

Handheld near-infrared spectroscopy used as an authentication technology for pharmaceuticals.



By F. G. Haibach

Abstract

Near infrared diffuse reflectance is a rapid, non-invasive method of investigating pharmaceutical raw materials and finished forms. The use of near-infrared to distinguish placebo and active formulations is over 15 years old. It is not surprising that in early 2001 a few independent groups presented results for counterfeit identification.

Handheld spectrometers allow the use of benchtop-like tools in the field. Screening for authentic and counterfeits is rapid and forensic investigations are facilitated by timely results. Specificity is excellent; authentic pharmaceutical tablets can be readily distinguished from counterfeits.

Introduction

According to the World Health Organization IMPACT, a counterfeit pharmaceutical is, “a medicine, which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.”¹

Counterfeit pharmaceuticals are an acute and global problem. The volume of counterfeit pharmaceuticals comprises from 1 to over 30% of the legal pharmaceutical trade depending on region.¹ The result of counterfeiting is a health problem for patients and consumers, from receiving sub-potent, placebo or substitute pharmaceuticals; a criminal problem, from health endangerment; a regulatory problem, from illegal trade; and an intellectual property problem as patents are violated and the identity and brand value of proprietary formulations is diluted.²

The US FDA recommends that pharmaceutical manufacturers protect their products using both an overt and a covert anti-counterfeiting technology. The report also recommends the use of track and trace, and authentication technologies. However, the FDA estimates that counterfeiters can subvert most security measures within 18-24 months.³

Near infrared spectrometers record the “color” of materials in the optical spectrum between 700 and 2500 nm. Portions of the spectrum are absorbed by exciting vibrations in the molecules in the material. In pharmaceutical tablets, these absorptions arise from excipients, actives and coatings providing a unique “fingerprint” of the whole tablet composition. The method was first discussed in 1993 for identifying placebos⁴ and applied to counterfeits 2001.^{5,6} A recent, and detailed discussion of how composition relates to spectra is provided by de Peinder, *et. al.*⁷ Others have indicated that it is possible to identify manufacturing sources for some products by NIR diffuse reflectance.⁸

The packaging also has its own unique fingerprint and can be used for additional confirmation. The tablet can also be identified through blister pack material.^{9,10} These capabilities make the subversion of near-infrared based methods difficult. The spectrum is often unique enough to even be able to distinguish individual manufacturing sources of some products.

Handheld near-infrared has the properties of an authentication, a forensic and a covert technology. Instrument portability allows the identification of the pharmaceutical at any point in the supply chain. The ease of use makes it possible to be used for authentication by field agents. The specificity allows on-site forensic investigation.

Usage Scenarios

Usage of the PHAZIR is dictated by the nature of the instrument, a handheld NIR spectrometer. It has been



Figure 1. Using a PHAZIR to evaluate a blister-packed tablet.

designed to be straightforward for the end-user, just “click and measure.” Results are typically presented in 5 seconds or less. Figure 1 shows the PHAZIR used to measure a tablet in a blister pack. For the laboratory manager and the developer, sophisticated chemometric tools and a US FDA 21 CFR 11 compliant database tool are provided.

Authentication

Pharmacists and other health-service professionals can use the PHAZIR to authenticate pharmaceuticals bought in bulk or repackaged by wholesalers. Forms packaged in blister packs can also be tested. The testing tool has a one-time cost and provides results for each measurement in approximately 5 seconds. The signature analysis can be easily updated and analysis evolved with advances in counterfeiting. The analysis can be created, validated and saved within minutes. Updates can be provided to end-users by email or web-based distribution.

Forensic

Because NIR has specificity sufficient to differentiate authentic and counterfeits manufactured at different locations, it is possible to identify pharmaceutical forms that originated from a single source. This level of analysis of data is not convenient in a handheld spectrometer, using a laptop to analyze the clustering of counterfeiting is possible. The

PHAZIR can archive all spectra in a US FDA 21 CFR 11 compliant database for later use.

