Article Original: Contrôle de qualité

Detecting counterfeit tablets by near infrared spectroscopy

Hakim Boudis[1], Alexandra Gaubert[2], Chantal Boyer[2], Jean-Pierre Dubost[2], Rachida GHEYOUCHE[1]

(1) Laboratoire de Chimie Analytique- Département de Pharmacie D'Alger- Faculté de Médecine – Université d'Alger 1
(2) Laboratoire de Chimie Analytique –UFR des Sciences Pharmaceutiques- Université Bordeaux 2

Hakim BOUDIS – <boudish2000@yahoo.fr>
Alexandra GAUBERT –<alexandragaubert33@gmail.com>;
Chantal BOYER - <Chantal.boyer@u-bordeaux2.fr>;
Jean-Pierre DUBOST - <jean-pierre.dubost@chimana.u-bordeaux2.fr>;
Rachida GHEYOUCHE -< gheyouche_rachida@yahoo.fr>

***ABSTRACT*- Counterfeit drugs are deliberately and fraudulently produced drugs without respect of their identity and/or source. Different analytical techniques exist to detect counterfeit drugs based on the pharmacopeia methods using for example HPLC and TLC. These techniques are time-consuming, not environment friendly and take into account only the chemical characteristics of the drug. Near InfraRed Spectroscopy (NIRS) is a technique which reflects both chemical and physical aspects of the drug.**

An example of counterfeit drugs of an inhibitor of platelet aggregation is given to demonstrate the approach combining NIRS and chemometrics. First, a mathematical model was developed to discriminate the drug from the various production sites. Then the model was developed to distinguish the genuine drug from degraded samples; this is an advantage as it allows detecting the usage of degraded drugs by the counterfeiters.

This method represents a real weapon against counterfeit drugs.

Keywords – Chemometrics, Contrefeit drugs, NIR Spectroscopy, Plavix, validation model

I-Introduction

The counterfeiting that is defined by different regulatory agencies.

First in France, ANSM, the drug regulatory agency defines counterfeiting as: "an intellectual property infrigement" so it only takes into account the legal aspect and its consequences.

Counterfeiting is generally defined as the product of fraudulent reproduction of others without their consent.

But define "counterfeit medicine" is more complex

Table 1: Definition of the WHO

Definition of the WHO	Different kind of counterfeit drugs
"*Counterfeit medicines are part of the broader phenomenon of substandard pharmaceuticals - medicines manufactured below established standards of safety, quality and efficacy. They are deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients*"	A counterfeit drug can contain: - Correct API but incorrect amount - Another API - No API - Fake packaging - Incorrect excipient - **At pharmaceutical grade or not**

II-COUNTERFEITING IN FIGURES

- In the world

– 10% of world market of pharmacy
– Up to 70% in Africa, eastern Europa and eastern Asia
– 50% realised on the net
– In 2008, almost 900000 counterfeit drugs seized by customs (France)
– In 2009, 1693 incidents caused by counterfeit drugs (7%

compared to 2008)

- Risks associated with counterfeiting

– Intellectual property Infringement
– Loss for Research
– Affect of Human Health
– Development of resistances

III-PROJECT

Table 2 : Presentation of project

• **Reference EA 4575 Analytical and Pharmaceutical Developments applied to Neglected Diseases and counterfeit drugs**		
Developments pharmaceutical & formulation for neglected diseases	Counterfeit drugs detection	Analytical development & green chemistry
Pharmaceutical Industrie		

III-1 MODE OF DETECTION

Observation of the primary packaging

Fig1 : inspection of packaging drug

Observation of secondary packaging

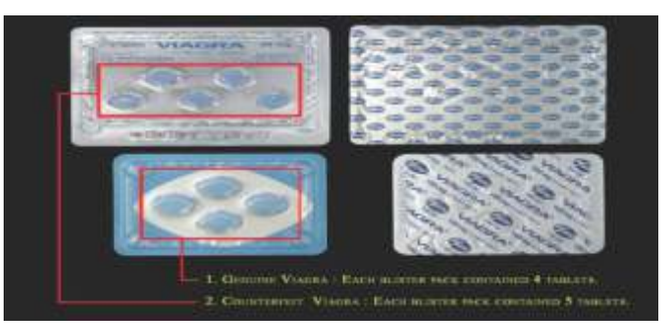


Fig 2 : Inspection of secondary packaging drug

Aspect of tablets

–Color
–Shape
–Marking

Fig 3 : Inspection of aspect tablet

Test chemical

–Research of API
–Based on Pharmacopeia method
oHigh Performance Liquid Chromatography
oThin Layer Chromatography, …
–Most used techniques

