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Nanogold in rapid tests

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ABSTRACT

Gold nanoparticles (AuNPs) have been successfully used as biosensors since the early 1990s, when researchers first demonstrated the use of AuNPs functionalized with DNA probes as a sensing platform for the detection of specific DNA sequences. Since then, gold nanoparticle-based biosensors have seen rapid advancements and have been applied in various fields, including medical diagnostics, environmental monitoring, and food safety. Where they are commonly applied as point of care rapid tests based on functionalised AuNPs, for use as highly specific, reliable, and simple to use rapid tests for the determination of pregnancy, diseases, allergies, and many others. This short review article offers a quick insight into the different types of rapid tests and their components.

Keywords: gold nanoparticles, AuNPs, functionalized, rapid tests, diagnostics.

1. Introduction

Rapid diagnostic tests play a key role in many analytical environments, such as clinical and biopharmaceutical diagnostics, environmental monitoring, food testing, and personal diagnostics (Wild et al., n.d.). This key role came to the forefront, especially with the outbreak of the COVID-19 pandemic, where the rapid, reliable, and selective recognition of the new coronavirus SARS-CoV-2 enabled the early recognition of the infection. This was important due to the complex transmission and limitation of the spread of the COVID-19 disease, as specific lateral flow immunoassay (LFIA) tests allow the identification of both symptomatic and asymptomatic persons. The identification of these persons was crucial to contain the spread of the disease, as due to the overnight increased hospitalization in the intensive care units, all medical institutions were overloaded (Moitra et al. 2020; Yu et al. 2020). This situation also led to the overloading of the primary diagnostic service, since in the initial phase of the epidemic, real-time polymerase chain reaction-based tests, generally referred to as RT-PCR tests, were exclusively used. This diagnostic method is otherwise extremely sensitive and very accurate. Its only weakness is the relatively long time it takes to perform a laboratory test, which also requires specialized equipment and professionally trained personnel who can interpret the results. As additional support for this method and as the first line of detection of the SARS-CoV-2 virus, LFIA tests began to be used in the middle of 2020, which enabled the detection of potential infection in the test subject in a relatively short time, from 5 to 30 min (Wen et al. 2020; Li et al. 2020; Nuccetelli et al. 2020; C. Huang et al. 2020; S. Cavalera, B. Colitti, S. Rosati, G. Ferrara, L. Bertolotti, C. Nogarol, C. Guiotto, C. Cagnazzo, M. Denina, F. Fagiolic, F. Di Nardo, M. Chiarello, C. Baggiani 2020). LFIA tests combine several key technologies and associated components: namely chromatography in the composition and distribution of the different membranes and pads used to capture and wick the sample, biotechnology for the isolation, choice and development of highly specific capture molecules that bind with the targeted analytes and nanotechnology for the development and production of nanoparticle labels, which allows for signal amplification. The combination of all these technologies together allow for a deceptively simple looking device, that offers high selectivity, high specificity and a high signal gain, resulting in a medical device that is both affordable, reliable and simple to use (Vashist SK 2020; Yang et al. 2023; Borse and Srivastava 2019).

2. Function of nanogold

AuNPs have a high surface-to-volume ratio. The effect of this is that the surface properties are more pronounced than the core properties. This influence increases markedly with decreasing size, especially in the case of round nanoparticles. At a certain size, surface

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effects become dominant (Vollath, Fischer, and Holec 2018). In the case of nanoparticles, shrinkage of the underlying crystal lattice also occurs. This refers to the phenomenon where the crystalline lattice of nanoparticles is compressed or shrunk compared to classical materials. This phenomenon can occur due to several factors, including surface tension, defects in the crystal structure, and changes in the electronic structure of the atoms on the surface of the nanoparticles. In general, lattice contraction in nanoparticles leads to higher surface energy and their higher reactivity (Ahmad and Bhattacharya 2009; Balerna 1985; Z. Huang, Thomson, and Di 2007). The surface area of nanoparticles determines their physical properties, such as stability, solubility, and reactivity.

