# Identification of counterfeit tablets and authentication of medicines in the international wholesaling supply chain using near infrared spectroscopy

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## Introduction

Counterfeit medicines are a global problem and are estimated to comprise about 10% of the world's market in medicines. One way to block the supply of counterfeit medicines in the international wholesaling supply chain is to test batches as they are bought, and only sell them on if they are authenticated. To provide such an authentication service to an international wholesaler, a near infrared (NIR) spectroscopic standard operating procedure (SOP) was developed to authenticate medicinal tablets, and has been in use for two years.

The pharmaceutical industry manufactures tablets to tight specifications and therefore the chemical and physical "fingerprints" of proprietary products is very constant. A counterfeiter must not only get the physical characteristics of the product the same as the authentic product (shape, size, weight, colour, marking etc.), but also the chemical makeup. This involves the same active pharmaceutical ingredient (API), and excipients, at the same concentrations and grades (polymorphic forms, particle sizes etc.). Thus, counterfeit proprietary medicines should be relatively easy to identify by NIR spectroscopy, which can detect physical as well as chemical differences between products.

Scafi and Pasquini[1] examined 15 different pharmaceutical products, using at least 10 different batches and measuring 25 samples of each product. Looking at between 10 and 200 spectra for each product, they concluded that at least 50 spectra must be present in the training set in order to obtain a 100% correct classification. They also found that the identification model should contain tablets exposed to many different humidities, so that it becomes robust to tablet water content. Their identification protocol involved principal component analysis (PCA) and soft independent modelling of class analogies (SIMCA) and their results were 100% correct in terms of identifying known samples of counterfeit drugs.

Vredenbregt and co-workers[2] used the simpler identification method of correlation in wavelength space (CWS) and suggested that the critical values for CWS used to categorise suspected

counterfeit Viagra tablets should be: >0.998 identical, >0.99 strongly similar, >0.98 similar, >0.95 slightly similar and <0.95 dissimilar. However, a subsequent study by them showed that the threshold of 0.998 was only applicable to tablets in their original packaging, as contamination could occur (e.g. moisture) in unpacked tablets when a threshold of 0.995 should be applied.[3]

The objective of the present work was to develop a method that would authenticate pharmaceutical tablet products provided by an international pharmaceutical wholesaler, using the minimum of authentic products.

## Materials and methods

Nine proprietary medicines were used as a model set of tablets to develop the authentication procedure: Effexor 37.5 mg, Lipitor 10 mg, Nexium 20 mg, Plavix 75 mg, Protium 20 mg, Risperdal 0.5 mg, Seroquel 25 mg, Singulair 10 mg and Zyprexa 2.5 mg. Reflectance spectra were run on a Foss NIRSystems 6500 NIR spectrometer equipped with a Smart Probe and Rapid Content Analyser (RCA), using a ceramic reference. Each spectrum was the mean of 32 scans in the wavelength range 1100–2500 nm, at 2 nm intervals. Various sample presentation methods, mathematical pre-treatment procedures and a number of chemometric identification procedures were examined. The final SOP was validated with known counterfeit samples of Viagra tablets from the Korean Food and Drug Administration. Samples have been tested for authentication from an international wholesaler.

