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Research Article

Non-Destructive Analytical Techniques for Detection of Counterfeit Pharmaceutical Preparations

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ABSTRACT

Analytical methods development and validation play important roles in the discovery, development, and manufacture of pharmaceuticals. The development of the pharmaceuticals brought a revolution in human health. These pharmaceuticals would serve their intent only if they are free from impurities and are administered in an appropriate amount. Currently, counterfeit medicine is a significant issue for the pharmaceutical world, and it targets all types of therapeutic areas. These pharmaceuticals may develop impurities at various stages of their development, transportation and storage which makes the pharmaceutical risky to be administered thus they must be detected and quantitated on spot even. For this analytical instrumentation and methods play an important role. Many of the methods require varying degrees of irreversible sample preparation (removal from sealed container or blister pack, crushing into powder, dissolution with solvent, etc.) and therefore cannot be used in non-destructive mode. Now, direct methods to detect counterfeit products and to analyze the properties of the product itself are available. This can either be achieved using laboratory-based testing of purchased or seized samples, or can increasingly be done using portable, non-invasive techniques. This review highlights the role of the analytical instrumentation and the analytical methods in assessing the quality of the drugs.

KEYWORDS

Non-Destructive Analytical Techniques, Pharmaceutical Counterfeit, Portable analytical techniques

1. INTRODUCTION

The counterfeiting of medicines has been known of since around 1990 and the problem has escalated – in both developing and developed countries. Currently, counterfeit medicine is a significant issue for the pharmaceutical world, and it targets all types of therapeutic areas. The World Health Organization (WHO), estimated that 5–7% of pharmaceutical products worldwide are counterfeit goods, has defined counterfeit drugs as those which are ‘‘deliberately mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products with counterfeit products including drugs with the correct ingredients or with the wrong ingredients; without active ingredients, with insufficient active ingredient or with fake packaging.’’ High-consumption, expensive and innovative drugs along with well established generic drugs are most readily affected. [1, 2]

Counterfeit concept: Counterfeit products are often produced with the intent to take advantage of the superior value of the imitated product. [3]

The increase in the number of counterfeits penetrating into the open market has created the need for a product authentication approach in tracing and tracking the product anytime, anywhere. [4] Many of the methods require varying degrees of irreversible sample preparation (removal from sealed container or blister pack, crushing into powder, dissolution with solvent, etc.) and therefore cannot be used in non-destructive mode. This can be a drawback for a number of reasons: there may not be the time or facilities during a field investigation to undertake complex sample preparation; the owner of the consignment to be checked may reasonably object to having their consignment opened so that a sample can be removed for analysis; if the product is packed and sealed in bulk, then opening it for examination could render it unsellable and represents a significant and unnecessary financial loss to the owner if the batch is subsequently confirmed as genuine. For these reasons, and often because of the cost and bulk of the instruments used, most of the techniques are used for secondary analysis of suspected counterfeits that have been identified in the field by other, usually non-destructive, methods are useful. [5,6] The ideal analytical tool or method for detecting counterfeit medicines should be of low cost and fast, and should have high level of reliability. It should avoid error in classifying counterfeit drugs as genuine and vice-versa. Spectroscopy is a light interacting with a matter as an analytical tool and now day’s works as a mobile spectroscopy. [7]

2. MATERIALS AND METHODS

Non-destroyable methods

These methods involve the analysis of pharmaceutical dosage form content without any sample preparation. The true and false identification of Pharmaceutical dosage forms could be performed with specific peaks and the absorption ratios of active ingredients. [8]

Figure 1: Various non-destroyable techniques

2.1. X-Ray Diffraction:

X-ray diffraction is based on constructive interference of monochromatic x-rays and a crystalline sample. These x-rays are generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate and directed towards the sample. The interaction of incident rays with the sample produces constructive interference. [9]

Portable instruments operate under the same technical principles as laboratory diffractometers, but using a small, portable X-ray source. By comparing the observed diffraction spectrum from the test sample with known spectra in a database, the machine can identify the presence or absence of key ingredients or contaminants. The portable XRD machines are not as cheap as the portable infrared machines. [10]

