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The use of dynamic thermal analysis to distinguish between genuine and counterfeit drugs

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ABSTRACT

WHO estimates that 10% of drugs are falsified. Economic and health factors arising from the use of counterfeit drugs lead to the development of new methods for distinguishing genuine medicines from falsified ones. The purpose of this study was to develop a new, fast, and inexpensive method to distinguish between original and fake drugs.

10 counterfeit Viagra® tablets were compared to 4 original pills (Pfizer). The drugs – both original and fake – were heated to 60 °C and then the dynamics of their temperature changes at ambient conditions was tested using a thermal imaging camera. The time constants τ showing the dynamics of temperature changes for Viagra® and the falsified drug were determined.

The thermokinetic parameters of drugs were determined in the temperature range of 60–22.2 °C. Both original and counterfeit tablets had different time constants: 171.44 ± 4.62 s and 182.71 ± 4.05 s, respectively. Differences in the dynamics of temperature changes as a function of time are particularly pronounced in the range of $t+2$ to $t+7$ min.

The comparison of the time constants τ enables to distinguish between genuine and counterfeit drugs. The proposed new method which uses dynamic thermal analysis is an effective, cheap and fast technique to distinguish genuine drugs from counterfeit ones.

1. Introduction

Counterfeit drugs are a huge problem because of the high risk of injury in a patient who takes them (Seiter, 2009; Blackstone et al., 2014). According to WHO the extent of drug counterfeiting cannot be clearly determined, but it is roughly estimated at 10% (WHO Brochure, 2008; Fernandez et al., 2008). The phenomenon of drug counterfeiting is much more common in developing countries than in the developed ones (Fernandez et al., 2008; Ranieri et al., 2014). Both original and generic medicines are falsified (Ranieri et al., 2014). Approximately 50% of medicines purchased online from retailers that do not have any physical address are falsified (Ranieri et al., 2014). Currently, numerous medicines and dietary supplements are skilfully falsified. Visual inspection, disintegration test or colour and shape analysis of tablets do not allow for 100% identification of counterfeit drugs.

WHO divides counterfeit drugs into six categories (WHO Counterfeit Drugs Guidelines, 1999):

1. Products without active ingredients, 32.1%.
2. Products with incorrect quantities of active ingredients, 20.2%.
3. Products with wrong ingredients, 21.4%.
4. Products with correct quantities of active ingredients but with fake packaging, 15.6%.
5. Copies of an original product, 1%.
6. Products with high levels of impurities and contaminants, 8.5%.

In order to assess whether a drug has been falsified, the drug itself (Fernandez et al., 2008) or its packaging (Kwok and Taylor, 2012) can be evaluated. Analytical techniques for determining the authenticity of a medicament generally focus on determination of the content of the active substance (active pharmaceutical ingredient (API)) and/or excipients. For this purpose, techniques such as high-performance liquid chromatography (HPLC) (Deconinck et al., 2013), mass spectroscopy (MS) (Fiori and Andrisanob, 2014), Raman spectroscopy (Sacréa et al., 2011) or Fourier transform infrared spectroscopy (FTIR) (Ortiz et al., 2013) are primarily used. They enable to quantitatively determine the amount of API, excipients or any impurities.

Although counterfeit drugs can be visually almost identical to the original ones, they almost always differ in terms of the active

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ingredient content and/or excipients. The use of other excipients and/or another active ingredient content entails a change in the heat capacity of the counterfeit solid dosage form. The proper mass heat capacity is the heat capacity determined on a per object mass basis. This value is intensive, which means that it is not dependent on the quantity but the kind of material. This enables to identify/distinguish the ingredients of solid dosage forms.

In order to evaluate the heat capacity of the test drugs, they were heated to a temperature of 60 °C and then the dynamics of their cooling down to room temperature (22.2 °C) was studied. The use of a relatively narrow range of temperatures (max. 60 °C) helped to prevent the drug from thermal degradation, which enabled to use it for further analysis. The temperature change was recorded using a thermal imaging camera - the image was recorded with a frequency of 60 Hz.

Thermal analysis techniques such as thermogravimetry (TG), differential thermal analysis (DTA), and differential scanning calorimetry (DSC) are the accepted methods of drug characterization. They are used to assess the purity of pharmaceutical substances, polymorphism, solvation and hydration, to evaluate the melting point and above all to predict the shelf life and half-life of a drug (Yoshida et al., 2010). It should also be noted that dynamic thermal analysis, as proved in this publication, can be used to characterize solid dosage forms and thus distinguish between genuine and counterfeit solid dosage forms.

The applied technique of dynamic thermal analysis, supported by mathematical methods and methods of image analysis and processing, enables to distinguish the original drug from the fake one with 100% probability. It should be emphasized that it is a non-destructive technique and it also enables to perform screening tests—a few, several dozen or a few hundred samples can be tested at the same time.

