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Application of NIR spectroscopy and chemometrics for revealing of the 'high quality fakes' among the medicines

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ABSTRACT

Counterfeit medicines of 'high quality' are the most difficult to detect as they have the same chemical composition as the genuine ones, but they are produced by underground manufacturers who violate technological regulations. Our approach is to consider a remedy as a whole object, taking into account the complex composition of APIs, excipients and manufacturing conditions. For rapid testing, the Near Infrared (NIR)-based approach is applied. It entails the acquisition of NIR spectra and processing of the collected data using a modern one-class classifier method called data driven soft independent modeling by class analogy (DD-SIMCA). We present an exemplary analysis of the suspected drugs, which have the same designation and a very similar chemical composition to the brand of a widely used medication used to treat allergies. We recognized the counterfeits using a model that had been previously developed and stored in a library for everyday monitoring in drugstores. We also describe the steps taken in development and validation of DD-SIMCA library models. In the case under consideration, the NIR-based analysis reveals 100% of counterfeits, and this result surpasses the results of the routine compedial tests. Additionally, we present a new instrument, VisCam, that is used in visual analysis of the primary and secondary packages. This instrument combines a tenfold web-camera with different light sources. It is shown that VisCam helps to reveal hidden violations in the primary and secondary packages.

1. Introduction

Counterfeiting poses a significant danger to public health and causes a huge economic and reputational damage to pharmaceutical companies. Due to European Medicines Agency (EMEA), "the phenomenon of falsified medicines is on the increase, with more and more medicines now being falsified" [1]. Fake medicines could be of different type: placebo, the medicines with lower concentration of active pharmaceutical ingredient (API), the drugs that do not contain the proper concentrations of excipients or contain wrong excipients, etc. Several years ago, World Health Organization (WHO) attempted to introduce a total term that should comprise all kinds of fakes. It was named "substandard/spurious/falsely-labeled/falsified/counterfeit (SSFFC)". Now, this phenomenon has obtained a simplified term that is 'substandard and falsified' (SF) medical product. According to the WHO definition, substandard is "authorized medical products that fail to meet either their quality standards or specifications, or both". Next to that, falsified means "medical products that deliberately/fraudulently misrepresent their identity, composition or source" [2].

Looking at counterfeiting from a recognition perspective, we can single out several types of fakes. They are (1) pills/tablets that can be recognized without any instruments, simply by a glance, or, at least, by an experienced glance; (2) medications that can be recognized due to special packages, holograms, a unique printing on the tablet surface, special shapes of pills and capsules; (3) fakes that can only be detected using chemical/physical testing of the drugs themselves.

Employment of a unique 2-dimension barcode and an anti-tampering device is a modern tendency used to protect the market from the SF medication. A law will be drawn up in the EU in the middle of 2019 year. It will cover the most of prescription medicines and certain non-prescription medicines [1]. In Russia, the project devoted to marking all secondary packages by the

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2-dimensional barcodes and tracing the movement of medication has been launched at the end of 2016 and is conducted by the Federal Service for Surveillance in Healthcare (Roszdravnadzor) [3]. This could definitely be an effective way to combat counterfeits and a good addition to special tokens, overt or covert, which are already used by various pharmaceutical companies. A complex approach to the analysis of a suspicious medicine is very important [4], a special workflow for the complex analysis is presented in [5]. However, the most reliable way to get evidence that a medicine is not a counterfeit is testing the drug itself. The compendia tests, or the tests used to accord the specification, are, ordinarily, time and labor consuming and sometimes ineffective. These tests are concerned with specific properties of a remedy, so they leave ample space for counterfeiting [6,7,8,9]. In general, the most difficult to reveal are 'the high quality fakes', which have a proper composition but are produced by underground manufactures with a violation of technological regulations.

Our general approach is to consider a remedy as a whole object, taking into account the complex composition of APIs, excipients, as well as manufacturing conditions, such as the degree of drying, homogeneity, etc. [10]. For rapid testing, the Near Infrared (NIR) measurements, accompanied by chemometric data processing, are applied [11–14]. NIR spectra carry information not only regarding chemical, but also physical phenomena. In some cases, NIR measurements are more sensitive in revealing falsified medication than routine laboratory tests [15,16].

