Journal of Pharmaceutical and Biomedical Analysis 53 (2010) 215–220

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

Counterfeit drugs detection by measurement of tablets and secondary packaging colour

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ARTICLE INFO

Article history:
Received 13 November 2009
Received in revised form 29 March 2010
Accepted 30 March 2010
Available online 27 April 2010

Keywords:
Counterfeiting
Colorimeter
Visible spectroscopy
Viagra
Levitra
Cialis

ABSTRACT

The growth of pharmaceutical counterfeiting is a major public health problem. This growth is resulting in a proportional increase in the number of samples that medicines control laboratories have to test. Thus the need for simple and affordable preliminary screening methods to be used by inspectors to decide in the field whether to collect a sample for further laboratory analysis or not. This paper intends to evaluate the possibility to employ for preliminary examinations of suspicious samples an optical spectrophotometer (colorimeter) used in the graphic industry, capable of measuring the reflectance visible spectrum of solid materials. The colorimeter was tested on original and counterfeited Viagra, Cialis and Levitra by measuring the colour of tablets' surface and of a specific spot of the packages. Various batches of the original drugs were employed both to investigate precision and robustness of the technique and to build spectral libraries. These libraries were used to compare suspicious samples to the corresponding original by means of a wavelength distance pattern recognition method. The method was eventually tested on suspicious samples sized by police authorities in order to evaluate its effectiveness. The device resulted precise and robust toward ambient conditions changes, although some limits emerged: the libraries of original samples need a frequent update and a lower precision is to be expected for tablets which surface is extremely convex.

1. Introduction

The pharmaceutical counterfeiting phenomenon is a major public health risk [1] which is being intensively debated these days [2]. To respond properly to the alarming raise of the phenomenon, WHO has created a global coalition of stakeholders and regulatory agencies called IMPACT (International Medical Products Anti-Counterfeiting Taskforce) [3] whose goal is mainly to forge international collaboration and raise awareness of the dangers posed by counterfeit medicines consumption.

Many different methodologies to detect counterfeiting by various analytical techniques have been reported to date [4–19]. However the raising concern about counterfeiting is resulting in a proportional increase in the number of samples that medicines control laboratories have to test. Thus the need for simple and affordable preliminary screening methods to be used by inspectors to decide in the field whether to collect a sample for further laboratory analysis or not. Moreover such methods would be of great advantage to developing countries where more effective testing procedures are often lacking. To this purpose in recent years colorimetry and refractometry on drug solution have been proposed with success [20–24] also in conjunction [25].

This paper intends to present another possible field method not yet reported: the detection of counterfeiting by measurement of tablet and packaging colour. This study investigated the effectiveness and reliability for in the field inspections of an optical spectrophotometer (colorimeter) capable of measuring the reflectance visible spectrum of solid materials. This particular instrument, which is generally used in the graphic industry, basically projects a light toward a solid surface, collects the reflected spectrum and digitally records it. Therefore in principle one can match the spectrum from the surface of a suspicious drug with the one of the corresponding original and, once the right statistical treatment of data is put in place, establish with a defined amount of confidence if the sample is genuine, fake, or deserves further investigations.

As a model three of the most counterfeited drugs were considered: Viagra® from Pfizer, Cialis® from Lilly and Levitra® from

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doi:10.1016/j.jpba.2010.03.044

Bayer. Colours of both tablet's surface and of secondary package (i.e. the carton box) were considered. An area of the package where the colour was more distinctive was chosen (i.e. the green side in the Cialis box, the violet in the Levitra and the blue in the Viagra).

2. Experimentals

2.1. Chemicals

Original Viagra®, Cialis® and Levitra® were mostly bought from Italian pharmacies; about a 10% of the samples were bought from online UK pharmacies in order to widen the variability among batches. More than one dosage for each drug was considered (i.e. 25, 50 and 100 mg for Viagra, 10 and 20 mg for Cialis and 10 and 20 mg for Levitra) and tested separately, in order to verify the influence of tablet dimension on the colorimeter performance. Also secondary packages were tested separately for each dosage because they might have come from different production lines. Ten to twenty batches were analysed for each dosage. Batches production date spanning 5 years were chosen to maximise heterogeneity. Tablets were scanned on the less carved side (which for Viagra and Levitra is the one indicating the brand, while for Cialis is the one not carved at all) to avoid introducing a source of heterogeneity.

For those tablets of irregular shape the operators were instructed to make the scan always on the same spot.

