

NIR-based approach to counterfeit-drug detection[☆]

O.Ye. Rodionova, A.L. Pomerantsev

There is no simple solution to the problem of counterfeit-drug detection. So-called “high-quality fakes” with proper composition are most difficult to reveal. Methods based only on quantitative determination of active ingredients are sometimes insufficient. A more general approach is to consider a remedy as a whole object, taking into account the complex composition of active ingredients and excipients, as well as manufacturing conditions (e.g., degree of drying). NIR measurement combined with chemometric data processing is an effective method but the superficial simplicity of its application may lead to wrong conclusions that undermine confidence in the technique. The main drawback of the NIR-based approach is the need to apply multivariate/chemometric data analysis in order to extract useful information from the acquired spectra.

This article provides an overview of the experience of different research groups in NIR drug detection and highlights the main issues that should be taken into account. The common problems to be dealt with are:

- (1) each medicinal product should be carefully tested for batch-to-batch variability;
- (2) the selection of a specific spectral region and the data pre-processing method should be done for each type of medicine individually; and,
- (3) it is crucial to recognize counterfeits as well as to avoid misclassification of genuine samples.

The real-world examples presented in the article illustrate these points.

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[☆]All medicines described in this paper are given their pharmaceutical names not their manufacturer names. This is done in accordance with agreement with the institution that provided us with counterfeit-drug samples.

^{☆☆}Raw spectra for datasets “Metronidazole” and “Pancreatin 2” are located at the web-site <http://rcs.chph.ras.ru/data/>

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1. Introduction

At present, drug counterfeiting is becoming more and more sophisticated. In the past, fake medicines were a common problem in developing countries where the main issue was often the tremendous lack of a specific remedy (e.g., antimalarial drugs). According to the European Agency for the Evaluation of Medicinal Products (EMA), the phenomenon has spread. More and more frequently, fakes are being revealed all over the world. In developing countries, the majority of counterfeited medicines are used to treat serious diseases (e.g., malaria, tuberculosis, and HIV/AIDS).

“In wealthy countries, fakes are mainly new, expensive lifestyle medicines, such as hormones, steroids and antihistamines. In recent years, fakes were revealed among expensive drugs, such as anti-cancer ones, and those highly in demand, such as antivirals,” according to EMA [1].

Counterfeit drugs are produced using modern pharmaceutical equipment in

packages of excellent printing quality. According to the World Health Organization (WHO) definition [2]: “A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging.”

The growing circulation and variety of counterfeit medicines all over the world forces analysts to design different methods to recognize fakes [3,4].

It is evident that the simplest way of testing is visual, based on special drug packages, holograms, and unique printing on the tablet surface. These methods are always used by manufacturers to protect their products. Unfortunately, everyday practice shows that such an approach is insufficient, though it is important as a first step against dissemination of fake medicines.

Testing a remedy itself leads to much more reliable conclusions. Traditional methods of rapid analysis include a simple disintegration test, simple qualitative reactions, and thin-layer chromatography (TLC). These basic drug-testing schemes were published by the WHO some 30 years ago, shortly after the report in 1982 about counterfeit drugs, mainly referring to developing countries. The testing methods were successfully implemented in Germany, Japan and the USA. However, at that time, the problem was prevalent in the developing countries, where many imported medicines (e.g., to treat malaria and tuberculosis) were fakes. To combat these counterfeit drugs, special testing kits [5] were developed for use by both foreign specialists and local laboratories.

Nowadays, these traditional methods are insufficient, as drug counterfeiting has become increasingly sophisticated. Even for the developing world, the problem is no longer straightforward, as “counterfeit antimalarial drugs are found in many developing countries, but it is challenging to differentiate between genuine and fakes due to increasing sophistication of the latter” [6].

Other analytical methods described in pharmacopoeia [e.g., gas chromatography (GC), high-performance liquid chromatography (HPLC), mass spectrometry (MS)] take time and are labor intensive, and they cannot generally be used for screening analysis. Analysts therefore have to design special methods, which are simple and rapid, and can be applied directly on site and face the challenge of the modern counterfeit market.

One such approach suggests using near-infrared (NIR) spectroscopy followed by chemometrics-based data analysis. At the end of the 1990s, NIR testing was included in pharmacopoeias of different countries (e.g., European Pharmacopoeia since 1997). NIR equipment is now widespread among analytical laboratories, as spectrometers have become cheaper and more reliable. On-site usage of inexpensive portable NIR spectrometers is feasible [6,7]. Especially well known is the Chinese experience in small mobile laboratories equipped with NIR spectrometers [8].