This study is conducted within a state project aimed at the monitoring of the quality of the medicines and at anti-counterfeiting. A part of this project involves establishing and managing a special NIR spectrometers network to monitor the quality of tablets and capsules. A central laboratory receives samples directly from the manufacturers; develops and collects the corresponding authentication models in a special library, which is extended and updated on a permanent basis. Nine mobile laboratories conduct the routine NIR tests of medicines directly in drugstores and warehouses. This monitoring system began its work in 2011. The main principles of the data collection, the model development and validation have been described in paper [12].

In this paper, we present an exemplary analysis of the suspects seized from a drugstore and illegal warehouse. All these samples had the same designation as the brand of a widely used medication for the treatment of allergies. In the course of the analysis, we recognized the suspects using a library model that had previously been developed for everyday monitoring of that brand name. In some cases, the NIR-based analysis was more specific than laboratory tests in revealing counterfeits. We also discuss the procedure of the library model development, which involves a comparison of a target medicine with its analogues produced by the other manufacturers. This study demonstrates the importance of the model validation against the similar but still alien objects, because this procedure trains the model to recognize counterfeits of various grades, not only rough and evident, but also 'the high quality' ones.

All calculations were conducted using free available MATLAB GUI tool "DD-SIMCA" [17].

2. Materials and methods

All objects are intact uncoated tablets of Loratadine (international nonproprietary name), an antihistamine medicine, packed in Polyvinyl Chloride (PVC) blisters. The commercial names of the tablets are not disclosed here for reasons of confidentiality. Instead, we use the 'L' name, presented here in versions L1, L2, etc, depending on the drug manufacturers, whose names and locations are also not disclosed.

2.1. Objects used for the library models

Tablets produced by 6 different manufacturers are denoted as L1, L2, …, L6. All producers employ the same amount of the API (10 mg) but different composition of excipients (see Table 1). Each producer is represented by a set of batches ranging from four to ten. Each batch consists of 7–10 tablets. Products L4 and L5 are tablets with an identical composition, which are produced by the same manufacturer at two different plants. All the tablet samples were provided by the manufactures, thus, there was no doubt about their authenticity.

Several years ago, the six models for classes L1–L6 have been developed and stored in the library. Now, they are used to recognize new objects that are presented in the following subsection.

2.2. New genuine and suspicious objects of class L6

Several suspicious tablets designated as the L6 medicine were seized from a drugstore. This set is marked as S1 in Table 2. Later on, other L6 suspects were found in an illegal warehouse, where they were located at different places (marked as shelves in Table 2). They constitute sets, marked as S2-S6 in Table 2.

All the samples were subjected to NIR analysis, routine laboratory tests in accordance with medicine specification, and they also were examined visually. In this research, we also use new L6 tablets provided by the manufacturer (marked as Ln in Table 2). The L6 model has been developed several years ago and 'fresh' genuine samples are employed to confirm that the model is still actual.

In total, we have 47 tablets in 7 sets that are listed in Table 2.

2.3. NIR measurements

The measurements are carried out through a PVC blister in the diffuse reflection mode. Spectra acquisition without damaging of the primary packaging provides a possibility to return tablets into circulation in case they passed the test. PVC blister influences the results of measurements in two different ways. Firstly, full contact between the probe tip and a tablet packed in the blister cannot be guaranteed. This circumstance mainly influences the shape of the spectrum background, and may cause a decrease in the absorbance intensities [18]. Such distortions are eliminated by the spectrum pre-processing. Secondly, PVC film has its own strong absorption peaks around 5570–6000 cm^{-1}, and close to IR range, (4450–4000 cm^{-1}, combination bands range) (see Fig. 1, curve 3). These peaks

Table 1
Summary of dataset, genuine tablets.

Name	Marker*)	Batches	Training	Test	Excipients	Mass, mg
L1	◆	5	37	10	Lactose monohydrate, microcrystalline cellulose, calcium stearate, sodium carboxymethyl starch	200
L2	▲	10	70	30	Lactose monohydrate, microcrystalline cellulose, magnesium stearate, corn starch, croscarmellose	200
L3	■	6	50	10	Lactose monohydrate, microcrystalline cellulose, calcium stearate, sodium carboxymethyl starch	140
L4	◆	5	40	10	Lactose monohydrate, croscarmellose sodium, calcium stearate, potato starch	100
L5	●	4	30	10	lactose monohydrate, croscarmellose sodium, calcium stearate, potato starch	100
L6	△	9	60	30	Lactose monohydrate, magnesium stearate, corn starch	100

*) Used in Figs. 2 and 3a.

Table 2
Summary of dataset, new and suspicions tablets of class L6.