2.2. Infrared Spectroscopy:

Infrared radiations lies between the visible and microwave portions of the electromagnetic spectrum. Infrared waves have wavelength longer than visible and shorter than microwaves. The infrared portion of the spectrum is commonly divided into three sub-regions, termed near, mid, and far based on their proximity to the visible spectrum. Near infrared refers to the part of the infrared spectrum that is closest to visible light and far infrared refers to the part that is closer to microwave region, while mid infrared is the region between these two. Each region of the spectrum can provide different information on the molecular structure of the sample.[11]

Measurements taken in a production facility or in the field, using portable or handheld devices, can be cross referenced to a database of known reference scans to identify the constituents of the sample. Most common non-destructive approach used to check pharmaceuticals in situ, while still in their packaging. [12]

Near Infrared (NIR):

Absorption bands corresponding to mid-IR region (4000-2500 cm-1) are used for the identification of compounds. Rapid and simple, because it involves minimal or no sample prep; very informative spectra which give information on both physical and chemical phenomena; different modes can be used depending on the type of sample transmittance, diffuse reflectance and scattering modes; offers onsite analysis through the use of fiber optic probes.

This method is more objective, and will help in minimizing errors of interpretation that abound in the highly subjective approach of visual examination of in homogeneity arising from differences in mode of drug preparation.[13, 14]

Table 1: Differentiable Regions of IR

No.	Region	Range cm^{-1}	Vibrational /Rotational Information
1.	Near IR	14000-4000	Changes in vibrational and rotational levels, electron transitions
2.	Mid-IR	4000-400	Changes in fundamental vibrational levels of most molecules
3.	Far-IR	400-20	Rotational energy level changes

Fourier Transform Infrared (FTIR) Spectroscopy:

FTIR, or mid-infrared spectroscopy, was the first vibrational spectroscopy technique to be widely used for material identification. FTIR has excellent selectivity.[15]

Attenuated Total Reflection Fourier-Transform infrared spectroscopy (ATR-FTIR) might be useful for the screening of counterfeit medicines since it is easy to use and little sample preparation is required. This study proposes a combination of ATR-FTIR and chemometrics to discriminate and classify counterfeit medicines.[16, 17]

2.3. Raman Spectroscopy:

In Raman Spectroscopy, a laser shone on a sample is scattered and this scattering leads to two principal types of processes known as stokes and anti-stoke: In the stokes process, which is parallel to absorption, scattered photons are shifted to lower frequency due to abstraction of vibrational energy by the analyte molecules. For the anti-stoke process, parallel of emission, scattered photons are shifted to higher frequency arising.[18]

As a non-destructive technique, the method was successfully applied to the determination of thickness of tablet coating under different coating conditions. A rugged, handheld instrument based on Dispersive Raman Spectroscopy (DRS) has been developed. This instrument can be used remotely and methods developed in one instrument can be transferred to another for application in tracking counterfeited drug preparations from picking up energy released from molecules. These effects are displayed as Raman Shift in a typical Raman spectrum.[19]

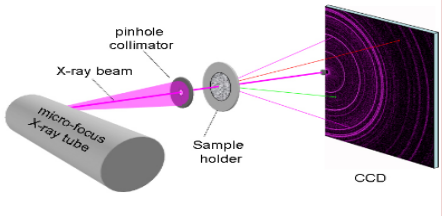
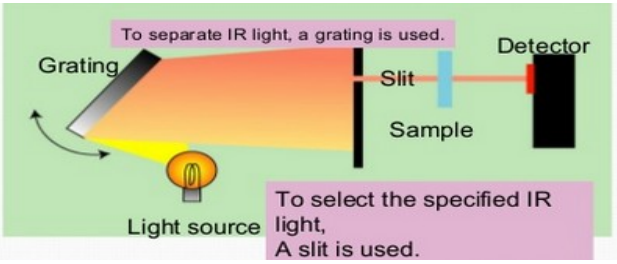
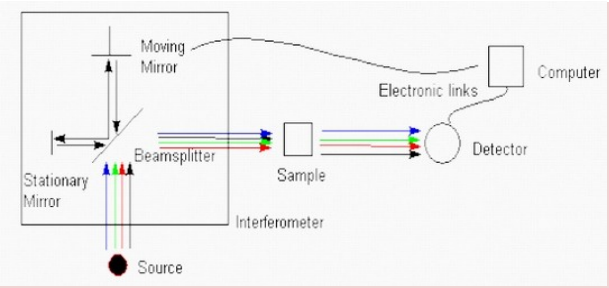
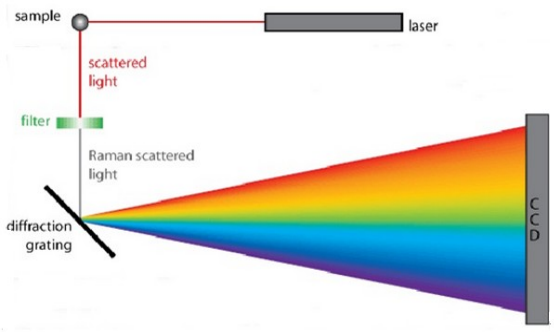
Raman spectroscopy can analyze substances through glass and plastic, allowing pills to be analyzed while still in blister packs or bulk API to be analyzed while double-bagged in drums. For portable devices, little or no sample preparation is needed before performing a Raman analysis. [20]