Several research groups [9–13] have reported promising results in applying NIR spectroscopy for counterfeit-drug detection. Some of the researchers follow a traditional analytical route and try to reveal fakes by determining the concentration of an active pharmaceutical ingredient (API), which is then compared to similar medicines produced by various manufacturers [14–17]. Nowadays, this approach is extensively utilized in China [18,19]. Another approach is to investigate the types of excipient and their concentrations [20].

We consider that a remedy should be investigated as a whole and that the methods based on determination of API alone are insufficient. Proper API concentration does not guarantee that a tablet is not a fake. As a rule, a remedy is a complex composition of API(s) and a number of excipients, all indispensable for therapeutic efficacy.

Not only are the proper ingredients important, but also the way the medication is manufactured. For example, the drug-release time is an essential characteristic for many types of medicines, so that the solid-state properties influence the stability and the dissolution of tablets and pellets [21]. We therefore adhere to the opinion stated in [21] that “the problem appears to be a simple one: to identify whether a drug sample is or is not the drug reported on the label”. NIR spectroscopy is an effective technique for this purpose.

Another aspect closely related to counterfeiting is generic medicines. The discussion of the pros and cons of generics is outside of the scope of this review. However, it is worth mentioning that counterfeiting refers to branded and generic drugs. Speaking of “original” or “genuine” sample, we mean legally produced and legally labeled drugs, as distinct from those that are “intentionally mislabeled so as to mislead the user with respect to composition and/or manufacturer” [22].

A more recent advancement would be NIR imaging. Theoretically, it is clear that NIR imaging is more informative [23–26], but, at the same time, it is more expensive when it comes to equipment and software requirements. It would be interesting to consider a case of counterfeit-drug detection where an ordinary NIR-based approach fails, while NIR imaging succeeds. For the moment, we do not have such an example to present.

2. NIR-based approach

NIR spectroscopy has been used extensively since the 1970s. Absorption bands in the NIR region (12500–4000 cm^{-1}) correspond mainly to overtones and combinations of fundamental vibrations, which occur in the mid-IR region [27]. Close attention is now being paid to application of NIR spectroscopy in pharmaceutical analysis and technologies [21,28,29]. Among the merits of NIR spectroscopy, the following are most important:

- measurements are rapid and simple, and they can be conducted without special, or minimal, sample preparation;
- spectra carry information regarding not only chemical, but also physical phenomena, making NIR spectroscopy very informative;
- depending on the samples and problem under consideration, acquisition of spectra may be conducted in transmittance, reflectance or diffuse reflectance mode;
- NIR spectra can often be obtained through blisters or ampoules without opening them; acceptable materials are glass and plastics, but metal foil is unacceptable.
- measurements can be performed using an integrating sphere as well as a fiber-optic probe, so testing can be performed not only in a laboratory but also on site.

The main drawback of NIR spectroscopy is a hidden way the information is presented in the acquired spectra. Multivariate/chemometric data processing is necessary to extract this information.

Sometimes the superficial simplicity of NIR testing leads to meaningless models and wrong conclusions, which explains why we do not speak of NIR spectroscopy as a rapid analytical tool, but present the entire NIR-based approach for counterfeit drug detection. This approach combines NIR measurements with chemometric data processing. There is a wide choice of chemometric methods and there are many publications devoted to this theme in specialized books [30,31], as well as chemometric and analytical journals. In the present review, we focus on crucial points that influence the final results of an NIR-based approach.

When the main goal of an investigation is to predict API concentration in a medicine, multivariate-regression methods are utilized. The most widely used approach is partial least squares (PLS) and its numerous modifications [31]. According to this approach, if the predicted concentration of API in a new sample differs from the calibration samples, the sample is considered a counterfeit. This method follows the pharmacopoeia tests, which aim to control a set of characteristics for a given remedy. However, proper API concentration cannot guarantee that a sample is genuine. Also information provided by NIR measurements is much more comprehensive.

Another approach within the framework of NIR-based methods is the two-class (or multi-class) discrimination between genuine and counterfeit drugs. Most frequently, PLS discriminant analysis (PLS-DA) is applied (e.g., as in revealing fake Lipitor [32] and antimalarial tablets [6]).

Various types of cluster analysis and Kohonen self-organizing map (SOM) [7] were successfully applied when it was necessary to divide tablets into several classes and separate genuine from counterfeit drugs. At the same time, this technique cannot be used to reveal a potential counterfeit that could be produced in the future.

