Nanoparticles Based Sensors for Pharmaceutical Impurity Detection

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Abstract

Oral solid dosage (OSD) forms are frequently used due to their stability, ease of administration and relatively cheap manufacture. Their safety and therapeutic efficacy, however, relies on control of pharmaceutical impurities such as degradation products, residual solvents, elemental impurities and genotoxic impurities like nitrosamines. Conventional methods like high performance liquid chromatography (HPLC), gas chromatography (GC), liquid chromatography–mass spectrometry (LC–MS) and inductively coupled plasma mass spectrometry (ICP–MS) offer high sensitivity and regulatory acceptance but often demand extensive sample preparation, high solvent use, laboratory analysis and are not compatible with real-time process monitoring. Nanotechnology advances have created nanoscales sensing platforms for quick and sensitive detection of impurities. The high surface-to-volume ratio, tunable surface chemistry, enhanced catalytic activity, plasmonic properties and excellent electrical conductivity make gold nanoparticles, graphene derivatives, carbon nanotubes, quantum dots and magnetic nanoparticles attractive. These properties enable the low-level electrochemical and optical detection of impurities at parts-per-billion or parts-per-trillion. The use of magnetic nanomaterials allows the preconcentration and separation of samples from complex matrices. Integration with pharmaceutical manufacturing may help achieve rapid response, miniaturization, process analytical technology (PAT) and continuous manufacturing, as well as real-time release testing. Nanotechnology could facilitate green analytical chemistry by decreasing the amount of solvent used, by providing a microscale platforms, and by synthesizing environmentally friendly platforms. The conventional analytical limitations, principles of nano sensing, recent progress in nanoparticle-based impurity detection, and their applications in the pharmaceutical manufacturing, stability monitoring and sustainable analysis are discussed.

KEYWORDS: *Electrochemical Sensors , Impurity Detection, Nanoparticles, Pharmaceutical Analysis, Pharmaceutical Impurities, Pharmaceutical Manufacturing.*

1. Introduction

Oral solid dosage (OSD) forms, such as tablets and capsules, are still the most common types of drugs because they are easy to use, stable, patients can follow them, they are cheap, and they can be made in large quantities *[1,2]*. Even though OSD products have some good points, their quality, safety, and therapeutic effectiveness depend heavily on strict control of pharmaceutical impurities. Even tiny amounts of chemicals that weren't meant to be there can have a big effect on the stability, bioavailability, and safety of drugs for patients *[3]*. Any part of a drug substance or drug product that is not the intended active pharmaceutical ingredient (API) or an approved excipient is called a pharmaceutical impurity *[2]*. These impurities may come from a few places, such as synthetic intermediates, by-products of chemical reactions, degradation during storage, leftover solvents from manufacturing processes, or contamination from raw materials and processing equipment *[4]*. In OSD formulations, additional risks like hydrolysis caused by moisture, oxidative degradation, API-excipient interactions, and thermal stress during compression make impurities even more likely to form *[5,6]*.
There are three main types of impurities: organic impurities (which come from the process or from things breaking down), inorganic impurities (like elemental contaminants and catalyst residues), and residual solvents *[7]*. Degradation products that form during long-term storage are especially important in OSD systems because they need to last a long time. Furthermore, recent global regulatory warnings about nitrosamine contamination in commonly prescribed oral medications have heightened scrutiny on genotoxic impurities that present carcinogenic risks even at nanogram exposure levels *[8,9]*. International regulatory agencies have set up strict rules for impurity control to protect patients. The International Council for Harmonization (ICH) guidelines Q3A(R2) and Q3B(R2) set the standards for reporting, identifying, and qualifying impurities in new drug substances and drug products *[10,11]*. ICH Q3D also talks about elemental impurities, and ICH M7 gives a way to evaluate and control mutagenic impurities *[12,13]*.

These regulatory requirements mean that we need to make analytical methods that are very sensitive, selective, and stable, and that can find impurities at very low levels. Because genotoxic contaminants, such as nitrosamines, can cause cancer at very low exposure levels, regulatory bodies also provide a ideas for identifying the presence of nitrosamine impurities with risk assessment, confirmatory testing and risk mitigation approaches on tight management of these substances. Regulatory agencies have recently stressed the need for strict control of genotoxic impurities, because even very low levels of exposure can cause cancer. These changing rules call for analytical methods that can find trace impurities at nanogram/gram levels with a lot of selectivity and consistency. As pharmaceutical synthesis and formulation have become more complicated, impurity profiling has gone from being a normal part of quality control to a very important part of science and regulation. High-performance liquid chromatography (HPLC), gas chromatography (GC), liquid chromatography–mass spectrometry (LC–MS) and inductively coupled plasma mass spectrometry (ICP–MS) are now important tools for finding, naming, and measuring impurities *[14]*.

2. Limitations of conventional analytical techniques

Pharmaceutical quality assurance relies on impurity profiling as its fundamental method which enables compliance with modern regulations that govern genotoxic impurities and residual solvents and elemental contaminants. Regulatory authorities now mandate detection of certain mutagenic impurities at parts-per-billion (ppb) or even nanogram-per-day exposure levels *[15,17]*. The traditional analytical methods which include HPLC and UHPLC and GC–MS have achieved excellent reliability and regulatory approval but their existing constraints create difficulties for continuous manufacturing and real-time quality assessment and sustainable testing methods *[16]*.

2.1 Dependence on Laboratory-Centric, Offline Analysis

Most traditional chromatographic methods are carried out as off-line methods in which samples are removed from the production line and transported to a central laboratory for analysis. This workflow includes several sample preparation steps and may delay the detection of impurities, thereby limiting the possibility to immediately correct during production. Such delays may reduce the responsiveness of the process in continuous manufacturing systems, where quality assurance is increasingly dependent on

real-time process monitoring rather than end product testing alone. Moreover, the conventional analytical systems that are based in laboratories are hardly integrated with Process Analytical Technology (PAT) systems, limiting their use for the continuous monitoring of impurity levels that are constantly changing *[18]*.

2.2 High solvent consumption and environment burden

Chromatographic impurity profiling depends a lot on organic solvents like methanol, acetonitrile, and dichloromethane. These solvents raise the cost of doing business, make dangerous waste, add to the toxicity of the environment, bring up worries about green chemistry programs *[19]*. As the global pharmaceutical industry focuses on sustainability and being environmentally responsible, analytical workflows that use a lot of solvents are being looked at more closely. Green analytical chemistry principles call for less use of solvents, smaller systems, and detection platforms that use less energy. Traditional chromatographic systems only partially meet these standards *[20]*.

2.3 Time intensive and multiple-step sample preparation

Finding ultra-trace impurities, especially genotoxic impurities and nitrosamines, often needs: Steps for preconcentration, Extraction in solid phase (SPE), derivatization, Cleaning up the matrix. These extra steps make the analysis more complicated and add variability. Also, they slow down throughput and make batch release timelines longer. This delay can have a big effect on supply chain efficiency and following the rules in places where a lot of things are made *[21,22]*.

2.4 Ultra-Trace Detection Has Limited Real-Time Sensitivity

Even though LC–MS/MS and GC–MS systems can find things at the ppb level, their sensitivity often depends on: Advanced tools, a lot of upkeep is needed, analytical skills that are very good, Strict rules for calibration excipients in (OSD) forms can make ultra-trace quantification even harder by interfering with the matrix. To get reliable detection at nanogram levels, you often need to spend a lot of money on mass spectrometric upgrades and advanced method optimization *[23]*.

2.5 Limited Portability and Scalability

Standard systems are: Big, uses a lot of energy, infrastructure-dependent. They don't work for: Screening for impurities on site, Quality control in-line, Manufacturing environments with few resources. As the production of drugs grows around the world, there is a greater need for portable, small, and cheap analytical tools that can work in decentralized settings *[24,25,26]*.