Name	Marker*)	Batch	Tablets	Comments
Ln	□	1	10	New genuine tablets of class L6
S1	■	2	4	Source: drugstore
S2	□	1	10	Source: illegal warehouse, shelf 2
S3	○	1	7	Source: illegal warehouse, shelf 3
S4	△	4	8	Source: illegal warehouse, shelf 4
S5	▲	3	3	Source: illegal warehouse, shelf 5. No secondary packages
S6	◇	2	5	Source: illegal warehouse, shelf 6. No secondary packages

*) Used in Fig. 3.

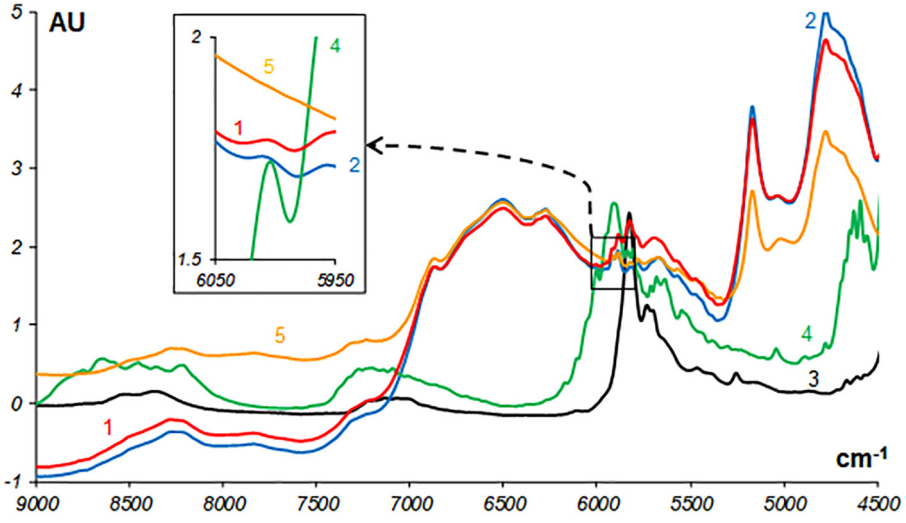

Fig. 1. Normalized spectra. (1, red) intact tablet through PVC; (2, blue) intact tablet without PVC; (3, black) PVC alone; (4, green) API; (5, yellow) lactose. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

partly mask the spectrum of the tablet itself. In other regions, PVC film is almost transparent to the NIR irradiation. It is worth to mention that usually a NIR spectrum of organic matter has wide overlapping peaks, so the tablet components are not presented by the isolated narrow bands, but are shown as broad peaks in several NIR ranges. Thus, the tablet measurement through the blister is reasonable.

A Loratadine tablet contains API in a rather low concentration, from 5 to 10 w/w%. The tablets produced by L6 have 10 w/w% of API and 70 w/w% of lactose. Therefore, the main spectrum profile is the spectrum of lactose. However, it is possible to single out the API absorption bands, for example, in the region round 6009 cm^{-1} (see insert in Fig. 1).

Measuring the tablet through the blister, we deal with a rather complex system, the entire spectrum of which is a combination of the API spectrum, the spectra of excipients, and the PVC spectrum (see Fig. 1, curve 1). As was mentioned above, we consider a remedy as an entire object, and analyze the complex spectra, which carry information regarding various tablet constituents.

NIR spectra are acquired in the interval 4000–12,500 cm^{-1} with a resolution of 8 cm^{-1} using the FT-NIR spectrometer (MPA by Bruker Optics) equipped with a handheld fiber-optic probe (FP). Each time triplicate readings are made to control reproducibility. Replicas are averaged for data analysis. The informative range 4150–9000 cm^{-1} was chosen for data analysis. Spectra are preprocessed by the standard normal variate (SNV) procedure [19,20].

2.4. Visualization instrument

VisCam is used for a visual analysis of the primary and secondary packages. This device was specially designed by the ArtPhotonics [21] company at the request of our laboratory. VisCam is a rather simple but helpful instrument, which combines a tenfold web-camera with different light sources: ordinary white light, and several narrow band sources with wavelengths at 256 nm, 540 nm and 740 nm. The device presents images on the connected computer and can save them in jpeg format.

