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Detection of Lipitor® counterfeits: A comparison of NIR and Raman spectroscopy in combination with chemometrics

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ABSTRACT

Research has been carried on the feasibility of near infrared (NIR) and Raman spectroscopy as rapid screening methods to discriminate between genuine and counterfeits of the cholesterol-lowering medicine Lipitor®. Classification, based on partial least squares discriminant analysis (PLS-DA) models, appears to be successful for both spectroscopic techniques, irrespective of whether atorvastatine or lovastatine has been used as the active pharmaceutical ingredient (API). The discriminative power of the NIR model, in particular, largely relies on the spectral differences of the tablet matrix. This is due to the relative large sample volume that is probed with NIR and the strong spectroscopic activity of the excipients. PLS-DA models based on NIR or Raman spectra can also be applied to distinguish between atorvastatine and lovastatine as the API used in the counterfeits tested in this study. A disadvantage of Raman microscopy for this type of analysis is that it is primarily a surface technique. As a consequence spectra of the coating and the tablet core might differ. Besides, spectra may change with the position of the laser in case the sample is inhomogeneous. However, the robustness of the PLS-DA models turned out to be sufficiently large to allow a reliable discrimination.

Principal component analysis (PCA) of the spectra revealed that the conditions, at which tablets have been stored, affect the NIR data. This effect is attributed to the adsorption of water from the atmosphere after unpacking from the blister. It implies that storage conditions should be taken into account when the NIR technique is used for discriminating purposes. However, in this study both models based on NIR spectra and Raman data enabled reliable discrimination between genuine and counterfeited Lipitor® tablets, regardless of their storage conditions.

1. Introduction

In recent years, counterfeit medicines are increasingly threatening public health especially since it has become more and more difficult to visually distinguish counterfeits from genuine products [1,2]. As these illegal medicines are not produced under good manufacturing practice (GMP) no guarantee concerning the quality of these products can be given. Besides, it hampers the work of pharmacists and nursing staff that have to provide reliable medical products. Finally, its production is illegal and for all these reasons, there is a growing need for fast screening methods to unambiguously determine the authenticity of medicines, preferably on the location where these are found, e.g. at the customs.

Two techniques that have been proposed to be useful for rapid counterfeit detection are Near infrared (NIR) and Raman spectroscopy [3]. NIR is a fast and non-destructive method and hence economically attractive. Several applications of NIR for drug quality control have been described in literature [4–7]. However, it turned out that NIR spectra are not always highly substance specific. For that reason, Raman spectroscopy has been studied as an alternative [8–13]. This technique is not only useful in the structural elucidation of unknowns [14], but also allows unambiguous identification of analytes. Furthermore, Raman spectra provide information into the low-wavenumber region, which is very useful for the identification and characterization of inorganic compounds, widely used as excipients in pharmaceutical tablets. Emerging techniques like spatially offset Raman spectroscopy (SORS) even allow for bulk and deep subsurface Raman spectroscopy of coated tablets and capsules [15].

A relatively new drug for which counterfeits have been traced is the cholesterol-lowering medicine Lipitor®. Authentic Lipitor® tablets contain atorvastatine as the active pharmaceutical ingredient (API) in a well-defined matrix. In contrast, falsifications usually exhibit various matrices, while the active component is often different, has an incorrect concentration or even is absent.

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Occasionally, lovastatine has been detected as the API in counterfeit Lipitor®. Currently, Lipitor® is amongst the 10 most often counterfeited medicines and this has initiated a growing demand for rapid screening techniques to discriminate counterfeits from genuine tablets. The potentials of NIR and Raman spectroscopy for such application have already been demonstrated and for that reason, it is a logical step to perform a feasibility study of both techniques to detect Lipitor® counterfeits. For this purpose, partial least squares discriminant analysis (PLS-DA) models have been constructed for both NIR and Raman spectra to distinguish between counterfeits and the genuine product. PLS-DA has been preferred over principal component analysis (PCA), since it focuses on the spectral variation that is relevant for the discrimination between the classes [3]. Besides, the corresponding regression vector in general contains spectral information on the chemical differences between the defined classes. With PCA the spectral variations are not necessarily related to the different classes. The relevant differences can easily be distributed over several principal components, thus frustrating the spectral interpretation. In this paper, the results obtained for both spectroscopic techniques are compared. The influence of the storage conditions of the tablets on the NIR [16] and Raman spectra have been included in this study, as counterfeits are often received unpacked and with unknown storage history. For this purpose, PCA was applied to the spectra of tablets that were stored under various conditions. Additionally, the value of Raman spectroscopy for the identification of atorvastatine is explored.