3. Emergence of Nanoparticle-Based Sensors in Pharmaceutical Impurity Detection

The drawbacks of conventional chromatographic methods have led to the emergence of alternative analytical platforms for high-throughput, sensitive and miniaturized impurity detection *[27,28]*. Nanoparticle-based sensing systems remain one of the most promising technologies in pharmaceutical techniques *[29]*. Nanoparticles are defined in conventional terms as materials with dimensions ranging from 1–100 nm, and they display quite different physicochemical properties compared to the bulk material [30]. These properties essentially stem from quantum confinement effects and a remarkably high surface-to-volume ratio that facilitates interaction with the analyte molecules *[31]*.

The nanoscale dimension endows nanoparticles with unique electronic, optical, magnetic and catalytic properties that enable them to act as signal transducers and amplifiers with tremendous utility in sensing applications *[32]*. During the last 10 years, especially between 2019 and 2025, nanomaterial-assisted analytical platforms have received considerable interest for impurity profiling in drug substances as well as finished dosage forms *[33,34]*.

4.1 Fundamental Properties Enabling Nano-Sensing

4.1.1 High Surface to Volume Ratio

The high surface to volume ratio of nanoparticles is a significant factor. This factor has the following consequences: Enhances adsorption of impurity molecules, Improves sensitivity for the detection of impurities at trace levels, Facilitates faster interaction between the analyte and the surface *[35]*. The high adsorption efficiency, in the context of pharmaceutical impurities, which could be present at ultra-trace levels (ppb, ppt), makes the nanoparticles very useful *[36]*.

4.1.2 Quantum Confinement and Electronic Modulation

The confinement of electrons in very small spaces causes the energy of the electrons and their movement to change *[37]*. This is known as the confinement effect, and it has the following consequences: Enhances fluorescence emission, Improves electrochemical reactions, Enables the modulation of the properties to perform specific tasks. The ability to perform specific tasks allows us to create sensors that could find specific pharmaceutical impurities *[38]*.

At the nanoscale, the electronic and hole motion of semiconductor nanomaterials are spatially confined, leading to discrete and size-dependent energy levels. This quantum confinement effect changes the optical and electronic properties and band gap of the nanomaterial *[30,36]*. Consequently, quantum dots can be fluorescent with intensities and tunable colors that are strong and useful, have an improved capability to transfer charge, and possess high sensitivity to changes in their local chemical environment.

The sensing mechanism is the interaction of the target pharmaceutical impurity with the functionalized nanomaterial, which changes its electronic or optical state. An impurity can, for instance, cause "quenching" or "enhancement" of the fluorescence, shift its emission wavelength, or alter electron-transfer processes. These measurable changes can then be correlated to the concentration of the target impurity. Surface modification with antibodies, aptamers, ligands or other recognition molecules can also offer a selective interaction with specific analytes *[30,39]*. So, quantum confinement cannot be directly attributed to an impurity, but rather, it brings tunable optical and electronic properties that allow for highly sensitive signal generation, whereas surface recognition chemistry gives analyte selectivity.

4.1.3 Catalytic and Redox Activity

Several carbon and metal-based nanoparticles have inherent catalytic properties [39]. When used in the context of electrochemistry, they have the following consequences: Accelerate the transfer of electrons, Reduce the overpotential, Increase the signals for the redox currents. When compared to conventional electrodes, the faster response and lower detection limits make them very useful *[40]*.

4.2 Key Functional Advantages in Impurity Detection

Sensing systems using nanoparticles provide several analytical benefits that directly solve the challenges associated with the use of traditional sensing approaches *[41,42]*.

4.2.1Enhanced Electron Transfer in Electrochemical Sensing

Metallic nanoparticles such as carbon nanotubes, graphene, and gold nanoparticles, when incorporated into the sensing electrodes, exhibit high electron transfer rates *[43]*. This is due to their catalytic ability and conductivity, which allow for the following benefits *[44]*. High signal-to-noise ratio, Fast rates of

electrochemical oxidation and reduction reactions of impurities, ppb and sub-ppb detection levels. These nanoparticles are best used in the detection of oxidative degradation products and genotoxic impurities *[45]*.

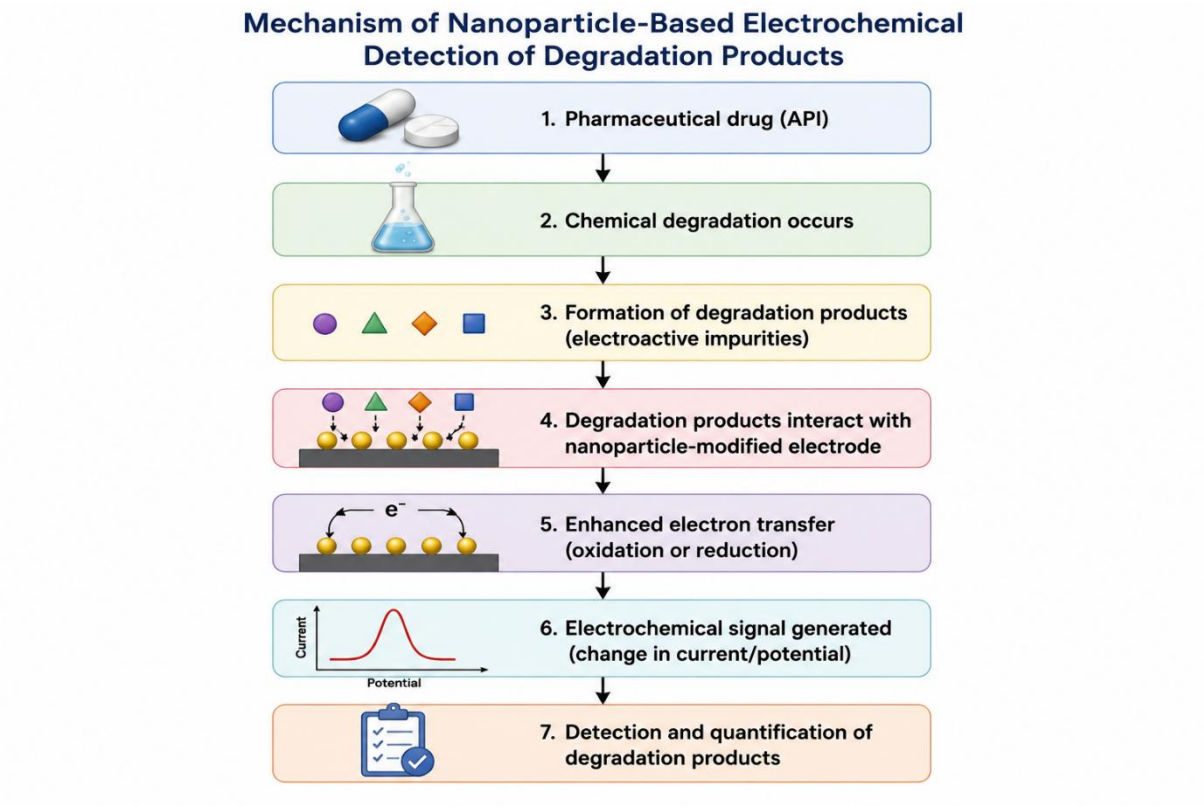

Fig. 1: Mechanism of nanoparticle-based electrochemical sensing of pharmaceutical degradation products

4.2.2 Surface Plasmon Resonance in Optical Sensing

Metal nanoparticles such as gold and silver nanoparticles exhibit localized surface plasmon resonance, where the free electrons in the nanoparticles oscillate in the presence of light *[46]*. This results in the following benefits *[47]*. High peaks in the absorbance spectra, Changes in color due to the binding of the analytes, High sensitivity in colorimetric assays. These sensing approaches are best used in portable sensing devices due to their optical properties, which allow for quick and naked-eye detection of impurities *[48]*.