2.5. Authentication procedure and chemometric analysis

To reveal an SF medicine we should answer the question whether a sample is, in fact, what it is declared to be. Thus, we should solve an authentication problem [22]. A special class of pattern recognition methods, called one-class classifiers (OCC), is used for this purpose. The distinct features of this approach are as follows. For each class of interest, referred to as a target class, a separate OCC model, a classifier, is built. The target class is defined by the representative set of genuine objects. These samples are collected in the training and test sets and they present possible variations inside the target class. Both training and test sets are used to develop a model and for estimation of model sensitivity, which is the share of correctly identified samples of the target class. It is desirable to apply an additional validation set, which consists of samples from extraneous classes. These samples are used to assess specificity, which is the portion of objects of an alternative class that are correctly identified as aliens with respect to the target class. Theoretically, alien objects may be as close to a target class as possible. Therefore, the choice of alien objects is important for assessing the model specificity.

The DD-SIMCA method [23] is used to develop a decision rule (threshold), which delineates the target class from all other samples. The method also provides a possibility to theoretically

Table 3
Summary of the basic features of the models.

Class	Number of PCs	Optimal α-value	Sensitivity (%)	β-value correspondent to the opt. α-value	Specificity (%)
L1	2	0.01	98	~0	100
L2	4	0.01	98	0.001 (L3)	100
L3	4	0.01	98	0.005 (L2)	100
L4	3	0.05	92	0.012 (L5)	100
L5	2	0.05	98	0.007 (L4) and 0.05 (L6)	100
L6	3	0.05	95	0.03 (L5)	100

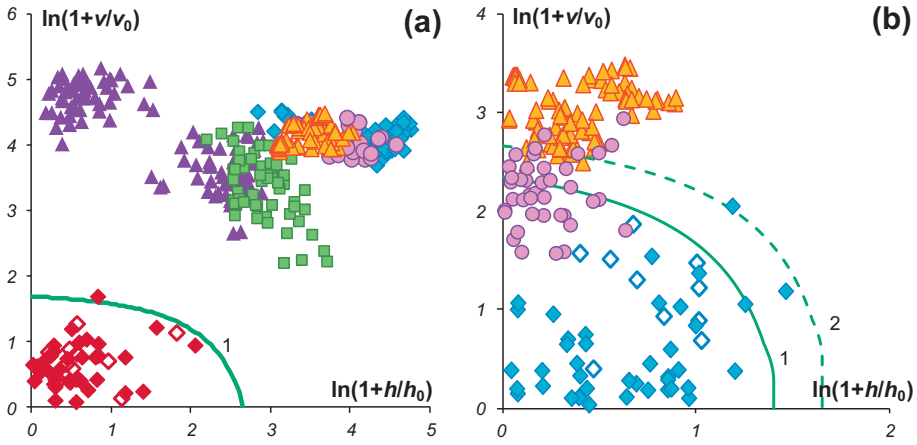

Fig. 2. DD-SIMCA results, the final L1 (a) and the interim L4 (b) models with 2 PCs. Markers are explained in Table 1. For a target class, closed markers present training objects and corresponding open markers present test objects. (a) Curve 1 is a threshold for α = 0.01. (b) Two thresholds: α = 0.05 (solid curve 1) and α = 0.01 (dotted curve 2).

calculate the model characteristics, such as the type I error, α, and the type II error, β [23,24]. The training data are collected in the $(I \times J)$ matrix **X**, where I is the number of samples and J is the number of variables (wavelengths). At the first step, DD-SIMCA applies the principal component analysis (PCA) to the **X** matrix. The number of principal components (PCs), A, determines the model complexity and this parameter essentially influences the quality of classification. The greater the A value, the greater part of the **X** variation is explained by the PCA decomposition. At the same time, including superfluous components in PCA may result in a model that accounts not only for the main class features, but also for irrelevant noise. Therefore, the parsimonious principle is often applied to choose the model complexity. At the second step, DD-SIMCA calculates two distances for each object from the training set. They are the orthogonal (Euclidean) distance, and the score (Mahalanobis) distance. DD-SIMCA finds data-driven estimates of parameters that characterize the distributions of these distances. It also establishes a threshold for the acceptance area in accordance to the given value of the type I error, α. In case an alternative class is available, DD-SIMCA provides the possibility to calculate the type II β error with respect to this class.

In the result, we obtain a classifier that is characterized by the model complexity, A, and the established threshold for the given α-value. Agreement between the given α-value and sensitivity, which is calculated post factum, is one of the important characteristic of the model quality.