We recommend another technique aimed at modeling each class of samples independently (i.e. the disjoint-class model) {e.g., unequal dispersed classes (UNEQ) [33], support vector machine (SVM) [34], and soft independent modeling of class analogy (SIMCA) [35]}. These methods construct an acceptance area for the genuine model(s) and help to detect any counterfeit sample regardless of the reason for dissimilarity from the genuine medicine (e.g., wrong API concentration, different composition of excipients, violations in production process). Construction of the acceptance area for such classes is a rather complicated problem and various authors solve it in different ways [36,37]. We apply a modified SIMCA approach [38], which provided the acceptance procedure for quantitative classification of

samples at a certain significance level (see example in Section 6 below).

3. Counterfeits of different quality

There are different types of false drugs (e.g., placebos, medicines with a reduced concentration of API, and drugs that do not contain the proper concentrations or types of excipient). The most typical classes of the “high-quality” counterfeit drugs differing in their degree of non-conformity with the genuine drugs are as follows:

- (1) medicines with wrong API(s);
- (2) medicines with proper API(s) but wrong in one or several excipients; and,
- (3) medicines with very similar chemical composition, which can hardly be discriminated from the genuine drug.

3.1. Specific examples

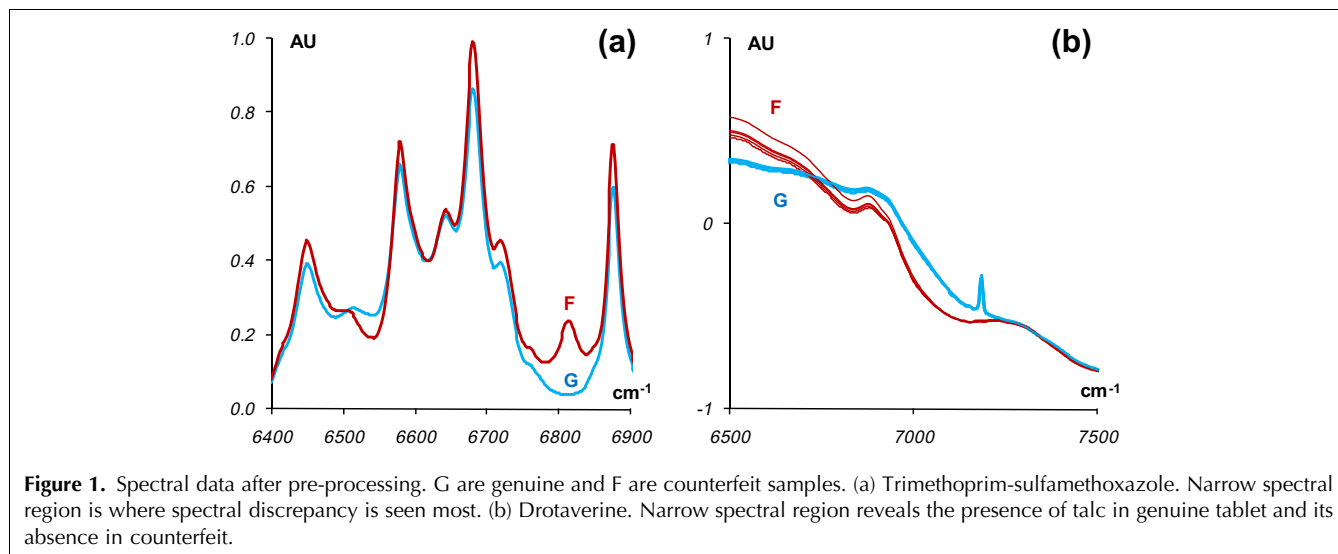
Specific examples that we obtained during our research help to illustrate these classes.

3.1.1. Trimethoprim-Sulfamethoxazole combination. The first case concerned uncoated tablets of complex antibacterial drug (Trimethoprim-Sulfamethoxazole combination) [39]. The data set comprised three batches of the genuine medicine (10 samples in each batch) and one batch of fakes (9 samples). In this case, one of the two APIs in the counterfeit tablets was of low quality. False tablets were easily detected by a regular pharmacopoeia test as well as by the NIR-based approach. The discrepancies in spectra were evident in the interval of 6400–6900 cm^{-1} (Fig. 1a).

There are numerous studies devoted to successful application of NIR analysis for the quantitative determination of API in different drugs [15,16,19]. The feasibility of this approach for low-dosage tablets has been presented [17].

