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Viagra® and Cialis® blister packaging fingerprinting using Fourier transform infrared spectroscopy (FTIR) allied with chemometric methods

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The production of counterfeit drugs is a criminal problem that carries serious risks to public health worldwide. Herein, the chemical fingerprinting of blister packaging using Fourier transform infrared spectroscopy (FTIR) of authentic and counterfeit samples of Viagra® and Cialis® is demonstrated. Fifteen commercial samples (Viagra® and Cialis®) and thirty two counterfeit samples (Viagra and Cialis) were analyzed, and the FTIR data was subjected to chemometric treatment *via* unsupervised pattern recognition methods (principal component analysis, and hierarchical cluster analysis) and a supervised pattern recognition method (partial least squares discriminant analysis). ATR-FTIR spectra of the blister packaging of authentic Cialis® and counterfeit Cialis samples showed bands at 2976, 2904, 1431, 1326, 1243, 973, 691 and 608 cm^{-1}, suggesting the presence of polyvinyl chloride (PVC) in its chemical composition. For authentic Viagra® and counterfeit Viagra samples, several distinct chemical profiles were observed in the ATR-FTIR spectra. Using unsupervised methods, samples were separated into three large groups: (i) counterfeit Viagra (seven samples made of PVC); (ii) authentic Viagra® (three samples made of poly(ethylene terephthalate)); (iii) Cialis (authentic and counterfeit) and some samples of Viagra (thirty seven made of PVC with additives of stearic acid derivatives, butyl hydroxy toluene or bisphenol A). Therefore, this suggests that three different types of forming films are used in the market for blister packaging used to contain inhibitors of PDE-5. Using supervised methods, all samples were correctly classified into their respective classes.

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1. Introduction

Sildenafil citrate (the active ingredient in Viagra®) was the first drug approved to treat male erectile dysfunction. Its mechanism acts by blocking the enzyme phosphodiesterase type 5 (PDE-5), which is involved in the erection process. It has vasodilating properties and effects blood pressure (BP), and like nitrates, it works through the nitric oxide cyclic guanosine monophosphate pathway.[1] It is estimated that erectile dysfunction affects between 48% and 52% of men from the age of 40 to 70 years old.

Viagra® was registered in the European Union in 1991 by Pfizer. In Brazil, despite the expiration of the patent in June of 2010, the production and the market of counterfeited drugs has become a continuous criminal problem that carries a serious risk to public health worldwide.[2] Tadalafil (the active ingredient in Cialis®) is another medicine commercialized as a PDE-5 inhibitor. Which according to the National Agency for Sanitary Vigilance (ANVISA), together with Viagra® are considered to be the main medicines made by counterfeit production found in the Brazilian market.[3,4] Between 2007 and 2010, the Brazilian Federal Police reported a large number of seizures (371 seizures) of counterfeit pills corresponding to *ca.* 600 pills, meaning that PDE-5 inhibitors account for an average value of 70% of the seizures of counterfeit medicines, followed by steroids, anabolics and inhibitors of prostaglandin (PG), see Fig. 1.

To control the quality of new pharmaceutical formulations and to distinguish between authentic and counterfeit tablets, several analytical methods have been reported in Viagra® and Cialis® tablet analyses such as Raman spectroscopy, nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy, liquid chromatography, mass spectrometry using

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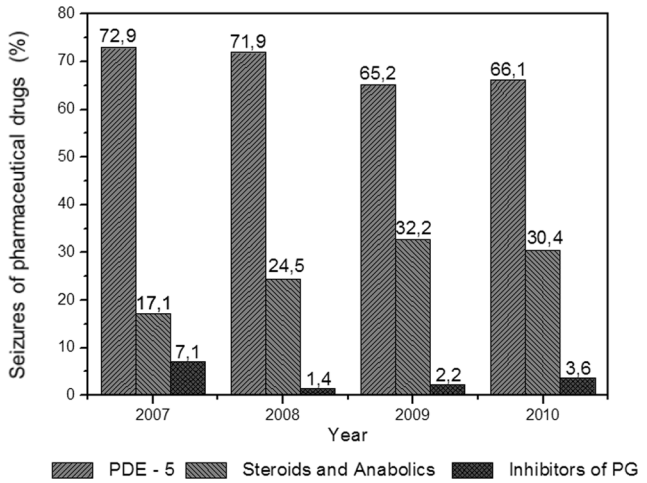

Fig. 1 Numbers of seizures of counterfeit pharmaceutical drugs (%) between 2007 and 2010, classified as inhibitors of PDE-5 and PG, steroids and anabolics.

electrospray ionization or fast-atom bombardment, and X-ray diffractometry.[4–9] However, most methods are time-consuming, and require extensive sample preparation, or sample destruction. Therefore, it is important to develop an analytical method to classify authentic and counterfeit Viagra® and Cialis® samples directly from blister packaging analyses, thus allowing the tablet to remain intact in its physical form.