Metal nanoparticles have an additional special property, namely surface plasmon resonance, which is particularly prominent in AuNPs, as their plasmon resonance coincides with the wavelengths of light visible to humans, which we see as a characteristic coloration (Figure 3) (Zeng et al. 2014; Jain et al. 2006; Zhu and Gao 2018). Surface plasmon resonance causes conduction electrons on the surface of nanoparticles to oscillate, which are excited resonantly (in phase) by the electromagnetic field of the incident light. Besides silver and copper nanoparticles, AuNPs are the most common nanoparticles exhibiting plasmon resonance in the human visible wavelengths of light (Figure 1) (Amendola et al. 2017). The effect of plasmon resonance enhances the radiative and non-radiative properties of nanoparticles (Mieszawska et al. 2013), such as scattering and absorption. The oscillation of conduction electrons around the surface of the particle causes charge differences in the atomic structure and creates a dipole oscillation in the direction of the electric field of the incident light. The collective oscillations of conduction electrons or the reverse oscillation of the plasma, is called a plasmon. The amplitude of the oscillations reaches a maximum at a certain frequency, which is called the surface plasmon resonance. The oscillation frequency is determined by: the crystal structure of the nanoparticle, the effective electronic mass, the electron density, and the shape and size of the charge distribution (Kelly et al. 2009; Mie 1908).

The main function of AuNPs in rapid tests is as a label, or in other words, as a pigment, to optically visualise a signal (either positive or negative). For nanoparticles to successfully function as labels in rapid tests, they are conjugated (chemically bound) to specific capture molecules. These conjugates, or in other words, functionalized AuNPs form AuNPs based biosensors.

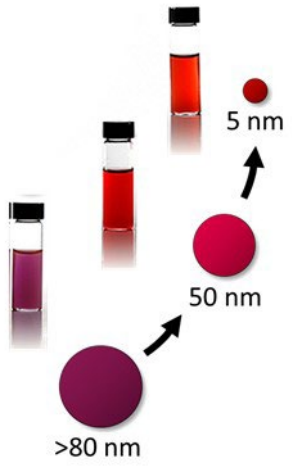

Fig. 1. Size to colour dependency of spherical AuNPs

Binding between capture molecules and AuNPs depends on the ionic attraction between negatively charged AuNPs and positively charged capture molecules – or vice versa, hydrophobic attraction and dative (coordinated) bonding between surface electrons of AuNPs and sulphur atoms of amino acids. Chemical interactions between antibodies and the nanoparticle surface are usually achieved by chemisorption via thiol derivatives, using bifunctional linkers, using ion coupling and using adapter molecules. Both covalent and non-covalent immobilization methods are used for this type of bioconjugation. Primarily, capture molecules or other functionalized groups non-specifically adsorb onto AuNPs through non-covalent binding modes based on a combination of electrostatic and hydrophobic interactions, which preserves the negative charge of AuNPs. In case of sufficient AuNPs charge, this can additionally provide stability in colloidal solutions (Byzova et al. 2020; Wen et al. 2020; Jazayeri et al. 2016). Typically, the capture molecules are antibodies or antigens, that offer highly specific binding to target analytes (Figure 2).