Test chemical and physical

–Near InfraRed Spectroscopy (NIRS)
–Raman

III-2 Comparison detection modes

Table 3: Comparaison detection mode of contrefeit

HPLC, TLC	NIRS
Chemical aspect Destructive sample preparation Time consuming Use of solvent	Chemical + Physical aspect None sample preparation Fast analysis Free solvent Eco-friendly

III-3 Tablets studied:

Inhibitor of platelet aggregation

Table 4: Composition and therapeutically indications of drug studied

Composition	Therapeutical indications
API Mannitol Macrogol CMC (Microcristalline Cellulose) Castor oil Opadry Hydroxypropyl cellulose Carnauba wax	Myocardial infarction Arterial Angina or acute coronary syndrome Stroke

IV-Near InfraRed Spectroscopy (NIRS) –

Instrumentation

4 essentials parts

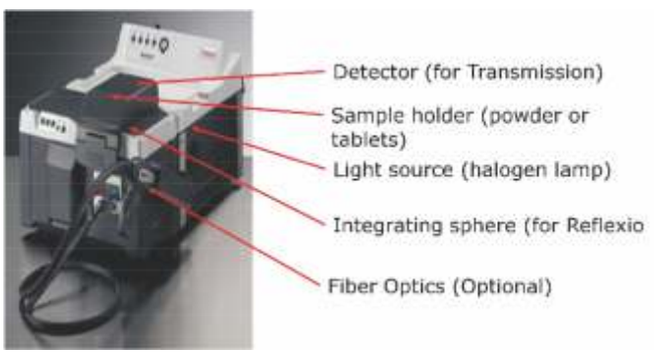
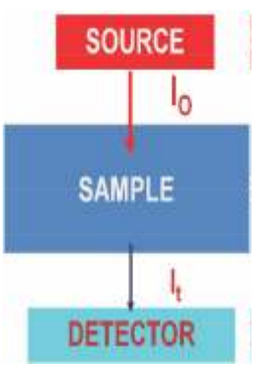
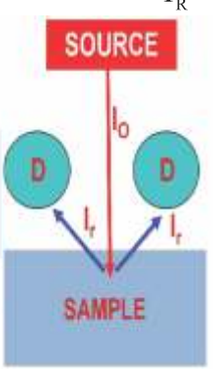


Fig 4 : NIRS instrument

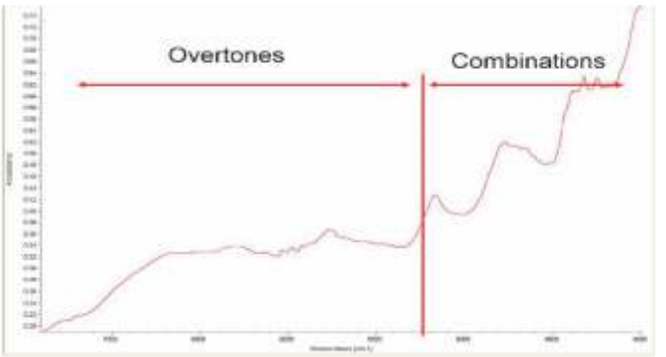
Acquisition modes

Table 5 : Differnts acquisition modes used

Transmission	Reflexion
Radiation passes throught sample (up to 1 cm thick) Measure: Absorbance	Radiation penetrates sample of 2 mm Measure: Absorbance $A = \text{Log} \frac{I_0}{I_R}$
	

NIRS Spectrum

Tablet spectrum in Reflexion



V-CHEMOMETRICAL TOOLS

Pre treatment

– Standard Normal Variate (SNV)

- Each spectrum compared to standard deviation

– Multiplicative Signal Correction (MSC)

