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Review Article

Counterfeit Drug Detection: Recent Strategies and Analytical Perspectives

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ARTICLE INFO | ABSTRACT

Pharmaceutical counterfeiting is becoming a significant and life-threatening issue both in developed and developing countries and comprises a major dispute for analytical laboratories to identify and characterize them. This review intends to give a peculiar overview of the techniques described in literature for rapidly screening samples suspected of being counterfeits. In addition to visual and simple chemical approaches, fast and sophisticated analytical techniques are usually required for successfully differentiate counterfeit medicines from the real stuffs. These are described under the headings of different strategies, including Raman spectroscopy, near Infrared Spectroscopy, Fluorescence and phosphorescence approach, Nuclear magnetic resonance, X-ray diffraction, Chromatography, Mass spectrometry. Conjunctive efforts should be positioned toward research and development in fast, low cost, and efficient ways of detecting substandard pharmaceutical preparations at different stages of its existence by using sophisticated instruments.

Keywords: Counterfeit, analytical tools, raman spectroscopy, near infrared spectroscopy, nuclear magnetic resonance

1. INTRODUCTION

According to WHO 6 percent of medicines in the world are counterfeited and 10 percent according to FDA [1]. Counterfeit drugs, as defined by The World Health Organization (WHO), are those which are "fraudulently and deliberately mislabeled with respect to their source and identity". Drug counterfeiting can apply for both branded and generic products and counterfeit medicines may include products with the wrong ingredients, fake packaging, without active ingredients, or with insufficient active ingredient" [2]. The primary counterfeited therapeutic categories are lifestyle drugs. The risks associated with these drugs are mostly due

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to the presence of impurities and toxic compounds, the presence of unexpected active ingredients, too high quantities of active ingredients, new unknown molecules, and wrong information concerning the application of the drug [3]. Other categories such as antineoplastic drugs or cardiovascular drugs, antibiotics, antimalarials, antiretroviral etc., have also been detected. The national and international authorities have to be supported with data about counterfeited samples from laboratory analysis.

Hence, several laboratories throughout the world have specialized in the analysis and detection of counterfeit preparations. More knowledge about these drug samples can lead to a better fight against counterfeiting and developing awareness of the risks by the patients. Several reviews have already been published in the domain of counterfeit pharmaceutical preparations. Most of them focus on a specific and particular technique; e.g., nuclear magnetic resonance [4], or on a specific type of counterfeited products, e.g., PDE-5 inhibitors [5]. A few more general reviews have been published, in which the different techniques that could be applied in the analysis of counterfeit medicines were discussed, with some applications [6]. Several analytical methods are employed for detection of drugs which may be substandard. They range from simple thin layer chromatography and colorimetry to more sophisticated techniques such as Raman spectroscopy and X-ray diffraction. This review intends to provide an updated review of the approaches used in the detection and characterization of counterfeit pharmaceutical preparations, with a focus on the role from few simple chemical approaches to sophisticated spectroscopic and the chromatographic approaches described in literature. These techniques have great potential in the analysis and characterization of counterfeit medicines and illegal pharmaceutical preparations, because they allow not only the quantification and detection of active ingredients, but also provide a final image of the sample composition. These characteristics have made the number one technique for risk evaluations of illegal substandard preparations.

2. SIMPLE CHEMICAL APPROACHES

Thinlayer chromatography and colorimetry are most common methods for analyzing drug quality. Colorimetry allows the active drug ingredient to be accredited by comparison with a known standard of drug. This technique is cheap, sensitive and specific .The intensity of a positive color reaction is proportional to drug concentration with visual assessment. Usually, color intensity can be measured by applying a portable filter photometer [7].

Green et al have described a colorimetric analysis to determine the quality of anti-malarial drug artesunate in South Asia. A little portion of a tablet is scraped into a tube having a base; a buffer is added with their agent [8]. A yellow color is generated indicating the presence of artesunate. They are also worked on analysis for mefloquine using tablet

disintegration behavior [9]. Counterfeit medicine may contain the sufficient amount of active ingredients but may fail the test for disintegration.