“Covert signatures”

The PHAZIR can be programmed with the unique signatures of particular pharmaceutical formulations or in the packaging. As with the discussion above, the signatures can be updated and the analysis evolved to match new anti-counterfeiting strategies. When updated, the PHAZIR can be used by minimally-trained customs, law enforcement and pharmaceutical manufacturer field agents to match the appearance of the pharmaceutical with its chemical signature. The user does not need to be an expert, as the result is simply “pass” or “fail.” Failed dosages can be submitted for forensic investigation.

Technical Analysis

Experimental

Materials

- PHAZIR™ 1624
- PhazirMG™
- Pharmaceutical tablets from known and suspect sources

Table 1: Results from PCA models (columns) on various tablet types (rows). Significant results are highlighted in color.

	PCA model								
	Cialis HK	Cialis US	Ecotrin	Lamisil US	Levitra US	Norvasc 5mg US	Viagra 100mg US	Viagra 50mg US	aspirin, generic 1
APAP tablet		0	0	0	0	0	0	0	0
Cialis HK	40/40	40/40	0	0	0	0	0	0	0
Cialis US	16/40	40/40	0	0	0	0	0	0	0
Cialis HK, counterfeit	0/40	0/40	0	0	0	0	0	0	0
Citracal	0	0	0	0	0	0	0	0	0
Ecotrin	0	0	40/40	0	0	0	0	0	0
Lamisil HK	0	0	0	7/40	0	0	0	0	0
Lamisil US	0	0	0	40/40	0	0	0	0	0
Levitra HK	0	0	0	0	9/40	0	0	0	0
Levitra US	0	0	0	0	40/40	0	0	0	0
Norvasc 5mg HK	0	0	0	0	0	0/40	0	0	0
Norvasc 5mg US	0	0	0	0	0	39/40	0	0	0
Norvasc 10mg HK	0	0	0	0	0	0/40	0	0	0
Sudafed	0	0	0	0	0	0	0	0	0
Sudafed PE	0	0	0	0	0	0	0	0	0
Viagra 100mg HK	0	0	0	0	0	0	0/40	0/40	0
Viagra 100mg US	0	0	0	0	0	0	40/40	34/40	0
Viagra 50mg HK	0	0	0	0	0	0	0/40	0/40	0
Viagra 50mg, US	0	0	0	0	0	0	13/40	40/40	0
aspirin, generic 1	0	0	0	0	0	0	0	0	40/40
aspirin, generic 2	0	0	0	0	0	0	0	0	0/40
naproxen, generic	0	0	0	0	0	0	0	0	0

Procedure

Tablets of commonly counterfeited pharmaceuticals were purchased from local pharmacies in the US and Hong Kong. One pharmaceutical, Cialis, was readily identifiable as a counterfeit by a misprint on the packaging. A random selection of analgesics was used to extend the challenge. Spectra were acquired using the PHAZIR. Spectra were processed, and analyzed using Savitzky-Golay 1st derivative and unit-vector normalization. Due to the sample collection procedure, moisture varied between tablets. The water band was deleted from all spectra. Individual principal components analysis (PCA) models were made from the US purchased tablets and Cialis from Hong Kong.

A second set of blister-packed capsules submitted to Polychromix for examination. The capsules were from two origins, one authentic and the other was identified as “counterfeit.”

Results & Discussion

Building PCA models for near-infrared spectra is straightforward. PCA is a procedure that captures variations in the spectra presented to it. With sufficient collection of tablet spectra, manufacturing variations are captured. By applying statistical tests on the magnitude of the variations, new spectra can be classified as typical (pass) or atypical (fail) at a particular confidence level. In Table 1, we summarize the results from the first study. We have used a 99.9% confidence limit to establish the pass/fail criterion.

PCA models were created for a tablet types that would be useful from an authentication perspective. Cells filled with a “0” provided no “pass” results. These cells would not be expected to have any “pass” results. Cells that could be expected to contain a “pass” are colored. Green indicates a positive and expected result. Yellow indicates a result worthy of further investigation and red indicates a result suggesting that action is needed.