- Each spectrum compared to mean spectrum

- **Discriminate Analyse**

– Supervised qualitative method

– Discrimination over similarity

– **Principal Component Analyse (PCA)**

– Non supervised qualitative method

– Discrimination of distant points

NIRS – Parameters optimization

- Resolution

– Ability to separate adjacent bands

- Scan number

– Increase gives more information about the sample

- Gain

– Better reading of spectra

– Background noise increased

NIRS – Optimised Parameters

- **Resolution:** 8 cm^{-1}
- **Gain:** 1

Studied faces: 1 & 2

Face 1 / Face 2

- **Pre treatment:** SNV
- **Spectra:** raw
- **Model**
  - Discriminate Analyse
  - Principal Component Analyse

§**Differentiation production site**

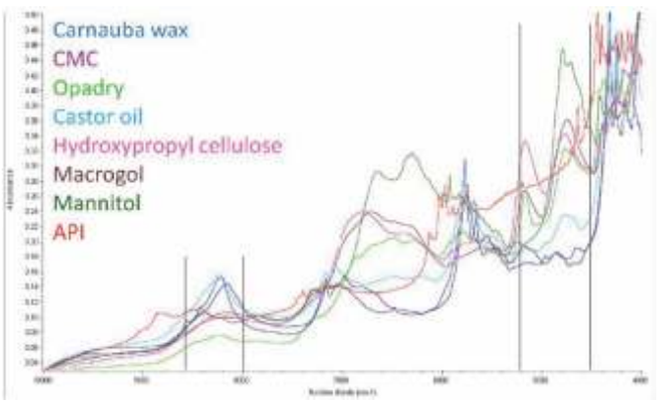


Fig 6: NIRS spectrum of different component

- **Spectral bands studied:**
  - 8600 to 8000 cm^{-1} and
  - 5237 to 4500 cm^{-1}
- **Differentiation production site**
- **Validated model**

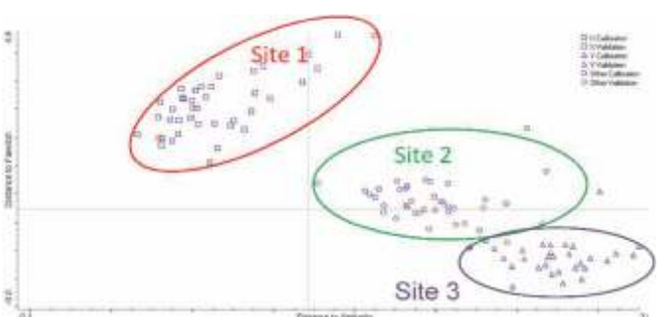


Fig 7 : Model « AD » validated

Study of tablets degradation

- Tablets studied
  - 3 tablets per batch 15 tablets per sites
    - 90° in oven
    - Spetra acquisition
    - T0, 1h, 2h, 4h and 3 days
    - Since 1h, tablets out of model

- Spectra comparison

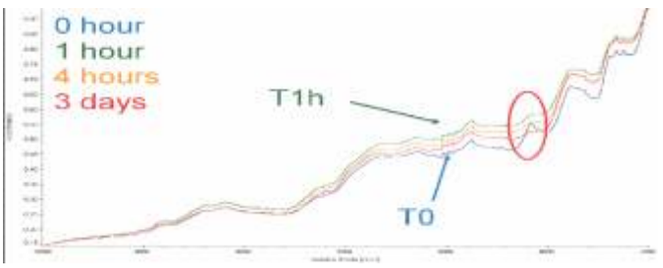


Fig 8: Spectra comparison between tablet genuine & tablet degraded**.**

Study of tablets degradation

- Differenciation between genuine/degraded drug

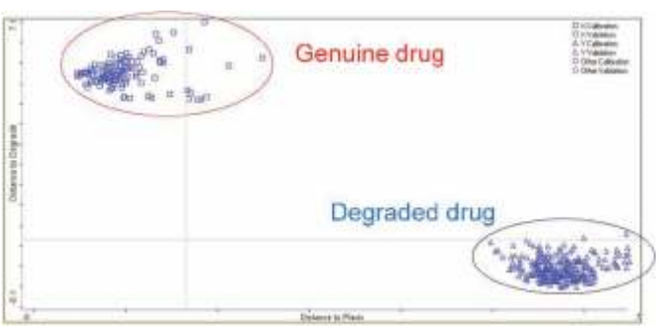


Fig 9: Model "AD" of defferentiation

V-Genuine/Counterfeit drug

Fig 10: Suspect sample in the world

Genuine/Counterfeit drug –Parameters

- Raw spectra
- Establishment of models
  - Genuine drug → Calibration
  - Counterfeit drug → Calibration