4.2.3 High Adsorption Capacity for Sample Preconcentration

The magnetic nanoparticles and carbon nanostructures are highly adsorbent materials owing to their porous structure and functionalized surfaces *[49]*. These nanostructures are capable of [50]: Selective adsorption of heavy metals, Adsorption of residual catalysts, Enrichment of genotoxic impurities before sample testing. This nano-compatible sample preconcentration will result in highly improved sample testing sensitivities with less solvent consumption and sample preparation process *[51]*.

4.2.4 Magnetic Separation Capability

In addition to the above advantages, the mono-dispersed Fe_3O_4 magnetic nanoparticles have the capability of magnetic separation *[52]*. This will result in: Effective sample cleanup, Minimized centrifugation, Faster integration into the workflow. The most promising applications of magnetic nano-adsorbents are in the monitoring of chemical synthesis reactions, where catalytic residues must be detected *[53]*.

4.2.5 Compatibility with Microfluidics and Portable Devices

Sensors based on nanoparticles are also compatible with: Platforms for lab on a chip , Electrochemical analyzers that are portable, Systems for microfluidic detection. This is because they are highly compatible with the development of continuous manufacturing and real-time release testing (RTRT) *[54]*.

4.3 Advanced Nanomaterials in Pharmaceutical Impurity Detection

Recent research has focused on specific nanomaterials that demonstrate exceptional analytical performance.

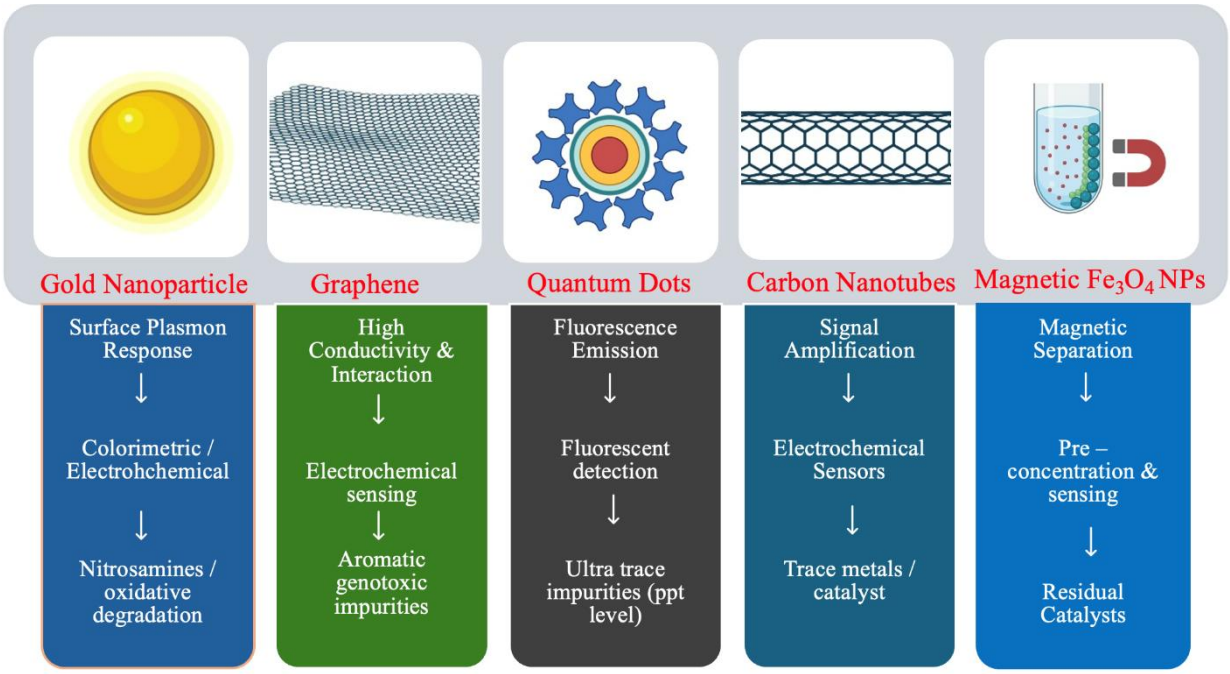

Fig. 2: Sensing platforms based on nanomaterials for the detection of pharmaceutical impurities

In pharmaceutical impurity analysis, the most important benefit of the nanomaterial-based sensing approach is not just the tiny size of the nanomaterial, but the selective capture of analytes, the amplification of their response, their ability to transfer electrons/energies quickly, and the efficient separation from complex pharmaceutical matrices. Based on the physicochemical properties of the impurity, various nanomaterials can be designed to recognize and concentrate the target compound for producing the optical, electrochemical or fluorescence signal. Therefore, nano sensing can be combined into a relatively small analytical platform that includes sample preparation, separation, recognition, and detection.

Gold nanoparticles (AuNPs) When the recognition of impurities can be correlated with an optical or electrochemical change of the nanoparticles, gold nanoparticles (AuNPs) are especially valuable. Ligands or recognition molecules bound to the surface of AuNPs can interact with oxidative degradation products, pharmaceutical impurities, and certain analytes related to nitrosamines. The binding of the target analyte may affect the interface electron-transfer properties or the surface charge of the nanoparticles, resulting in a change of electrochemical response or colour that is detectable *[55–59]*. AuNPs decorated with specific ligands may, for instance, focus tiny metal particles from a formulation and the variation in the optical response that occurs for the surface plasmon may give a quick readout of the contaminant. In the same manner, AuNP modified electrodes can also improve the electron transfer and increase the electrochemical response of the electroactive degradation products. Thus,

AuNPs can be used both as recognition surfaces and as signal amplifying transducers, resulting in a greater sensitivity of impurity detection.

Graphene oxide (GO) reduced graphene oxide (rGO) and other graphene derivatives are especially useful for contaminants that have a high affinity for carbon surfaces. Due to adsorption capability, large accessible surface area, π–π interaction, hydrogen bonding, electrostatic interaction, etc., the surface forces, they can adsorb and accumulate aromatic and conjugated pharmaceutical impurities *[60–62]*. This is especially significant for the analysis of aromatic degradation products, genotoxic impurities and residual organic compounds that may be present in a complex formulation matrix at trace levels. By using graphene-based materials in electrochemical sensors, the analyte accumulated is brought into a closer proximity to the conductive sensing interface, which helps with electron transfer and amplifies the signal that can be measured. Hence, graphene-based nano sensors can be employed to enhance both preconcentration and detection which will minimize the matrix component effect and allow the detection of trace-level.

Quantum dots (QDs) the process of impurity identification is especially important with quantum-dot based sensing when relying on the variation in fluorescence. Whereas quantum dots can be excited and emit their own light when they are illuminated by light of a specific wavelength, they can also be linked to recognition molecules that are specific to a target analyte. The interaction with the impurity can cause fluorescence quenching or enhancement or cause a shift in the wavelength, which can be related to the concentration of the analyte *[63,64]*. It could be useful for the identification of elements of minor concentration such as degraded products or trace impurities, which would not be detectable by standard fluorescence techniques. Furthermore, the capacity for molecular recognition elements to be combined with quantum dots offers the potential for selective identification in complex mixtures, beyond the measurement of overall impurity content.

Carbon nanotubes (CNTs) Impurity detection is done mainly by carbon nanotube (CNTs) which allows for fast electron transfer at the electrochemical interface. They can be incorporated into electrode surfaces to increase the interaction area between the sensing platform and the analytes and enhance the electrical response of the electroactive impurities *[65–67]*. This is especially important for trace amounts of the catalyst residues, redox-active degradation products and other electrochemically detectable contaminants. Selectivity may also be further enhanced by the functionalization of the surfaces of CNTs with appropriate ligands or recognition groups. Therefore, using CNT-based platforms, the weak chemical interactions can be amplified to generate strong electrochemical responses and impurities can be detected at levels that might be difficult to detect by an unmodified electrode.