2. Experimental

2.1. Samples

All compounds studied are listed in Table 1. Each batch consisted of five tablets. Batches 1–9 of Lipitor® tablets in 10-, 20- and 40-mg strength in closed blisters were obtained from Pfizer (The Netherlands). These samples have been used as genuine reference tablets. Batches 10 and 11 of 20 mg were received from the United Kingdom (Medicines and Healthcare products Regulatory Agency, London) and batches 12–14 (10, 20 and 40 mg) from Australia (Therapeutic Goods Agency, Canberra). These batches were analyzed since the packages of the suspected samples in this study suggest that they originate from these two countries. Batches 15 and 16, both containing five potentially counterfeited 20 mg Lipitor® tablets, were received from the Dutch Health Care Inspectorate (IGZ).

The pure compounds atorvastatine–calcium-trihydrate (Pfizer, The Netherlands) and lovastatine (Merck-Sharpe-Dome, The Netherlands) have been used as API references. The molecular structures of these compounds are depicted in Fig. 1.

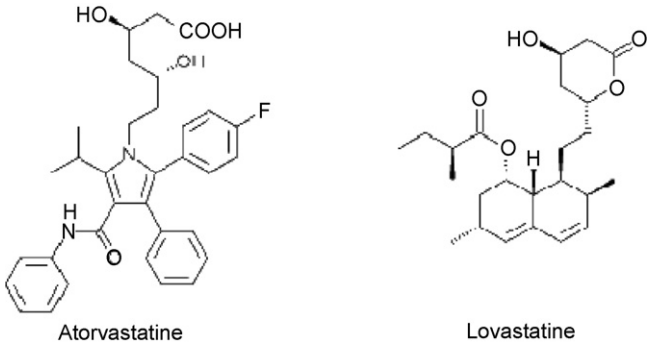

Fig. 1. The molecular structure of atorvastatine (left) and lovastatine (right).

2.2. Near infrared spectroscopy

NIR spectra were recorded on a Spectrum Identicheck FT-NIR system (PerkinElmer, Beaconsfield, Bucks, England) equipped with a PbS detector and an identicheck reflectance accessory (ICRA). Measurements were carried out in the diffuse reflection mode with an optical resolution of 16 cm^{-1} over the spectral range of 12,000-3000 cm^{-1} and 64 scans were co-added for each spectrum. Spectralon was used as the reflectance reference.

2.3. Raman spectroscopy

Raman measurements were performed on a HoloLab Raman spectrometer equipped with a microscope, a 785 nm laser and a Peltier cooled CCD detector (Kaiser Optical Systems Inc., Lyon, France). Spectra were recorded with a 10× objective in the spectral range 4000–200 cm^{-1} with a data point resolution of approximately 2 cm^{-1} resolution. The exposure time was 10 s and 10 scans were accumulated for each spectrum using a laser power at the sample of 10 mW.

2.4. Measurements

All samples were measured as received. NIR analysis was carried out on the front side and the backside of the intact tablets, while Raman scanning was performed on the outside and the inside of the tablet after cutting. From each batch, Raman spectra were recorded from three tablets and NIR from five tablets, all immediately after

Table 1
List of reference and counterfeit Lipitor samples, including origin, API, dose (in mg/tablet) and the number of tablets analyzed per batch

Batch	Description	Dose (mg)	Analyzed tablets (NIR)	Analyzed tablets (Raman)	API	Origin
1	Reference	10	5	3	Atorvastatine	NL
2	Reference	10	5	3	Atorvastatine	NL
3	Reference	10	5	3	Atorvastatine	NL
4	Reference	20	5	3	Atorvastatine	NL
5	Reference	20	5	3	Atorvastatine	NL
6	Reference	20	5	3	Atorvastatine	NL
7	Reference	40	5	3	Atorvastatine	NL
8	Reference	40	5	3	Atorvastatine	NL
9	Reference	40	5	3	Atorvastatine	NL
10	Reference	20	5	3	Atorvastatine	UK
11	Reference	20	5	3	Atorvastatine	UK
12	Reference	10	5	3	Atorvastatine	Australia
13	Reference	20	5	3	Atorvastatine	Australia
14	Reference	40	5	3	Atorvastatine	Australia
15	Counterfeit	17	5	3	Atorvastatine	IGZ[a]
16	Counterfeit	18	5	3	Lovastatine	IGZ[a]

[a] Dutch Health Care Inspectorate.

removal from the blister. Since, the 10 mg tablets were too small to analyze directly with NIR, a tablet holder with a 5-mm hole was used for these samples. The 40-mg tablets were measured without a tablet holder. The 20-mg tablets were measured with and without a tablet holder in order to evaluate the effect of the tablet holder.

In view of the relatively small sample area that is probed with Raman microscopy, additional line scan measurements were carried out to determine the effect of the inhomogeneity of the tablets on the Raman spectra. Line scans of 10 points were taken from the inside of three different tablets, one reference and two counterfeits containing atorvastatine and lovastatine, respectively.