Blister packaging is formed by two main components: a forming film and a lidding material (see Fig. 2).[10,11] The forming film is the packaging component that contains the product in deep drawn pockets, made of a polymeric material and a coating agent. The lidding material is formed of inks, print primer and a sealing agent, providing the base or main structural component upon which the final blister packaging is built.[10,11]

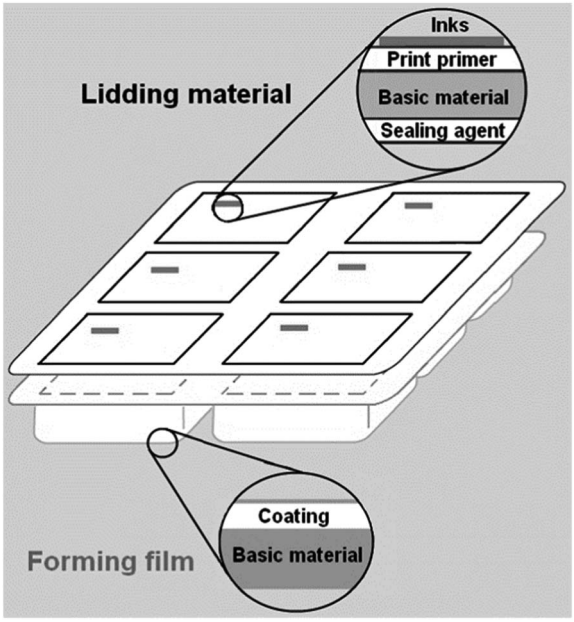

Fig. 2 The basic composition of blister packaging (adapted from ref. 10).

The basic polymeric material applied to the forming films can be produced from thermoforming a plastic such as PVC, polypropylene, and poly(ethylene terephthalate) (PET), which supports coating materials containing aluminum. It can appear colorless or transparent, but can also be obscured for use in child resistant packages or to protect light sensitive drugs. Generally, the forming web for blister packaging is nearly always PVC, sometimes coated or laminated with additional components that enhance the oxygen and water-vapor barrier (aluminum, paper/aluminum and paper/PET/aluminum). On the other hand, the lidding material can be a clear or printed plastic such as 1-mil foil (for push-through blister types), paper/foil or paper/PET/foil laminations (for child-resistant peel–push types).[10,11]

There are some analytical methods that have been employed for pharmaceutical medicines packaging analyses,[12–16] however, they are not related to studies used for intelligent forensic profiling, since no correlation between the chemical composition of the blister packaging and the register of seizures was performed. Therefore, in this paper we have demonstrated the chemical characterization of blister packaging of authentic and counterfeit samples of Viagra® and Cialis® using FTIR allied with chemometric methods. To test this ability, fifteen commercial samples (Viagra® and Cialis®) and thirty two counterfeit samples (Viagra and Cialis) were analyzed, and the data subjected to chemometric treatment *via* unsupervised pattern recognition methods (principal component analysis (PCA) and hierarchical cluster analysis (HCA)) and a supervised pattern recognition method (partial least squares discriminant analysis (PLS-DA)). The results obtained were also compared with the chemical profile of sildenafil citrate and tadalafil tablets.[3,4]

1.1 Chemometric methods theory: pattern recognition

Generally, the term pattern recognition tends to refer to the ability to assign an object to one of several possible categories, according to the values of some measured parameters. In statistics and chemometrics, however, the term is often used in two specific areas: unsupervised pattern recognition and supervised pattern recognition. A simple example will serve to make this distinction between unsupervised and supervised pattern recognition clearer. Given a collection of objects, each of them is described by a set of measurements defining its pattern vector. Cluster analysis seeks to provide evidence of natural groupings or clusters of the objects in order to allow the presence of patterns in the data to be identified. The number of clusters, their populations, and their interpretation are somewhat subjectively assigned and are not known before the analysis is conducted. With supervised pattern recognition, the number of parent groups is known in advance and representative samples of each group are available. With this information, the problem facing the analyst is to assign an unclassified object to one of the parent groups. There are several algorithms to perform unsupervised pattern recognition and supervised pattern recognition. In this work, unsupervised pattern recognition was used. Hierarchical Cluster Analysis (HCA) and Principal Component Analysis (PCA) methods and the supervised

pattern recognition partial least squares discriminant analysis (PLS-DA) method were used, which will be discussed below.