2.4. Terahertz Imaging:

Terahertz technology has the advantages of being non ionizing, non destructive, and able to image at depth. The technique's ability to act as both an analytical tool as well as for monitoring or inspection applications has fuelled interest in many markets including security, military, medical, and pharmaceuticals.[21]

The region of the electromagnetic spectrum between infrared and microwaves, (1mm-30 micron) at frequencies around 1 Terahertz, has recently been exploited for non-destructive testing devices, which allow imaging of solid dosage forms in three dimensions.[22, 23]

Terahertz pulsed spectroscopy (TPS) and terahertz pulsed imaging (TPI) are two novel techniques. These are used for the physical characterization of pharmaceutical drug materials and final solid dosage forms. [24]

Technique	Working	Device (Example)
X-Ray Diffractometer		
Near Infrared		
FTIR		
Raman Spectroscopy		

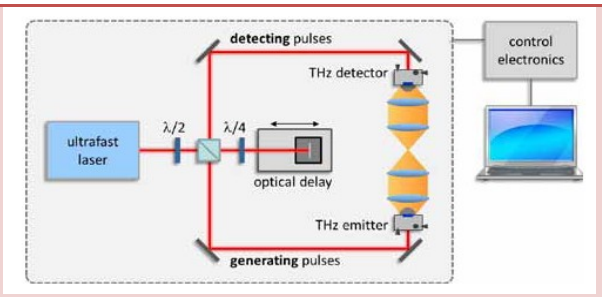
Terahertz Imaging	 

Figure 2: Non-destructive techniques with their working principle and instruments

2.5. Other Miscellaneous Methods

In addition to the various techniques established above for tracking counterfeited items of pharmaceutical origin, there are numerous other methods that are employed for this end.

- Multidimensional atomic force microscopy (m-AFM) can then be employed to track these patterns as a way of fighting Counterfeits.[25]
- To complement 2H NMR, quantitative 13C NMR was also employed for the investigation of counterfeiting in drug preparations.[26, 27]
- Fourier-transform infrared imaging in combination with electrospray ionization linear ion trap mass spectrometry. This method was recently applied for the analysis of counterfeit antimalarial tablets with high sensitivity of detection.[28]
- To detect trace levels of drugs with high rapidity and sensitivity, ion mobility spectrometry and direct analysis in real time (DART) spectrometry can be used.[29]
- One technique that has the ability to efficiently ionize both polar and non polar analytes is called desorption atmospheric pressure photo-ionization (DAPPI) in which sufficiently high MS spectrum could still be obtained from drugs placed afar from MS extension inlet than conventionally practiced.[30]
- Capillary electrophoresis (CE) became popular in the 1980s, different applications can now be found in the pharmaceutical arena.[31]
- While some compounds are fluorescent in nature therefore, a sensitive method based on Light Induced Fluorescence (LIF) was proposed for determining the API contents in tablets.[32, 33]
- The molecules in several pharmaceutical tablets were directly analyzed using nanospray desorption electrospray ionization mass spectrometry (nano-DESI MS). Nano-DESI is an ambient surface sampling technique which enables sampling of molecules directly from the surface of the tablets without any sample pretreatment.

2.6. Advantages of portable, non-destructive methods

Advantages of portable, non-destructive technologies are several: [34, 35]

- ✓ Spot checks can be made quickly and without warning.
- ✓ Evidence is provided almost immediately, allowing rapid seizure of suspect items without recourse to brand owner verification.
- ✓ It is not necessary to equip every customs post or train every officer.