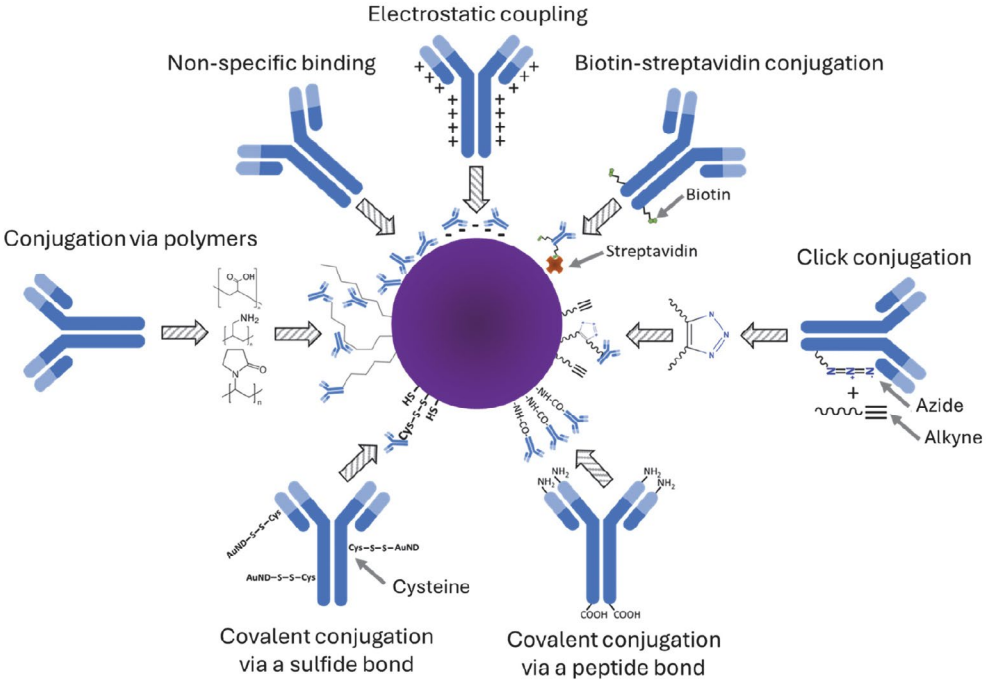

Fig. 2. Schematic of different mechanisms of conjugation of proteins or specific IgG antibodies on to a AuNPs surface.

3. Types of nanogold based rapid tests

The simplest form of immunoassay is an immunometric assay (Figure 3). Capture molecules immobilized on the surface of the substrate capture the test analyte from the sample. After a short incubation time, which ensures a sufficient degree of binding with the analyte, a conjugate of the label and the capture molecule, which is specific to another part of the analyte molecule, is added. This is the basis of the signal generation system. After a short incubation time between the label/capture molecule conjugate and the analyte, the unbound components are removed by a washing process. The difference in the intensity of the staining of the label before and after washing represents a signal for determining the content of the analyte. The intensity is thus determined based on a change in colour, as is the case for AuNPs labels, but alternatively, depending on the type of label, fluorescent radiation, a magnetic field, or a radioactive source can also be used to determine the signal (Wild et al., n.d.; Vashist and Luong 2018; Bjerner et al. 2004).

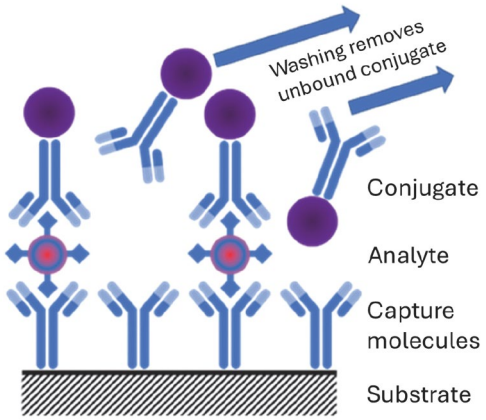

Fig. 3. Schematic representation of a simple immunocolloidal test

For capture molecules, various proteins are most often used, such as antibodies or even proteins that appear on the surface of viruses. These can be immobilized on the substrate and thus capture specific antibodies for this virus from the sample. These types of assays work well when the target analyte is a large molecule with sufficient surface area to accommodate two antibody molecules (Bjerner et al. 2004). For immunoassays designed to detect smaller compounds, such as drugs or drugs, a different approach is required. These tests use only one antibody, which is present in a limited amount. Another key reagent, called a tracer, is made from a target analyte labelled with an appropriate signal-generating material, such as a radioisotope or an enzyme. The proportion of the tracer that binds to the restricted sites of the antibodies is inversely proportional to the concentration of the analyte in the sample. This is known as a competitive immunoassay. In this type of assay, precise amounts of immobilized antibody and labelled analyte are critical. In immunoassays, the analyte to which antibodies bind is often called an antigen, although the word “antigen” refers to a substance capable of eliciting an antibody response. In many competitive immunoassays, the analyte molecules are too small to elicit an antibody response in animals and must be chemically linked (conjugated) to a larger molecule, usually a protein, to generate antibodies (Chen et al. 2019). Once antibodies are generated, antibodies may be found in some or all vaccinated animals that bind only to the analyte. In this case, the analyte is called a hapten. A molecule used to immunize an animal, whether it is a pure analyte or a conjugated version, is called an immunogen. So far, every type of immunoassay described has depended on the separation of the unbound tracer before the bound signal is measured. All these assay formats are examples of a heterogeneous immunoassay. Some non-separation assays have been developed in which the tracer produces a signal only when it binds to the analyte in an immunometric assay or to an antibody in a competitive assay (Wild et al., n.d.). AuNPs can also be used to enhance the functionality of existing diagnostic processes, such as the PCR process, where the subsequent addition (after PCR amplification) of functionalized AuNPs enables the visualization and detection of specific DNA sequences, by using AuNPs functionalized with DNA probes that are complementary to the target DNA sequence. These DNA probes can be single-stranded oligonucleotides that are designed to hybridize specifically with the target DNA sequence. The presence of the DNA-gold nanoparticle complexes can be visualized through various methods (Vu, Litvinov, and Willson 2008; Low, Karimah, and Yean 2013). One common method involves the aggregation of AuNPs upon binding with the target DNA, leading to a colour change from red to blue or purple. This colour change can be easily observed with the naked eye or measured using a spectrophotometer (Sattarahmady et al. 2016).

