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A literature review of analytical methods used for identification and determination of counterfeit drugs

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Abstract: Drug counterfeiting is a serious problem in developed and developing countries. Different types of drugs are produced factitiously and endanger the health of the patients. Quick inspection methods for counterfeit drugs are of vital necessity. Since counterfeit drugs are becoming increasingly more sophisticated, additional analytical techniques are necessary to detect these counterfeits. Qualitative and quantitative analysis of pharmaceutical active ingredients could be achieved by chromatographic and spectroscopic methods. Various analytical techniques such as Liquid Chromatography/Mass Spectroscopy, Gas Chromatography/Mass Spectroscopy, Nuclear Magnetic Resonance and Raman/ Infrared Spectroscopy are used to determine the counterfeit product. In this study, analytical methods used for identification and determination of counterfeit drugs were summarized.

Keywords: Counterfeit drugs, chromatography, spectroscopy, analytical methods, drug determination, counterfeiting

Introduction

Counterfeit drugs are threatening public health globally in recent years. The lack of global definition complicates the problem. To solve this problem WHO is defined the counterfeit drugs which is accepted globally as pharmaceutical products that have ‘‘been deliberately and fraudulently mislabeled with respect to identity and/or source‘‘ (http://apps.who.int/iris/bitstream/10665/65892/1/WHO_EDM_QSM_99.1.pdf). Counterfeit drugs are medical products and drugs which were produced as substandard therefore they underwhelm the treatment (http://www.who.int/medicines/services/counterfeit/overview/en).

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Different types of drugs including anticancer drugs, antibiotics, hypertension drugs, cholesterol lowering drugs, hormons, streoids, cheap versions of painkillers and antihistaminics are produced factitiously and endanger the health of the patients. After all it is more serious that in developing countries the fatal drugs like AIDS, tuberculosis and malaria drugs are prevalently exposed fraud (http://www.who.int/medicines/services/counterfeit/overview/en).

There is also a growing interest to herbal drugs and food supplements apart from the above mentioned drugs. Problems including contamination, additives, toxicity, effective dose errors or incorrect tagging are on the agenda for these products as well as all the issues for the pharmaceutical preparations. Turkey has a wide variety of herbal species due to the climate features. Therefore, there are a lot of different herbal based "nutraceutical", "supportive food", "food supplement" types which were released with a license by Turkish Ministry of Food, Agriculture and Livestock. Since these products might contain a large number of chemicals in different variants; it is obvious to have ilnesses and even deaths caused by side effects (Turkmen et al., 2014).

In order to struggle with counterfeiting and counterfeit drugs and to distinguish the actual product from the fake, fast and precise analytical methods are essential. In this review the types of drug counterfeiting and the methods used for the identification and the determination of counterfeit drugs were discussed.

Types of Drug Counterfeiting

Drug counterfeiting could be grouped into six categories below in terms of fraud types and sizes and different analytical methods could be used for identification (Degardina et al., 2014)

1. Products that do not include active substance: 32.1 %

2. Products that include the wrong amount of the active substance: 20.2 %

3. Products that are produced with the wrong material: 21.4 %

4. Products that are made with correct amount of the active substance but fake packaged: 15.6 %

5. The original copy of the exact product: 1 %

6. Products containing high amounts of contaminants: 8.5 % (2)

It could also clearly be seen in the following table how drug counterfeiting diversifies depending on the drug type and quality objectives (Table 1).

Table 1. The different types of counterfeit drugs on the market (Degardina et al., 2014)

	Fraud Types	**Properties**
Drugs	Drugs with no active ingredient	The original drug counterfeiting in industrialized countries
	Drugs containing wrong active substance	Generic drug counterfeiting in developing countries
	Drugs containing correct active substance with wrong dose	
	Shadow copies	Lifestyle drugs sold over the internet in industrialized countries
	The original drugs with expired dates	Drugs packaged with fake dates
	Hybrid fake drugs	Drugs containing used materials
Active substances	Active substances sold as approved but unapproved materials	
	Active substance produced with a different process	
	Active substance produced by off the record firms and labeled fraudly	
Medical devices	Drugs produced with copied original packaging	
Packaging	A copy of original packaging	
Documentation	Fake documents (certificate of conformity, import status, etc.)	

Identification of Counterfeit Drugs

Fast, precise and practical analytical methods are essential to identify counterfeit drugs. Liquid/gas chromatographic and nuclear magnetic resonance (NMR) /infrared (IR) spectroscopic methods could be used for fast qualitative and quantitative analysis of pharmaceutical active substances.