The powdered reference materials atorvastatine and lovastatine were measured with NIR as delivered in a 4-ml glass vial with screw cap (Alltech/Applied Science Group, Hoogeveen, The Netherlands). The Raman spectra of these materials were recorded directly from a powdered layer on a microscope slide.

In order to investigate the influence of the storage conditions of the tablets on the NIR spectra of genuine Lipitor® tablets (batches 1–9), three tablets were taken from each batch, i.e. 9 tablets of 40 mg, 9 of 20 mg and 9 of 10 mg. After NIR measurement, one tablet from each batch was stored for 24 h at ambient conditions, one in a stove at 40 °C and one in a desiccator over silica gel. The 27 tablets, treated this way, were analyzed with NIR in the same way as the 'freshly' unpacked tablets, i.e. at two sides with the sample holder (10 and 20 mg tablets) and without (20 and 40 mg tablets). The effect of the storage conditions on the Raman spectra was studied in parallel. For this study, three tablets from batches 5 and 13 have been analyzed after storage for 24 h at ambient conditions in the same way as the freshly unpacked tablets.

For reference purposes, the API concentration in the genuine and counterfeit medicines was determined for all batches by liquid-chromatography combined with mass spectrometric detection (LC–MS). Details on the corresponding sample pre-treatment and measurement protocol can be found elsewhere [17].

2.5. Chemometrics

PCA was applied to the 30 Raman spectra, acquired from line scanning three tablets, in order to determine the effect of inhomogeneity. PCA was also applied to study the effect of the storage conditions on the NIR and Raman spectra. Models were obtained from the spectra recorded after 24 h of storage at different conditions. Next, these models were applied to the spectra obtained directly after unpacking. PLS-DA models were constructed from all NIR and Raman spectra, including the ones obtained from tablets stored at different conditions for 24 h, to distinguish counterfeit from genuine tablets.

All data processing and modeling was performed in MatLab 7.0 (The Mathworks Inc.) using the PLS Toolbox 3.5 (Eigenvector Research Inc.). All models were built after pre-processing the data with multiplicative signal correction (MSC) followed by mean centering (MC). A baseline correction by subtracting a polynomial fit (2nd order) was applied to the Raman spectra. To allow 'spectral' interpretation of the model loadings and regression vectors, a derivative was not applied. Modeling of the NIR spectra has been applied on the spectral range 10000-4000 cm^{-1}, while for the Raman spectra the region 3150–250 cm^{-1} has been used.

3. Results and discussion

3.1. The effect of inhomogeneity

The results of PCA of the 30 Raman spectra obtained from the lines scans of the core of three different tablets (one reference and two different counterfeits; batches 5, 15 and 16, respectively) are illustrated by the score plot of PC1 versus PC2, presented in Fig. 2. PC1 and PC2 explain almost 83% of the variance. As appears, the three different tablets are clearly separated in clusters. Besides, the spectra of the counterfeit tablets with lovastatine (▽) and atorvastatine (+) show more variation than those of the reference tablet (●). It indicates that the variations in the Raman spectra as result of inhomogeneity will probably not obstruct discrimination between counterfeits and references. Furthermore, the score on the 2nd PC seems to be related to the differences between the lovastatine and atorvastatine containing tablets. This is confirmed by several peaks present in the corresponding loading depicted in Fig. 3. Comparison with the Raman spectra of both API's in Fig. 4 reveals that the peaks at 3054, 1600, 1521 cm^{-1} are characteristic for atorvastatine and the peaks at 3008 and 1645 cm^{-1} for lovastatine. In contrast, the band at 1083 cm^{-1} seems not to be representative for the difference between the Raman spectrum of lovastatine and atorvastatine. It illustrates one of the common problems with straightforward interpretation of PCA loadings and emphasizes that this should be done with extreme care.

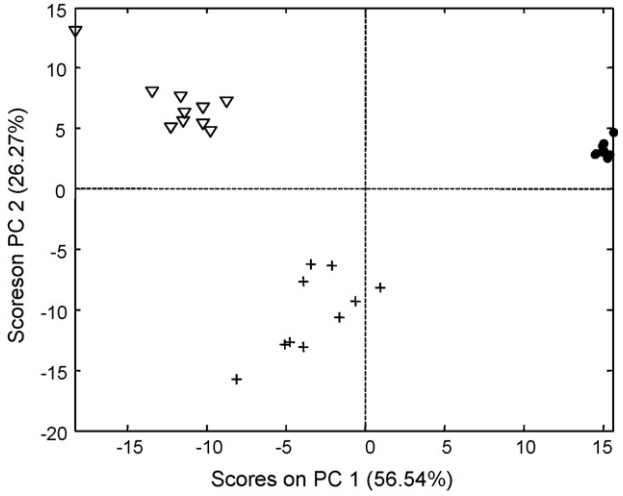

Fig. 2. Score plot of PC2 vs. PC1 of the PCA of the Raman spectra (line-scan) of batch 15 counterfeit containing atorvastatine (▽), batch 16 counterfeit containing lovastatine (+) and batch 5 a genuine Lipitor® reference tablet (●).