The most common and simplest form of this type of test for the user is the LFIA test, or immuno-serological lateral flow test. Scientific knowledge in the field of nanomaterials in the last five years has enabled the transfer and use of LFIA tests in medicine, where high accuracy and sensitivity of diagnosis are required. If research is carried out with the same intensity in the future, the LFIA tests could thus represent the basis for the transition to the technological challenge of setting up a completely different laboratory system. LFIA stands for lateral flow immunoassay. This is a type of rapid diagnostic test used to detect the presence of specific substances, such as antibodies or antigens, in a sample. The target use of LFIA tests is for on-site testing, as results are obtained in a relatively short time, i.e., after a few minutes. LFIA tests consist of a strip or cassette with a porous membrane that contains specific molecules, such as antibodies or antigens, that can bind to the target substance, or the analyte being sought. The sample is usually a body fluid such as blood, saliva, or urine and is applied to the test strip and flows through the membrane via capillary action. If the target substance is present in the sample, it will bind to specific molecules on the test strip (Wild et al., n.d.). The LFIA assay typically contains a label conjugate and capture molecules that bind to target substances. As the sample continues to flow through the membrane, it reaches an area where a line of capture molecules is positioned. These capture molecules will bind to the label and consequently form a line of sight. The colour of this line indicates a positive result and confirms the presence of the desired analyte. LFIA tests are widely used for a variety of purposes, including the detection of infectious diseases (such as COVID-19, HIV and influenza), pregnancy testing, drug testing and food safety testing. They are particularly useful in situations where rapid results are required, in emergency departments and in remote or resource-constrained environments (Wild 2013; Parolo et al. 2020; Mohit, Rostami, and Vahidi 2021; Vashist SK 2020). The operation of a well-designed LFIA is simple: a sample is applied to a sample pad, ensuring that the sample properties match those required for optimal detection (pH, ionic strength, viscosity, purity, and concentration of blocking agents). The sample then begins to travel along the strip and reaches the conjugate pad, which releases the labelled detection bioreceptor (an antibody conjugated to the detection nanoparticle). Wetting the dry conjugate pad releases the labels and allows the first interaction between the analyte and the bioreceptor. The sample then travels through a nitrocellulose membrane (also called a detection pad). In most LFIAs, there are at least two lines on the membrane: a test line, where the capture bioreceptor binds the analyte of interest, producing a line that is most often visible to the naked eye and indicates the presence or absence of the analyte; and a control line with a selective bioreceptor that confirms the correct operation of the LFIA. Finally, the excess sample reaches the absorbent pad, which provides sufficient bed volume for complete sample flow (Parolo et al. 2020; Wild et al., n.d.; Bahadır and Sezgintürk 2016). When choosing the basic components of the rapid LFIA test, special attention should be paid to the selection of appropriate membranes that provide lateral traction of the sample within the rapid test (Parolo et al. 2020; Wild et al., n.d.; Bahadır and Sezgintürk 2016).