The column indicates a particular test and the rows indicate tablet types that were checked against that model. For the Cialis tablets, the US sourced tablets exhibited a 99.9% confidence interval large enough to overlap with the Hong Kong tablets; the same was not true for a PCA model built on the Hong Kong tablets. The counterfeit was clearly different from the two authentic tablets, as shown in the scatter plot in Figure 1. The spectra are clearly different as seen in Figure 2. Similar conclusions could be drawn about many of the other formulations if given more information. Uncoated aspirin tablets from different manufacturers are particularly well separated. The spectra from aspirin tablets are very uniform.

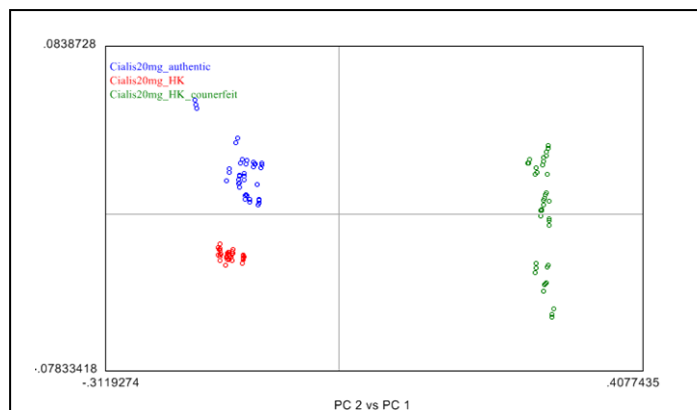


Figure 2. PCA score plot showing how the different Cialis tablet types relate to each other.

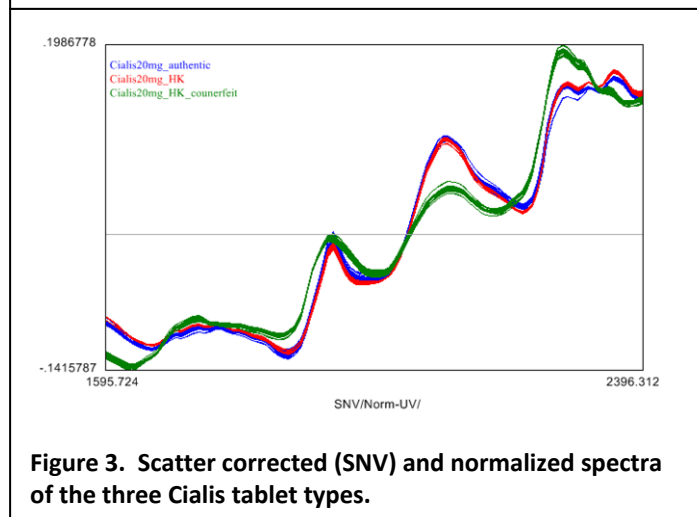
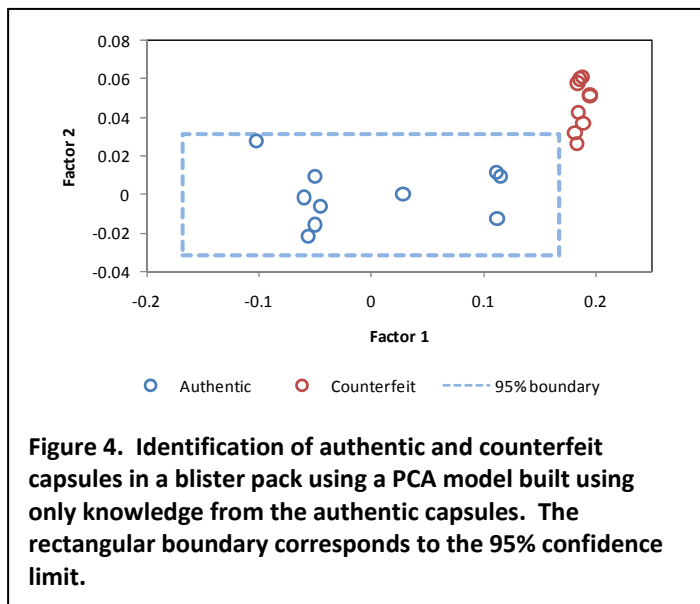


Figure 3. Scatter corrected (SNV) and normalized spectra of the three Cialis tablet types.