Magnetic nanoparticles an added bonus is that the magnetic Fe_3O_4 nanoparticles can be used to both remove impurities and detect them. If their surfaces are modified with chelating groups, antibodies or aptamers, Fe_3O_4 nanoparticles can selectively recognize target impurities in complex pharmaceutical matrices *[68–71]*. Finally, when the external magnetic field is applied, the impurity-bound nanoparticles can be recovered in a short time, while the components of the unbound formulation are left in the sample solution. Subsequent analysis of the impurity can then be performed by an optical, electrochemical, fluorescence or other detection method to determine the amount of impurity trapped. This results in a capture–separate–detect strategy, especially for trace contaminants and catalyst residues in chemically complex formulations. For instance, the Fe_3O_4 nanoparticles can be functionalized with ions or residues of catalysts which can then be separated using magnetic force and detected by instrumental methods. During this process, matrix interference can be reduced, which can increase analytical selectivity and detection reliability.

The key contribution of nanomaterials to pharmaceutical impurity analysis can thus be considered as a three-layer process of targeting, separation of the matrix, and generation of the signal. AuNPs can be used for recognition and optical/electrochemical signal amplification; graphene-based materials can be used to improve adsorption; highly sensitive fluorescence-based responses can be obtained using quantum dots; CNTs can be used to improve electrochemical transduction; and magnetic Fe_3O_4 nanoparticles can be used to physically separate target impurities from complex matrices before

detection. These functions can also be combined in hybrid nanocomposites. For example, a magnetic nanoparticle may capture and isolate an impurity and a gold or graphene section may amplify the signal that can then be detected. This can decrease the number of preparation steps required, remove matrix interference, increase selectivity and facilitate fast detection of organic impurities, degradation products, residual catalysts, elemental contaminants, and various other trace pharmaceutical impurities.

Therefore, the use of nano sensing for pharmaceutical impurity detection is not limited to the use of a conventional sensor replaced by a smaller material, but rather in the ability to convert the conventional detection into a capture–recognition–separation–transduction workflow. This is especially helpful in the case of impurities that are present at very low levels, where efficient and selective preconcentration and recognition are crucial for the ability to identify the ingredient**.**

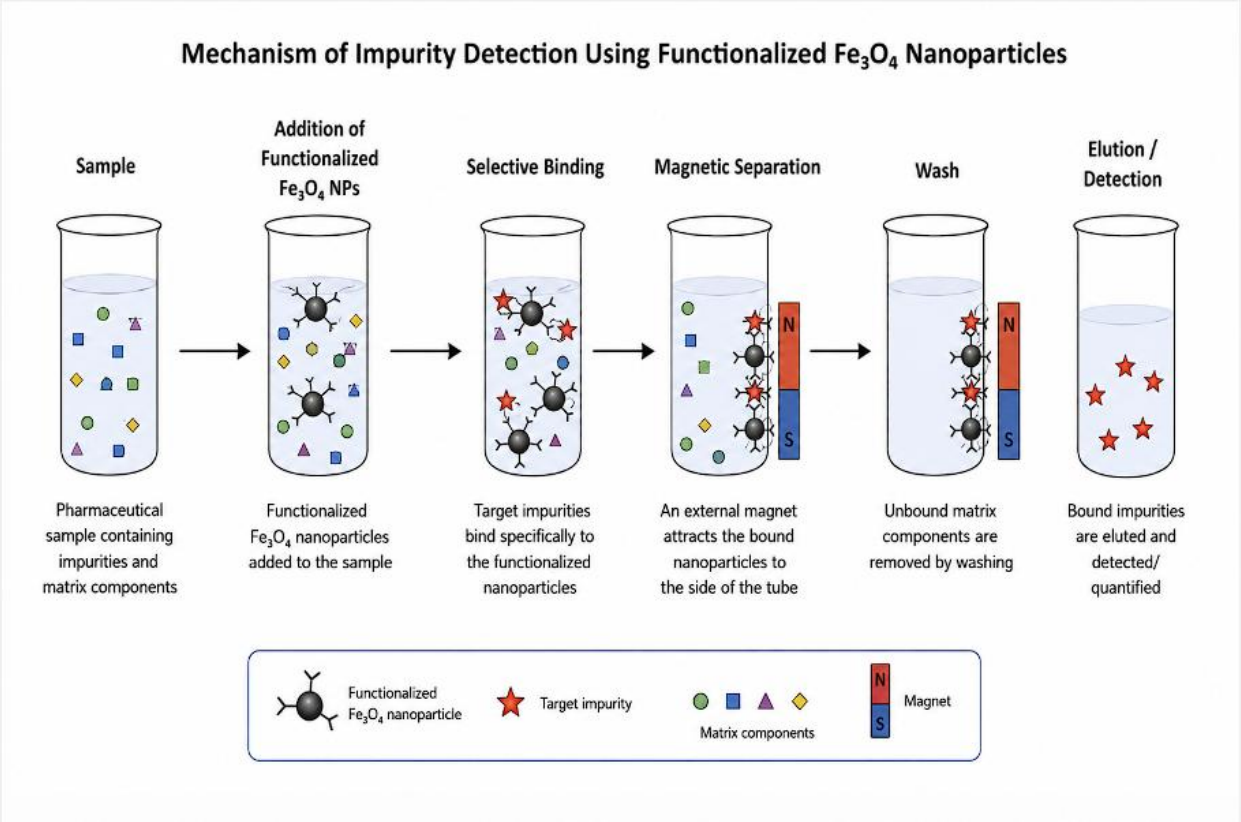

Fig. 3 : Mechanism of detection of pharmaceutical impurities by functionalized Fe3O4 nanoparticles.

Table 1. Classification of Pharmaceutical Impurities and Regulatory Threshold:

Impurity Type	Source	Typical Detection Requirement	Regulatory Reference
Organic (process-related) impurities	Synthetic intermediates and process-related by-products	Depends on the applicable reporting, identification, and qualification thresholds	ICH Q3A(R2)

Degradation products	Storage instability and degradation during manufacturing or shelf life	Depends on the applicable reporting, identification, and qualification thresholds	ICH Q3B(R2)
Residual solvents	Incomplete drying and solvents used during manufacturing	ppm levels, based on solvent-specific limits	ICH Q3C(R8)
Elemental impurities	Catalysts, raw materials, and manufacturing equipment	Based on permitted daily exposure (PDE), expressed in µg/day	ICH Q3D(R2)
Genotoxic impurities	Reactive process impurities and potentially mutagenic contaminants, including nitrosamines	Risk-based, compound-specific limits; often expressed as ng/day for potent mutagenic impurities	ICH M7(R2); FDA/EMA nitrosamine guidance

5.Fundamentals of Nanoparticles in Sensing

Due to the different physicochemical properties at the nanoscale, nanoparticles can act as flexible transduction elements for analytical sensing. At the sub-10 nm scale, materials are found to be different from their bulk properties, and particles are classified as nanoparticles, where the diameter is less than or equal to 100 nm.

Due to the ability of nanoparticles for signal amplification, selective binding, and rapid response for the next generation, nanoparticles act as excellent injectable agents for ultra-sensitive analysis of pharmaceutical impurities, such as degeneration toxins.

5.1 Physicochemical Properties Relevant to Sensing

The sensing ability of nanoparticles is mainly controlled by the surface chemistry, catalytic activity, and electronic structure of the nanoparticles. Their analytical ability is controlled by several related factors.

