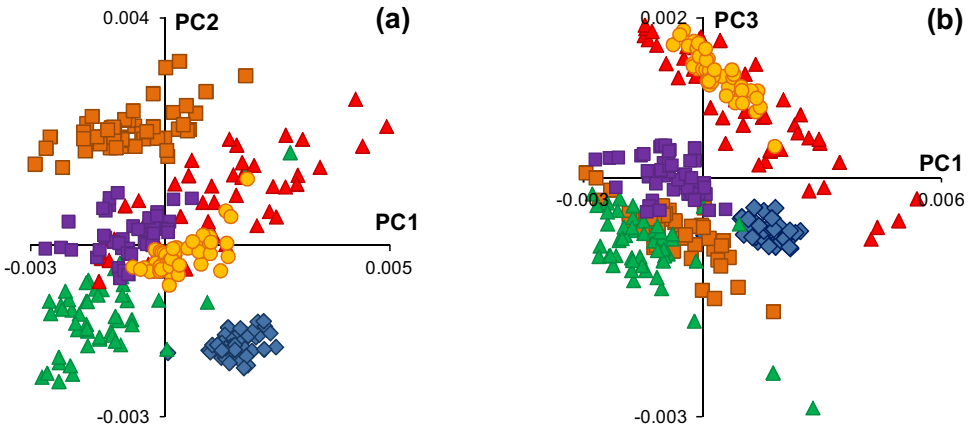

Fig. 3. Score plots for the joint PCA analysis of all data: (a) PC1 vs. PC2, (b) PC1 vs. PC3.

Table 3
"Spectral matching". Total and partial specificities (%).

Target class	Total specificity		Partial specificities for CC = 0.99					
	CC = 0.95	CC = 0.99	A1	A2	A3	A4	A5	A6
A1	**80**	100		100	100	100	100	100
A2	**40**	90	100		100	90	**70**	90
A3	**24**	100	100	100		100	100	100
A4	**36**	**78**	100	90	**80**		0	**20**
A5	**20**	**78**	100	100	100	90		**0**
A6	**20**	**62**	100	100	100	**0**	**10**	

cation. Also, we can conclude that even the proper threshold value CC = 0.99 does not provide reliable solutions for classes A4, A5, and A6.

4.3. DD-SIMCA procedure

This method provides a possibility to develop a decision rule [16] for a given value of type I error, α, and then to calculate the type II error, β, for any alternative class. Certainly, the posterior assessment of selectivity and specificity is also available.

Firstly, we consider a simple instance, when the authentication model in case A2 is the target class. Applying PCA to the training samples from A2 and using score and orthogonal distances (Eq. (4)) we calculate total distances, *c* (Supplementary materials Eq. (S2)), and obtain a cut-off level for a given α-value (Supplementary materials Eq. (S3)). The number of PCs is selected using cross-validation and taking into account the principle of parsimony. The ultimate external validation is conducted using test samples, i.e. the target samples from a batch, which is not used for model training. Test objects from all other classes are considered as new objects and used to evaluate the performance of the model. Samples from the alternative class, which is closest to the cut-off values, can be used for calculation of the type II error β (Supplementary materials Eq. (S8))

Fig. 4 demonstrates the acceptance areas developed for two PCs in PCA. The regular curve (2) represents the area obtained for α = 0.01. It can be seen, that all A2 objects are properly recognized as the members of the target class. In case we set α = 0.05 (dashed curve, 1), the acceptance area shrinks a little. The value α = 0.05 means that we could expect 5% of the training objects to be out of the acceptance area. In our case, 5% of 40 training objects gives two, and that is exactly the result we observe. From Fig. 4b, we see that, even for α = 0.01, the objects from all other classes are located very far from the acceptance area. Therefore, there is no need to increase α. Finally, for α = 0.01, selectivity equals 100%, and the total specificity equals 100%. These results are better than those obtained by the Spectral Match procedure (compare with Table 3, row "A2").