3. Results and discussion

3.1. Development of the models

In this section, we explain the principles of the library model development using the cases of L1-L6 products. For each manufacturer (see Table 1) we develop an individual OCC model using the DD-SIMCA method. A genuine medicine of a certain manufacturer defines the target class. A representative sample set, which takes into account both within batch and between batches variations, constitutes the training set. A test set consists of the genuine samples from the same manufacturer selected from other batches. Both the training and test sets are used to develop a model. Ideally, one more (validation) set should be involved in the modeling. This set includes the tablets, which are substandard or falsified with respect to the target class. However, it is often difficult to find falsified tablets for each target class. In paper [12], we suggested using the tablets of the same type, but produced by other manufactures in validation. These samples simulate the 'high quality fakes' from different sources and of various grades.

The models obtained for all six manufacturers are summarized in Table 3. The optimal value of α was chosen in a way to reach 100% specificity. The β value was calculated in accordance to the optimal α for each alternative class separately. Namely, in the case when L1 is the target, classes L2-L6 are used as the alternatives. In Table 3, the closest alien class is indicated in brackets after the β value. Some alternative classes are reliably separated from the target class, but other classes are located close to the threshold. For the models' validation, we focus on those alternative classes, which cause the difficulties in recognition.

For illustration of various difficulties met in the course of development of the models, we present three of six models in details.

3.2. The L1 model

In this case, the target class is easily separated from all other classes. Thirty-seven samples from four batches are used as the training set and ten samples from one batch are used as the test set. The model with 2 PCs reliably describes the target class at α =0.01 with a sensitivity of about 98%. All samples from the alternative classes are located far from the threshold. The model specificity equals 100%. Using the parsimonious principle we

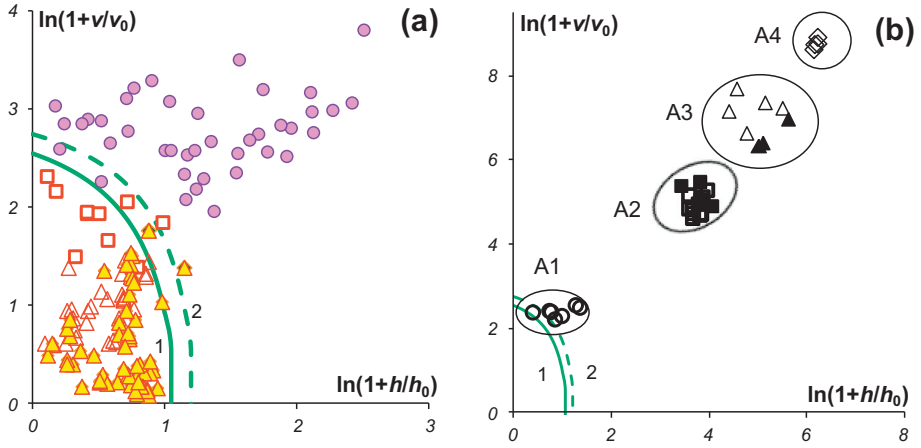

Fig. 3. DD-SIMCA results, the L6 model, 3PCs, two thresholds: $\alpha = 0.05$ (solid curve 1) and $\alpha = 0.01$ (dotted curve 2). (a) Target class L6 (yellow triangles), class Ln (red squares), extraneous class L5 (dots); (b) Recognition of the suspicious samples. Markers are explained in Table 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Analysis of suspicious samples.

Group	Set	Number of samples	β-value
A1	S3	7	0.083
A2	S1 + S2	14	~0
A3	S4 + S5	11	~0
A4	S6	5	~0

consider that the model with 2 PCs is an admissible solution (Fig. 2a). The L1 model is the simplest case we have encountered in the study of Loratadines.

3.3. The L4 model

The L4 and L5 tablets have the same composition; they are produced by one manufacturer but at different sites. The manufacturer has registered these two types of tablets as different products. The similarity in composition causes difficulties in modeling of individual classes.

Forty tablets from four batches are collected in the L4 training set. Ten tablets from another batch, not used in the training, are employed for the model testing.