- Principal Component Analyse

Spectral bands studied

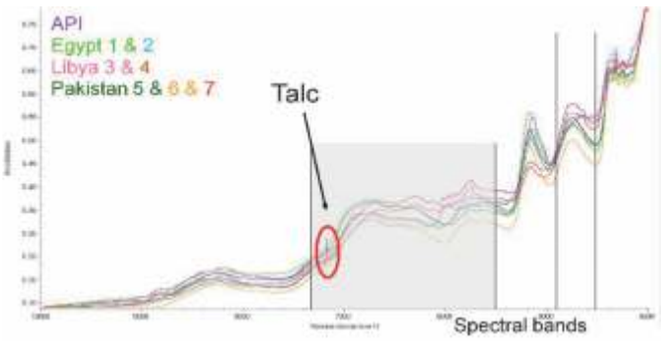


Fig 11 : NIRS Spectrum of suspect sample

As indicated previously in reflexion we studied two spectral bands which present the most variability.

Moreover, in the largest spectral band a characteristic peak is observable. After some research, we find out that it was talc.

It will be useful for the identification of counterfeit.

Development of the model

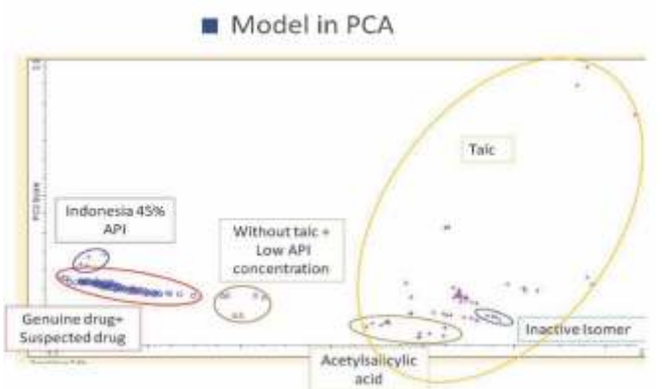


Fig 12: Model "ACP" validated

The established model allows a differenciation between the genuine drug, counterfeit drugs containing talc or not.

In the genuine drug group, we can find suspected drugs which were in a second time consider as genuine drug.

The sample coming from Indonesia and containing talc and 45% API are separated very close to genuine drugs in every models perhaps due to the process fabrication.

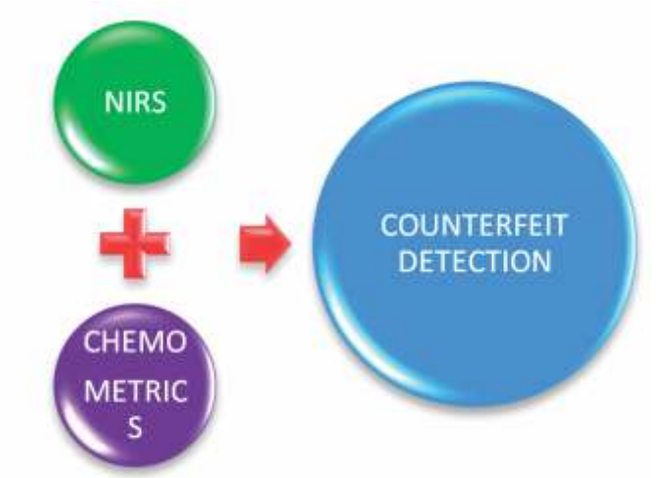
Here, you can see samples without talc and with low API concentration

And at you right the group of counterfeit drugs containing talc.

Among this counterfeit drugs, two groups are noticeables.

The first one contains acetylsalicylic acid as API and the second one an inactive isomer.

VI-CONCLUSION



In conclusion, we have seen the impact of counterfeiting both for the pharmaceutical industry and patient. Different methods are available to detect counterfeit drugs: general aspect, chemical and physical characteristics.

NIRS and chemometrical tools are able to detect counterfeit drugs rapidly without harming the environment. The obtained results in reflexion as well as in transmission show the ability of this method to differentiate genuine and counterfeit drugs.

So this is worth further investigation on this medicine but also on other medicines.

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