5.1.1 High Surface Area and Enhanced Analyte Interaction

The very high surface-to-volume ratio of nanoparticles is one of the most important advantages of nanoparticles *[72]*. A high percentage of the atoms in a material are on the surface rather than inside the core of the material when it is in nanoparticle form. This is one of the important features of nanoparticles that enables them to interact well with the molecules around them *[73]*. This is due to the increased number of active binding sites that are a result of the larger surface area of the nanoparticles. Therefore, the ability of the nanoparticles to adsorb the impurities is increased *[74]*. The rate at which the analyte molecules are able to reach the active sites of the sensing material is also increased due to the increased rate of mass transfer resulting from the larger surface area. This leads to an increased rate of response for the nanoparticle-based sensors *[75]*. Impurities such as genotoxins, degradation products, or trace heavy metals have been detected in pharmaceutical systems at very low levels, often in the parts per billion (ppb) or parts per trillion (ppt) range. It is only possible to detect very low levels of substances by employing highly sophisticated analytical tools *[76]*. Because of their high surface reactivity, which facilitates strong interactions with trace impurities, nanoparticles are very useful in this context. In addition, the materials used in nanoparticles have been seen to be very effective in terms of preconcentration. It is noteworthy that nanoparticles play a very important role in enhancing the performance and reliability of sensing systems employed in pharmaceutical analysis *[77]*.

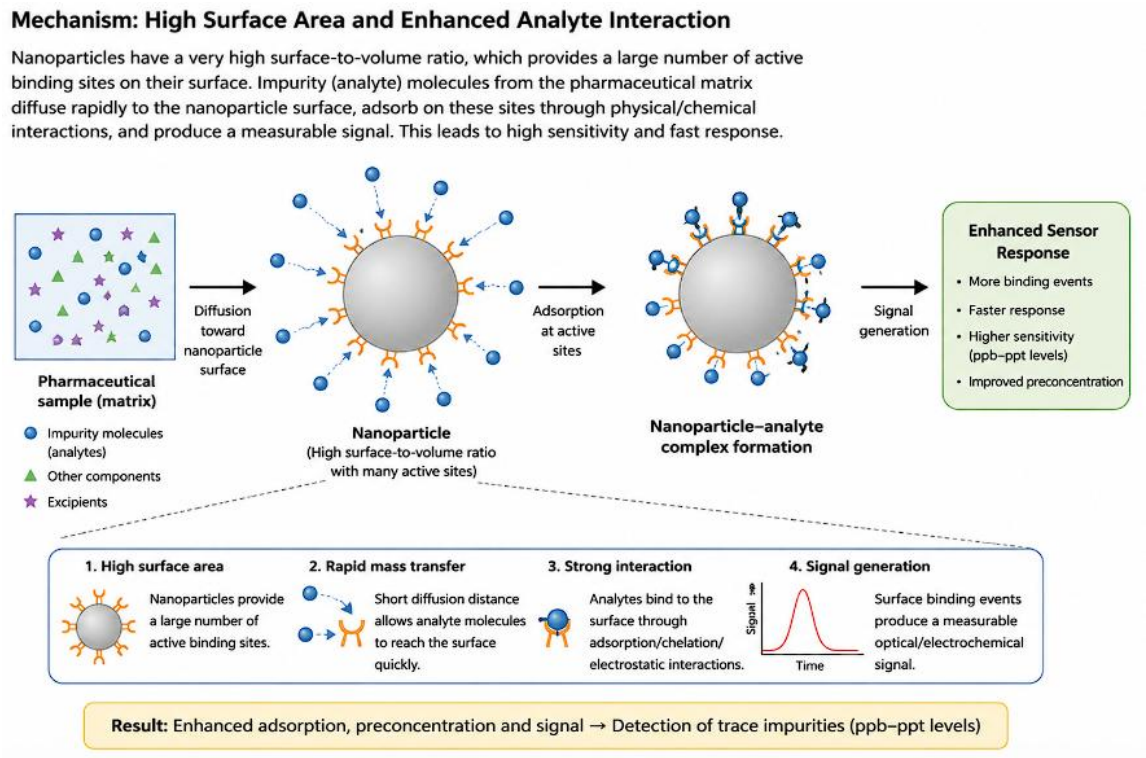

Fig 4: Mechanism of high surface area and enhanced analyte interaction in nanoparticle based sensing.

5.1.2 Tunable Surface Chemistry for Selective Binding

It is also possible to introduce different functional groups to the surface of nanoparticles with the aim of increasing their interaction with specific target molecules *[78]*. These include the introduction of thiol, amine, and carboxyl groups, as well as biomolecules like antibodies and synthetic receptors like molecularly imprinted polymers. These are crucial in increasing the selectivity of nanoparticle-based sensing systems. By adjusting the surface chemical composition of nanoparticles, it becomes possible to develop materials that can specifically interact with specific impurities, without interacting with any of the other components of the sample mixture. These include the introduction of thiol, amine, and carboxyl groups, as well as biomolecules like antibodies and synthetic receptors like molecularly imprinted polymers.

For example, gold nanoparticles that are functionalized with molecules that contain thiols have a strong affinity for certain heavy metal ions, such as mercury (Hg^{2+}). This is because sulphur atoms in thiol functional groups are able to form stable bonds with metal ions *[79]*. This is useful in the efficient capture and detection of heavy metals. Moreover, graphene and its derivatives can be chemically modified in such a way that they have improved interactions with certain aromatic compounds. This is useful in the efficient detection of certain genotoxic impurities, which are normally present as trace contaminants in pharmaceuticals. This is because nanoparticle-based sensors have tunable surface properties. This is useful in the efficient and precise targeting of certain impurities. This is useful in the efficient and precise targeting of certain impurities. This is useful in the efficient and precise targeting of certain impurities. This is useful in the efficient and precise targeting of certain impurities. This is useful in the efficient and precise targeting of certain impurities *[80]*.

5.1.3 Enhanced Catalytic Activity

When materials are taken down to the nanoscale, it is often seen that their catalytic activity is significantly enhanced compared to their bulk counterparts *[81]*. This is mainly because of the increased surface energy and the proportion of atoms on the surface. As the size of the particles is reduced, there

is an increased number of sites that are exposed for chemical interactions, which might help in speeding up the reaction. Apart from this, it is also seen that there are changes in the electronic structure, which might help in enhancing the catalytic activity. This is the reason why metallic nanoparticles like gold, silver, and platinum are used as nano-catalysts in many analytical techniques. By providing catalytic sites that enhance electron transfer mechanisms, these nanoparticles can catalyse redox reactions, thus speeding up the process. These catalytic nanoparticles can enhance the performance of sensors when they are used in electrochemical sensors. These nanomaterials can also enhance the process of electrochemical sensors by reducing the overpotential required for oxidation or reduction reactions, thus enhancing the efficiency of the electrochemical process. At the same time, an improvement in the intensity of the current that is measured during the redox reaction is also achieved due to the catalytic properties of these nanoparticles. An improvement in signal strength is therefore achieved due to these catalytic nanoparticles. As a result, sensors that incorporate these catalytic nanoparticles can have much lower detection limits when compared to conventional sensors, thus making them very effective in detecting impurities in pharmaceuticals, among other applications.