The proposed fast and non-destructive technique allows for the quick withdrawal of the counterfeit drug from the market using relatively inexpensive tools and without the need for time-consuming chemical procedures. This technique, after validation, does not require any special preparation of samples or qualified personnel. It can be therefore used at border crossings, in drug control offices and by other authorities to verify the authenticity of drugs.

2. Material and methods

2.1. Tablets

Original and fake tablets of one of the most counterfeited drug – Viagra® manufactured by Pfizer – were compared. The original drug was purchased at a pharmacy in Poland. The study used Viagra® with the highest dose of sildenafil citrate—100 mg. The counterfeit drug was purchased on the black market from a seller who advertised on the Internet. According to the information given on the counterfeit drug packaging it should also contain 100 mg of sildenafil citrate. Fig. 1 shows the original and counterfeit drugs. 10 counterfeit Viagra® tablets (marked as $V_{count}1 - V_{count}10$) and 4 original Viagra® pills (marked as $V_{org}1 - V_{org}4$) were examined. Both original and counterfeit tablets had almost identical mass: 620 mg ± 15 mg and 624 mg ± 20 mg respectively and the size and shape of the tablets were almost identical (Fig. 1). Volume of the original and counterfeit tablets were also similar: 444.73 mm^3 and 517.4 mm^3, respectively. The volume of the tablets was determined using 3D scanner Steinbicher COMET L3D.

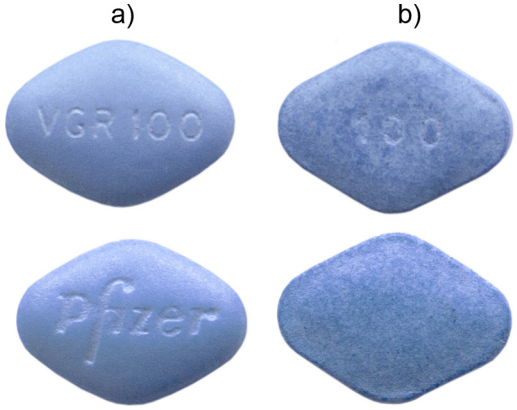

Fig. 1. Genuine (a) and Counterfeit (b) Viagra® tablets.

2.2. Heating

Original and counterfeit tablets were heated to 60 °C using Memmerit UFB 500 sterilizer. The use of a sterilizer with forced air enabled even heat distribution in the heated tablets. The tablets were heated for 10 min—the time was sufficient to reach the stable temperature of the tablets. The original and fake tablets were placed at the same time in the sterilizer on a cardboard tray. The tablets were placed on a tray in such a manner so as to prevent thermal influences between test samples. Then after 10 min of heating in the sterilizer preheated to 60 °C the tablets were taken out together with the tray on which they were previously placed. Acquisition of thermal images started immediately after their removal from the sterilizer.

2.3. Data collection

In the applied research model, the tablets were heated with the use of an infrared radiation. Object excitation (heating) occurred in a specified period of time—t_1.

$$Up(t) = A \times (\Phi(t) - \Phi(t - t_1)) \quad (1)$$

where A, excitation amplitude; Φ, heaviside, step function.

As a result of heating, the temperature of the tablets changed in accordance with the thermal properties of the material from which they are made. Taking into consideration a single point of the tablet, its temperature is represented as follows:

$$S_k^p = S_{n+c}^p = S_n^p \cup S_c^p = \{S_1^p, S_2^p, S_3^p, \ldots, S_n^p\} \cup \{S_{n+1}^p, S_{n+2}^p, S_{n+3}^p, \ldots, S_{n+c}^p\} \quad (2)$$

where n, total number of samples measured during heating; c, total number of samples measured during cooling; p, index of a measurement point.The area of the test tablets indicated the measurement area. Measurement parameters were adjusted to the thermal imaging camera resolution, the used lens, the distance of the camera detector from the analysed object and the thermal properties (emittance) of the test tablets.

The FLIR T420 thermal imaging camera operating in the wavelength range of 7.5–13 μm was used for the acquisition of infrared images. The acquired image resolution was 320 × 240 pixels and the thermal camera resolution was <0.045 °C. The images were registered at 60 frames per second. Measurements were made at room temperature of 22.2 °C and relative humidity of 65%. The room was adjusted to infrared measurements—no windows, no heat or cold sources, the lack of air-moving devices. Data acquisition was performed using FLIR ResearchIR software version 3.5.

As for the interpretation of thermograms, Fig. 2 it should be noted that colour coding for a given temperature is only valid per figure as given on the colour-coded temperature scale to the right in each thermogram.