Bulk properties of matter include weight, density, viscosity, solubility, optical rotation and refractive index. These can be easily measured by rugged and low cost equipment. Green's group has applied refractive index (RI), pH, solubility and crystal morphology to distinguish counterfeit from real artesunate tablets. This technique involved pulverizing and weighing the tablet before suspending in alcohol. The filtered extract is applied for performing various analyses. Comparisons were achieved with chloroquine, acetaminophen and aspirin tablets, all are of similar size, shape and weight to artesunate tablets. Real tablets had a pH 3.5 while counterfeit artesunate, acetaminophen and chlroquine were 6.5 while aspirin had a pH of 2.0. Solubility was determined by the addition of alcoholic extract to water and a light meter was applied to measure precipitation. By plotting the number of drops of sample against signal, it was easy to differentiate the counterfeit medicine from genuine. Counterfeit samples generate very dense precipitates while the former generates a milky precipitates. Crystal morphological studies were performed by allowing crystals for settle after standing for a few hours. Genuine drug samples showed rod-shaped crystals while counterfeit samples did not crystallize [10].

The refractometer is a portable and simple instrument which utilizes the principle of refraction. Differences in refractive index value were multiplied by two conversion factors: excipient compensation factor and artesunate specific conversion. The results of the determination of 33 tablets showed specificity and sensitivity were 90% and 83% respectively.

3. SPECTROMETRIC APPROACHES

Several spectrometric techniques have been widely applied to detect counterfeit drugs ranging from simple Ultraviolet spectroscopy to more sophisticated Raman spectroscopy technique. The below mentioned figure clearly illustrate the combined efforts of the all spectrometric approaches used in counterfeit drug detection [6].

3.1 RAMAN SPECTROMETRIC TECHNIQUE

Raman spectroscopy provides specific information on the identification of analytes, characterization of sample matrices, and molecular spectroscopic information useful in the structural elucidation of unknowns [11]. Raman spectrometric technique explains the shift in wavelength of a small fraction of radiation scattered by molecules, having different frequency from that of the incident beam [12]. This shift in wavelength depends upon the chemical structure of the molecules responsible for scattering. Raman spectroscopy utilizes scattered light to gain knowledge about molecular vibrations which can provide information regarding the structure, symmetry, electronic environment and bonding of the molecule, thus permits the quantitative

and qualitative analysis of the individual compounds [13]. Aided by relentless instrumentation advances, these techniques have now applied common use for the study of solid samples [14]. Raman spectroscopy has achieved many applications in the pharmaceutical industry such screening of polymorphism, quantitative determination of active pharmaceutical ingredient (API) content, solid state analysis [15] and distribution of active ingredients by Raman mapping [16, 17]. Raman spectroscopy can be widely used in a laboratory for quality control application and also for on-line analysis [18, 19].

Raman is complementary to many methods. More anti-malarial drugs bought in Nigeria and Ghana has failed quality control measurements employing Raman Spectrometric measurements than with physical examination [20]. Unlike the case of NIRs where long duration exposure of drugs lead absorption of water from the outer atmosphere which affects the NIRs analytical results, Raman has low vibrational activities due to presence of water [21]. This technique can be applied remotely and developed method on one instrument can be transferred to another one for application in detecting counterfeit medicine. Structural differences in imipramine tablets based on raman microscopic evaluation techniques was explained [22].

The tablets containing imipramine hydrochloride as active drug and excipients were microcrystalline cellulose, hydroxypropylmethylcellulose as binder, maize starch and magnesium stearate as lubricant. 7 different manufacturing procedures were applied. The mechanical behaviors of the tablets were analyzed with device Pharma Test PTB-311, measurements of 10 tablets for every compression. Raman-mapping spectra were observed. For spectral acquisition and optical imaging, objectives of $10\times$ and $100\times$ were applied. Since results indicate that different manufacturing technology result in morphological and polymorphism variations may help to trace the technique used for purpose of production. Presence of moisture is the only one reason responsible for change in morphology of API. When active ingredients are compressed without performing any wet granulation, the spectrum of the imipramine particles indicate same morphology as observed in the original API. RSD of <9% in HS granulation and >17% in any other batch is because API forms a homogeneous layer upon drying the particles of the excipients. Hence, the smaller the RSD value, there is more homogeneous particle distribution will occur.

Research has been carried out on the feasibility of Raman spectroscopy and near infrared (NIR) as rapid screening technique to differentiate between counterfeits and genuine of the cholesterol-lowering Lipitor. Classification, based on partial squares discriminant analysis (PLS-DA) models, proved to be successful for both spectroscopic tools, irrespective of whether lovastatine or atorvastatine has been used as the active pharmaceutical ingredient (API) [21].

Raman spectroscopy combined with chemometrics has been utilized for the detection and chemical profiling of counterfeit drugs. Method in two steps has been executed here. The first step explains the identification of pharmaceutical tablets and capsules and the detection of their counterfeits. A nonlinear classification technique, the Support Vector Machines (SVM), is computed along with a correlation with the database and the determination of Active Pharmaceutical Ingredient (API) peaks in the suspicious product. If a counterfeit is observed, the second steps enable its chemical profiling among former counterfeits in a forensic intelligence purpose. For this second step, a classification based on correlation distance measurement and Principal Component Analysis (PCA) is applied to the Raman spectra of the counterfeits [23].