The first study does not contain enough examples for a thorough validation. Using leave-one-tablet-out subsets confirms the results.

The second study, of capsules still enclosed in a blister pack was more challenging. The spectra are shown in Figure 4. It is difficult to control presentation of the tablet inside the blister pack. This adds a variable contribution to the spectrum from the blister pack and the tablet. A PCA model was built using the same preprocessing as used for the previous study. Results from the first two factors are shown in Figure 4. The counterfeit is distinguishable from the authentic formulation at the 95% confidence level.



Focusing on particular portions of the near-infrared spectrum that are specific to the tablet composition enables improved discrimination. Pharmaceutical manufacturers have detailed knowledge of their own formulations, and this knowledge can be used to optimize model building. Spectral ranges should be chosen to maximize information from the capsule contents and minimize the effect of packaging. Selecting preprocessing and wavelength ranges for analysis allows the building of PCA and linear discriminant models that capture important features of the capsule content.

Conclusions

Handheld NIR spectrometers can provide laboratory capabilities in the field. This is useful for authentication, forensic investigation and the identification of covert signatures. The technique is sensitive enough to provide differentiation of authentic product from individual manufacturing sites for the example shown.

Development and updating of the analysis, a PCA model, is extremely rapid. Polychromix provides a software package that allows for rapid development and validation of created methods.

Acknowledgements

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¹ WHO, "Counterfeit Medicines: an update on estimates" 15 November 2006

² "The Economic Impact of Counterfeiting and Piracy." OECD Publishing, 2008.

³ US Department of Health and Human Services, "FDA's Counterfeit Drug Task Force Interim Report" October 2003.

⁴ M.A. Dempster et al., "Near-Infrared Methods for the Identification of Tablets in Clinical Trial Supplies," *J. Pharm. Biomed. Anal.* **11**, 1087–1092 (1993).

⁵ W.L. Yoon, R.D. Jee, G. Lee, A. Charvill, A.C. Moffat, "A non-destructive method to detect counterfeit medicines using near-infrared spectroscopy." *AAPS Pharm. Sci.*, **3**, 1800 (2001).

⁶ S.H.F. Scafi, C. Pasquini, "Identification of counterfeit drugs using near-infrared spectroscopy." *Analyst*, **126**, 2218 – 2224 (2001).

⁷ P. Depeinder, M.J. Vredendregt, T. Visser, D. de Kaste, "Detection of Lipitor counterfeits: A comparison of NIR and Raman spectroscopy in combination with chemometrics." *J. Pharm. Biomed. Anal.* **47**, 688-694 (2008).

⁸ B.A. Olsen, M.W. Borer, F.M. Perry, R.A. Forbes, "Screening for Counterfeit Drugs Using Near-Infrared Spectroscopy." *Pharm. Tech.* **6**, 62 (2002).

⁹ J.-P. Conzen, A. Schmidt, J.Q. Wang, "Non-destructive quality control of pharmaceutical tablets by near-infrared reflectance spectroscopy," *Near-infrared Spectrosc.: Future Waves, Proc. Int. Conf. Near-infrared Spectrosc.*, 7th, A.M.C. Davies, P.C. Williams, Eds., 378–385, 1996.

¹⁰ M.L. Sun, B.R. Xiang, D.K. An, "A near-infrared diffuse reflectance analysis method for the noninvasive quantitative analysis of ambroxol hydrochloride tablets." *Yao Xue Xue Bao*, **39**, 60-63 (2004).