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ANALYTICAL METHODS USED FOR IDENTIFICATION AND DETERMINATION COUNTERFEIT MEDICATIONS: A COMPREHENSIVE REVIEW

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ABSTRACT:

Fake medicines have become an increasing global health problem, affecting confidence in the public, patient safety, and medical systems.These counterfeit medications are often hazardous or ineffective as they consist of wrong, spurious,or missing active therapeutic agents. financial incentives, regulatory errors, advanced developing techniques, And an increase in online transactions are the main causes of the rise in counterfeit drugs. Different instrumental techniques have been developed to adress this problem. Chromatography techniques, mainly High Performance Liquid Chromatography (HPLC), are used for identification, ingredient separation and accurate detection of any differences from documented formulations. Spectroscopic methods such as Raman, Fourier-transform Infrared (FTIR), and Near Infrared (NIR) Spectroscopy provide fast, harmless analyses of chemical and physical characteristics, providing unique fingerprints for medication testing.FTIR spectroscopy is used for rapid detection of chemical and physical properties which give unique molecular fingerprints for drug authentication. Several advanced techniques, such as microtomography and Raman microscopy,provide detailed surface and internal examinations, revealing structural and compositional irregularities. Additionally general methods such as visual inspection, physical testing, and thorough documentation verification help these techniques. Despite developments in technology, problems arise. Bcause of counterfeiters' shifting methods, inflated costs, and the world's limited authority to regulate. Therefore, ongoing development, validation, and use of affordable, portable analytical tools are crucial, as are increased

enforcement and international collaboration. In order to effectively detect, prevent, and regulate counterfeit pharmaceuticals and ultimately protect public health and sustain pharmaceutical quality worldwide, an integrated multi-technique strategy is essential.

KEYWORDS: HPLC, Spurious, Molecular fingerprints, Fourier-transform Infrared (FTIR)

INTRODUCTION:

A complex and rapidly rising global health issue, counterfeit drugs have a major effect on the health of the population, economic stability, and consumer trust in healthcare systems across the globe[1]. These counterfeit medications are Intentionally manufactured and marketed to mimic original pharmaceuticals, but they often have dangerous or inaccurate ingridents or None at all[2].They are an increasing problem in developed as well as developing nations due to a different factors, including busines incentives, regulatory imperfections, technology Developments in falsification,and rising online medication sales[8]. The Problem of fake medications has long been acknowledged as a major obstacle to guaranteeing the efficacy and safety of pharmaceuticals[11].Patients, healthcare systems,and reputable pharmaceutical businessesall suffer large financial losses as a result of the equally enormous economic impact[14].Falsified and poor medicines also damage the trust of the people, which results in a decreased commitment to treatment plans and suspicion of medical services[27]. In addition, the use of inappropriate or hazardous Substances in counterfeit medications may end up inadverse health outcomes which include allergic reactions, toxicity,or overdose, which can occasionally be more dangerous than the original ailment being treated[9].The growth of digital platforms and online pharmacies increased the situation by making it easier for counterfeit drugs to directly reach consumers[1]. With the use of complex packaging, holograms, QR codes, and digital identifiers that are difficult to identify without specialized tools, falsification techniques have become more complicated[20]. This requires the development of dependable identification approaches and technological solutions, such as analytical procedures like mass spectrometry, spectroscopy, chromatography, and more recent portable sensors, which help in on-site drug verification[9][16]. Despite these developments,there are many challenges to overcome in the fight against counterfeit drugs, including the international nature of the trade, the high cost of technological solutions, and the limited regulatory capacity. Illegal manufacturing facilities and organized crime networks exploit this weakness, enabling the international trade of counterfeit drugs;

therefore, to effectively combat this illegal transport, strict law enforcement and international cooperation are required[17].