Now, we consider A6 as the target class. From Table 3, row A6, we conclude that this is a challenging class. We employ PCA models with two and three PCs. The two PCs model performs perfectly on the training set, however two out of ten samples are misclassified for α = 0.01 (Fig. 5a solid curve) in the A6 test set. Objects from all other classes are properly classified as aliens. To accept these outliers we could extend the acceptance area (Fig. 5a, dashed line), but the value of α, which forms this area is unreasonably low and equals 10^{-5}. Instead of this, we can increase the complexity of the model and consider a model developed for 3 PCs (Fig. 5b). Here, for α = 0.01, we obtain a selectivity of 100%, and the total specificity of 100%. No misclassification has occurred. The closest alien class is A4 and we can estimate the value of β for the selected acceptance area. β is equal to 0.007, this means that the risk of misclassification, which is the wrong acceptance of the A4 objects as the members of class A6, is negligible.

It is worth noting that the type I and type II errors are connected. Increasing the value of α we increase the risk of wrong rejection of the target objects, and, at the same time, decrease the risk of wrong acceptance of aliens, and vice versa. DD-SIMCA provides a possibility to balance the risks for each particular model.

Another challenging class is A4. The model with 2 PCs and α = 0.01 wrongly attributes 8 objects of class A6 as the members of the target class. The model with 3 PCs solves this problem and provides a selectivity of 100% and specificity of 100%.

Taking into account the principle of parsimony, we construct models with 2 PCs for classes A1, A2, A3, A5, and models with 3 PCs for classes A4 and A6. All these models show a selectivity of 100% and specificity of 100% for α = 0.01.

5. Conclusions

Whenever we use a one-class classifier approach, we should account for the risk of misclassification of alien objects. It might

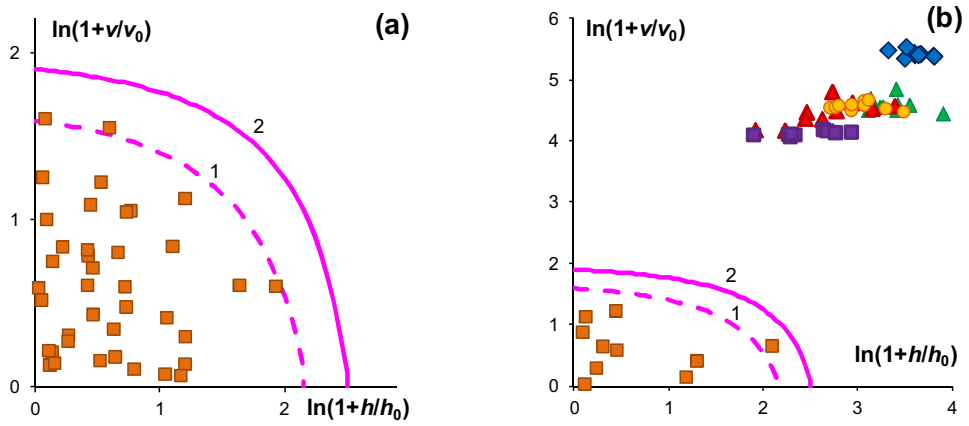

Fig. 4. DD-SIMCA model for class A2, 2 PCs. Two cut-off levels are shown: α = 0.05 (dashed line, 1) and α = 0.01 (solid line, 2). Plot (a): training set, (b) test sets.