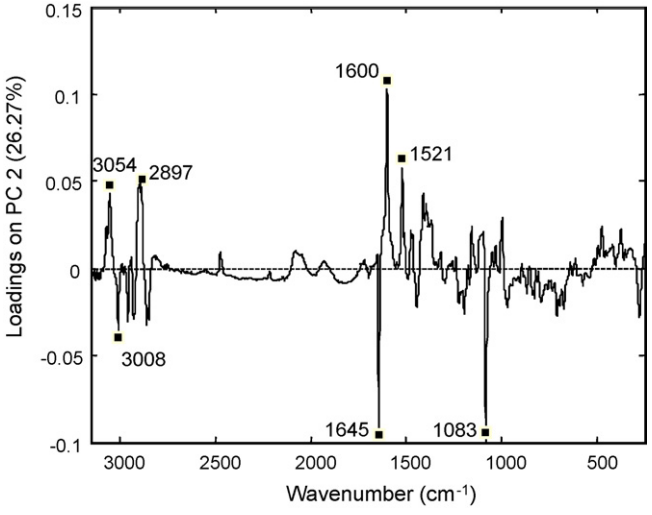

Fig. 3. The 2nd principal component (PC) of the PCA model applied to the Raman spectra of counterfeit containing lovastatine, counterfeit containing atorvastatine and genuine Lipitor® batch 5, 15, and 16, respectively.

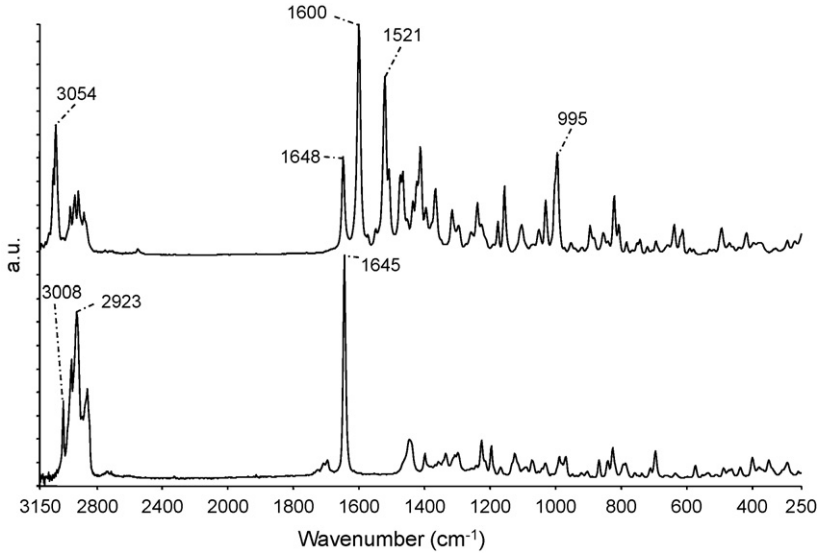

Fig. 4. Raman spectra of atorvastatine–calcium trihydrate (upper trace) and lovastatine (lower trace) in the range 3150–250 cm^{-1}.

3.2. The effect of storage conditions

The effect of different storage conditions on the NIR spectra of genuine Lipitor® tablets (10–40 mg) is shown in Figs. 5 and 6. First, PCA was applied to the spectra of the tablets that were stored under different conditions after unpacking from the blister. The largest variation captured by the 1st principal component (PC) described 74% of the variance and did not reveal any trend related to the storage conditions. Fig. 5 depicts the 2nd PC (17%) of this PCA model. The peaks at 7068 and 5200 cm^{-1} can be assigned to changes in OH vibrations, induced by the intermolecular interactions between tablet constituents and atmosphere substances, most likely water vapor. Adding the spectra of the 'freshly' unpacked tablets to this model resulted in the score plot shown in Fig. 6. The scores on PC2 of the spectra recorded from tablets stored at ambient conditions (□) in a stove (▽) and in a desiccator (+) are shown on the left side (spectra 1–72). The scores of the spectra, recorded immediately after opening the blisters (●), are plotted on the right side (spectra 73–232). From this plot, it is clear that the effect of the storage conditions on the tablets increases from storage in a desiccator (+), to stove (▽) and atmospheric conditions (□), although the scores for stove and desiccator partly overlap. As such, it confirms the hypothesis that the bands at 7068 and 5200 cm^{-1} are the result of water adsorption (Fig. 5). Based on these results, it can be concluded that the spectra, recorded from freshly unpacked tablets, mostly resemble the spectra of tablets stored for 24 h in a stove at 40 °C. This not only confirms the effect of water adsorption, but, more important, demonstrates that there is a significant influence of the storage conditions on the appearance of the NIR spectra. It follows that this parameter might affect classification results in case a comparison is made between a genuine and a suspected counterfeit sample.