In the case of Trimethoprim-Sulfamethoxazole, these approaches successfully recognized the API quality in counterfeit drugs as the main difference.

3.1.2. Drotaverine. In the second case, we considered uncoated anti-spasmodic tablets containing Drotaverine as API [10]. The data set comprised five batches of the genuine medicine (10 samples in each batch) and one batch of fakes (10 samples). The API concentration in the counterfeit samples was identical to that in genuine samples, but the tablets differed in excipients. The talc peak was distinctly seen in the spectra of the genuine tablet and was absent in the spectra of the fake tablets (Fig. 1b). In this case, a regular pharmacopoeia test did not detect a fake. As for the NIR-based approach, counterfeits could be easily revealed by a direct comparison of NIR spectra as well as using the score plot



(t_1 – t_2), where two groups of samples were well separated [10].

Often drugs contain a complex mixture of excipients which are good indicators of the genuine product. Comparison of the excipients by the NIR-based approach was applied in Moffat's group at the University of London [13]. NIR was applied for determination of different chemical forms of the most frequently used excipients (e.g., cellulose and lactose) in illicit ecstasy production [20].

3.1.3. Metronidazole. In the third case, film-coated tablets of antibiotic drug (Metronidazole) were studied [39]. The data set consists of 17 batches of genuine medicine (5–10 samples in each batch) and two batches of fakes (5 samples for a batch). This data presented a “high-quality” counterfeit. Tablets were very similar and the standard pharmacopoeia tests could not recognize the counterfeits. NIR spectra also looked very similar, and only chemometric NIR data analysis succeeded in detecting the counterfeit drug (see Section 6). A group of scientists from the USA and the UK also came across the problem of “high-quality medicine” [6].

4. Pre-processing of NIR data and variable selection

Before chemometric analysis is applied, it is important to decrease the influence of various sources that are not related to the chemical or physical information carried by raw spectra. They may be from instrumentation (e.g., light scattering, particle-size distribution, packing density, or the effect of tablet face and tablet position in relation to a probe beam). Usual pre-processing techniques are used to remove these effects. The most popular among them are the first and second derivatives,

multiplicative scatter correction (MSC) and extended MSC, and standard normal variate (SNV) transformation [31]. As the performance of these methods is known to depend on the nature and the extent of the variations, in a real-world case, various techniques and their combinations are applied and tested to provide a better solution [17,40]. An attempt at detailed investigation of the efficacy of the empirical pre-processing methods in connection with physical sources that cause spectra variations is available [41].

The influence of standard blisters [42,43], bottles [44] and other packaging materials can sometimes also be removed through a pre-processing method. However, when liquid samples in amber plastic bottles were investigated [44], it was noted that the model had to be recalibrated if the bottle material was changed.

We came across a more complicated case, in which API was tested through closed polyethylene (PE) bags [45]. The samples of Taurine, a non-essential sulfur-containing amino acid, were measured in drums by FT-NIR spectrometer fitted with a hand-held diffuse reflectance fiber-optic probe in the 4000–10000 cm⁻¹ region in the drums. Primary PCA analysis classified 40% of the original samples as outliers. Further investigations showed (Fig. 2) that the PE peak in the central part of the NIR region (first overtone around 5770 cm⁻¹) significantly shifted the API peak to the mid-IR region and the second PE peak (combination bands around 4300 cm⁻¹) amplified the corresponding API peak. Due to varying thickness of the PE package caused by folds, the influence of the PE spectra on the routine measurements resulted in different distortions of the main API peaks. Spectra were analyzed after SNV pre-processing, but, in this case, formal mathematics failed to give an explanation. For proper classification, it was necessary to use two calibration sets: NIR spectra with low PE influence