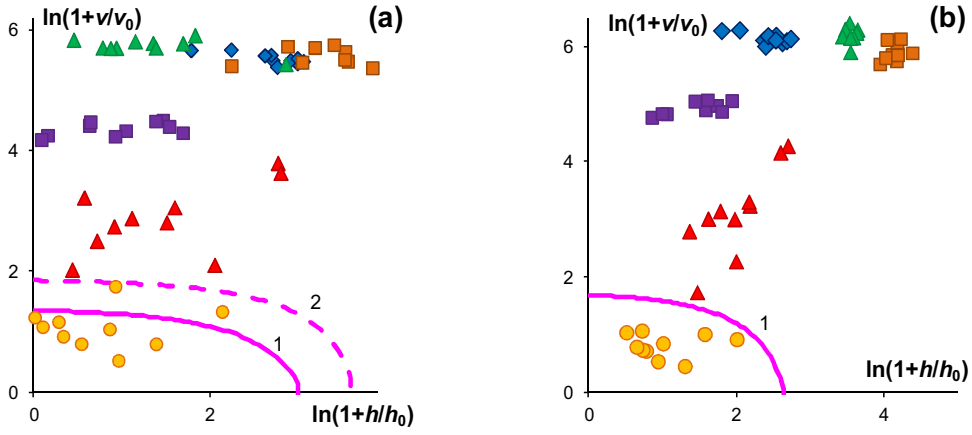

Fig. 5. Test sets in the DD-SIMCA models for target class A6. Plot (a): 2 PCs, α = 0.01 (solid line, 1), α = 10 – 5 (dashed line 2). Plot (b): 3 PCs, α = 0.01 (solid line, 1).

happen because the model is developed for a specific target class, but not for recognition of aliens, which, in principle, can be very close to the selected acceptance area. Therefore, it is important to both validate the model using an independent set of the target objects, and to verify the model against a wide variety of alien objects.

The internal spectral matching procedure based on the correlation coefficient assessment is a very simple and straightforward method. The only parameter which is possible to vary is the threshold value. The simplicity of the method is also its main drawback. Spectral matching performs well in case the compared spectra are rather different. For more or less similar spectra it is hard to yield satisfactory results. It is also important to note that the presented example shows that a simple "push a button" approach, in which the CC threshold value is selected automatically, leads to unsatisfactory results. Even a simple manual tuning of the threshold value improves the situation.

The application of DD-SIMCA requires more efforts when it comes to model development, however this method yields much better results and also provides additional possibility of quantitative assessment of the risk of wrong decisions.

The successful solution of the presented authentication problem confirms that the initial spectra do carry information that allows delineation of the considered objects. DD-SIMCA helps to extract this information. In this case the handheld NIR device should be utilized in pair with a laptop running the software implementation of the DD-SIMCA, this makes the testing routine more complex than application of the handheld instrument itself. At the same time in comparison with the now used FT-NIR instruments mounted into special vehicles, the proposed complex is much more mobile.

The chemometrics aided approach helps to enhance the applicability of miniaturized NIR instruments.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jpba.2016.08.008.

References

[1] World Health Organization, Definitions of SSFFC Medical Products, 2016 (accessed 15.02.16) http://www.who.int/medicines/regulation/ssffc/definitions/en/.
[2] Interpol. int, Operation Pangea/Operations/Pharmaceutical Crime/Crime Areas/Internet/Home – INTERPOL, 2016 (accessed 15.02.16) http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Pangea.
[3] R. Martino, M. Malet-Martino, V. Gilard, S. Balayssac, Counterfeit drugs: analytical techniques for their identification, Anal. Bioanal. Chem. 398 (2010) 77–92.
[4] B. Krakowska, D. Custers, E. Deconinck, M. Daszykowski, Chemometrics and the identification of counterfeit medicines—a review, J. Pharm. Biomed. Anal. 127 (2016) 112–122, http://dx.doi.org/10.1016/j.jpba.2016.04.016.
[5] M. Blanco, I. Villarroya, NIR spectroscopy: a rapid-response analytical tool, TrAC Trends Anal. Chem. 21 (2002) 240–250.
[6] O.Ye. Rodionova, A.L. Pomerantsev, NIR-based approach to counterfeit-drug detection, TrAC Trends Anal. Chem. 29 (2010) 795–803.
[7] A.P. Arzamastsev, N.P. Sadchikova, A.V. Titova, Current state of IR spectroscopy applied to pharmaceutical analysis, Pharm. Chem. J. 42 (2008) 466–470.