To determine the effect of storage conditions on the Raman spectra, a slightly different approach was followed. This relies on the fact that, in contrast to NIR, Raman spectroscopy is merely a surface technique. As a consequence, the spectra taken from the outside of the tablets clearly differ from the ones of the inside. For that reason, two models were developed in parallel, one for the Raman spectra from the coating and one for the spectra from the tablet core. The

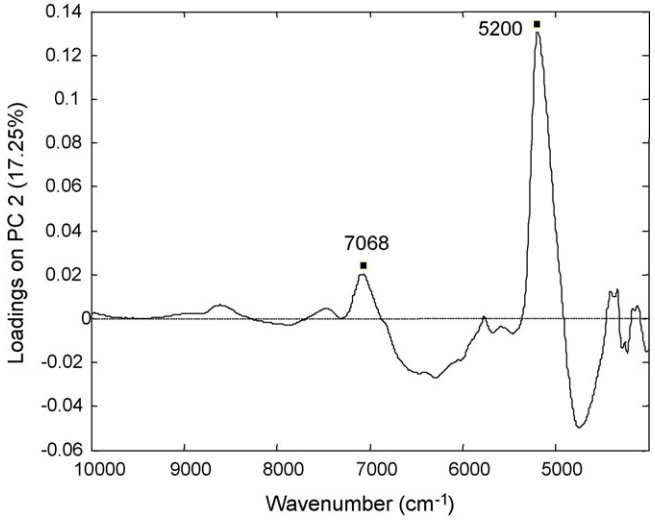

Fig. 5. The 2nd principal component (PC) of the PCA model applied to the NIR spectra of the tablets after 24 h at different storage conditions.

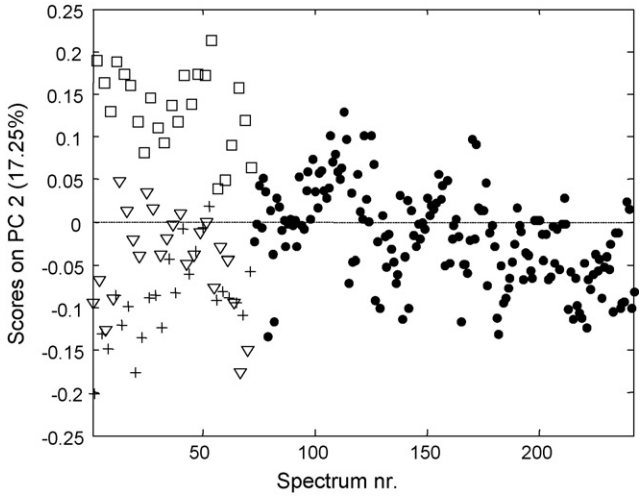

Fig. 6. Effect of storage conditions on the score plot of PC2 vs. the sample number for the NIR spectra of all reference tablets. Desiccator storage (+), stove storage (▽), atmospheric storage (□) and freshly unpacked samples (●).

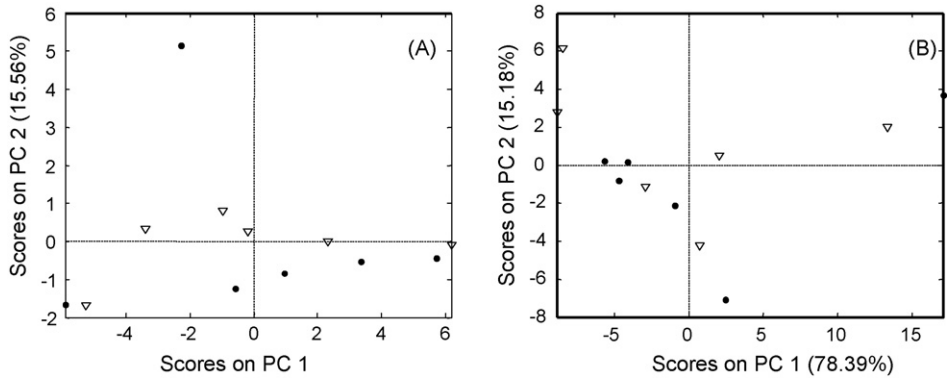

Fig. 7. Effect of storage conditions on the plots of PC2 vs. PC1 of the PCA of the Raman spectra of genuine Lipitor®. Models based on the spectra of the tablet coating (A) and the tablet core (B), recorded immediately after unpacking (▽) and after 24 h storage at ambient conditions (●).