Counterfeit Drugs

A counterfeit drug is defined as a medication that has been intentionally and fraudulently mislabeled in relation to its identity and/or source, modifying the identity, active ingredient, or contents of the genuine product (e.g., incorrect ingredients, no active pharmaceutical ingredient, improper or insufficient active ingredient, etc.) and/or the representation of the real product (e.g., packaging, labeling, documentation, etc.)[14]. Counterfeit drugs are dangerous and pose a serious risk to public health, as they may be harmful or inefficient. They ultimately interfere with treatment and impact the general public's health. According to the WHO, drugs that are purposefully and fraudulently mislabeled with regard to their identification and/or source are considered counterfeit[28].

Types of Drug Counterfeiting:

Depending on the substance, packaging, and purpose of deception, counterfeit medications can be classified into different of categories. Counterfeit pharmaceuticals have been characterized by the World Health Organization (WHO) as healthcare products that are intentionally and unlawfully mislabeled with respect to identification and/or source[28]. The main types of counterfeit medications are as follows:

Absence of Active Components:

There are no active pharmaceutical ingredients (API) in these imitation drugs. They may be entirely ineffective as they are made of inert substances like wheat, starch, or other fillers[2]. Since there is no therapeutic advantage for patients, these products pose a serious health risk.

Incorrect Quantity of Active Ingredients:

The active ingredient quantities in these medications is either over or under which are documented. While overdosing products toxicity or negative consequences, underdosing medications can cause treatment failure and contribute to drug resistance[14]. Antibiotics using lower-than-recommended dosages or fake antimalarials are two examples.

Inaccurate or Fake Active chemicals:

Some fake medications have entirely different active chemicals that could be harmful or useless[11]. For example, a drug which claims to treat malaria may include falsified material or irrelevant pharmacological substances that could be spurious or lack any therapeutic effect.

Counterfeit Packaging:

With little variations from original packing there may be a few slight variations, such as poor writing, mistakes in spelling, or modified logos, the packaging for these fake drugs is similar to that of genuine products[25]. The technique often tricks consumers and authorities by resembling original branding.

Contaminated or Impure Drugs:

Because of substandard manufacturing techniques or purposeful adulteration, some counterfeit goods may include hazardous substances or impurities which result in toxicity or serious responses.

Substandard Medicines (Closely Related Category):

These are genuine goods that fall short of quality standards, frequently as a result of substand ard handling, storage, or production, which reduces their effectiveness [14].

Adetailed types and examples are discussed in Tab no.1

Tab no.1-General Types and Examples of Counterfiet Drugs.

Type of Counterfeit Drug	Properties	Example Drugs
Drugs with no active ingredient	The original drug counterfeiting in industrialized countries	Fake Viagra, counterfeit antimalarials
Drugs containing wrong active substance	Generic drug counterfeiting in developing countries	Antibiotics with wrong compounds, fake antimalarials
Drugs containing correct active substance with wrong dose	Shadow copies	Substandard antibiotics, under-dosed antimalarials
The original drugs with expired dates	Drugs packaged with fake dates	Expired hypertension drugs repackaged
Hybrid fake drugs	Drugs containing used materials	Recycled or reprocessed pills
Active substances sold as approved but unapproved materials	Falsely labeled unauthorized ingredients	Unapproved steroids, hormones
Active substance produced with a different process	Alternative synthesis routes	Illegally synthesized generics
Active substance produced by off-the-record firms and labeled fraudulently	Unauthorized manufacture	Fake branded erectile dysfunction drugs
Medical devices produced	Fake medical devices	Counterfeit glucose meters

with copied original packaging		
Packaging	A copy of original packaging	Fake packaging of popular brands like Lipitor
Documentation	Fake certificates, conformity documents	Fake regulatory approvals and import permits

General Methods

Visual Inspection:

One of the basic method to identify counterfeit medications is visual inspection, which involves thoroughly examining the product and the packaging for any possible signs of manufacturing or abnormalities. Global health organizations, including the World Health Organisation and medication regulatory agencies, strongly advise this approach as an essential first phase in the screening process[7].

The packaging is checked visually for irregularities including misspelled words, irregular fonts, poor writing, and missing or incorrect data like batch or lot numbers, manufacturing details, and expiration dates. The physical state of the packaging is also important; broken, resealed, or abnormally light or heavy packaging may be signs of substitution or tampering.