Identification of counterfeit drugs usually begins with a quick visual inspection. Pharmaceutical product packaging is reviewed in detail and compared the original with the suspected packaging. Analyses of packaging products such as boxes, blisters, bottles and brochures consist of studies like bulk data, printing, holograms and logos (Degardina et al., 2014). Then physical characteristics of drugs such as weight, shape, and color are evaluated and compared with the reference. Chemical-physical tests, colorimeter and dissolution tests, density or viscosity measurements are sometimes very effective, cheap and fast methods however do not provide much information about the content (Rodomonte et al. 2010; Kaur et al. 2010; Al-Hussain, 1996).

Since the time is an important factor for the detection of counterfeit drugs, the use of solid vibration spectroscopy has been increased in recent years. It is possible to obtain results by Mid Infrared (MIR), Near Infrared (NIR) and Raman spectroscopy measurements within minutes. The spectra of the counterfeit drugs taken with these methods could be compared with the spectrum of original product and the fraud could be determined.

Recently among the fast analytical methods the use of X-ray Diffraction with Mass Spectrometry, Ion Mobility Spectrometry, Direct Analysis In Real Time (DART) and Desorption Electrospray Ionization (DESI) are seen frequently (Likar et al. 2011; Santamaria- Fernandez et al. 2009). In addition, isotope determination methods could help to determine the profiles of synthesis as well as the fake common origin (Marini et al. 2010).

Fake drugs fast diagnosis and control for portable Raman Spectroscopy and Fourier Transform Infrared Spectroscopy (FTIR) is one of the commonly used methods (Feng et al. 2013; Deconick et al. 2012; Sacre et al.2011; Custers et al. 2014; Ortiz et al. 2013; Anzanello et al. 2014).

Jung et al. were used a new approach with image processing and statistical analysis for automatic classification of fake Viagra and Cialis tablets (Fig.1). A high-resolution VSC5000 device and the combination of morphological operators with bridging technique have been used to process of displaying of tablet from the floor (Jung et al. 2012).

Figure 1. Images taken from sample Viagra and Cialis tablets. The first three pillars are of the original tablets whether others fake (Jung et al. 2012).

In the study by Feng et al., three types of counterfeit drugs were used where the first type does not contain the active substance but the ingredients (sucrose, dextrin, etc.). The second type of drugs contains completely different type of substance than the original one (e.g., the original drug is hypoglycemic sulfonyl ureas, glimepride etc. but the drug contains metformin), the third type of drugs contains cheaper active substance with a similar structure to the original (e.g. glimepiride instead of Glibenclamide). These three types of counterfeit drugs were analysed by using portable Raman spectroscopy with modified regional flat-line viewing ("Local Straight-Line Screening"; LSLS) and primary component analysis (PCA). The LSLS algorithm based on infrared spectroscopy were used to identify the synthetic drug blended to herbal medicine. Detection of the suspected counterfeit drugs was achieved by LSLS method which adapted to Raman spectroscopy by weighing made false positive false negative ratios modification (Feng et al. 2013).

Spectroscopic techniques are preferable due to the fast and specific detection of counterfeit drugs with little sample and without sample preparation. Raman spectroscopy were used by Veij et al. (Deneckere et al.2008) for the detection of fraud Viagra®, by Trefi et al. (Trefi et al. 2008) for the detection of fraud Cialis® and by Roggo et al. (Roggo et al. 2010) for the identification of the pharmaceutical tablets with different manufacturing technologies.

Vredenbregt et al. (Vredenbregt et al. 2008) were used the near infrared spectroscopy (NIR) scans to identify homogeneity of Sildenafil Citrate in the original Viagra®. Storme-Paris et al. (Storme et al.2010) and Chong et al. (Chong et al. 2009) were also used the same technique for identification

of counterfeit antibiotics. The counterfeit Lipitor® identification was achieved by the comparison of Raman Spectroscopy with NIR results by Peinder et al. (Peinder et al. 2008). Maurin et al. (Maurin et al. 2007) were determined the presence of Sildenafil Citrate and/or certain additives in fraud Viagra by X-Ray powder diffraction (XRD). In the study conducted by Pierre et al. 55 counterfeit and 9 real Viagra®, 39 counterfeit and 4 real Cialis® were analyzed by Raman, NIR and FT-IR spectrometer and the technique or combination of techniques were determined for the detection of illegal drugs in forensic investigation by authorities for the identification of the fake Viagra® and Cialis®. Samples were visually divided into groups and compared with originals in Table 2 (Sacre et al.2010).