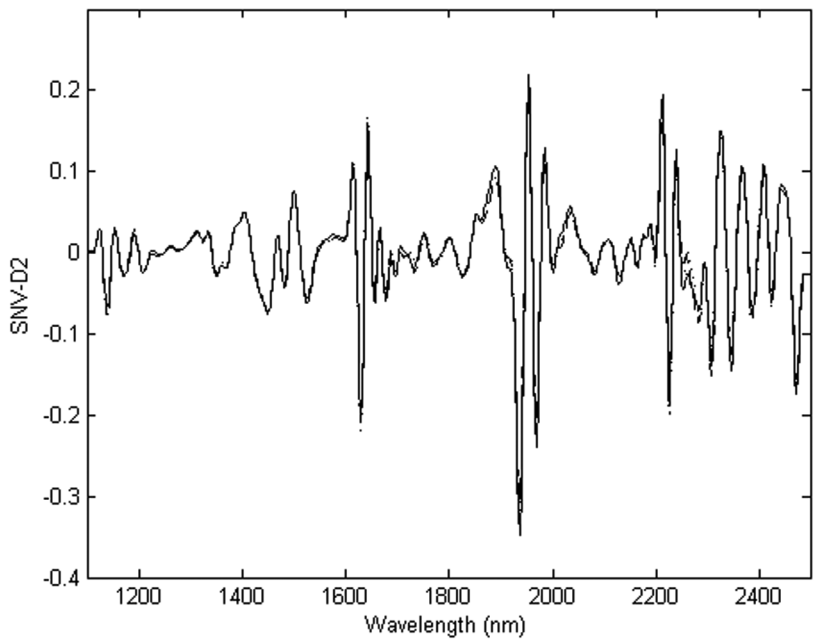


**Figure 1.** SNV-D2 NIR spectra of Bayer's Ciprobay 250 mg tablet from Lebanon (solid line), Bayer's Ciproxin 500 mg from the UK (dotted line) and Bayer's Ciproxin 750 mg from the UK (dashed line) which are completely superimposed.

## Results and discussion

The probe, regardless of its position, gave more noisy spectra than the RCA, especially beyond 2200 nm. The RCA was therefore used in all further work. Second derivatives of the standard normal variates (SNV-D2) of the spectra were used as mathematical pre-treatments.

The mean of twenty spectra, of 10 tablets (measuring once on each side) was optimum in terms of the quality of mean spectra, accuracy of authentication, and time taken for analysis.

The method of authentication was validated by setting up a library of mean spectra of authentic products, and testing them with other batches of authentic and counterfeit tablets of the same product. Batches of authentic products have always given values of CWS in excess of 0.95 when compared to the library authentic samples of the same product. A good example of the similarity of spectra for related products from the same manufacturer of different dosages and countries of manufacture can be seen in Figure 1. The SNV-D2 NIR mean spectra of Bayer's Ciprobay 250 mg tablets from Lebanon, Ciproxin 500 mg tablets from the UK and Ciproxin 750 mg tablets from the UK are completely superimposed.

CWS values for tablets that were eventually found by subsequent conventional analysis to be counterfeit were always less than 0.94, except for one batch of known counterfeit Viagra tablets, that gave CWS values of 0.98, when compared with 27 authentic batches from different parts of the world. However, PCA can be used to distinguish authentic from counterfeit Viagra tablets (Figure 2).

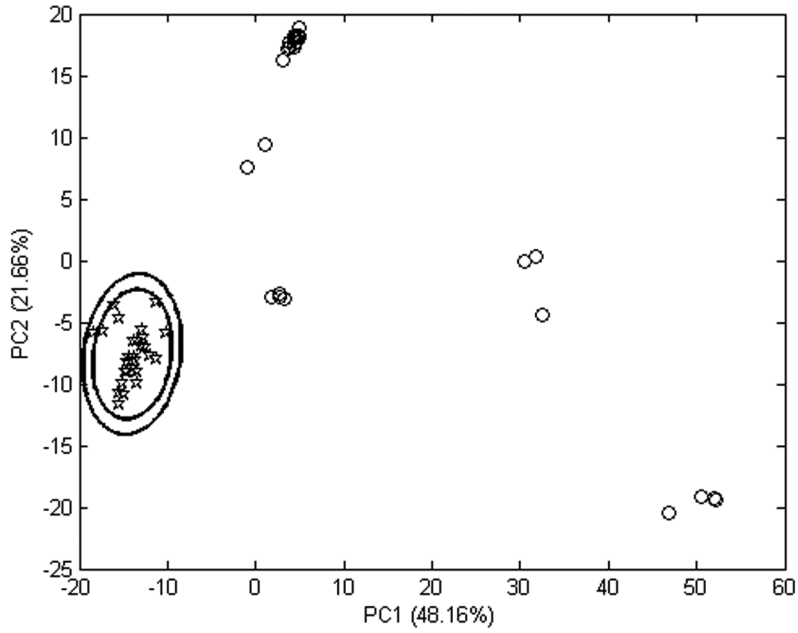


**Figure 2.** Authentic batches (stars) and counterfeit batches (open circles) of Viagra Tablets 100 mg with the 95% and 99% equal frequency ellipses.