In order to identify tiny flaws that counterfeiters could miss, including misplaced print, wrong colors, or incomplete logos, inspectors frequently compare packaging with a real reference. The medicine itself needs to be inspected in addition to the package. The size, shape, color, markings, texture, and coating of authentic pills and capsules are all the same. Due to subpar manufacture, counterfeit medications may exhibit irregular forms, uneven coloring, cracking, or cracks[1][11]. Occasionally, there may also be differences in flavor or fragrance. These physical differences from the original product are important markers.

Visual inspection is still a crucial and useful screening method even though it cannot ensure the detection of counterfeit pharmaceuticals because many counterfeiters create extremely convincing fakes. It presents qualitative information about drug identity and inflates discrepancies that call for additional physical and chemical testing. For those involved in dispensing or regulating medicines, being familiar with the authentic product's visual and physical characteristics enhances the likelihood of identifying counterfeits early and protecting public health[27].

Physical Tests

Examining the observable and quantifiable features of the medicine dosage form to find discrepancies with genuine items is one of the physical tests used to identify counterfeit drugs[16]. These tests evaluate the drug's mass and physical characteristics in addition to visual evaluation.

Typical physical examinations consist of Dimensions and Weight Measurements:

In accordance with established production requirements, pharmaceutical tablets or capsules from a legitimate batch have exact and consistent weight, size, and form.The onsistency of individual tablet weights within a batch is evaluated using weight variation testing. Significant variations could indicate subpar production or fraud. Similar to this, counterfeit goods may differ in tablet diameter, thickness, or capsule size as a result of inadequate quality controls during manufacturing[12][26].

Disintegration and Dissolution Testing:

Disintegration time is a measure of the breakdown of a pharmaceutical compound into smaller particles at the desired site, usually in a liquid medium, mimicking the stomach or intestinal environment[1]. Genuine medications meet the Pharmacopoeial requirements for disintegration, allowing proper drug release. Bioavailability may be influenced by counterfeit medications which disintegrate too fast or too slow, or none at all. Dissolution testing measures how quickly and to what extent a pharmaceutical drug dissolves in a solution, which is an important measure of drug efficacy, which often fails in counterfeit medicines[19].

Hardness and Friability

Tablet hardness testing gauges a tablet's mechanical strength by measuring the force needed to smash it. A tablet's propensity to crumble or break during handling and transit is evaluated through friability testing[16]. While counterfeit tablets may be excessively soft or brittle as a result of subpar formulation or processing, genuine tablets have constant hardness and low friability to guarantee stability.

Density and solubility

Density tests measure the mass of tablets or powders per unit volume, which is a measure of the uniformity of the formulation[1]. The degree to which a drug material dissolves in a specific solution is determined by solubility testing. Both are essential to the effectiveness of drugs and may be erroneous or contradictory in fake medications.

Documentation Checks

In pharmaceutical quality assurance and regulatory procedures, documentation checksare a key method for identifying Fake drugs[20]. These processes guarantee validity, traceability, and adherence to set standards; their failure Frequently reveals phony or counterfeit medications.

Key Documentation Check

Techniques Batch Manufacturing Record (BMR) Verification

Batch Manufacturing Record (BMR) verification plays a key role in detecting counterfeit drugs by carefully checking the accuracy and correctness of manufacturing documentation. In correlation with approved master formulas, genuine BMRs include accurate and verifiable records of batch numbers, raw material sourcing, production stages, operator signatures, packaging data, and quality checks. Differences in these records, such as missing or imitated batch data, mismatched signatures, and unexplained variations, tend to be evidence of counterfeit drugs. Verification includes checking online data, such as blockchain entries or serial numbers, with physical papers and looking for relevant audit trails[20]. Possible counterfeiting is indicated by discrepancies between the BMR and the real product or by missing approvals. In order to verify the authenticity of medications, this documentation check is an essential first step in the detection of counterfeit goods, supporting chemical and physical studies.