Principal Component Analysis (PCA)[17,18] is a technique which, quite literally, takes a different viewpoint of multivariate data. In fact, PCA defines new variables, consisting of linear combinations of the original ones, in such a way that the first axis is in the direction containing the most variation. Every subsequent new variable is orthogonal to previous variables, but again in the direction containing most of the remaining variation.

Cluster analysis is based on the principle that distances between pairs of points (*i.e.*, samples) in the measurement space are inversely related to their degree of similarity.[3,19] The starting point for a hierarchical clustering experiment is the similarity matrix, which is formed by first computing the distances between all pairs of points in the data set. Each distance is then converted into a similarity value (eqn (1))

$$s_{ik} = 1 - d_{ik}/d_{max} \quad (1)$$

where s_{ik} is the measure of similarity between samples i and k, d_{ik} is the Euclidean distance between samples i and k, and d_{max} is the distance between the two most dissimilar samples, which is also the largest distance in the data set.

PLS-DA is a supervised classification technique that classifies samples based on their spectral similarity to modelled classes (*e.g.*, ref. 20–26). A set of spectra is selected from each class for training (calibrating) the model, and a second set of spectra is reserved for testing (validating), or verifying, the model. The input matrix for modelling can be the whole spectrum, selected wavelengths, or peak ratios. This input matrix (X matrix) is regressed against a second matrix (Y matrix) that contains information about each class. Commonly in PLS-DA, the Y matrix contains 1s and 2s, with 1s indicating that the corresponding spectrum from the input matrix is a member of that class. In this work, the Y matrix contains 1s to 4s for the four classes in the data set: authentic Cialis®, false Cialis, authentic Viagra® and false Viagra.

2. Methods and materials

Fifteen authentic samples of Viagra® and Cialis® blister packaging containing 50 mg of sildenafil citrate (9) and 20 mg of tadalafil (6), respectively, were supplied by Pfizer Ltd and Eli Lilly of Brazil Ltd Laboratories. Thirty two blister packs containing counterfeit samples (registered to seizures named Cialis I (2),† II (3), III (5), IV (7) and V (3); and Viagra I (2), II (1) and III (9)) were supplied by the Brazilian Federal Police. Fig. 3 shows pictures of blister packaging of authentic and counterfeit samples of (a and b) Cialis® and (c and d) Viagra® that were analyzed by FTIR allied with chemometric methods, respectively. Note that the FTIR analyses were performed directly on the surface of the forming films, where the lidding material had been removed previously.

† The value in parentheses corresponds to number of samples analyzed.

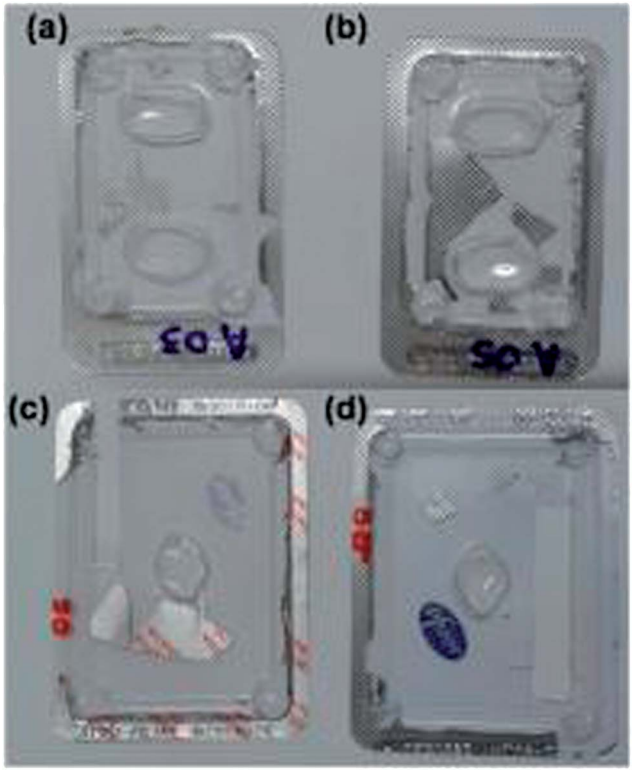

Fig. 3 Pictures of blister packaging corresponding to authentic and counterfeit samples of (a and b) Cialis® and (c and d) Viagra®, respectively.