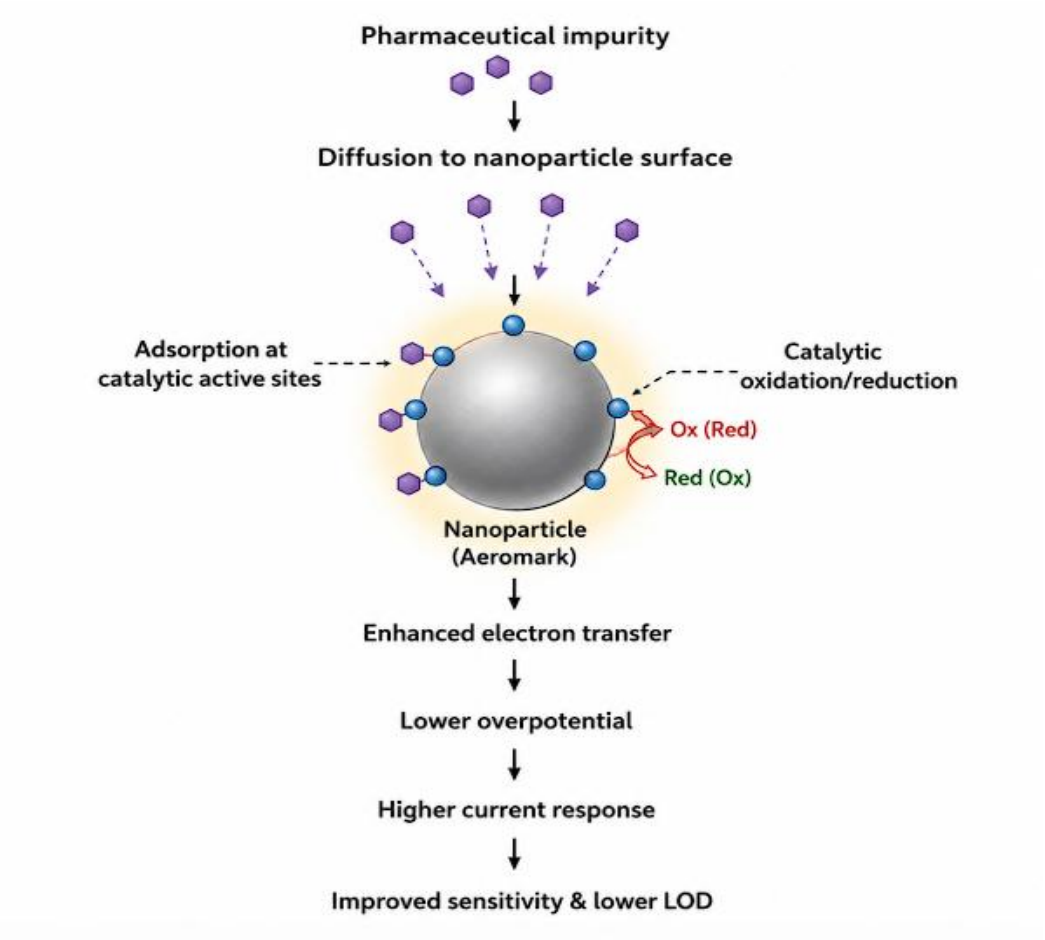

Fig. 5: Mechanism of the boosted catalytic activity of nanoparticles in electrochemical sensing.

5.1.4 Plasmonic Optical Properties in Noble Metals

The special optical properties of noble metal nanoparticles, in particular gold and silver nanoparticles, are attributed to a phenomenon referred to as localized surface plasmon resonance (LSPR). This is a process in which the conduction electrons on the surface of the nanoparticles collectively oscillate in reaction to certain wavelengths of light *[82]*. As a result of the oscillation, these nanomaterials have strong absorbance in the visible part of the electromagnetic spectrum. The optical property related to LSPR is also related to the colour of the nanomaterials. Gold nanoparticles, in particular, are bright red

when dispersed in a solution. However, it is important to note that the optical properties of the nanomaterials are highly sensitive to any events occurring on the surface of the nanoparticles.

As the optical properties of gold nanoparticles are observed to change upon interacting with the target analytes, gold nanoparticles are considered more appropriate for sensing purposes. The gold particles are observed to aggregate or change the interparticle distance as certain contaminants or chemical species attach themselves to the surface of the gold particles. The optical properties of the gold particles are observed to change due to even a minute change in the interparticle distances. This changes the colour from red to blue. There are a number of colorimetric sensing methods based on gold particles. Plasmonic gold nanoparticle-based sensors have been extensively explored for the sensing of contaminants such as heavy metals, catalyst residues, and nitrosamine due to the high sensitivity and simple sensing principle of these sensors. The gold particles are observed to aggregate or change the interparticle distance as certain contaminants or chemical species attach themselves to the surface of the gold particles *[83]*. The optical properties of the gold particles are observed to change due to even a minute change in the interparticle distances. This changes the colour from red to blue.

5.1.5 Excellent Electrical Conductivity in Carbon-Based Nanomaterials

Due to the unique electrical and structural properties, carbon-based nanomaterials such as graphene and carbon nanotubes have received a lot of interest for the development of advanced electrochemical sensors *[84]*. The unique properties of these nanomaterials, such as high electrical conductivity and high electron mobility, allow for the efficient transfer of electrons across the sensing surface. The use of these nanomaterials in the development of electrochemical sensors enables the efficient transfer of electrons between the analyte and the electrode surface. This enables the development of a stable electrochemical signal during the sensing process. The unique properties of these nanomaterials, such as high electrical conductivity and high electron mobility, allow for the efficient transfer of electrons across the sensing surface *[85]*.

This high capacity for adsorption of the analyte molecules is further supported by the high surface area of the graphene, a sheet of carbon atoms arranged in a hexagonal configuration *[86]*. The high capacity for adsorption of the analyte molecules increases the probability of interaction between the target compounds and the sensing material. On the contrary, the carbon nanotubes have a tubular configuration that provides a means for the conduction of electrons. The structural and electrical properties of the nanotubes have thus provided a means for improving the current response, thereby enhancing the performance of the sensor *[87]*. Therefore, the use of graphene and CNT-based electrochemical sensors has thus provided a high probability for the detection of trace impurities even in complex pharmaceutical samples *[88]*.

5.1.6 Magnetic Properties for Separation and Enrichment

Owing to their unique magnetic properties at the nanoscale, magnetic nanoparticles, such as iron oxide nanoparticles, have generated significant interest in analytical and separation techniques *[89]*. These materials exhibit superparamagnetic properties at very small sizes, which means they have the ability to respond strongly to an external magnetic field with little to no residual magnetism once the magnetic field has been removed. Therefore, magnetic nanoparticles have the ability to be isolated quickly from complex matrices with the aid of a simple magnetic source, avoiding the need for time-consuming centrifugation and filtration steps. These materials exhibit superparamagnetic properties at very small sizes, which means they have the ability to respond strongly to an external magnetic field with little to no residual magnetism once the magnetic field has been removed *[90]*.

The ability of Fe3O4 nanoparticles to extract and concentrate target analytes in a sample is another important benefit *[91]*. This is because the particles have the ability to selectively bind with certain contaminants or target substances when functionalized with the correct chemical groups. This will enable the enrichment of the target analytes before the actual analysis by magnetically separating the

target analytes attached to the nanoparticles. This will help in reducing interference from other substances in the sample. This is important in pharmaceutical impurity analysis because trace amounts of contaminants in the drug substance might be very hard to detect because of interference by the presence of excipients in the drug product. This is because trace amounts of contaminants in the drug substance might be very hard to detect because of interference by the presence of excipients in the drug product. Magnetic nanoparticles will be very useful in the effective preconcentration of the target analytes *[92]*.

Mechanism: Complex pharmaceutical sample → Functionalized Fe_3O_4 nanoparticles added → Selective impurity binding → External magnetic separation → Washing → Elution/enrichment → Improved detection

The key mechanism is **selective capture + magnetic separation + preconcentration**, which reduces matrix interference and improves detection of trace impurities.

5.2 Synthesis Approaches for Nanoparticles

Since particle size, morphology, crystallinity, and surface functional groups all directly affect sensing efficiency, synthesis techniques have a significant impact on the performance of nanoparticle-based sensors. Conventional chemical methods and green synthesis approaches are two broad categories of nanoparticle synthesis strategies *[93]*.

5.2.1 Conventional Synthesis Methods

Chemical Reduction

Chemical reduction is one of the widely used techniques for the synthesis of metallic nanoparticles. In this method, metal salts like $HAuCl_4$ are chemically reduced to their corresponding metallic nanoparticles by using chemical reducing agents *[94]*. Some of the reducing agents that are commonly used include sodium borohydride, citrate, hydrazine, etc. During the reduction process, the metal ions present in the solution react with the reducing agents by gaining electrons, resulting in the formation of metallic nanoparticles. This method of synthesis of metallic nanoparticles is widely preferred by researchers due to its ability to control critical parameters of nanoparticles by varying conditions like temperature, concentration of reactants, and reaction time. These parameters are critical for nanoparticle stability. Among various chemical reduction techniques, citrate reduction of gold nanoparticles is widely used for various sensing applications. This method of reducing gold ions to their corresponding nanoparticles offers better stability, thus making it more suitable for constructing reliable nanoparticle-based sensing devices *[95]*.