The model with two PCs and $\alpha = 0.05$ fairly classifies the L4 samples with two extreme objects. This corresponds to the selected value of the type I error, because 5% of 40 training samples exactly equal 2. For $\alpha = 0.01$, only one training object is classified as an extreme. All the test objects are recognized as the target class members. Interrupting the model development at this point (the rigorous approach [25]), we can conclude that the obtained model can reliably classify objects from class L4. At the same time, in case we want to avoid not only false negative decisions (reject genuine sample), but (even more important) to avoid false positive decisions (accept counterfeit sample), we should validate the model against alien objects (the compliant approach [25]). For this purpose, we use all other classes as a collection of extraneous objects. The model with 2 PCs and $\alpha = 0.01$, accepts 34 out of 40 tablets from class L5 as the members of the target class L4 (Fig. 2b). This is not a surprise because the L4 and L5 samples have the same composition. Moreover, 3 samples from class L6 are also wrongly attributed to the target recognized as the target class objects. Samples from the remaining classes are located far away from the L4 acceptance area. With a purpose to improve the recognition, we have developed a new model with 3 PCs. For $\alpha = 0.01$ all the L4 samples (both the training and test sets) are reliably classified as the target samples. All the L6 objects are now located far from the acceptance area. Only two of forty class L5 samples are wrongly attributed to the target class. To avoid this misclassification, we can decrease the acceptance area, by choosing α=0.05. In this case, no false positive decisions are obtained, but two samples from the test set are wrongly classified as aliens. This example demonstrates a possibility of the risk management in model development. Decreasing the acceptance area, i.e. increasing α value, we increase a chance of false negative decision, but, at the same time, decrease a chance to accept falsified tablets as the genuine ones.

3.4. The L6 model

This model deserves special attention. Firstly, the L5 samples are hardly separated from the L6 class. The second reason is that just this model is used for the analysis of the suspicious samples (S1-S6) which have been labeled as the L6 tablets.

Sixty L6 tablets from six different batches are collected in the training set. Thirty L6 tablets from the three other batches comprise the test set. The model with 2 PCs, reliably recognizes all the samples from the training and test set, but it demonstrates low specificity, because the samples from the alternative class L5 are located close to the threshold. For $\alpha = 0.01$ nine of the forty L5 samples are misclassified as the target objects. For $\alpha = 0.05$, three L5 samples are wrongly accepted as target objects. The model with 3 PCs and $\alpha = 0.05$ provides a sensitivity of 98% and specificity of 100% (see Fig. 3), and it is used as the ultimate model for L6 class.

4. New and suspicious samples

4.1. NIR based analysis

For the NIR based analysis we apply the library model for L6 (see Table 3). Due to our previous study, this is the most reliable model, which provides a stable recognition of alien objects, even those which are very similar to the L6 samples. However, the L6 model has been developed several years ago, so it should be validated against new genuine tablets, Ln (see Table 2). The validation shows that 2 out of 10 Ln samples are misclassified as aliens. However, these extremes are located very close to the threshold (the red open squares near curve 1 in Fig. 3a). Since the L6 model employs α=0.05, the value of 2 hits the binomial range for the tolerance of 0.95 [23]. Extending the acceptance areas for $\alpha = 0.01$

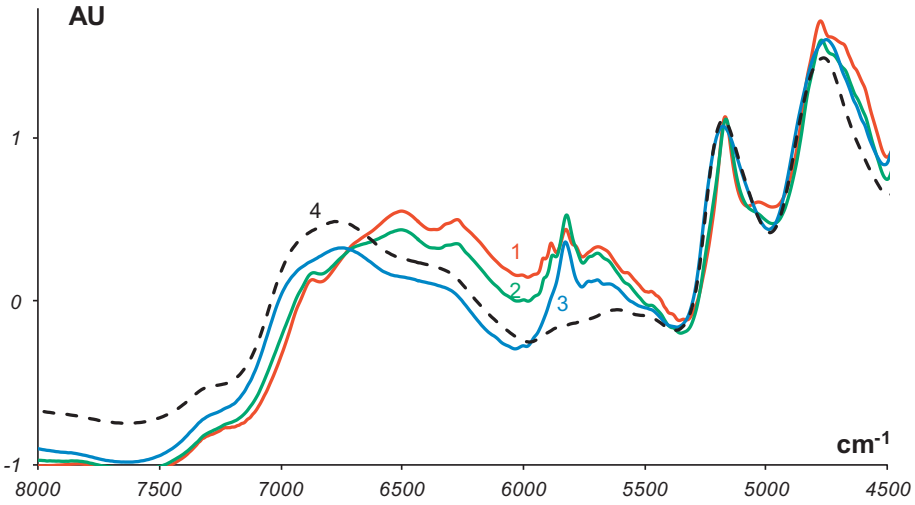

Fig. 4. NIR spectra after SNV correction. (1, red) average genuine spectrum for class L6; (2, green) average spectrum of group A2; (3, blue) average spectrum of group A4; (4, dotted) spectrum of microcrystalline cellulose. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