2.1 FTIR

An ABB BOMEN IR (FTLA2000-102 model) coupled with a MIRacle attenuated total reflectance accessory (ATR) was used for the FTIR studies. Blister packaging samples were inserted under a single reflection crystal plate and a total of 32 scans were taken, thus producing ATR-FTIR spectra recorded from 4000 to 630 cm^{-1} with a resolution of 4 cm^{-1}. The background was performed under air and acquired before the analysis of each sample. The ATR-FTIR spectra were acquired using the GRAMS/AI software (Thermo Galactic).

2.2 Chemometric methods

Pattern recognition methods were applied to the ATR-FTIR data to classify the tablets between authentic Cialis®, false Cialis, authentic Viagra® and false Viagra. The results were submitted to the multivariate statistical analysis methods of principal component analysis (PCA), hierarchical cluster analysis (HCA) and partial least squares discriminant analysis (PLS-DA) using Matlab 6.5 software with PLS Toolbox, version 4.21, from Eigenvector Technologies.

All of the spectra recorded were used in the multivariate statistical analysis methods, resulting in 1748 points (variables) and 47 samples. Some pre-processing strategies (baseline correction, mean center, smoothing and first derivative) of the spectral data were evaluated and the best results were obtained using mean center for PCA and first derivative with a Savitzky–Golay filter (second-order polynomial and 15 window points) for

HCA and PLS-DA. The sample set was divided into calibration (22) and validation (25) subsets by applying the SPXY (sample set partitioning based on joint *x*–*y* distances) algorithm[27] to use PLS-DA. Detection and elimination of outliers were done using score, residual and leverage plots.

3. Results and discussion

Fig. 4a and b show typical ATR-FTIR spectra of blister packaging of samples of authentic Cialis® and counterfeit Cialis (registered as Cialis I–V). The main bands identified in the ATR-FTIR spectra are: (i) 2976 cm^{-1}: C–H stretching of a CH–Cl group; (ii) 2904 cm^{-1}: aliphatic C–H stretching of a CH_3 group; (iii) 1431 cm^{-1}: CH_2 deformation (wagging); (iv) 1326 and 1243 cm^{-1}: C–H deformation corresponding to a CH–Cl group; (v) 973 cm^{-1}: rocking of a CH_2 group; and (vi) 691 and 608 cm^{-1}: CH–Cl stretching.[28,29] The assignments are also shown in Table 1. Therefore, these results suggest the presence of PVC in the chemical composition of the forming films of the blister packaging. Also, other additional bands are identified: bands of lower intensity at 1726 cm^{-1} and 1539 cm^{-1} (C=O and aromatic skeletal stretching, vii) and at 3402 cm^{-1} (O–H stretching, viii) can be associated with the presence of lubricants such as stearic acid derivatives magnesium and zinc stearate[30,31] or of antioxidants such as butyl hydroxy toluene (BHT) and bisphenol A,[32–34] respectively, Fig. 4 and Table 1. Generally, a similar chemical profile of ATR-FTIR spectra is observed between authentic and counterfeit Cialis® samples.