4. Sample pad

The sample pad represents the part of the LFIA where the sample is applied. This component has two key functions, namely, to ensure uniform sample flow and standardization of sample buffer conditions. The material and design chosen for the sample pad can significantly affect the overall system. The geometry and characteristics of the sample pad are important for controlling sample flow and for the design thickness, porosity, and overall dimensions of the pad. An additional feature of the sample pad is the degree of retention of particles relative to their sizes. The pad can remove larger particles to allow adequate filtration of the sample. If the selected sample pad does not provide the desired level of particle retention, it is possible to install an additional pad (e.g. blood filtration membranes). There are two main types of material used in commercially available sample pads: cellulose fibres and woven meshes. Cellulose fibre sample pads are usually thicker (≥ 250 μm) and less expensive, but are more difficult to handle, especially when wet. They typically have larger bed volumes (≥ 25 μl/cm2) and have a greater tolerance for chemicals present in the buffer. Sample pads made of woven meshes such as fiberglass have good tensile strength and allow uniform distribution of the sample across the conjugate pad. In addition, the woven meshes can also act as a filter to remove particles from the sample, prevent blockage of further pads and retain minimal sample volumes thanks to their low bed volumes (≤ 2 μl/cm2). The sample pad should be selected based on the type of analyte to be detected, the amount of sample available, and the type of sample. If the analyte is in the micrometre size range (bacteria and cells), the sample pad must have a large volume (cellulose fibres) to allow the analyte to flow along the LFIA strip. The same is true for a sample that requires consistent buffering. In contrast, for the analysis of small amounts of samples, the pad must be thin (woven mesh) (Parolo et al. 2020; Wild et al., n.d.; Bahadır and Sezgintürk 2016; Merck Millipore 2013).

5. Conjugate pad

The most commonly used conjugate pad material is fiberglass, although cellulose and polyester can also be used. Several factors must be considered when selecting a conjugate pad material, such as thickness, pad volume, and resistance to non-specific binding. A thicker pad means more volume (assuming a similar pore size), and this allows for more label to be stored for detection, slower flow and higher sensitivity. This also means that the mechanical strength of the conjugate pad in the wet state is lower. Buffer and reagents for stabilization and redissolution are often added to the conjugate pads in addition to the conjugated nanoparticles. The key components of the conjugated buffer are sugars, especially sucrose and trehalose, which have the main function of maintaining the natural conformation of dehydrated proteins (hydroxyl groups of sugar molecules replace the water around the protein after drying) and enabling their rapid re-dissolution after rehydration. They are usually used in concentrations of 1% to 10% by volume. Once an appropriate buffer is selected, the bioreceptor-nanoparticle conjugate can be applied to the membrane either by spraying or by a dipping process. Air jet dosing is the most reliable non-contact method for the application of nanoparticles, as it ensures quantitative coverage of the entire membrane. The immersion method is used when the air jet method is not possible. Its main drawback is that the achieved nanoparticle coverage is not uniform and can lead to high assay variability. The subsequent drying process is crucial to maintaining the stability of the dried conjugate and determines the release efficiency from the membrane. If the conjugate pad is not completely dried, a syrup-like solution may form that cannot flow through the membrane. The most suitable methods for drying the conjugate pad after application are warm air (T < 37 °C) or vacuum drying. For mass production of LFIA, hot air is the preferred method and is usually fixed at 37 °C so as not to affect bioreceptor stability (Parolo et al. 2020; Wild et al., n.d.; Bahadır and Sezgintürk 2016; Merck Millipore 2013).

6. Chromatographic membrane

Commercial chromatographic membranes are generally defined by capillary flow time, which is the time required for the front of the sample to cover the length of the membrane (typically 4 cm) and is generally expressed as s/4 cm. In general, the longer the capillary flow time, the slower the flow rate. This parameter is not only crucial for the overall duration of the test but also plays a fundamental role in determining the sensitivity and specificity of LFIA. High capillary flow times allow a longer interaction time between the target molecule and the bioreceptor, thus increasing the sensitivity of the assay. At the same time, long capillary flow times also increase the possibility of non-specific binding. Therefore, it is crucial to evaluate membranes with respect to different capillary flow times. The chosen material of the chromatographic membrane determines the type of interactions that govern the functionality of the membrane with the capturing bioreceptors (for both the test and control lines). Nitrocellulose is the most commonly used material for membranes due to its strong binding to proteins including antibodies and adjustable absorption properties (variable capillary flow times and the possibility of changing the surfactant content) (Parolo et al. 2020; Wild et al., n.d.; Bahadır and Sezgintürk 2016; Merck Millipore 2013).