Certificate of Analysis (CoA) Authentication

Certificate of Analysis (CoA) verification is an essential step in identifying counterfeit pharmaceuticals by verifying that the test results and quality data match the manufacturer's original records. A comparison of batch numbers, product specifications, and test results with official manufacturer and regulatory databases are approaches to CoA authentication. Finding indications of fabrication, such as irregularities in fonts, logos, signatures, or security elements like watermarks or embossed seals, is the main goal of physical analysis of CoA documents[1][20]. Digital verification techniques verify the legitimacy and integrity of the CoA data via blockchain, QR codes, or secure electronic records. Conflicting quality standards, conflicting batch information, or a lack of verifiable permission are examples of discrepancies that may point to phony or inferior medications[10]. This documentation validation is critical for counterfeit drug detection and supports chemical and physical testing.

Analytical and Instrumental Techniques

Near-Infrared (NIR) Spectroscopy

Near-infrared (NIR) spectroscopy is a potent, non-destructive analytical method that is being increasingly used to identify fake drugs by evaluating the physical and chemical properties of pharmaceutical items[2]. Its implementation in counterfeit drug detection follows a structured procedure for accurate and reproducible results. To guarantee accuracy and consistency, the NIR equipment is then calibrated using common reference materials. In order to account for possible ambient fluctuations that could impact the spectral data, a baseline spectrum of the measurement environment is gathered. This step is essential for producing reliable and reproducible measurements when screening pharmaceutical samples. The construction of a spectral library is a crucial stage in this procedure. This involves acquiring and storing NIR spectra from authentic reference samples of the drug. These reference spectra serve as benchmarks for comparison with the test samples. For robust counterfeit screening, the library should ideally cover a range of legitimate product batches and contain data on known counterfeits to ensure comprehensive chemometric modeling. To analyze a sample, the pharmaceutical item is placed on the sample holder of the NIR spectrometer. Spectral data in the NIR band, typically between 780 and 2500 nm, are gathered by the device. Controlling external variables like temperature and humidity during acquisition is crucial for correct results because these might affect the components of spectral fingerprints, especially water content. The acquired NIR spectra are then processed using specialized software. To improve the quality of the spectral data, preprocessing techniques including data smoothing, baseline correction, and normalization may be used. Then, using sophisticated chemometric methods like Principal Component Analysis (PCA) or Partial Least Squares Regression (PLSR), statistical models are constructed that can distinguish between authentic and counterfeit medications based on their distinct spectral fingerprints. Following examination, the spectral profile of suspected samples is compared with that of the recognized reference library. The product is considered authentic if a match is discovered; notable departures from the reference point to a high probability of counterfeiting[1][2].

The procedure is validated with a variety of blinded real and fake samples to guarantee reliability, and a report is generated summarizing the findings of the analysis stating whether a sample matches authentic references or is suspected to be counterfeit. In field applications, portable NIR spectrometers can provide almost immediate identification, empowering regulatory, customs, and quality assurance teams to act quickly against counterfeit pharmaceuticals.

Chromatographic Techniques

High-performance liquid chromatography

High-performance liquid chromatography (HPLC) is a decisive analytical technique for identifying and measuring counterfeit pharmaceuticals because of its accuracy and sensitivity in separating pharmaceutical components[3][22]. To extract the active pharmaceutical ingredient (API) and other components, a tablet or capsule suspected of being counterfeit is first carefully prepared by weighing it, powdering it if necessary, and dissolving it in an appropriate solvent[5][13]. This solution is then filtered to remove any particulate matter, yielding a clear extract ready for analysis[19].

The prepared sample is injected into the HPLC instrument, where it is carried by a liquid mobile phase through a chromatographic column filled with stationary phase material. The mixture's components interact differently with the stationary and mobile phases as it passes through the column under high pressure, causing separation according to their chemical characteristics[16]. The instrument's detector, which usually uses ultraviolet (UV) absorbance, detects the unique retention time at which each component elutes. The detector creates chromatograms with peaks that represent each material in the sample[24]. It is possible to definitively determine the identity and quantity of the API and to identify any deviations, impurities, or undeclared substances that might point to counterfeiting by comparing the retention times, peak areas, and spectral characteristics of the sample with those of authentic standard substances run under identical conditions[16]. HPLC can also quantify the amount of active ingredient, thus identifying sub- or super-potent formulations, often seen in counterfeit drugs[24]. Method validation, which covers specificity, accuracy, linearity, and detection limits, ensures reliability for regulatory and forensic purposes[19]. Through this systematic approach, HPLC enables the rigorous and reproducible detection of counterfeit pharmaceuticals and protects patient safety[24][13].