Fig. 5a–d show the ATR-FTIR spectra of blister packaging for (a and b) authentic Viagra® and (c and d) counterfeit Viagra samples. Among the authentic Viagra® samples, two distinct chemical profiles are observed, Fig. 5a and b. For Fig. 5a, the ATR-FTIR spectrum is in good agreement with those of the Cialis samples, Fig. 4. The only difference is related to the 3400 cm^{-1} region, where no band is detected for Viagra®. For Fig. 5b, a specific chemical profile is observed: (ix) 3400 cm^{-1}: O–H stretching of diethylene glycol or ethylene glycol end-groups; (x) 2960 and 2866 cm^{-1}: aliphatic C–H stretching; (xi) 1730 cm^{-1}: carbonyl C=O stretching; (xii) 1234: C(O)–O stretching of an ester group; (xiii) 1142 cm^{-1}: rocking of a CH_2 group; and (xiv) 736 cm^{-1}: this region is associated with the out of plane deformation of two carbonyl substituents on an aromatic ring, Table 1. These results suggest, therefore, the presence of another polymer in the chemical composition of the forming films, *i.e.* PET.[35]

Fig. 5c and d show the ATR-FTIR spectra of the blister packaging of counterfeit Viagra samples (Viagra I and II (c); and

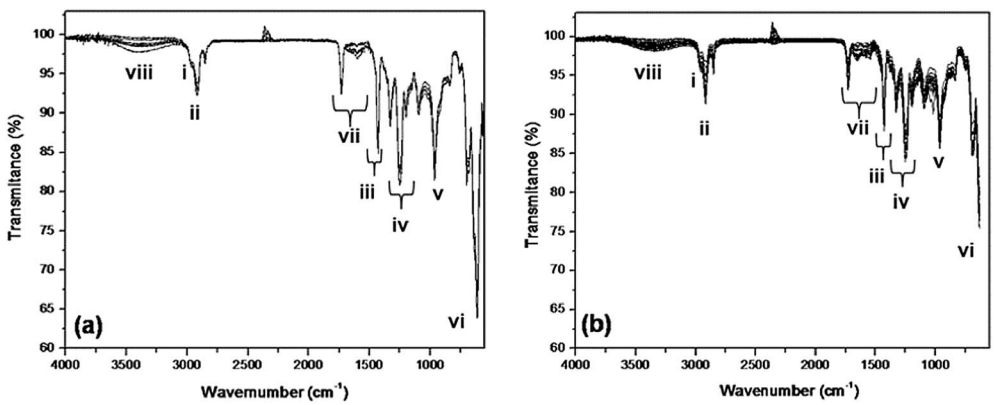

Fig. 4 ATR-FTIR spectra of blister packaging for (a) authentic Cialis® and (b) counterfeit Cialis samples (Cialis I–V).

Table 1 Band assignments for the ATR-FTIR spectra of blister packaging samples. *Numbering corresponds to Fig. 4 and 5

Peaks*	Wavenumbers (cm^{-1})	Assignment
i	2976	C–H stretching of a CH–Cl group
ii	2904	Aliphatic C–H stretching of a CH_3 group
iii	1431	CH_2 deformation (wagging)
iv	1326 and 1243	C–H deformation corresponding to a CH–Cl group
v	973	Rocking of a CH_2 group
vi	691 and 608	CH–Cl stretching
vii and xi	1726 and 1730	C=O stretching
vii	1539	Aromatic skeletal stretching
viii and ix	3402 and 3400	O–H stretching
x	2960 and 2866	Aliphatic C–H stretching
xii	1234	C(O)–O stretching of an ester group
xiii	1142	Rocking of a CH_2 group
xiv	736	Region associated with the out of plane deformation of two carbonyl substituents on an aromatic ring