results are shown as score plots of PC1 versus PC2 in Fig. 7A and B, respectively. As can be seen in both plots, the spectra of the freshly unpacked tablets (▽) and the ones obtained from tablets exposed to ambient conditions for 24 h (●) are randomly scattered. Since, for both models, the PC1 and PC2 describe more than 85% of the variance and no distinct clusters are observed, it is concluded that the influence of the storage conditions on the Raman spectra is very small. Close examination of higher PC's confirms that the difference due to the storage conditions is negligible small.

The virtual discrepancy between the results from NIR and Raman can be easily explained by the high activity of water vibrations in NIR, whereas these are practically inactive in Raman. Besides, it illustrates the complementary character of both spectroscopic techniques.

3.3. Discrimination of genuine and counterfeit tablets

After pre-processing the NIR spectra of all tablets, including the counterfeits and the (genuine) references that have been stored under different conditions described previously, a PLS-DA model based on 3 latent variables (LV's) was constructed. The three LV's accounted for more than 90% of the spectral and binary variation. The counterfeits (●) could be easily distinguished from the genuine tablets (▽) in the class prediction plot in Fig. 8A. The corresponding regression vector is presented in Fig. 8B. The positive contributions are more present in the counterfeited than in the genuine tablets, whereas the negative ones are more apparent in the genuine tablets. The broad positive contributions at 6996 and 5124 cm^{-1} can be assigned to OH overtone and combination bands, while the sharp 7188 cm^{-1} band most likely originates from an OH vibration of talc [18], a substance which is commonly used as a mould release agent in tablet manufacturing processes. Based on these results, it is concluded that the counterfeits can be discriminated by their NIR spectra, but that this is mainly based on differences in the matrix used in these tablets. Besides, the classification is not affected by differences in storage conditions or the use of a sample holder. Furthermore, since half of the counterfeit tablets contain the original API atorvastatine and the other half lovastatine, the API characteristics cannot be the discriminating factor in this model.

Raman spectroscopy also turned out to be a valuable tool to discriminate counterfeits and genuine tablets. This is illustrated by the PLS-DA class prediction plot in Fig. 9A, which is based on three latent variables (LV's). The three LV's accounted for 70% of the spectral and 90% of the binary variation. Even though all Raman spectra were used for modeling in order to obtain a robust model that is independent of whether spectra have been recorded from the surface or from the inner tablets, a clear separation into genuine tablets (▽) and counterfeits (●) is acquired. The corresponding regression vector is shown in Fig. 9B. Similar to the regression vector for the NIR spectra in Fig. 8B, the positive peaks correlate more with the counterfeits, whereas the negative bands reflect the characteristics of the genuine tablets. It should be noted that the peculiar bands around 2000 and at 2500 cm^{-1} originate from a luminescence effect instead of Raman scattering. This phenomenon is exclusively observed in the Raman spectra of the lovastatine containing counterfeits (batch 16).

3.4. Discrimination of counterfeits containing atorvastatine or lovastatine

In order to distinguish between counterfeits containing Atorvastatine or Lovastatine (batches 15 and 16) as the API, PLS-DA models

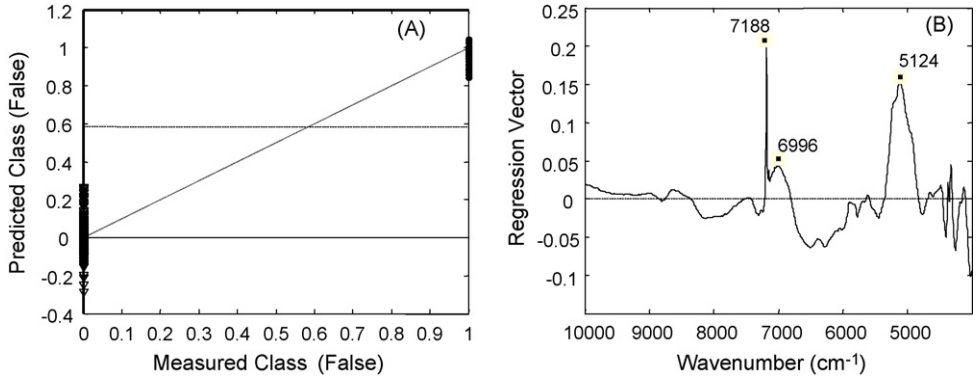

Fig. 8. Class prediction plot (A) and regression vector (B) of the PLS-DA model of NIR spectra based on three LV's to discriminate counterfeits (●) and genuine tablets (▽).