Imaging and Microscopy

The detection of fake medicines is becoming more common with imaging and microscopic tools, providing clear views without damaging the medication or packages[4]. First, people check tablets, capsules, or wrappers for flaws on the surface, odd colors, also poor printing using a regular microscope. Some counterfeit drugs are made to look just like real medicines; however, using magnification might show tiny changes in how words are stamped, feel of the surface, and evenness of outer layers you can't see normally. Fancy scanning tricks, such as micro-CT, provide a clearer view inside the material. With this 3D scan method, you can check how the pharmaceutical medication is built, spot changes in thickness, yet see if ingredients are spread right. It shows hidden layers without breaking them apart while highlighting uneven spots or gaps where the mix did not stick. On average, how bright or dark a tablet looks, along with its texture, gives clues about real vs fake medicines; measurements make this clear. Instead of guessing, you see differences through visible flaws like cracked spots inside the tablet[7]. Because it doesn't damage the sample, the method works well when checking if copies match the original chemically. It also shows whether each batch was mixed evenly during production, not just once, but every time.

Raman microscopy and Fourier-transform infrared (FTIR)

Raman microscopy works well for spotting fake meds - no damage needed[30]. Instead of using "and," it maps where chemicals sit inside pills by scanning tiny areas. A laser hits the sample, then checks how molecules vibrate; each bond reacts differently. That pattern acts like a signature, showing what’s really in the pill. Scientists use these traces to stack up fakes against real ones, swapping comparison for verification. Missing medicine parts, wrong fillers, or hidden junk pop up clearly this way[30].

A big plus of Raman microscopy is that it spots tiny chemical variations and checks samples right through clear wrappers or layers, keeping proof intact[30]. Crime scene work proves today’s Raman tools, like handheld ones, quickly tell real items apart from fake copies by comparing unique spectral fingerprints, even if the knockoffs copy the original mix almost perfectly[15]. Smarts built into software sharpen results by weighing small spectrum shifts, whereas scanning features pinpoint exact zones where a pill may be tampered with or uneven inside.

FTIR imaging checks how drug samples soak up infrared light at different wavelengths[30]. Because every compound reacts differently, you can map where each one sits inside the pill. Instead of just spotting active ingredients, it flags organic impurities most tools miss. While Raman sees some things well, FTIR catches what it doesn’t - so using them side by side gives a fuller picture[30]. These methods don’t damage the sample, which means evidence stays intact for court or inspection later. Labs testing meds, border agents checking shipments, and crime labs all depend on this pair daily.

CONCLUSION

In conclusion, the identification and detection of counterfeit drugs necessitate a toolbox of analytical and instrumental methodologies to be applied, as a result of the higher technology in use for counterfeiting pharmaceuticals. Methods including the chromatographic (e.g., HPLC and GC-MS), spectroscopic (UV-Vis, Raman-, FTIR-spectroscopy), and imaging (various types of microscopy) techniques are accurate and reliable analytical tools for evaluating authenticity of pharmaceuticals' . Chromatographic methods enable quantification as well as determination of the quality and purity level of active substances and impurities. Spectroscopic or imaging technologies are widely used for non-destructive characterization at high resolution, providing detailed chemical and structural information. The use of such complementary analytical tools further improves the ability and validate real drugs versus counterfeits and greatly assists regulatory agencies, forensic laboratories, and QC units by differentiating between them when looked at together. In view of the changing tactics adopted by counterfeiters, there is a need for continued research, validation, and growth of rapid, economical, and portable analytical methods that can be employed as preferred tools to protect public health. This integrated method is the foundation of current anti-counterfeiting work and is crucial for drug safety and effectiveness worldwide.

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