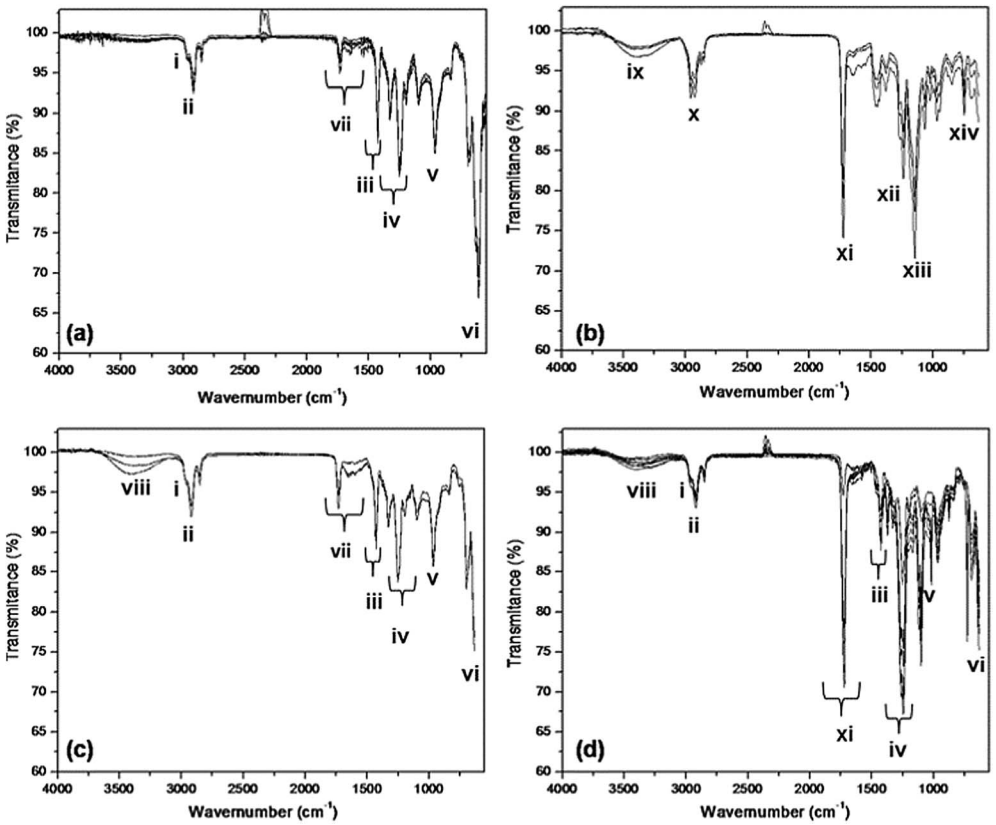

Fig. 5 ATR-FTIR spectra of blister packaging for (a and b) authentic Viagra® and counterfeit Viagra samples (Viagra I and II (c); and Viagra III (d)).

Viagra III (d)). The chemical profile of the ATR-FTIR spectrum of Fig. 5c (Viagra I and II) is similar to the authentic Viagra® samples corresponding to Fig. 5a. For the other registered seizure (Viagra III), Fig. 5d, the chemical profile is similar to the ATR-FTIR spectra corresponding to Fig. 4. However, an intense band, in the 1700 cm^{-1} region, was detected, and can be correlated to other chemical additives: compounds derived from anthraquinone. It could explain the bluish tones observed in the forming films of the blister packaging of counterfeit Viagra samples, Fig. 3d.

The ATR-FTIR data were subjected firstly to chemometric treatment from unsupervised pattern recognition methods: PCA and HCA, Fig. 6 and 7. Both were used to statistically evaluate the performance of the ATR-FTIR spectra in classifying sildenafil citrate and tadalafil samples for quality control

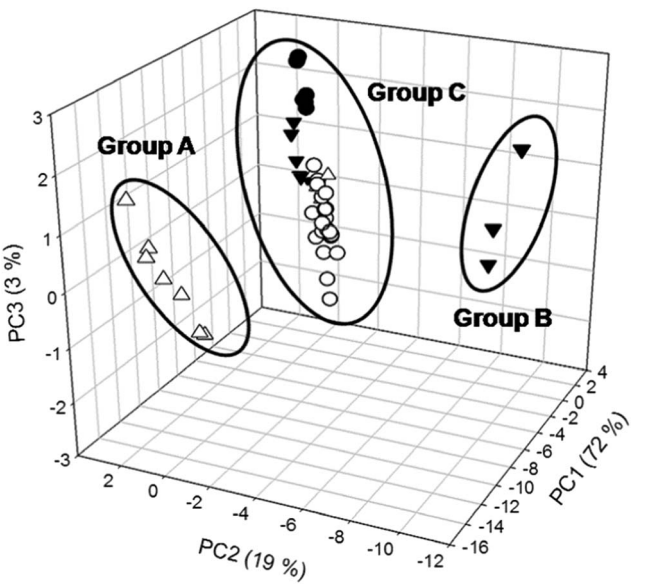

Fig. 6 PCA 3D scores plot of the ATR-FTIR data where the symbols (Δ) and (○) correspond to counterfeit Viagra and Cialis samples and (▼) and (●) to authentic Viagra® and Cialis® samples, respectively.