3.2 NEAR INFRARED (NIR) TECHNIQUE

Infrared spectral measurements have been used for a broad range of applications – from analysis of liquids, gas compositions and solid substances to detailed characterization of each physical state. One of the fundamental properties of chemical bonds is that they exhibit vibrations at distinct frequencies. The vibrational frequency of a chemical bond is intrinsic to the chemical bond of interest [24].

NIRsretains many advantages like, it possess minimal or no sample preparation; informative spectra provide information on both physical and chemical incidents; several modes can be applied depends upon the type of, offers onsite through the use of fiber optic probes; diffuse reflectance and modes of scattering. Detection of counterfeit antimalarial tablets was accomplished in one application. 62authentic artesunate tablets and 55 substandard tablets obtained from the market of south-East Asia were identified and analyzed [25]. The diastereomer of tadalafil was first time identified in counterfeited pharmaceuticals preparation with the aid of near infrared spectroscopy [26].

Classical least square analysis [27] was utilized to analyze the measurements obtained from near infrared chemical imaging of Heptodin tablets. The main advantage of this method is that no any previous information and data regarding the origin of the counterfeit medicine is required in order to obtain good result. Clear difference had observed between tablets with high contents of the active drug contain lamivudine, and those with low content. A recently developed statistical image analysis method and symmetry parameter image analysis, was described [28]. These methods have more objective, and will help in minimizing interpretation errors. A review on the applications of chemometrics and near infrared spectroscopy in pharmaceutical applications was previously prepared [29]. NIRs based chemometric technique proposed for the fast screening and determination of sildenafil citrate, the active ingredient in Viagra formulations [30]. The main demerit of this method is the high possibility of false positives. This technique is able to correctly forecast the presence and

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absence of the active ingredient for at least 98% of the analyzed 103 samples of different compositions and origins.

3.3 FLUORESCENCE AND PHOSPHORESCENCE TECHNIQUE

Due to the high cost of camptothecin (CPT), anticancer drug, are frequently a subject of counterfeiting which has low water solubility and toxic effects. For the determination of camptothecin as trace contaminant in anticancer preparation containing irinotecan and topotecan, a method based on room termparature phosphorimetry has been applied [31]. Prior to this, a fast method based on light induced fluorescence had developed for the analysis of pharmaceutical active ingredients [32]. An example for this is the reaction between fluorescamine and nonfluorescent oseltamivir phosphate to produce an adduct which is quantifiable at 485 nm using excitation of 380 nm [33]. Laser-induced fluorescence was utilized for the trace determination of camptothecin in anticancer pharmaceutical preparations [34]. A recent method for the application of small array for discriminate between functional groups in drug molecules was published [35]. The arrays produced from 3 reactive cruciform fluorophores in 6 different solvents, were able to distinguish 10 different carboxylic acid [36]. A technique for identification of heparin counterfeiting has been proposed based on the sensor molecule heparinase I inhibition by over sulfated chondroitin sulfate and polymer-H [37]. When heparin is incubated with heparinase I, the resulting fluorescence intensity can be applied for the determination of heparin. These all methods are depending on the characteristics of the bulk compounds, a method was described which was capable to constitute the elemental profiles of pharmaceutical formulations in addition to thickness of coating determination [38]. X-ray fluorescence (XRF) is a suitable technique for characterization of the presence of metals. This method has advantageous features like multi elemental capability, short analysis time, high precision, good detectivity, and is nondestructive, which makes it perfect to be extended to variety of samples. Thus XRF presents an excellent analytical methodology for detection of active ingredients, excpients and covering agents as calcium phosphate, titanium oxide and iron oxide (P, Ca, Ti and Fe) that can be detected directly by XRF.

A light Induced Fluorescence (LIF) method was described for determining the active drug contents in tablets [39]. This method predicts total content fluorescent active drug of tablets, was applied for two sets of ingredients. One set contains triamterene with colloidal silicon dioxide and lactose as excipients. The second set contains caffeine with magnesium stearate, microcrystalline cellulose and lactose as excipients.