Table 2: Some photos for fraud Viagra and Cialis tablets and the originals (Sacre et al.2010).

Viagra®-like Sample photos	
	Professional imitations
	Non-professional imitations
	Original
Cialis®-like Sample photos	
	Professional imitations
	Non-professional imitations
	Original

Determination of Counterfeit Drugs

Chromatographic and spectroscopic methods are used for the

determination of the content (Gaudiano et al. 2008; Nyadong et al. 2008; Arthur et al. 2004). The choice of the method depends on the amount of an existing substance and the laboratory resources.

In GC-MS studies mostly the content of residual solvents like ethanol, 2-propanol, acetone, ethyl acetate, chloroform, carbon tetrachloride, benzene, dichloromethane, toluene and ethylbenzene were determined and compared with original tablets (Deconinck et al.2013; Custers et al. 2014; Deconinck et al.2012). Deconinck et al. were determined above mentioned solvents by using Phenomenex 624 capillary column (60 m×0.32 mm; 1.8 µm film thickness) with an oven temperature program from 60°C (held for 5 min) to 270°C at 25°C/min and 270°C was held for 10 min. The temperatures of the injection port, the ion source, the quadrupole and the interface were set at 160, 230, 150 and 280°C, respectively. For the identification of the solvents present in the samples the mass spectrometer was operated in full scan mode. For quantification and validation the mass spectrometer was operated in SIM mode (100 ms dwell times) (Deconinck et al.2012).

In the study by Custers et.al, head-space gas chromatography was used. The samples were incubated in a 10 mL headspace vial and shaken at 120°C for 15 min. Next, 1 mL of the vapor phase was injected in to the GC–MS system in a split injection mode (split ratio 6.8:1). The temperatures of the headspace loop, the transfer line and the EPC volatiles interface were set at 135, 145 and 160°C, respectively. The solvents were separated on a Phenomenex 624 capillary column (60 m x 0.32 mm; 1.8 mm film thickness). The oven temperature was programmed from 60°C, which was held for 5min, to 270°C at 251°C/min. 270°C was held for 10 min, making a total run time of 23.4 min (Custers et al. 2014).

The high-performance liquid chromatographic methods used for the counterfeit drug determination were based on reverse phase chromatography. Rozet et al. were determined Viagra fraud using HPLC-UV. In this study the development and validation of a fast method to detect and quantify the three authorised phosphodiesterase type 5 inhibitors and five analogues were described. The method was based on the use of a sub-2 microns polar-embedded column with a gradient using acetonitrile as organic modifier and 10 mM ammonium formate buffer (pH 3.5) as aqueous

component of the mobile phase. The separation was achieved in less than 4.5 min. The method was compared to the registered HPLC method for the assay of Viagra® which was considered as the reference method. The method was also compatible with on-line coupling mass spectrometry and will significantly reduce analysis times and solvent consumption (Rozet et al.2011). Hollein et al. were developed an HPLC method for the determination of five most widely used antimalarial drugs amodiaquine, mefloquine, proguanil, artemether and lumefantrine (Hollein et al. 2014). 18 nonsteroidal anti-inflammatory drugs, five preservative, paracetamol, chlorzoxazone, caffeine and salicylic acid were determined by Mbinze et al. with a fast and specific HPLC method. These molecules were the most common counterfeit drugs that are used alone and/or in combination. In the study, several HPLC separation conditions were optimized for targeted subsets of 27 molecules used alone or in combination. In order to provide faster analysis, method was transferred to ultra high performance liquid chromatography (UHPLC). The robustness of the methods firstly developed with conventional HPLC system was found mandatory to permit the geometric transfer. For the validation of the developed HPLC methods, the accuracy profile as decision tool for the determination of four compounds was used for a common NSAIDs combination marketed in some African countries consisting of capsules containing paracetamol, ibuprofen, caffeine and potentially 4-aminophenol (Mbinze et al. 2012).