- ✓ Expensive equipment can be controlled and monitored securely.
- ✓ Opportunities for corruption can be minimized.

2.7. Limitations

The limitation of CD3, X-ray Diffraction, Raman, and NIR portable devices is that they depend on the use of reference libraries of pharmaceuticals to identify falsified and substandard products. These libraries must be routinely updated when new generics or new compounds come to market, which may limit their feasibility. X-ray diffraction is currently only used in the laboratory settings. [36, 37]

3. CONCLUSION

The prevention of counterfeiting is largely based on deterrence, and a high likelihood of detection increases the risks for the criminals who are producing fake drugs. As counterfeiting is a multibillion dollar business, albeit heinous, the perpetrators will continue to develop ingenious ways to circumvent regulatory systems. Because of this, relentless effort should continue to be directed toward research and development. In low cost, fast and efficient means of detecting counterfeit drugs at their points of origin, in transit or on delivery, to give the regulatory bodies an edge in this fight against the heinous profession of 'selling death to humanity'. So, the identification of suspect, fake, or altered packaging is often a useful when looking for counterfeit medicines themselves, the rapid, nondestructive, and unequivocal detection of the counterfeit dosage forms directly is very essential.

4. REFERENCES

1. Andrei A. Bunaciu & et al (2013). Spectroscopic Analytical Methods for Detection of Counterfeit Pharmaceutical Preparations – A Mini-Review. Journal of Science. 26, 3, 407-417.
2. ICC Counterfeiting Intelligence Bureau, The International Anti-counterfeiting Directory, ICC Commercial Crime Services 2008.
3. Ye Rodionova and A. L. Pomerantsev (2010). NIR based approach to counterfeit-drug detection. Trends in Analytical Chemistry.29, 8, 795-803.
4. K. Deisingh (2005). Pharmaceutical counterfeiting. Analyst. 130, 271-279.
5. A. Nuhu Abdulmumin (2011). Recent analytical approaches to counterfeit drug detection. Journal of Applied Pharmaceutical Science. 01, 05, 06-10.
6. B. Berman (2008). Strategies to detect and reduce counterfeiting activity. Bus Horizons. 51, 191-199.
7. Priyanka P. Patel, Divyang G. Sanghadiya, Bharat Tank (2013). Study the analysis of solid oral dosage forms including the different modern analytical techniques. JPRBS. 2, 5, 45-53.
8. Masoom Raza Siddiqui, Zeid A. Al Othman Nafisur Rahman (2017). Analytical techniques in pharmaceutical analysis: A review. Arabian Journal of Chemistry. 10, S1409–S1421.
9. Ashish Chauhan & Priyanka Chauhan (2014). Powder XRD Technique and its

Applications in Science and Technology. J Anal Bioanal Tech. 5, 5.

10. Jan K. Maurin and et al (2007). The usefulness of simple X-ray powder diffraction analysis for counterfeit control. The Viagra· Journal of Pharmaceutical and Biomedical Analysis. 43, 4, 1514-1518.

11. Yves Roggo, Pascal Chalus & et al (2007). A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies. Journal of Pharmaceutical and Biomedical Analysis. 44, 683–700.

12. J. Luypaert, D.L. Massart, Y. Vander Heyden (2007). Near-infrared spectroscopy applications in pharmaceutical analysis. Talanta. 72, 865–883.

13. Javed Ali, Pramod K, SH Ansari (2010). Near-Infrared Spectroscopy for Nondestructive Evaluation of Tablets. Sys Rev Pharm. 1, 20-26.

14. Gabriele Reich T (2005). Near-infrared spectroscopy and imaging: Basic principles and pharmaceutical applications. Adv. Drug Del. Reviews. 57, 1109– 1143.

15. Faten Farouk and et al (2011). Fourier transform infrared spectroscopy for in-process inspection, counterfeit detection and quality control of anti-diabetic drugs. Spectroscopy. 26, 297–309.

16. Graham Lawson, John Ogwu (2014). Counterfeit Tablet Investigations: Can ATR FT/IR Provide Rapid Targeted Quantitative Analyses? J Anal Bioanal Tech. 5, 5.