Sol–Gel Methods

The sol-gel method is one of the most employed methods in the synthesis of nanomaterials, especially metal oxide nanoparticles. In the sol-gel method, metal alkoxides or similar materials are subjected to a hydrolysis reaction followed by a condensation reaction. As a result, a stable colloidal suspension is formed, referred to as a sol *[96]*. As the reaction proceeds, the sol gradually changes into a three-dimensional structure referred to as a gel. One of the most important advantages of the sol-gel method is that it can produce nanoparticles with a uniform distribution and well-defined structural features. Moreover, it is possible to control the porosity of the nanoparticles, which is an important factor in certain applications *[97]*. As a result, the sol-gel method is highly advantageous in the synthesis of metal oxide nanoparticles. It is also commonly used in the synthesis of silica-coated nanoparticles and catalytic nanoparticles.

Hydrothermal Synthesis

Hydrothermal synthesis is one of the most employed techniques for the synthesis of nanomaterials through chemical reactions, where the chemical reactions are carried out using aqueous solutions at high temperatures and pressures. Chemical reactions are generally carried out using sealed reactors called autoclaves, where the system is maintained at high pressure. At such high temperatures and pressures, the chemical precursors are dissolved and react, forming nanostructures *[98]*. One of the most important advantages of using the hydrothermal technique for the synthesis of nanoparticles is that it allows for the formation of highly crystalline nanoparticles of uniform size and shape. Moreover, the reaction conditions such as temperature, pressure, and time can be adjusted to control the structural properties of the synthesized materials. In addition, it has been found that nanoparticles synthesized using the hydrothermal technique show enhanced catalytic properties due to the crystal structure formed. For these reasons, this technique has been widely used for the synthesis of magnetic nanoparticles and other metal oxide nanostructures *[99]*.

5.2.2 Green Synthesis Approaches

Green synthesis of nanoparticles has gained more attention in recent years, especially because of the increased interest in environmentally friendly and green pharmaceutical production practices *[100]*. Unlike the conventional methods of nanoparticle synthesis, which require the use of potent chemical reductants, green synthesis makes use of natural biological sources such as plant extracts and biomolecules such as proteins and polysaccharides *[101]*. These biological agents contain several phytoconstituents such as flavonoids and phenolic compounds, which can reduce as well as stabilize the metal ions during nanoparticle synthesis. This leads to the formation of stable nanoparticles without aggregation *[102]*. One of the major advantages of this method is the reduction of the amount of toxic chemicals used, which helps to reduce the environmental impact of the method *[101]*. Additionally, the green method of synthesis is cost-effective since the materials used are readily available in nature. The nanoparticles synthesized using this method have also been found to have a high level of biocompatibility, which is advantageous for the application of nanoparticles in the fields of biology and medicine. It has been found through recent studies that gold nanoparticles synthesized using the green method can sense materials like those synthesized using the traditional method, especially for the detection of heavy metals. This shows that the green method of synthesis is not only advantageous for the environment but also for the principles of green chemistry *[102]*.

Table 2. Representative Electrochemical NP Sensors

Nanomaterial	Target Impurity	Detection Limit	Regulatory Reference
AuNP-modified electrode	Nitrosamines	0.5 ppb	[19]
Graphene oxide composite	Heavy metals	1 ppb	[18]
CNT-based electrode	Phenolic degradation products	0.8 ppb	[20]

6 Applications in Pharmaceutical Manufacturing and Storage

An important development in quality assurance techniques is the incorporation of nanoparticle-based sensing systems into pharmaceutical production and storage *[103]*. Unlike conventional laboratory-

bound analytical methods, nano-enabled sensors offer rapid response, portability, and compatibility with real-time monitoring systems, making them highly suitable for modern pharmaceutical production environments *[104]*. The integration of nanoparticle-based sensing systems into pharmaceutical manufacturing and storage represents a significant advancement in quality assurance strategies.

6.1 In-Process Catalyst Monitoring

Many active pharmaceutical ingredients use metal catalysts such as palladium, platinum, nickel, and copper in their synthesis. Although these metal catalysts are important in enhancing the chemical reactions during the synthesis of the active pharmaceutical ingredients, the presence of trace amounts of the metals in the active pharmaceutical ingredients may remain if they are not effectively removed during the purification process. The presence of these metal catalysts in the active pharmaceutical ingredients is viewed as a potential safety issue, as the prolonged exposure to these metal catalysts may be a potential cause of toxicity. This is the reason why the ICH Q3D guideline on elemental impurities in pharmaceuticals severely limits the levels of elemental impurities in pharmaceuticals *[105]*. Traditionally, sensitive analytical techniques such as Inductively Coupled Plasma Mass Spectrometry are used. Nonetheless, although these catalysts are vital in promoting chemical reactions during the synthesis, trace amounts of the metals may be left in the end product if they are not fully removed during the purification process *[106]*. The presence of these metal catalysts in the end product is viewed as a potential safety issue due to the potential toxicological risks that may be exhibited if one is exposed to these metals over a long period *[107]*. For this reason, the ICH Q3D Guideline for Elemental Impurities strictly regulates the levels of elemental impurities in drugs *[108]*.

Significant advancements have been reported in the field of nanotechnology that have provided an opportunity for developing sensing systems that can monitor the amount of residue in the catalysts by using nanoparticles. Nanomaterials have been designed that can selectively react with specific metal ions, providing an opportunity for developing sensors that can sense even traces of impurities in the catalysts. Nanoparticles have been used for developing interactions with specific metal ions that can change their optical or electrical properties for improving the sensitivity of sensors for specific metal ions *[109]*. Graphene electrodes or gold nanoparticles have been reported for developing sensors that can monitor optical changes for sensing palladium ions by modifying their electrochemical properties. Magnetic nanoparticles, such as iron oxide, have also been reported for the selective concentration of metal ions from complex matrices for their sensing applications. The ability to engineer the properties of nanoparticles for the selective interaction with specific metal ions enables the creation of sensing technologies that are able to detect the impurities present in the catalyst at the molecular level. These sensing technologies use the nanoparticles to increase the interaction with the target analyte, which in turn enables the increase in the sensitivity of the detection based on the changes in the optical signal and the electrical current *[110]*. Graphene and gold nanoparticles have been reported for the detection of palladium ions based on the changes in the optical absorbance and the electrochemical properties, respectively.

There are many benefits that can be derived from the use of nanoparticle-based sensor technology in the pharmaceutical manufacturing process. For example, it is quite easy and almost real-time to monitor the catalyst residues in the pharmaceutical manufacturing process, thanks to the sensor technology that can be closer to the process line *[111]*. This will, in turn, enable those operating these processes to easily identify any problems that may come up, thus reducing the chances of the pharmaceutical products being rejected, all within the legal framework. Additionally, these kinds of monitoring techniques are quite beneficial for the quality management of pharmaceutical products, as discussed in the Quality by Design approach. This system allows for the fast or even real-time monitoring of residues present in the catalysts during synthesis, as this system can function closer to the line. With the aid of this facility, appropriate changes can be made to the processes. These systems can function closer to the line *[112]*.

6.2 Integration with Continuous Manufacturing and Process Analytical Technology (PAT)

Continuous manufacturing processes are gradually replacing the traditional batch-wise manufacturing processes in the pharmaceutical industry. This change is mainly due to the need to increase the efficiency and control over the manufacturing processes and the quality of the products. At the same time, the regulatory authorities are also promoting the use of new quality management tools such as Process Analytical Technology, which involves the real-time monitoring of the critical quality attributes during the manufacturing process. This will help the companies gain a better insight into the manufacturing processes and control the quality of the products better during the entire manufacturing cycle *[113]*.