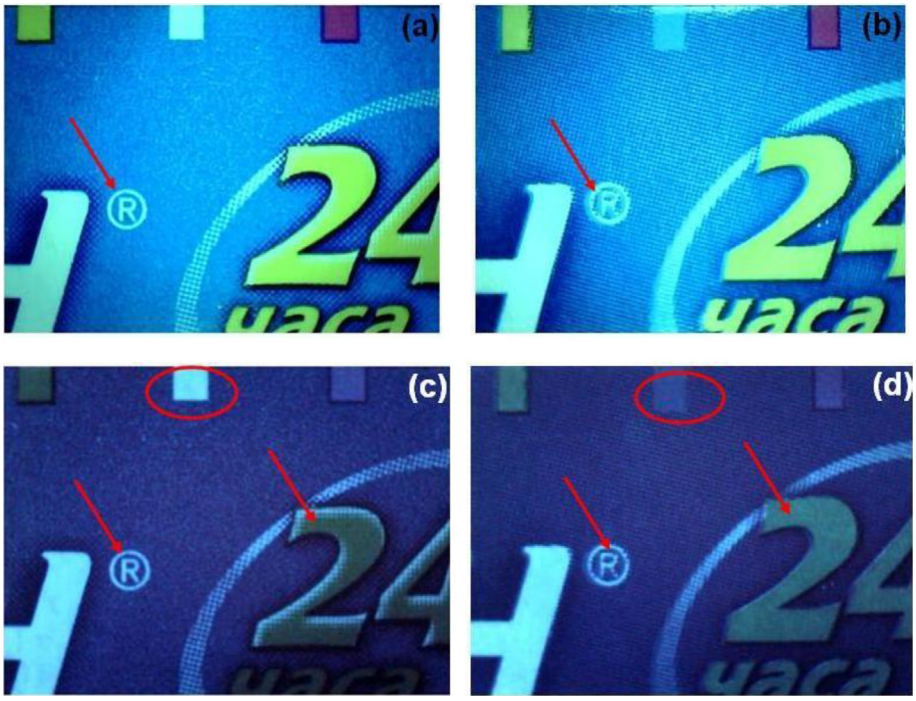

Fig. 5. Tenfold images of secondary packages. Differences are marked in red. a) Genuine box illuminated by white light; b) Falsified box illuminated by white light; c) Genuine box illuminated by UV light; d) Falsified box illuminated by UV light. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(curve 2 in Fig. 3a) we can decrease the risk of wrong rejection of the target objects. Really, in this case we observe that only one sample is wrongly rejected and the binomial distribution confirms that this is an admissible result. Therefore, we can conclude that the L6 model is still actual, although it gives somewhat worse results than was initially expected. We can suppose that this is due to some anticipated changes in the manufacturing process and, in the future, this model should be updated.

Application of the L6 model to the suspicious samples is presented in Fig. 3b. It can be seen that we are dealing with the suspicious samples of various grades. The DD-SIMCA method provides a possibility to reveal groups inside the alien objects and to calculate the β value for each alien group separately [24]. The results are collected in Table 4.

DD-SIMCA determines tablets from set S3 (open dots in Fig. 3b) as a specific group, further referred to as group A1. It is located very close to the threshold. The NIR spectra of the S3 samples and genuine samples are difficult to distinguish visually. For α=0.05, all tablets from group A1 are classified as aliens and β-value equals 0.083. In case we extend the acceptance area, choosing α=0.01, one suspicious tablet is recognized as a member of the target class L6 and the corresponding β-value increases to 0.21. It is interesting that the S3 samples have the same batch number as suspicious samples from the drugstore, referred to as the S1 set.

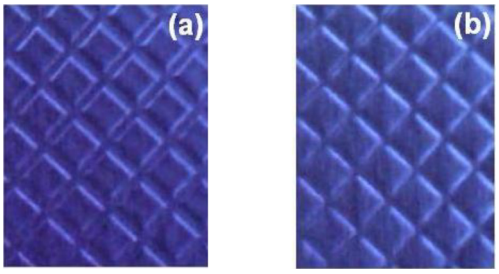

Fig. 6. Visual comparison of blister backside. a) Genuine; b) SF.