7. Absorption pad

The last pad in the LFIA test is the absorbent pad. Its role is to control the amount of sample that the LFIA test strip can accept. If there is no absorbent pad, when the liquid reaches the end of the membrane, the flow stops, and the liquid evaporates homogeneously along the strip. This means that any marks that have not reached the back of the detection pad can accumulate on the tape and cause background signal noise. It is in this part that the absorbent pad ensures that all the markings and the entire pattern reach the end of the tape. The dimensions of the absorbent pad must be evaluated according to the amount of liquid that must pass through the membrane. Thus, for example, in the case of an LFIA assay where the use of a wash buffer is required, the absorbent pad must provide sufficient bed volume to ensure complete washing of the membrane (Parolo et al. 2020; Wild et al., n.d.; Bahadır and Sezgintürk 2016; Merck Millipore 2013).

The choice of types of membranes and any potential modifications performed on them can have significant effects on the overall efficacy of a rapid test.

Conclusions

Overall, the use of AuNPs in rapid tests and for other detection methods shows some common distinct advantages across the different methods:

1. **High sensitivity:** AuNPs-based detection methods offer high sensitivity, allowing for the detection of very low concentrations of target compounds.
2. **Ease of detection:** The visual detection of AuNPs immobilisation or aggregation provides a simple and rapid method for result interpretation, eliminating the need for specialized equipment.
3. **Versatility:** AuNPs can be easily functionalized with different compounds, enabling the detection of a wide range of target compounds.
4. **Ease of use:** The use of rapid tests is very simple and does not require the use of expensive equipment. Making them uniquely suitable for use in challenging and remote

environments with personnel that require minimal training.

5. **Price performance:** Rapid tests offer a relatively cheap and fast alternative to more sophisticated methods. While they cannot outright replace more accurate methods, they still offer a significant benefit in terms of speed and price compared to other analytical methods.

While LFIA tests offer several distinct advantages, as a technology they are also susceptible to several factors that limit their use:

1. **Sensitivity:** LFIA tests may lack sensitivity compared to laboratory-based assays such as ELISA (Enzyme-Linked Immunosorbent Assay).
2. **Specificity:** LFIA tests may exhibit cross-reactivity or non-specific binding, leading to false-positive or false-negative results. Cross-reactivity occurs when the test reacts with substances other than the target analyte, compromising the specificity of the assay.
3. **Sample interference:** Certain sample characteristics, such as viscosity, turbidity, or the presence of interfering substances, can affect the performance of LFIA tests.
4. **User variability:** LFIA tests rely on the visual interpretation of results by the end-user, which introduces the potential for subjective interpretation and variability in result interpretation. Variations in lighting conditions, colour perception, and user experience can impact the accuracy and reliability of results.
5. **Limited shelf life:** LFIA tests often have a limited shelf life due to factors such as antibody stability, degradation of detection reagents, or deterioration of the test components over time.

Rapid tests have become a mainstay for professional and personal medical diagnosis. The COVID pandemic has highlighted several issues regarding the use of rapid tests that have opened potential avenues for further development. One such key area is the waste management of rapid tests, while a single test represents a relatively small investment of material mass, the sheer volume used during the pandemic, highlighted the need to bring the industry up to speed towards a circular economy. Either through advanced recycling technologies, advanced multiplexed rapid tests, that enable the detection of several diseases in one package, or advancements in electronic sensors, that use significantly less materials and offer better signal to noise results. While AuNPs have been the dominant marker used in rapid tests, new developments in magnetic, fluorescent and quantum dot markers, used in combination with electronic detection equipment, may offer better signal to noise ratios than traditionally used spherical AuNPs. Advancements in AuNPs production methods have enabled the synthesis of several different shapes of nanoparticles, such as nano-rods, nano-shells, and nano-urchins, all retaining the classical visible surface plasmon resonance albeit at different wavelengths. Au nano-shells seem especially promising, offering an intense colour, or in other words, an intense signal. While there are some lingering questions about the perceived accuracy of rapid tests, they will remain a mainstay in the medical arsenal, with new advancements only offering better solutions to existing issues.

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