LC-MS/MS is one of the common used method for the determination of drug fraud. It is possible to reliably assay a large number of counterfeit drugs in a short period of time due to the speed and sensitivity of the method. Lebel et al. were developed a method for simultaneous determination of 71 counterfeit erectile dysfunction (ED) drugs and 11 natural excipients. The method was achieved by using Orbitrap XL mass spectrometer in a short period of time as 10 minutes. The separation was achieved in 10 min using 2.6 µm fused-core C18 particles in a 100 × 2.1 mm column coupled to an LTQ Orbitrap XL mass spectrometer operated in positive electrospray mode. The sample extraction (tablets, capsules, oral liquids and herbal products) was achieved by using methanol. The results obtained were compared with traditional HPLC-UV and GC-MS methods. The intra- and inter-assay precision were ≤3.2% and 10.4% respectively across three concentrations of standards (50, 250 and 1000 ng/mL) measured for 4

representative drugs spiked into a tablet-based matrix. The mass accuracy was less than 3 ppm. The developed LC-MS/MS method for ED drugs was successfully applied to 32 samples and the drug identifications were in 100 % agreement with those obtained by the conventional methods HPLC-UV and GC-MS. (Lebel et al. 2014).

A study of six corticosteroid (betamethasone 17-valerate, beclomethasone, beclomethasone dipropionat, methylprednisolone, budesonide, flunisolid) was conducted using UHPLC-MS/MS to determine these substances in order to prevent the illegal use in the cosmetics and natural products. Since the corticosteroids are banned in cosmetics, effective analytical methods are required to rapidly screen over the counter products in health care shops for counterfeit corticosteroids. The separation was achieved on a C18 column (150 mm×2.0 mm I.D.) by using the following mobile phase: A (0.1% formic acid in acetonitrile), B (0.1% formic acid in water) in a linear gradient (from A–B 25:75, v/v to A–B 95:5, v/v in 30 min) at the flow rate of 0.3 mL/min. The detection was performed with an ion trap (IT) mass spectrometer in positive polarity, total ion current (TIC) and tandem mass modalities for qualitative purpose; single ion monitoring (SIM) mode was used for quantitative analysis on the ESI generated most abundant ion for each steroid. The method having 29 – 95 ng/mL LOQ levels was fully validated. The developed method was the first study for this mix of glucocorticoids in cosmetic products by using a fully validated method (Fiori et al. 2014).

In another study 43 commercial erectile dysfunction drugs (Viagra, Cialis, Lazar, Libiden, Maxfil, Plenovit, Potent 751, Rigix, Vimax, Pramil 75 and Pramil) and 65 fake medicines (Viagra and Cialis) were analyzed using a similar method. In this work, methanol extracts of crushed tablets were investigated by ultra performance liquid chromatography (UPLC) with diode array detection (DAD) coupled with eletrospray ionization in the positive ion mode (ESI(+)) quadrupole time-of-flight (Q-Tof) mass spectrometry (MS). It was observed in most cases the presence of other active pharmaceutical ingredients (APIs) than specified on the package (TAD and SLD). Additionally, high concentrations of TAD and SLD were detected in counterfeit samples when compare with observed values for a typical commercial product. (Ortiz et al.2013).

A recent study was conducted by Cho et al., to determine 26 anabolic-androgenic steroids (AASs). Ultra-liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) method was developed and validated for screening for the presence of 26 AASs and quantification of the detected AASs in counterfeit drugs and dietary supplements. In addition, the developed method was applied to real products that are designed to improve muscle mass and strength (Cho et al. 2015).

Discussion

Drugs contain different active ingredient written on the label and/or contain the actual substance in different doses and/or with no active substance and/or with fake labels are defined as counterfeit drugs and are serious hazard and threat for human life and health. Fast, precise and practical analytical methods are essential to identify and determine the drug counterfeiting in our country and around the world. Qualitative and quantitative analysis of pharmaceutical active ingredients could be achieved by chromatographic and spectroscopic methods. Advanced analysis techniques such as liquid chromatography/mass spectroscopy, UHPLC, gas chromatography/mass spectroscopy, liquid chromatography/time of flight mass spectroscopy, Nuclear Magnetic Resonance and Infrared Spectroscopy are used to determine the chemical structure of the product.

Conclusion

By the implementation of required regulations, practices and policies and enlightment of the public about the harms of counterfeit drugs, drug counterfeiting could be prevented in the world. In order to struggle with counterfeiting and counterfeit drugs and to distinguish the actual product from the fake ones, fast and precise analytical methods are essential. In this review the types of drug counterfeiting and the methods used for the analysis of counterfeit drugs were discussed.

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