2.2. The colorimeter

The colorimeter employed was the *eye-one* model by *X-rite* (Regensdorf, Switzerland). A first typical entry-level use of this kind of colorimeter is to calibrate pc monitors and video-projectors to get the accurate set of colours even on a different monitor from that on which the image was created. A second typical use is the monitor-to-printer matching, a process that ensures photographers and designers that the colour they are seeing on the PC monitor display will be the same on their printed output.

This instrument is indeed portable: It is a very small object and it can be connected to every personal computer through a standard USB port, through which it is powered without the need for a dedicated battery.

The Gretag Macbeth *i1Match* monitor profiling software was employed. It permitted to have a description of each scanned colour in terms of many different scales. Most importantly it permitted to export data in Microsoft Excel format as *reflectance vs wavelength*. This data format was employed during this study in every calculation concerned.

The colorimeter covers the whole visible spectrum, from 380 to 730 nm in 10 nm steps (i.e. it scans 36 points). In Fig. 1 spectra from Cialis 20 mg, Viagra 100 mg and Levitra 10 mg tablet surface are depicted.

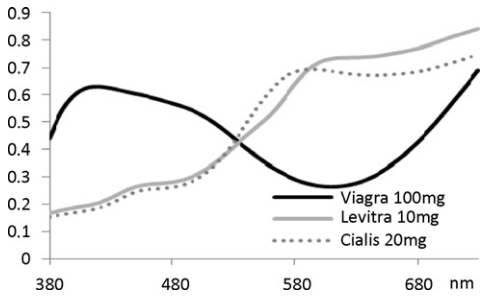

Fig. 1. Reflectance spectra obtained from tablets of Viagra, Levitra and Cialis.

Spectrum acquisition is performed placing the ocular upon the surface to be scanned, making it adhere perfectly in order to avoid interferences from ambient light (see Fig. 2).

The scanning requires not more than a couple of seconds.

Since the response to ambient light conditions was unknown prior to this study, all the analyses were performed in homogeneous conditions putting the scanner under a *GTI Mini Matcher* (GTI Graphic Technology, Inc., 211 Dupont Avenue, Newburgh, NY – www.gtilite.com) which is a booth that provides a calibrated and reproducible type of lighting (daylight, office, incandescent illumination or ultra-light).

Every 10 scans a calibration of the colorimeter was performed on a white barium sulphate tile.

2.3. Validation

2.3.1. Precision

To gain a better knowledge of method performances a validation was deemed necessary. In particular precision and ruggedness studies were devised.

The precision study was designed with the purpose of estimating method imprecision and comparing it with the batch to batch variability. It was also designed in order to try to evaluate which step of the analysis contributed most to the overall imprecision.

In order to do this a three-factor nested ANOVA experiment was conducted, the three factors being operators, days and replicates. Specifically, for every dosage of each drug considered three operators made 10 replicates in two different days on each batch available. Then a precision value was calculated for each dosage of the three drugs.

This procedure permitted to know for each batch separately both the total method precision and its various components (namely inter-operator precision, inter-day precision and repeatability). The pooling of the total precisions of each batch provided

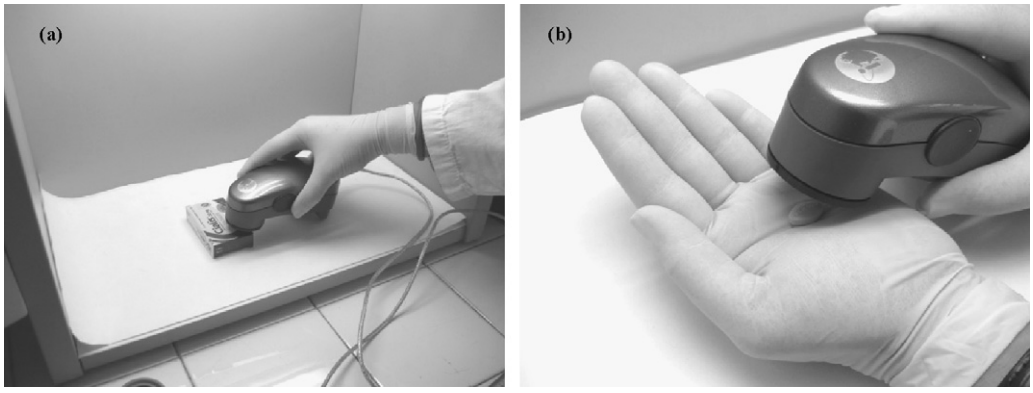

Fig. 2. (a) The scanning of Cialis 20 mg secondary packaging. (b) The scanning of a tablet.