[8] H. Storme-Paris, M. Rebiere, C. Matoga, P. Bonnet, M. Tissier, et al., Challenging near InfraRed spectroscopy discriminating ability for counterfeit pharmaceuticals detection, Anal. Chim. Acta 658 (2010) 163–174.
[9] A. O'Neil, R.D. Jee, G. Lee, A. Charvill, A. Moffat, Use of a portable near infrared spectrometer for the authentication of tablets and the detection of counterfeit versions, J. Near Infrared Spectrosc. 16 (2008) 327.
[10] M. Alcalà, M. Blanco, D. Moyano, N.W. Broad, N. O'Brien, D. Friedrich, F. Pfeiferd, H.W. Sieslerd, Qualitative and quantitative pharmaceutical analysis with a novel hand-held miniature near infrared spectrometer, J. Near Infrared Spectrosc. 21 (2013) 445–457.
[11] J.A. Fernández Pierna, P. Vermeulen, B. Lecler, V. Baeten, P. Dardenne, Calibration transfer from dispersive instruments to handheld spectrometers, Appl. Spectrosc. 64 (2010) 644–648.
[12] Viavisolutions.com, MicroNIR™ Pro Spectrometer [Internet], 2016 (accessed 17.02.16) http://www.viavisolutions.com/en-us/osp/products/micronir-spectrometers.
[13] Thermoscientific.com, MicroPHAZIR™ RX Analyzer, 2016 (accessed 17.02.16) http://www.thermoscientific.com/en/product/microphazir-rx-raw-material-identification-analyzer.html.
[14] Bruker.com, Bruker Corporation: MPA Overview – FT-NIR Multi Purpose Analyzer, 2016 (accessed 15.02.16) http://www.bruker.com/ru/products/infrared-near-infrared-and-raman-spectroscopy/ft-nir/mpa/overview.html.
[15] Middletonspectral.com, Hyperspectral Imaging Cameras and Systems | Middleton Spectral Vision, 2013 (accessed 29.05.16) http://www.middletonspectral.com/.
[16] O.Ye. Rodionova, K.S. Balyklova, A.V. Titova, A.L. Pomerantsev, Quantitative risk assessment in classification of drugs with identical API content, J. Pharm. Biomed. Anal. 98 (2014) 186–192.
[17] M. Dyrby, S. Engelsen, L. Nørgaard, M. Bruhn, L. Lundsberg-Nielsen, Chemometric quantitation of the active substance (Containing CN) in a pharmaceutical tablet using near-infrared (NIR) transmittance and NIR FT-Raman spectra, Appl. Spectrosc. 56 (2002) 579–585.
[18] P. Chalus, Y. Roggo, S. Walter, M. Ulmschneider, Near-infrared determination of active substance content in intact low-dosage tablets, Talanta 66 (2005) 1294–1302.
[19] F.E. Dowell, E.B. Maghirang, F.M. Fernandez, P.N. Newton, M.D. Green, Detecting counterfeit antimalarial tablets by near-infrared spectroscopy, J. Pharm. Biomed. Anal. 48 (2008) 1011–1014.
[20] P. de Peinder, M.J. Vredenbregt, T. Visser, D. de Kaste, Detection of Lipitor® counterfeits: a comparison of NIR and Raman spectroscopy in combination with chemometrics, J. Pharm. Biomed. Anal. 47 (2008) 688–694.
[21] O.Ye. Rodionova, A.P. Titova, A.L. Pomerantsev, Discriminant analysis is an inappropriate method of authentication, TrAC Trends Anal. Chem. 78 (2016) 17–22.
[22] SN, Y. Deming, D.L. Michotte, L. Massart, B.G.M. Kaufman, Vandeginste, Chemometrics: A Textbook, Elsevier, Amsterdam, 1988.
[23] T. Naes, T. Isaksson, T. Fearn, Multivariate Calibration and Classification, Wiley, 2002.
[24] A.L. Pomerantsev, Acceptance areas for multivariate classification derived by projection methods, J. Chemom. 22 (2008) 601–609.
[25] A.L. Pomerantsev, O.ye. Rodionova, Concept and role of extreme objects in PCA/SIMCA, J. Chemom. 28 (2014) 429–438.
[26] A.L. Pomerantsev, O.Ye. Rodionova, On the type II error in SIMCA method, J. Chemom. 28 (2014) 518–522.
[27] DD-SIMCA, Software. http://rcs.chemometrics.ru/SIMCA/, 2016 (accessed 15.02.16).