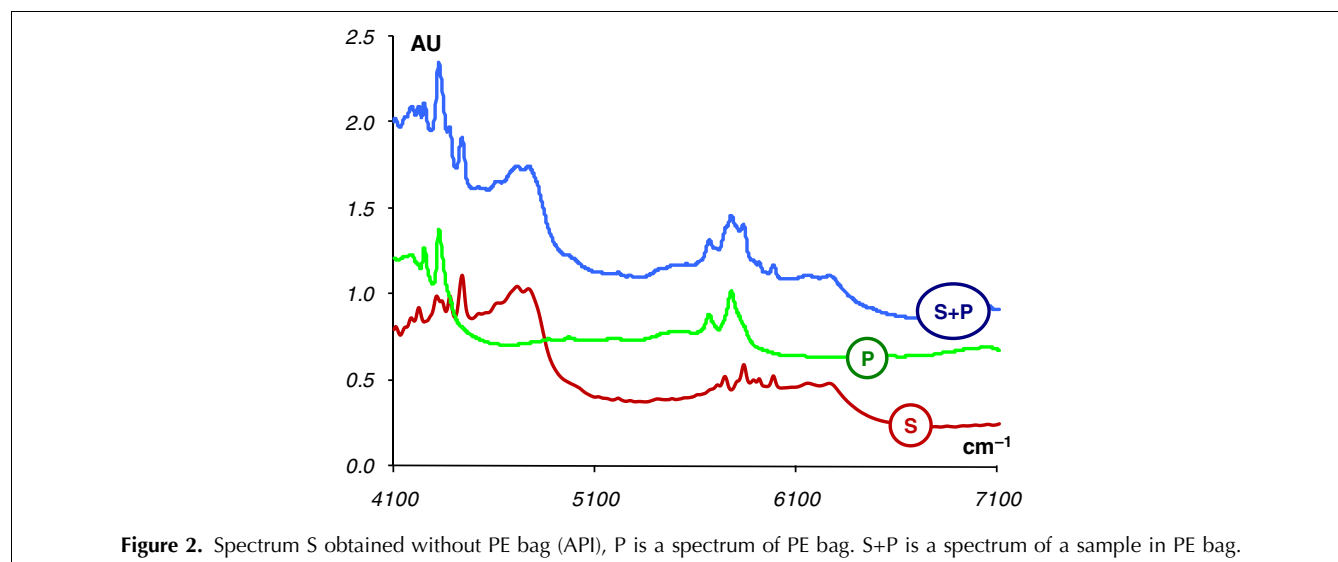


Figure 2. Spectrum S obtained without PE bag (API), P is a spectrum of PE bag. S+P is a spectrum of a sample in PE bag.

and those with intensive PE influence. Afterwards a special two-stage classification procedure [45] was applied to avoid misclassification.

Variable selection is another important issue that has a strong influence on proper pattern recognition and improvement of the multivariate calibrations based on NIR data. Relevant literature on the multivariate approach, in general, and on NIR applications, in particular, is very extensive [46,47]. Comparison of four variable-selection algorithms aimed to improve the precision of calibration models built for the NIR-transmission measurements of intact tablets [48]. These methods were iterative PLS, genetic algorithm, uninformative variable elimination by PLS, and interactive variable selection for PLS. The largest reductions of RMSEP values were found when using the genetic algorithm or interactive variable selection for PLS. A discrete cosine transform was proposed to improve the PLS calibration model for quantification of antidepressant tablets [49]. In [43], direct application of PCA failed to reveal data irregularity, but the application of the Sequential Projection Pursuit helped to reveal the heterogeneity of tablets, which were measured through their blister packages. A special optimization algorithm, which helped to remove continuous NIR spectral regions critical to the validity of the model was used in the case of piroxicam tablets [50].

The conclusions are that variable selection is important for a successful analysis of NIR data and that the lack of variable selection can spoil classification and regression results. Special attention should be paid to selection of the appropriate spectral interval. We strongly recommend not relying on automatic variable selection presented in software packages. For example, for the film-coated tablets of Sildenafil, an oral therapy for erectile dysfunction, such a selection resulted in misclassification (See Fig. 3a), as software selected a very

narrow spectral interval and one batch of genuine drug was classified as a counterfeit.