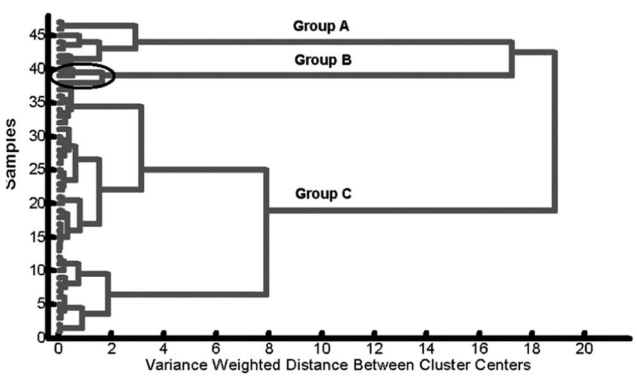

Fig. 7 HCA plot of the ATR-FTIR data.

Table 2 Summary of the classification errors obtained by PLS-DA.

Subset	Group	N^a	M^b	ME^c (%)
Calibration	Authentic Cialis® (class 1)	3	0	0
	Counterfeit Cialis (class 2)	10	0	0
	Authentic Viagra® (class 3)	3	0	0
	Counterfeit Viagra (class 4)	6	0	0
Validation	Authentic Cialis® (class 1)	3	0	0
	Counterfeit Cialis (class 2)	10	1	10
	Authentic Viagra® (class 3)	6	6	100
	Counterfeit Viagra (class 4)	6	0	0

[a] Number of drugs in each group/subset. [b] Number of misclassified drugs. [c] Misclassification error (percentage of misclassified drugs).

purposes. Fig. 6 shows PC1 × PC2 × PC3 scores, where the 3 first PCs account for *ca.* 94% of the total variance. In general, a separation into three large groups is observed corresponding to: group A – counterfeit Viagra (Viagra III (7)); group B – authentic Viagra® (3); and group C – Cialis samples (authentic and counterfeit) and some Viagra samples (6 authentic and 4 counterfeit samples). Therefore, this suggests the existence of three different types of forming films applied to blister packaging.

Fig. 7 shows the results of the HCA method on the ATR-FTIR data. As can be observed, although the HCA was carried out using all of the data, the results obtained were similar to those from the PCA: counterfeit Viagra (group A), authentic Viagra® (group B); and Cialis samples and authentic Viagra® (group C). In this last group, some blister packaging samples correspond to authentic tablets which were classified as counterfeit.

In 2012, Romão and collaborators[3] analyzed the inorganic chemical profile of forty six Viagra® and Cialis® tablets *via* X-ray fluorescence spectrometry (XRF). When the XRF data were also subjected to chemometric treatment *via* PCA and HCA, separations into seven groups were observed: three large groups corresponding to counterfeit Cialis tablets, two groups to counterfeit Viagra, and two other groups to authentic Cialis® and Viagra® tablets, respectively.[3] Therefore, it is evident that a better and richer classification is obtained when the organic composition of the tablets is used instead of the blister packaging. With the goal of improving the classification of Viagra and Cialis tablets between authentic and counterfeit samples using solely blister packaging analyses *via* ATR-FTIR, the data were subjected to chemometric treatment using a supervised pattern recognition method: PLS-DA. Table 2 shows the results of the PLS-DA method.

Table 2 shows a summary of the classification errors obtained by PLS-DA, where for the calibration process, all of the samples were correctly classified into their respective classes ((a) class 1: authentic Cialis®, (b) class 2: false Cialis, (c) class 3: authentic Viagra® and (d) class 4: false Viagra). A misclassification error (percentage of misclassified drugs) of 0 was obtained for classes 1 and 4, having been correctly-classified for validation of each subset. However, a higher misclassification error was observed (10% and 100%) for the validation samples corresponding to classes 2 and 3.

4. Conclusion

In this work, it was demonstrated that Fourier transform infrared spectroscopy is a powerful analytical tool for chemical characterization of blister packaging for identifying between authentic and counterfeit samples of Viagra® and Cialis®. Three different types of blister packaging are typically used in the PDE-5 inhibitor market. Using unsupervised methods (such as principal component analysis and hierarchical cluster analysis), three large groups were formed. In an attempt to improve the classification of Viagra® and Cialis® blister packaging, the data were subjected to chemometric treatment from a supervised pattern recognition method: PLS-DA. The result was that all of the samples were correctly classified into their respective classes. For the validation method, samples corresponding to authentic and counterfeit Cialis and counterfeit Viagra were correctly classified in their respective classes.

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