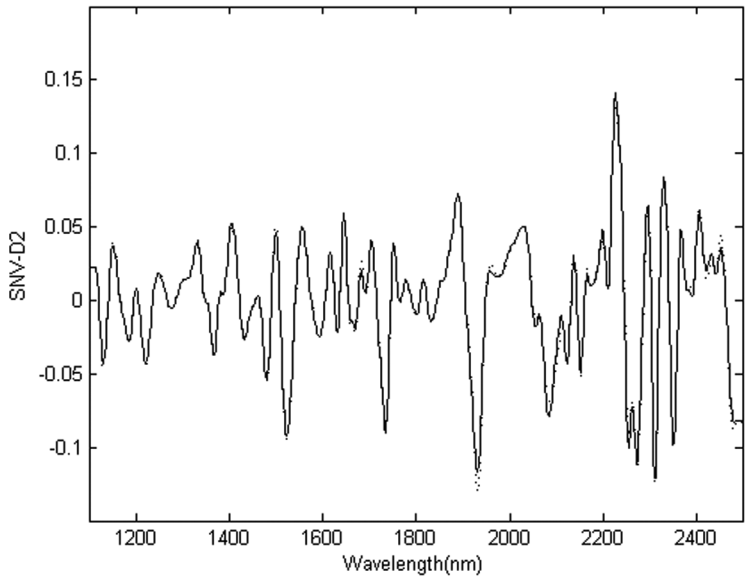


**Figure 3.** SNV-D2 NIR spectra of authentic Plavix Tablets 75 mg and test tablets which turned out to be Plavix Tablets 75 mg ($r = 0.997$).

The SOP has been used for two years, providing a service for an international pharmaceutical wholesaler who wanted to have batches of suspicious batches of tablets authenticated before they were bought and sold on. Of 104 samples submitted for analysis, eight were reported as failed, i.e. they gave CWS values of $< 0.95$. With this information, the wholesaler either did not buy that batch or had it examined further by other techniques. In some cases this further analysis proved that the batch was indeed counterfeit. Typical examples of the analyses of two batches of Plavix Tablets 75 mg submitted for analysis, one which turned out to be authentic and the other which turned out to be counterfeit, are given in Figures 3 and 4.

Of the 104 samples examined, five products were not in blister packaging. Four products were clear passes and were reported as such. However, the test rosiglitazone tablets of 4 mg had a CWS value of 0.919 when compared with authentic tablets. To remove any possible effects due to possible different water contents of the two batches of tablets, the regions in the spectra where water absorbs (1476–1516 nm and 1918–2089 nm) were removed from the two mean spectra and they were then compared again. In this case the CWS value was 0.8979 and the product was reported as failed.

## Conclusion

The SOP was validated by means of known authentic and counterfeit products. Of the 104 samples submitted by the international wholesaler, eight were reported as counterfeit.

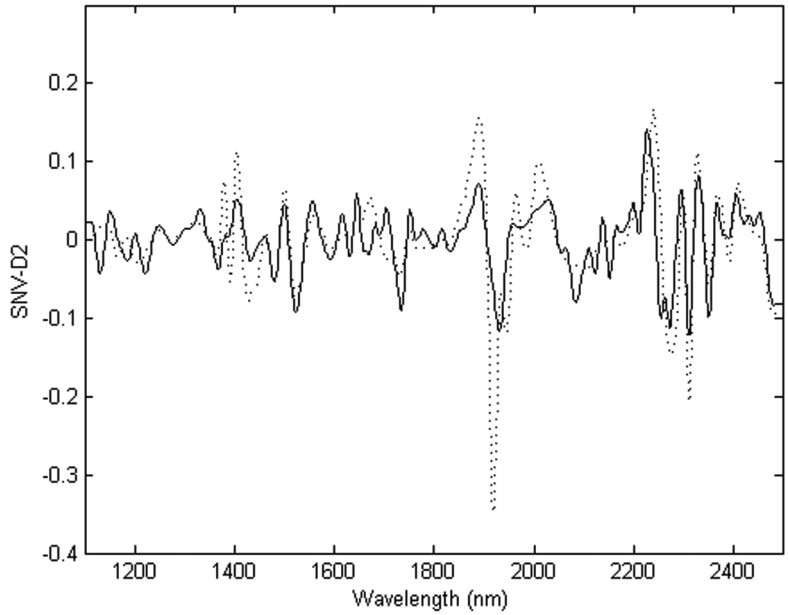


**Figure 4.** SNV-D2 NIR spectra of authentic Plavix Tablets 75 mg and test tablets which turned out to be counterfeit Plavix Tablets 75 mg (r = 0.712).

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