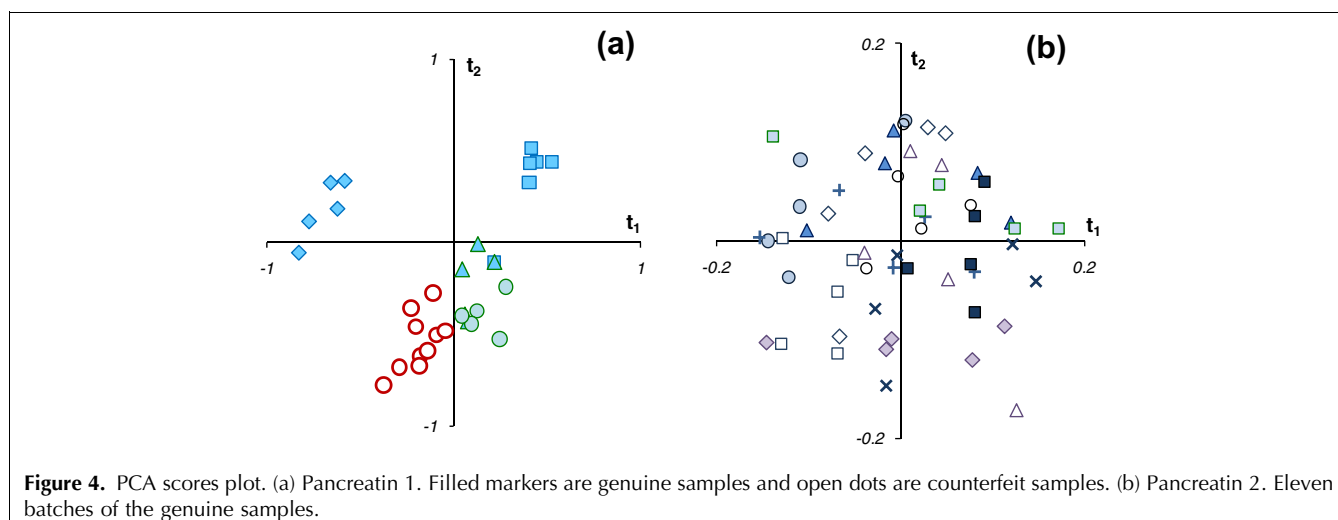
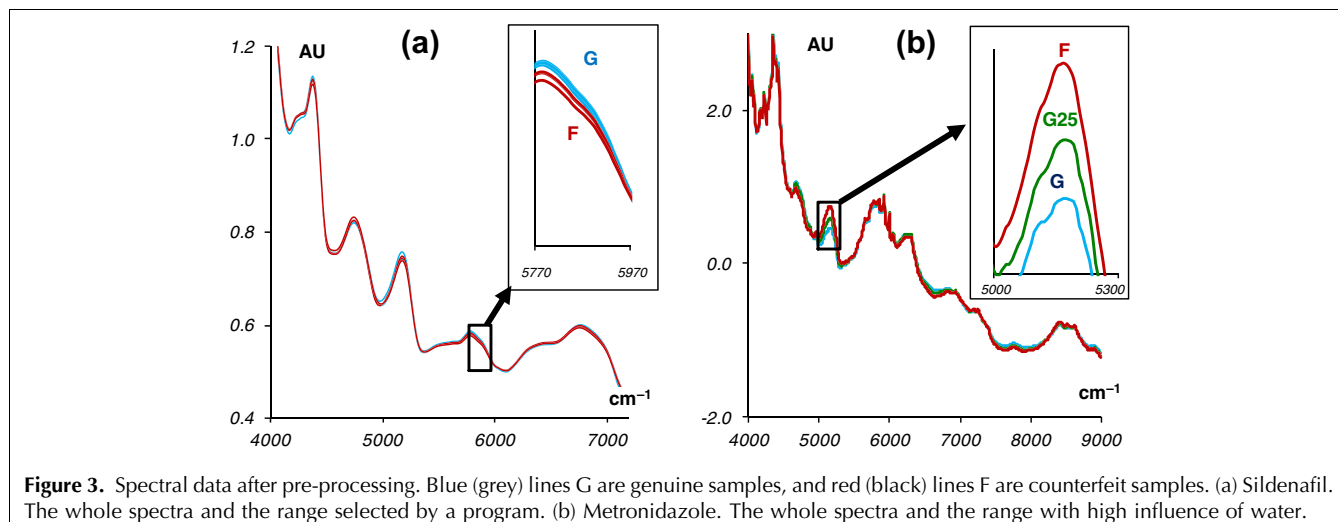
At the same time, data analysis without variable selection may also lead to misclassification. As an example, consider the case of Metronidazole (introduced in Section 3). Chemometric analysis showed that one genuine batch (G25) was classified as a fake. The reason was the higher moisture contents in this batch compared with the other genuine batches. Fig. 3b shows the spectra obtained and a narrow region, where strong moisture absorbance bands were present. Misclassification was corrected after excluding this spectral region, 5000–5300 cm^{-1} , from data processing (see Section 6). Here, we can state that, if the moisture variability in the genuine tablets was conventional, then exclusion of the water-related spectral region was necessary. Alternatively, where moisture variability does not meet technical requirements, spoilage in production has been revealed occasionally.

5. Variability of genuine drugs

One of the obstacles in counterfeit-drug analysis is batch-to-batch variation in the original product. This issue is of vital importance where counterfeit drugs are of “high quality”.