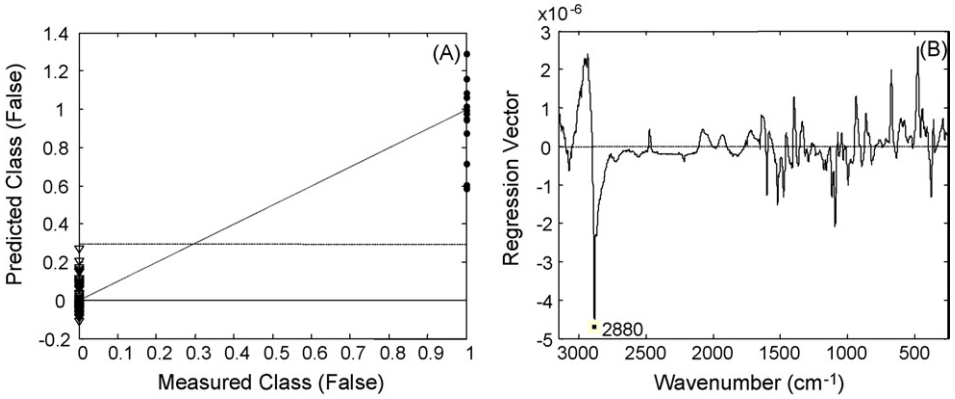

Fig. 9. Class prediction plot (A) and regression vector (B) of the PLS-DA model of Raman spectra based on three LV's to discriminate counterfeits (●) and genuine tablets (▽).

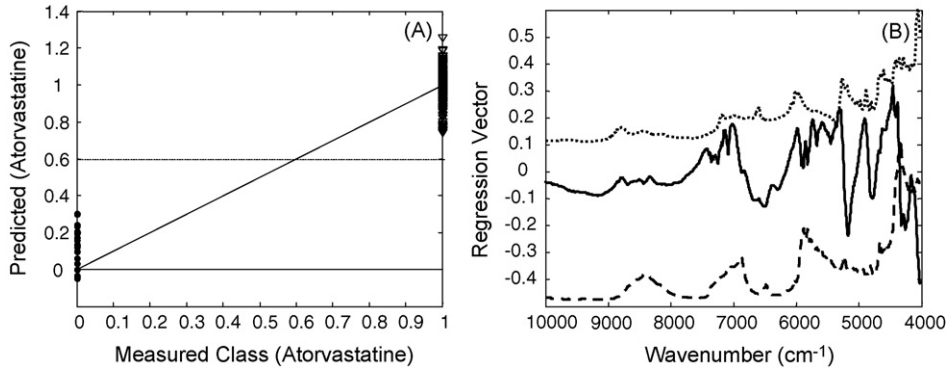

Fig. 10. Class prediction plot (A) and regression vector (B) of the PLS-DA model of NIR spectra based on four LV's to discriminate counterfeit tablets containing lovastatine (●) from counterfeit and reference tablets containing atorvastatine (▽). The NIR spectra of lovastatine (- - -) and atorvastatine (···) are plotted in B for comparison with the regression vector (—).

were developed for the NIR and the Raman spectra of all available tablets including genuine tablets. As illustrated in Fig. 10A, for NIR, the tablets can be easily distinguished for the two different API's with a PLS-DA model based on four LV's. The four LV's accounted for 99% of the spectral and 86% of the binary variation. The discrimination between the genuine and counterfeit tablets containing atorvastatine (▽) and the adulterated tablets containing lovastatine (●) is based on the regression vector presented in Fig. 10B. In this figure, the relation between the regression vector and the API's is shown by overlaying the regression vector with the NIR spectra of the two pure API's. The majority of the negative contribution of the regression vector is characteristic for lovastatine (- - -) and the positive parts for atorvastatine (···). It can be concluded that both API's can be detected with NIR in tablets at a level of 20 mg (and most likely also for 10 and 40 mg tablets). Hence, NIR offers a tool to discriminate batches that only differ in the type of API. Obviously, the limit of detection (LoD) will decrease with the variety of the matrix.

