

Comparison and combination of spectroscopic techniques for the detection of counterfeit medicines

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Introduction :

Counterfeit medicines are more and more present since the last decade. In developed countries, the most popular counterfeit drugs are lifestyle medicines like the phosphodiesterase type 5 (PDE-5) inhibitor drugs: sildenafil citrate (Viagra®), tadalafil (Cialis®) and more recently vardenafil hydrochloride (Levitra®).

In this study, 55 counterfeit and imitations of Viagra®, 9 genuine Viagra®, 39 counterfeit and imitations of Cialis® and 4 genuine Cialis® were analysed by Raman-, NIR- and FT-IR spectroscopy. It has been investigated which technique combination of these techniques was the best to (1) detect counterfeit Viagra® and counterfeit Cialis® and (2) to make clusters in illegal medicines which can be useful for forensic investigations by authorities.

Measurements :

All IR measurements were performed three times on the pulverised tablet. All NIR measurements were performed once on the core of three different tablets of each sample and all Raman measurements were performed on three different locations of the core of one tablet of each sample. Only the fingerprint region of the IR spectra (1800-400cm⁻¹) and the 7000-4000cm⁻¹ region of the NIR spectra were used because of their high variability and their richness of information. The Raman spectra were taken with an exposure time of ten seconds on the core of the tablets at three different locations per tablet.

Results :

Case study one: Viagra®

The samples have been divided in groups according to their visual aspect.

FT-IR:

A good separation between genuine and counterfeit or imitations is obtained. In spite of the differences of dosage, the genuine samples are relatively close to each other. This indicates that the separation is not related to the sildenafil citrate concentration.

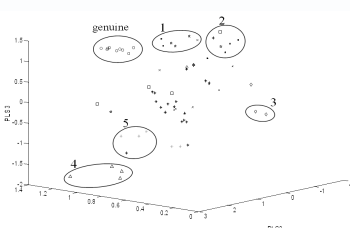
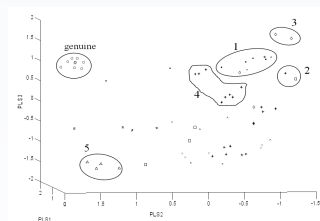
NIR:

the separation in groups by PLS factor 1 was due to microcrystalline cellulose (4732 cm⁻¹), sodium laurylsulfate (5130 cm⁻¹) and sildenafil citrate (5250 cm⁻¹). The separation by PLS factor 2 was due to a cellulose derivative (5180cm⁻¹). The whole spectrum was taken into account for the separation by PLS factor 3.

Raman:

The Raman spectroscopy was able to distinguish genuine from illegal medicines. Illegal samples were widespread and no cluster has been identified except two samples that are apart from other ones.

Group number	Sample photo	Symbol in plots	RIVM Class
1		•	Non professional counterfeits
2		X	Professional imitation
3		□	-
4		*	Professional imitation
5		Δ	Professional imitation
6		☆	Professional imitation and one mixed imitation
Other		○	-
genuine		○	-



Case study two: Cialis®

The samples have been divided in groups according to their visual aspect.

FT-IR:

Cluster 1 contains imitations that are visually similar without distinction between conventional tablets and chewable tablets. Cluster 2 contains the counterfeit samples. Cluster 3 contains samples from the same manufacturer (according to the packaging) that are visually similar the chewable tablets were separated from other samples (arrow 3). Cluster 4 contains samples that are neither counterfeit nor imitation samples. The chewable version of these tablets is not comprised in the cluster (arrow 4). Cluster 5 contains the other samples except three of them that are widespread in the plot. They are not similar between them but quite close to each other. They probably have the same chemical composition and the same manufacturer.

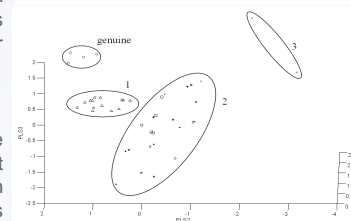
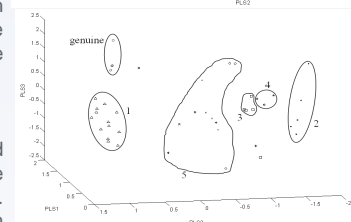
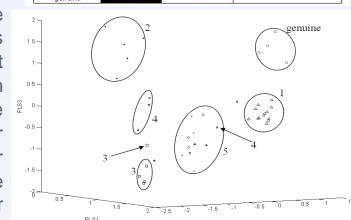
NIR:

Clusters 1 and 2 are very clearly separated from other samples but the clustering of the illegal samples is not clear (clusters 3, 4). These 2 clusters are very close to each other. Once again, the counterfeit samples (cluster 2) are clearly separated from other samples.

Raman:

Raman spectroscopy permits the distinction between genuine and counterfeit samples. This distinction was greater when the region between 1400-1190cm⁻¹ was selected.

Group number	Sample photo	Symbol in plots	RIVM Class
1		•	Mixed counterfeits
2		X	Professional imitation
3		□	Professional imitation
4		*	Non-professional imitation
5		Δ	Professional imitation
6		☆	Non-professional imitation and two mixed imitations
7		☆	Non-professional imitation
other		○	Professional imitation and mixed imitations
genuine		○	-



Conclusions :

For the Viagra® samples the conclusion is that the association of NIR and FT-IR spectroscopy provides the best results. Indeed, the many clusters observed with NIR and FT-IR alone were reduced to 4 clusters showing the most variability between the samples. This variability is correlated to both physical and chemical information.

For the Cialis® samples, the association of NIR spectroscopy (region between 7000-4000 cm⁻¹) and Raman spectroscopy (region between 1400-1190 cm⁻¹) was the most useful association of techniques. This association permitted a very good separation between genuine and counterfeit or imitation samples. The classification performed allows the distinction between very bad counterfeits, very good imitations and other samples from genuine samples.