To illustrate this aspect, we consider two similar medicines, which were coated tablets containing Pancreatin, produced by different pharmaceutical companies. Data set Pancreatin 1 comprised four batches of genuine pills (5 samples in each batch) and one batch of fakes (10 samples). Data set Pancreatin 2 comprised 11 batches of genuine medicine (5 samples in each batch) and four batches of fakes (5 samples in each batch).

PCA analysis of NIR spectra (see Fig. 4) showed that, for Pancreatin 1, the variability inside the original



tablets (filled markers) was greater than that of the “high-quality fakes” (open dots). Three isolated groups of genuine samples are clearly seen in the PCA-score plot (Fig. 4a).

A detailed study of Pancreatin 2 showed that the technological process was steady and the batches produced during two consequent years were similar. The samples from each batch were denoted by individual-marker type in the PCA-score plot (Fig. 4b). In this case, the NIR-based approach was suitable for counterfeit recognition.

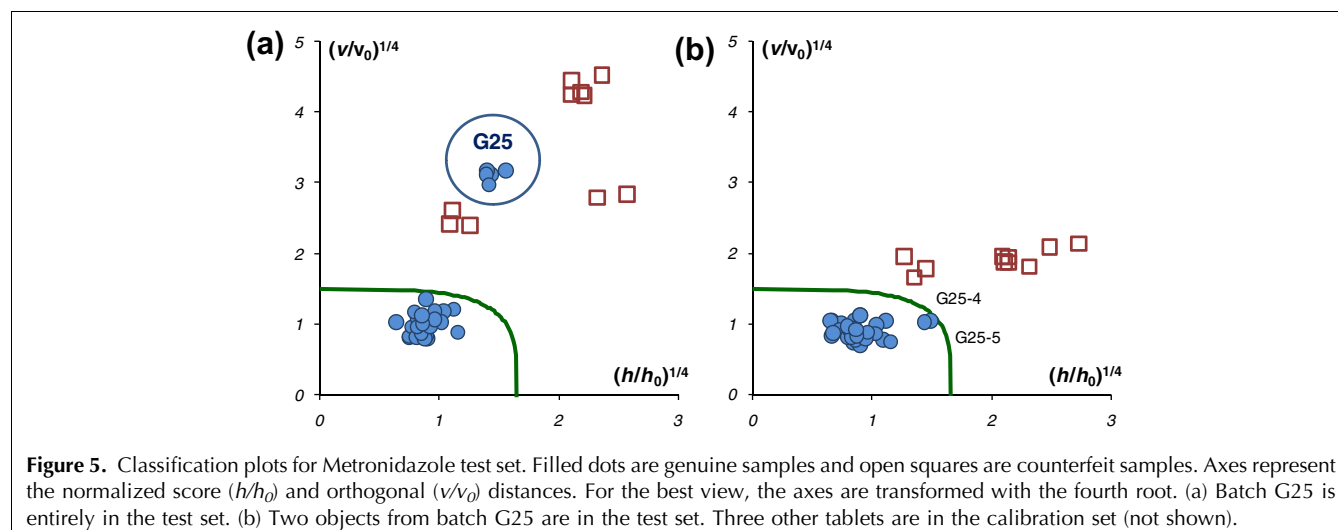
It is known that drugs are produced with some tolerance in API concentration and possible variations in excipients. This should be taken into account when collecting a calibration set. For example, in [50], 22 batches were utilized in order to cover the expected variation in the product over its shelf life. The production batches included retained ones (up to 24 months old at

the time of analysis) and fresh ones (less than one month old). In [9], it was also stressed that the calibration set should contain a number of spectra to consider the natural variability found among the composition of a given medicine.

However, the recommendation that at least 50 spectra must be present in the training set in order to obtain a correct classification for the additional test set seems questionable to us. We consider that the size of a calibration set greatly depends on the nature of the remedy being investigated, technological stability and aging conditions.

6. Classification

For a reliable classification, it is important not only to collect a representative data set, but also to distribute the



samples between the calibration set and the test sets in a proper way. Different studies have applied this issue to the counterfeit-drug detection (e.g., [51]).

Special attention to this aspect is also paid in the Guidance of the European Medicines Agency [52]. To illustrate this, we consider the case of Metronidazole that we discussed in Sections 3 and 4. The data set included 99 genuine samples and 10 counterfeit samples. It is clear that all fakes as well as some of the genuine batches should be placed in the test set that serves for validation. As was explained in Section 4, batch G25 was a troublesome subset that contained extra moisture. The problem was partly corrected by excluding the water-related spectral range, but G25 still slightly differed from other genuine batches. This is clear from Fig. 5a, which represents a SIMCA plot for test-set classification. In this case, the PCA model with 4 components was built based on the calibration set that comprised 69 samples (12 genuine batches without batch G25). The test set includes 30 samples from 5 genuine batches (including G25, filled dots) and 10 counterfeits (open squares). The acceptance area corresponds to the type I error $\alpha = 0.01$ (green curve).