3.4 NUCLEAR MAGNETIC RESONANCE (NMR) TECHNIQUES

Quantitative NMR was utilized with good reproducibility to the detection of various drugs in reasonable time [40]. Where many techniques fail, NMR can give valuable information

for resolving the structures of related compounds. The principles of the different NMR methods for studying complex mixtures spectra can be found elsewhere [41]. A comprehensive review on recent applications and techniques of quantitative NMR spectroscopy has been described [42]. Characterization of analogue of vardenafil was carried out using NMR approach [43]. ^{2}H NMR, quantitative ^{13}C NMR was also proposed for the investigation of counterfeit pharmaceutical preparations [44]. For this application ^{13}C profiles were constituted for two active ingredients, aspirin and paracetamol [45]. All short-comings have been addressed with the advent of the proposed method. Its application to ibuprofen has produced a precise site-specific ^{13}C isotope profile. This was achieved through application of 180° adiabatic composite refocusing pulses with improved refocusing of the chemical shift of ^{13}C along pulsesequence. A poly nuclear nuclear magnetic resonance may be more complex andrequires complex statistical analysis and may prove very vital in the identification of counterfeit drugs of various origins. Wawer et al [46] have described a poly-nuclear NMR consist of ^{13}C, ^{1}H and ^{15}N for the determination of sildenafil base and citrate in pharmaceutical dosage forms.

3.5 X-RAY DIFFRACTION (XRD) AND RADIO FREQUENCYMEASUREMENT TECHNIQUE

X-ray powder diffraction (XRPD) is a well suited analytical technique for the detection of pharmaceutical counterfeit. Now recent developments, such as ultra-fast X-ray detectors, make this a strong tool for quality control applications. Applications cover monitoring for structural changes that occur during policing, production, packaging or storage, and identification of counterfeit drugs. XRPD is a sensitive, versatile, and rapid method that provides detailed information regarding the chemical composition and crystallographic structure of natural and manufactured materials. It allows qualitative and quantitative phase analysis of the various constituents of the complete solid drugs, including the API and the fillers, with low detection limits and control of the final dosage form. X-ray diffraction (XRD) and radio frequency measurements can serve individually of Raman and IR spectroscopy in the analysis of counterfeit medicines. The operational principles of diffraction patterns for the study of different types of materials have currently been explained in details [47]. Recently, XRD was employed in the identification of sibutramine, rimonabant polymorphs and their analogs available in counterfeit products bought via the internet [48]. Magnetically molecularly imprinted polymers were prepared and used for the extraction of sildenafil due to its high recognition site specificity and high binding capacity for sildenafilmolecule [49]. A new method describing DNA fingerprinting is developed for the counterfeit drugs authentication [50]. Acierno et al [51] overcomed the possible alteration of molecular structures of the drugs due to exposure to electromagnetic radiation. Even after 72 hour exposure of insulin to electromagnetic field from RFID

tracing systems, no differences observed in the test and control samples. One of the drawbacks of the RFID technique is the possible cloning of RFID tags. To overcome financial loss, mechanisms for clones detection should be keep in place by RFID-chip manufacturers. Some of the routes by which clones can be detected have been accumulate in a current review [52]. Currently, a hardware-enabled technology has been developed which would enable the creation of physically-unique RFID tags and make them nearly impossible to exactly clone [53]. This certificate of authenticity method serves as a fingerprinting mechanism that uses random 3D scattering structures which are unique and special for individual compounds in drugs.

3.6 CHROMATOGRAPHIC APPROACHES

3.6.1 Thin Layer Chromatography (TLC):

TLC has been used for the identification of essential drugs such as paracetamol, acetyl salicylic acid, ibuprofen, prednisolone, dexamethasone and hydrocortisone in preparations and betamethasone, hydrocortisone acetate and metamizol. TLC combination with ultraviolet (UV) detection and microcrystal tests was extensively used for identification of phentermine (Ionamin) adulteration. The identification showed that the counterfeit capsules contained only phenylpropanolamine and caffeine [54]. Recently Hu et al. [55] proposed a fast chemical identification system consisting of two TLC systems and two chemical color reactions for the characterization of counterfeit macrolide antibiotic preparations. This technique is able to distinguish 14-membered and 16-membered macrolides basedon the color reactions. The TLC systems are then used to identify the concerned macrolide.

Moriyasu et al. [56] described another application using TLC for the identification adulteration of sildenafil in health supplements. After identification of sildenafil, high-performance liquid chromatography– diode array detection (HPLC–DAD) expose doses ranging from 25 to 45 mg of sildenafil citrate per tablet. Wu et al [57] described one example for the detection of the counterfeit herbal medicine called Curculigo Orchiode. For this objective TLC and UV spectrometry were applied along with the classical morphology test.