The samples from the drugstore, set S1, are marked as the black squares, and they are assigned to group A2 by DD-SIMCA. The A2 group also includes the S2 tablets seized from the warehouse. All groups except A1 are located rather far from the acceptance area; and they do not cause any difficulties for the NIR analysis. The values of the type II error for these groups are close to zero.

Samples from the S4 and S5 sets comprise group A3. Although group A2 is located far from the threshold, its spectra are close to the genuine ones (see Fig. 4).

The S6 samples form group A4, and their NIR spectra (the blue curve 3 in Fig. 4), notably differ from the genuine ones (the red curve 1). Analyzing the spectra, we can assume that in these tablets lactose monohydrate (the main excipient) has been substituted with microcrystalline cellulose (curve 4 in Fig. 4).

The results of NIR analysis allow us to conclude that all tablets in sets S1-S5 are the SF samples.

4.2. Routine laboratory tests

The HPLC tests have confirmed that all the suspicious samples do contain Loratadine as an API. The S4 and S6 samples fully comply with the L6 specification. It is worth to emphasize, that the specification protocols make no provision for the analysis of excipients. This is the reason why the samples, like those from set S6, have passed the specification tests, in spite of the fact that their spectral profiles differ from the genuine L6 spectrum.

For other suspicious samples, the main violated indicators are the average mass, and the uniformity of dosing.

Thus, paradoxically, the routine laboratory tests could only detect the SF samples in groups A1 and A2, which are the most similar to the target class L6 (see Fig. 3b) .

The possible lack of conventional tests' sensitivity and/or specificity is also underlined and reported in references [6,7,26].

4.3. Visual inspection

The VisCam visual inspection of the PVC blisters as well as the secondary packages confirms an illegal nature of the suspicious samples. For groups A1, A2, and A3 the secondary packages, carton boxes, manifest evident differences in the printing quality. The differences can be found in the enlarged images illuminated by white light (Fig. 5a and b). Even more evident are the differences that can be seen under the UV illumination (Fig. 5c and d).

The group A4 tablets have been seized without the secondary packages. In this case, the inspection of the blister backside can help to reveal differences. The examination of the blister folio using the UV illumination (see Fig. 6) shows the inversed patterns – upwards and downwards convexes. This fact shows that the genuine and the SF tablets have been packed using different equipment.

The usefulness of a similar handheld instrument have been previously announce by the US Food and Drug Administration (FDA) Forensic Chemistry Center. A special Counterfeit Detection Device 3 (CD-3) was developed and tested [27]. However, there is no serial production of these tools.

Table 5
Summary of dataset, new and suspicions tablets of class L6.

Name	Marker	NIR classification	Routine tests	Visual analysis
S1	■	Rejected	Failed	Differences in secondary packages
S2	□	Rejected	Failed	Differences in secondary packages
S3	○	Rejected*)	Failed	Differences in secondary packages
S4	△	Rejected	Passed	Differences in secondary packages
S5	▲	Rejected	Failed	Differences in blister backside
S6	◇	Rejected	Passed	Differences in blister backside

*) Located close to the acceptance area.

We can conclude that application of a carefully developed model, which has been validated against very similar, but still alien objects, helps us to recognize that all the seized tablets are not the members of the target L6 class. It can be supposed that the group A1 tablets have been produced by a genuine manufacturer, and afterward packed illegally. We can only guess that the producer committed violations in the technological process and this batch was rejected as defective. The same conclusion can be reached with respect to groups A2 and A3. However, in these cases the standards' violations are more significant. It can be supposed that the tablets from groups A2 and A3 have a common origin. Group A4 manifests an evident dissimilarity in composition of excipients and therefore its origin differs from the other SF samples. The summary of the suspected tablets analysis is given in Table 5.

5. Conclusions

1. NIR-based analysis is an effective method to monitor medicine quality, as it analyzes a drug as a whole, taking into account not only the chemical composition, but also the physical properties of the sample.
2. Compliance of a drug to its specification or to the compendial tests can be insufficient for a conclusion that the medicine has a genuine origin. It is often when the specification does not contain the compulsory tests for the composition of excipients.
3. Barcodes, overt, and covert printed signs help to identify counterfeit medicines, but leave ample space for falsification, for example, by repeatedly applied packages.
4. The SF medicines are a complex and multifaceted problem, and there is no single approach and solution on how to combat counterfeiting. Application of various methods helps to confirm the findings of different tests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.forc.2018.02.004.

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