In spite of the water-influence correction, all samples from batch G25 were not recognized as the originals. This signaled that batch G25 cannot be excluded from the calibration set. However, it would be a mistake to place the whole G25 into the calibration set. This batch bears very important features of variability in the genuine drugs, so batch G25 should be shared between the calibration set and test set as a valuable piece of data, which serves both for calibration and validation.

Fig. 5b illustrates this approach. The PCA model with 4 components uses 69 samples for the calibration set (including three samples from batch G25). The test set comprises 30 genuine samples (including two samples

from G25) and 10 counterfeits. It can be seen that, in this case, genuine and counterfeit samples are separated correctly.

7. Discussion

Surveying the whole procedure of counterfeit-drug detection using the example of Metronidazole case, we can underline all critical points of the NIR-based approach as a general technique. The representative data set comprised 17 different batches of genuine tablets that were produced in 20 months.

Exploratory analysis of the acquired NIR spectra demonstrates production stability, so chemometric modeling may be effective for such data.

As measurements were conducted on the intact coated tablets, SNV pre-processing of the raw spectra removes the influence of the tablet position as well as the light-scattering effect. Variable selection in this example is tightly connected with the pertinent distribution of objects between calibration and validation subsets.

PCA analysis using the whole NIR region singles out batch G25 as a strong outlier. At the same time, exclusion of batch G25 from the calibration set is undesirable, as this could lead to misclassification for genuine medicine in the future. We removed the strong water peak (region around 5000 cm^{-1} , Fig. 3b) and added objects from batch G25 to the calibration set. Subsequent PCA analysis showed that these objects could be treated as essential extreme samples, which help to span calibration variations. It is worth mentioning that the influence of moisture content is much more complicated in NIR spectra and the exclusion of strong water-absorption bands centered at 7000 cm^{-1} and 5000 cm^{-1} solves the problem only partly.

As was mentioned in Section 6, proper separation of data into calibration and test sets could be of critical importance. It is clear that all counterfeit samples should be placed in the test set. The more varying fake tablets we have, the more reliable the classification results are. At the same time, the problem of misclassification of genuine drugs is also very important. As for batch G25, three samples are included in the calibration set to span model variation and two samples are put in the test set for model validation. The samples from four other genuine batches are placed into the test set as well. They were produced at various times and do not overlap with the calibration objects. This simulates a possible future situation when routine procedure is applied to new tablets of the original drug.

8. Conclusions

The NIR-based approach is a rapid technique for recognizing counterfeit drugs, both evident (e.g., placebo) and sophisticated. NIR equipment is becoming common in analytical laboratories and portable NIR instruments provide their application on-site. At the same time, the efficiency of the NIR approach is determined by the quality of data processing. The following main factors should be taken into account and often define the success of the overall procedure:

- (1) There is a great variety in the quality of drug counterfeiting. The most difficult to reveal are the “high-quality fakes” with proper composition. Methods based only on quantitative determination of API are insufficient. It is necessary to investigate a remedy as a complex system (e.g., involving API, excipients and technology).
- (2) The collection of a representative calibration set is a necessary step that has a great influence on pertinent model building and therefore on classification results. Variability in the production of genuine drugs should be fully investigated and accounted for in the model to avoid misclassification and the impact of human factors.
- (3) NIR spectra should be pre-processed before any chemometric analysis. We recommend methods such as SNV or MSC. Application of derivation should be done with care as this pre-processing method adds noise to the data. Variable selection is a much more complicated task. We recommend not to trust standard software solutions, but rather to conduct case-derived spectral analysis.
- (4) Among the chemometric methods, SIMCA is one of the most convenient for counterfeit detection. A proper choice of the acceptance area within the approach is of great importance. A trustworthy classification can be made only if proper type I error accounting has been performed.
- (5) Model construction requires representative sample distribution between calibration and test sets. This should be made with respect to variability in manufacturing the genuine drug and tested on both various counterfeit objects and new genuine batches.

All these issues depend on the specific medicine, so establishing the classification model cannot be carried out formally, as a “one press-button” procedure. However, when the classification model is built, revealing a fake version of a specific drug becomes a simple routine procedure.

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