3.6.2 Liquid Chromatography (LC):

Liquid chromatography (LC) is often used in the detection and characterization of counterfeit pharmaceutical products. LC, in combined with different detectors, is applied in this domain for several objectives. The first is a method for target analysis (for presence of one or more known compounds) and as a quantification method. LC combined with MS is often applied in screening of counterfeit samples and structural elucidation. Another application of LC is the use of chromatographic fingerprints. Chromatographic fingerprints are often explained in the quality control of herbal products, and in the determination between the necessary plants and those sold as counterfeits.

3.6.3 Liquid Chromatography-Ultraviolet Spectroscopy (LC-UV):

L with UV or DAD is an important technique for the characterization of illegal pharmaceutical preparations. In literature, several methods are discussed for the analysis of active ingredients in counterfeit preparations and for impurities and not registered analogs. HPLC–UV/DAD has extensively and widely been used in the determination of counterfeited, adulterated and imitation samples containing PDE-5 inhibitors.

Nagaraju et al. [58] described a technique that is able to quantify and separate sildenafil and its impurities. They were able to determine sildenafil in a chromatographic run of 15 minutes and its process related impurities, both in pharmaceutical formulations and bulk products. Park and Ahn [59] screened 105 counterfeit drug samples, seized in Korea, for the presence of sildenafil and tadalafil applying HPLC–UV. The observations showed that 73 of the 105 samples contained sildenafil in doses ranging from 4.3 to 453.2 mg per tablet. 7 samples contained tadalafil in doses from 2.2 to 40.4 mg per tablet. The ratio of cases having more than 100 mg sildenafil was 50% and 78% had more than 20 mg of tadalafil. Gratz et al. [60] developed an HPLC–UV technique for the quantification and detection of PDE-5 inhibitors after confirmation of their presence with LC–MS. 40 botanical products were screened by this group, from which half were identified positive for PDE-5 inhibitors. The majority of the samples contained active ingredients. Gaudiano et al. [61] used HPLC–DAD for the quality control of antimalarial tablets purchased from the market of Goma. The results showed not only that the tablets contained only 88.6% of the amount of quinine, but also that many impurities were found in amounts higher than the reference samples and the samples purchased on the Italian market. Mikami et al. [62] described an HPLC–UV method for the screening of benzodiazepines in herbal products.

3.6.4 Liquid Chromatography-Mass Spectroscopy (LC-MS):

LC–MS is the method of choice when dealing with counterfeit pharmaceutical preparations. This method allows both target analysis and screening of unknown preparations for the presence of drug compounds. A lot of non-registered analogs and impurities have been detected from the group of PDE inhibitors. The majority have been detected using LC–MS, combined with IR and NMR techniques. Bogusz et al. [63] described an LC–MS-MS method for screen herbal medicines for the presence of synthetic adulterants. The described method was able to screen for adulterants of different clinical groups including analgesic drugs, antidiabetic, antibiotics, aphrodisiacs, antiepileptic drugs, anabolic and hormonal drugs, psychotropic drugs and weight reducing compounds. Chen et al. [64] developed a LC–linear ion trap (QTRAP)-MS technique to screen health supplements for the presence of lipid lowering and blood pressurea gents, anti-diabetic drugs, sedative drugs,

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aphrodisiac drugs and weight reducing compounds. Another application was described by Hall et al. [65], who applied LC–MS for the characterization of artesunate tablets purchased from Asian countries; 23 of 34 samples did not contain artesunate; 10 of the 11 that contained artesunate in the correct dose. From the 23 samples not containing artesunate, 5 contained paracetamol and 8contained erythromycin. Wang et al.[66] described LC–MS to perform a review of 22 herbal weight reducing preparations for the presence of sibutramine and its analogs, fenfluramine, phenolphthalein and orlistat. Out of the 22 samples, 10 were positive for sibutramine, 3 for phenolphthalein and 2 for N-mono-desmethyl sibutramine.

4. CONCLUSION AND FUTURE DIRECTION

In conclusion, all techniques, spectroscopic and chromatographic, have their applications in the detection of counterfeit pharmaceutical preparations, based on the purpose of the study. For normal counterfeit detections spectroscopic methods are very useful, but they have some disadvantages in the detection of adulterations. Separation techniques have the advantage to allow a complete analysis of the sample: detection of active substances, classification as illegal, imitation or genuine and risk prediction. The drawbacks are the limited possibilities for miniaturization and application in portable devices. In general, it can be concluded that health practitioners, authorities and patients should be sincere. Analytical results concerning these substandard products are necessary to support health authorities in their decisions and prevention campaigns, and also as part of legal dossiers for pharmaceutical crime.

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