17. Custers D, Cauwenbergh T & et al (2015). ATR-FTIR spectroscopy and chemometrics: An interesting tool to discriminate and characterize counterfeit medicines. J Pharm Biomed Anal. 10, 181-189.

18. Pushkar P. Kalantri, & et al (2010). Raman spectroscopy: A potential technique in analysis of pharmaceuticals. Der Chemica Sinica.1, 1, 1-12.

19. J. K. Mbinzea, P. Y. Sacréa (2015). Development, validation and comparison of NIR and Raman methods for the identification and assay of poor-quality oral quinine drops. Journal of Pharmaceutical and Biomedical Analysis. 111, 21–27.

20. Izake EL (2010). Forensic and homeland security applications of modern portable Raman spectroscopy. Forensic Sci Int. 202, 1-8.

21. M. Kalra, M. Khatak, S. Khatak (2011). Recent advanced -smarter techniques of Analysis. Int. J. of Pharma Professional's Research. 2, 2, 23-29.

22. J. A. I, Zeitler & et al (2007). Analysis of Coating Structures and Interfaces in Solid Oral Dosage Forms by Three Dimensional Terahertz Pulsed Imaging. J. Pharm. Sci. 96, 2, 330–340.

23. C. J. Strachan & et al (2008). Terahertz applications for the analysis of solid dosage forms. Pharm. Tech. Eur. 18, 11, 26–32.

24. R. P. Cogdill & et al (2006). An efficient method-development strategy for using teratertz pulse spectroscopy. J. Pharm. Inno. 1, 1, 63–75.

25. Lal R, Ramachandran S and Arnsdorf MF (2010). Multidimensional Atomic Force Microscopy: A Versatile Novel Technology for Nanopharmacology Research. The AAPS J. 12, 716-728.

26. Holzgrabe U (2010). Quantitative NMR spectroscopy in pharmaceutical applications. Prog Nucl Mag Res Sp.57, 229-240.

27. U Holzgrabe and M Malet-Martino (2011). Analytical challenges in drug counterfeiting and falsification-The NMR Approach. J Pharmaceut Biomed. 55, 679–687.

28. Ricci C, Nyadong L, Fernandez FM, Newton PN and Kazarian SG (2007). Combined Fourier-transform infrared imaging and desorption electrospray-ionization linear ion-trap mass spectrometry for analysis of counterfeit antimalarial tablets. Anal Bioanal Chem. 387, 551–559.

29. M. D. Likar, G. Cheng, N. Mahajan and Z. Zhang (2011). Rapid identification and absence of drug tests for AG-013736 in 1mg Axitinib tablets by ion mobility spectrometry and DARTTM mass spectrometry. J Pharmaceut Biomed. 55, 569–573.

30. T.J. Kauppila, A. Flink, M. Haapala, and R. Kostiainen (2011). Desorption atmospheric pressure photoionization–mass spectrometry in routine analysis of confiscated drugs. Forensic Sci Int.210, 206–212.

31. T. G. Morzunova (2006). Capillary Electrophoresis in Pharmaceutical Analysis (A Review). Pharm Chem J-USSR. 40, 158-170.

32. R. Domike, S. Ngai and C.L. Cooney (2010). Light induced fluorescence for predicting API content in tablets: Sampling and error. Int J Pharm.391, 13–20.

33. Carlos Cardoso-Palacios and Ingela Lanek off (2016). Direct Analysis of Pharmaceutical Drugs Using Nano-DESI MS. Journal of Analytical Methods in Chemistry. 3, 2, 53-58.

34. Rakesh Kumar (2014). Recent Applications of Analytical techniques for counterfeit drug analysis: A Review. Int. J. Pharm Tech Res. 6, 2, 646-665.

35. D. Bansal, S. Malla, K. Gudala K. P. Tirari (2013). Anti-Counterfeit Technologies: A Pharmaceutical Industry Perspective. Sci Pharm. 81, 1, 1-13.

36. M. Davison (2011). Pharmaceutical Anti-Counterfeiting: Combating the Real Danger from Fake Drugs. First. John Wiley & Sons, Inc.

37. C. Cahyadi, A. D. Karande, L. W. Chan, PWS Heng (2010). Comparative study of nondestructive methods to quantify thickness of tablet coatings. Int J Pharm. 398, 39-49.