Traditionally, conventional analytical techniques, such as chromatographic methods, have been employed for the analysis of impurities in pharmaceutical systems. However, such methods are generally associated with off-line sampling and longer analysis times, which could delay the availability of the analytical results *[111]*. Therefore, such methods may not be best suited for the framework of real-time monitoring, as they are generally associated with off-line sampling and longer analysis times, which could delay the availability of the analytical results. In continuous manufacturing, timely feedback is critical to ensure that any variation in the process is recognized and corrected without interrupting the process. Recent advancements in nanotechnology have led to the development of novel sensing platforms, which may help solve the aforementioned challenges. Nanoparticle-based sensors, such as electrochemical and optical nano sensors, have several characteristics that may be beneficial for the monitoring of processes. For instance, the small size and large surface area of such sensors may allow for faster response rates, which may be between seconds and minutes. Moreover, such sensors may require smaller sample volumes for analysis.

For example, it has been demonstrated that graphene-modified electrochemical sensors have the ability to detect changes in chemical composition during reaction processes when they are used in flow-based systems *[112]*. Plasmonic nanoparticles have also been shown to produce optical effects when there is a change in the environment on the surface of the particles. This means that there is an ability to observe the formation of impurities in real time.

Incorporating such nano sensor technologies in the pharmaceutical manufacturing process may revolutionize the approach used in the monitoring of impurities. This is because the ability to monitor critical analytes in real time will allow the levels of impurities to be monitored during the entire process and not at the end product alone. This may also be used in the implementation of the concept of Real time release testing, where the quality of the product is guaranteed in real time through the use of continuous process verification as opposed to end product testing alone. Nanoparticle sensing technologies have the potential to improve the robustness of the manufacturing process through faster feedback and better process understanding, which could improve the robustness of the manufacturing process and the strength of pharmaceutical quality systems.

6.3 Smart Packaging for Detection of Volatile Degradation Product

Storage stability is an important factor for oral solid dosage forms, and degradation mechanisms including oxidation, hydrolysis, and photolysis can result in the generation of volatile compounds. Nanoparticle-based sensors have also been considered for the development of smart packaging materials. Nano sensors have been integrated into the packaging materials for the following applications *[110]*. Volatile compounds resulting from degradation, Moisture pickup, Oxidative products, pH changes in the package.

Gold nanoparticles, quantum dots, or metal oxide nanoparticles have been integrated into polymer thin films for colorimetric or fluorescence changes in response to degradation gases.

Smart packaging materials have been developed for: Real-time monitoring of stability, monitoring shelf life, Detection of compromise, Safety benefits for patients.

This method of monitoring shifts the focus from laboratory-based periodic analysis to continuous monitoring of the environment.

6.4 Stability-Indicating Rapid Screening

Stability studies are vital for the approval of a drug. However, conventional methods for the stability-indicating properties of a drug are mostly based on chromatography, which is a time-consuming task *[114]*. Rapid screening of the degradants of a drug by nanoparticle-based sensors can be achieved by: Detection of oxidative species using electrochemistry, Observation of the spectrum changes in the presence of plasmonic nanoparticles, Quantification of impurities by nano-enhanced fluorescence.

7. Green Chemistry and Sustainability in Nano-Enabled Impurity Detection

Sustainability has emerged as a major focus area for pharmaceutical manufacturing and analytical chemistry. Nanoparticle-based sensor technology follows the principles of green chemistry, which emphasizes environmentally friendly synthesis and lower resource utilization for analysis [113].

7.1 Green Synthesis of Nanoparticles

In conventional synthesis, harmful reagents like sodium borohydride or hydrazine are used, which produce harmful by-products during synthesis.
In green synthesis, these reagents are replaced with: Vegetal extracts, which contain flavonoids and phenolic compounds, Microbial metabolites, Biopolymers, Natural antioxidants
In green synthesis, phytochemicals are used as reducing agents that reduce metal ions into nanoparticles *[100]*.
The advantages of green synthesis of nanoparticles are: Lower quantity of toxic reagents is used, Energy consumption is minimized, Very little waste is generated, Nanoparticles have better biocompatibility. Green synthesis of nanoparticles has been found to have equal sensing capabilities as chemically synthesized nanoparticles for sensing heavy metals and impurities, thus validating their use in pharmaceutical analytical applications.

7.2 Reduced Solvent Consumption and Micro-Scale Analysis

Traditionally, chromatographic techniques involve the use of huge quantities of organic solvents, resulting in environmental degradation and higher costs of operation.
Nano-enhanced sensing platforms enable micro-scale analytical techniques that involve: Micro-scale sample volume requirements, Low or no organic solvent requirements, Dry-state or electrochemical detection modes, Mitigation of waste generation *[111]*.
Some of these techniques include: Electrochemical nano sensors that operate in aqueous solutions with negligible organic solvent requirements, Microfluidic nano-devices that operate with micro-liter volume requirements, resulting in a drastic reduction of required reagents, Magnetic nanoparticle-based preconcentration techniques that eliminate repetitive steps in sample preconcentration *[112]*.
This reduction of organic solvents also corresponds with the green analytical chemistry approach, which focuses on: Waste reduction, Safe chemical practice, Energy efficiency, Mitigation of environmental impact.

7.3 Contribution to Sustainable Pharmaceutical Manufacturing

Nano-enabled sensing helps in the achievement of sustainable development goals by:

Prevention of batch rejection, Reduction of reprocessing, Continuation of manufacturing efficiency, Real-time quality monitoring, Reduction of analytical waste. The combination of green synthesis methods and solvent-free detection systems in nanoparticle-based sensors offers a double benefit in terms of analytical performance and environmental sustainability *[113,114]*.

Conclusion

Nanoparticle-based sensing platforms is a promising emerging method for pharmaceutical impurities detection and monitoring. The high surface area, tunable surface chemistry, optical properties, electrical conductivity, and magnetic responsiveness allow for recognition and enhancement of signal of specific analytes. The different sensing mechanisms include colorimetric, plasmonic, fluorescence, electrochemical and magnetic separation based detection is provided by the gold nanoparticles and graphene based nanomaterials, carbon nanotubes, quantum dots and magnetic Fe_3O_4 nanoparticles respectively. These features make it possible to analyze trace contaminants, degradation products, elemental impurities and other impurities in pharmaceutical products quickly and sensitively. Nanoparticle-based sensors can be superior to the conventional analytical methods like HPLC, GC, LC–MS, ICP–MS in terms of rapid response, less sample/solvent requirement, miniaturization, portability and possible integration with microfluidic and process analytical technology (PAT). The selectivity of functionalized nanoparticles can be further enhanced by tuning the interactions with the target analytes and the separation of analytes from the complex pharmaceutical matrix. They have also been found to be potential contributors to greener analytical workflows, which will help develop more sustainable methods for pharmaceutical quality assessment.

Although there are these benefits, there are some issues that need to be addressed before it can be widely adopted. Analytical performance can be affected by different methods of synthesis, aggregation of nanoparticles, functionalization of their surfaces, matrix interference, sensor stability, sensor reproducibly, and long-term storage. Moreover, many reported systems are still at the laboratory-development stage and their performance needs to be further confirmed with real pharmaceutical matrices and reference methods. In practical applications for the pharmaceutical industry, standardized validation protocols, better batch-to-batch reproducibility, and better understanding of the regulatory requirements will therefore be essential. At present, it appears that the use of nanoparticles as sensors is not a panacea and, for most applications, is still a complementary method to existing analytical techniques. Additional developments in the field of nanomaterial functionalization, portable instrumentation, microfluidics and integration of sensors could make them useful for quick screening of impurities, process monitoring, and even real-time pharmaceutical quality assessment. Ongoing dialogue between nanotechnology, analytical science, pharmaceutical manufacturing and regulatory disciplines will be crucial for advancing these promising platforms from the laboratory to reliable and real-world deployable analytical technologies.

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Conflict of Interest

Declared none.

Author Contributions

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