For the Raman spectra of the same tablets, the score plot of the PLS-DA model based on four LV's in Fig. 11A also clearly shows two API classes, representing on the one side the genuine and counterfeited tablets with atorvastatine (▽), and the lovastatine

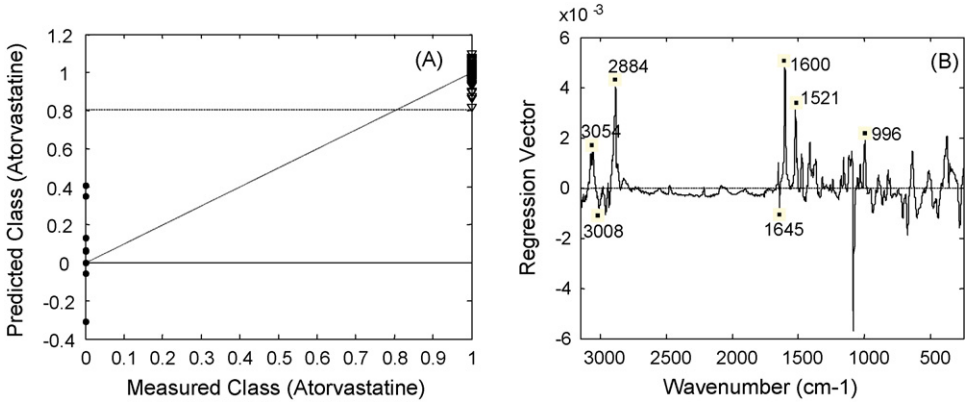

Fig. 11. Class prediction plot (A) and regression vector (B) of the PLS-DA model of Raman spectra based on four LV's to discriminate counterfeit tablets containing atorvastatine (▽) and lovastatine (●).

(●) containing tablets on the other side. Again, both the spectra form the surface and the tablet cores were included in the same modeling process, to obtain a versatile model. The four LV's accounted for more than 90% of the spectral and binary variation. The corresponding regression vector is presented in Fig. 11B and shows atorvastatine characteristics as positive contributions and the lovastatine features as negative peaks. The correctness of these correlations is illustrated by the Raman spectra of both API's in Fig. 4. Evidently, the Raman bands at 1600 and 1521 cm^{-1} in the spectrum of atorvastatine–calcium trihydrate perfectly match with the positive contribution of the regression vector in Fig. 11B. Hence, it is concluded that the tablets can be easily discriminated on the API by both Raman and NIR spectroscopy. It should be noted that the reliability of the classification of the Raman models can be enhanced, for instance by using spectra from either the coating or the tablet core. Alternatively, improvement can be achieved by averaging the spectra of a line scan or by extending the irradiated area [19]. However, as demonstrated for the data sets in this study this appeared to be unnecessary.

4. Conclusions

Summarizing the results of this study, it is concluded that both NIR and Raman spectroscopy in combination with chemometric analysis of the spectral data can be used to distinguish between genuine and counterfeited Lipitor® tablets. Classification, based on PLS-DA models, appears to be irrespective of whether atorvastatine or lovastatine has been used as the API. The discriminative power of NIR largely relies on the spectral differences that are the result of the tablet matrix used, but for Raman, such a correlation is less evident. This is attributed to the fact that NIR probes a much larger sample volume in terms of sample area and penetration depth than Raman microscopy. Besides, the excipients are, in general, more NIR than Raman active. In contrast, the aromatic rings of both API's are strong Raman scatters compared to the polar excipients. The application of either atorvastatine or lovastatine as API in counterfeits can also be easily distinguished with PLS-DA models based on either NIR or Raman spectra. The Raman spectra in particular are very useful to identify the API used, since it exhibits several characteristic bands that are directly correlated with the molecular structure of the substance of interest. An advantage of using a Raman microscope is the high spatial resolution, which offers the possibility to selectively record spectra of at different positions on the cross section of a tablet. On the other hand, line scanning reveals that the spectrum might change with the position of the laser on the tablet in case the sample is inhomogeneous. Evidently, a larger laser spot and/or spectral averaging will reduce this effect. However, the robustness of the PLS-DA models obtained turned out to be sufficiently large to allow reliable discrimination.

Unpacking the tablets from the blister and exposure to ambient conditions for a longer period appears to affect the NIR spectra as result of water adsorption from the atmosphere. It implies that, in principle, storage conditions should be considered when applying the NIR technique for discriminating applications. However, in this study falsifications could be easily discriminated from original Lipitor® tablets regardless of the storage conditions. The same holds for Raman spectroscopy. Here the effect of storage is negligible as result of the inherent low Raman activity of water related vibrations.

Finally, it is concluded that the use of a 5 mm sample holder results in a lower signal to noise ratio and some base line effects in the NIR spectra. However, in combination with the applied pre-processing, the NIR spectra are still sufficiently discriminative to divide the genuine and counterfeit tablets in two distinct classes.

Acknowledgements

Pfizer (Netherlands) kindly donated three different batches of genuine Lipitor® tablets in 10-, 20- and 40-mg strength in closed blisters and the pure compound atorvastatine–calcium trihydrate. The MHRA (London, United Kingdom) and the TGA (Canberra, Australia) kindly donated an authentic (genuine) sample from their market. The Dutch Health Care Inspectorate (IGZ) is greatly acknowledged for their support for enlarging their initially request for the analysis of one suspect counterfeit sample to an exploration of existing techniques to anticipate future developments.

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