Talanta 152 (2016) 410–422

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Colorimetric detection based on localised surface plasmon resonance of gold nanoparticles: Merits, inherent shortcomings and future prospects

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ARTICLE INFO

Article history:
Received 27 November 2015
Received in revised form
3 February 2016
Accepted 4 February 2016

Keywords:
Gold nanoparticles
Localised surface plasmon resonance
Colorimetric detection

ABSTRACT

Localised surface plasmon resonance (LSPR) of gold nanoparticles (AuNPs) has been exploited for two decades in analytical science and has proven to be a powerful tool for the detection of various kinds of substances including small molecules, ions, macro biomolecules and microbes. Detection can be performed by visual colour change observations, photometry or resonance light scattering. A wide range of applications have been studied in the areas of environmental, pharmaceutical and biological analysis and clinical diagnosis. In this article, some fundamental aspects and important applications involving LSPR of AuNPs are reviewed. Several inherent shortcomings of these techniques and possible strategies to circumvent them are discussed.

Contents

1. Introduction

Gold nanoparticles (AuNPs) have unique chemical and optical properties such as self-assembly [1], biocompatibility [2], localised

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http://dx.doi.org/10.1016/j.talanta.2016.02.015
0039-9140/

surface plasmon resonance (LSPR) absorption [3], and resonance light scattering (RLS) [4]. These properties offer the means for fast detection of a variety of substances including small ions and molecules, biomolecules and microbes, and have attracted significant interest in analytical science. Numerous studies have been conducted on the fabrication of bare and functionalised AuNPs and their subsequent applications in LSPR-based colorimetric detection of various analytes. LSPR-based detection methods offer some significant advantages. These include applicability to a wide range of analytes, ease of use, elimination of the use of toxic organic solvents, point-of-care applications, as well as high sensitivity in the detection of some biological species. These benefits derive from the excellent functionalisation properties of AuNPs and their strong and highly selective interaction with the analytes when functionalised with proper moieties [5].

A number of reviews on the application of LSPR of AuNPs for the detection of various analytes have been published [6–10]. These include the detection of small molecules or ions [6,11], nucleic acids [12,13], proteins and other biomaterials [6,13], cells [14], and compounds of interest in clinical diagnostics [13,15]. Some of the reviews have focused on the fabrication and application of DNA–AuNP conjugates which have exhibited outstanding performance in the detection of various analytes [6,14,16].

The present review provides a brief introduction to the synthesis and functionalisation of AuNPs and critically discusses different aspects of their application in colorimetric detection. Various strategies for the detection and quantification of small molecules, ions and biomolecules are outlined. These include the use of bare and functionalised AuNPs, the use of aggregation and anti-aggregation strategies, the use of small molecules and biomolecules for functionalisation of AuNPs, and specific target recognition with biomolecules. Some important methods, regarding the application of biomolecules that have contributed to the development of such techniques, are highlighted. Finally, several inherent limitations of colorimetric detection methods utilising AuNP-based approaches are discussed. These include the poor linearity of the calibration fits in numerous reported methods, the questionable high sensitivity claimed by some authors, the limited number of functionalities with proper selectivity, the lack of ability for multiple detection in homogeneous methods, possible matrix interference in the analysis of real samples, and the lack of technology for large scale synthesis of AuNPs with uniform properties for special application. Possible strategies for dealing with these problems are suggested on the basis of the discussions presented in this review.

2. Synthesis, stabilisation and functionalisation of AuNP probes

2.1. Synthesis

AuNPs used in colorimetric detection are normally synthesised by reducing tetrachloroauric acid ($HAuCl_4$) with trisodium citrate in an aqueous medium [16]. AuNPs obtained by this method have a loose citrate ion shell on their surface that can be easily replaced by another desired ligand [16]. The size and size distribution of the AuNPs can be controlled by experimental parameters such as pH, the concentration of $HAuCl_4$ and the reducing reagent used [17]. AuNPs are also synthesised using other reducing agents such as sodium tetraborohydride ($NaBH_4$) in the presence of a stabiliser like polyvinyl alcohol [18]. The reduction with $NaBH_4$ is much faster due to its higher reductivity than citrate.

The particle size of the AuNPs has a significant effect on the sensitivity of the corresponding colorimetric assays [19]. Lee et al. compared different particle sizes (6, 14, 23, 40, 57, and 97 nm) and observed that the interaction of 14 nm sized particles with the analytes produced the most noticeable spectral change at longer wavelengths [19]. This result is in line with the fact that most publications on this methodology use AuNPs of similar size (e.g. 13 nm). The widespread use of 13 nm citrate capped AuNPs in colorimetric detection is also due to their narrow particle size distribution and to the sharp plasmon absorption band at around 520 nm [20].

Apart from the size, the shape and composition of AuNPs play a major role in defining their spectral properties [9]. However, performance of colorimetric methods is mainly determined by the property of aggregates rather than the dispersed AuNPs and the majority of published work uses Au nanospheres. This review will mainly focus on Au nanospheres and their LSPR applications in colorimetric detection.

2.2. Stabilisation and functionalisation

Surface functionalisation of AuNPs with different molecules has been employed as a popular strategy for the development of a wide range of highly selective AuNP-based assays. It can further improve the stability of AuNPs at high salt concentrations and broaden the application of AuNPs by immobilising various moieties for interaction with different analytes. A pioneering work in this area is the immobilisation of thiolated DNA on AuNPs [21]. Functionalisation of AuNPs is based on their bonding with functional groups such as thiol (–SH) [22], amino ($-NH_2$) [23], hydroxyl (–OH) [24], phosphine ($-PH_2$) [25], $S_2O_3^{2-}$ [26], and $P_2O_7^{4-}$ [27]. Among these, sulphur-containing ligands, such as cysteine (Cys), peptides and thiolated nucleotides, bond most firmly to AuNPs and offer a convenient self-assembly process *via* the Au–S covalent bonding. The functionalisation process has conventionally been carried out by immobilising functionalities on citrate-capped AuNPs, but such a process usually requires a long incubation time. Consequently, it is now often performed concurrently with the AuNP synthesis [28].

3. Colorimetric detection with AuNPs

3.1. Detection of small molecules and ions with bare or functionalised AuNPs

Colorimetric detection using AuNPs is based on the distance-dependent surface plasmon resonance property of AuNPs, i.e. the aggregation of AuNPs induced by an analyte and the resultant alteration of the solution colour and absorption spectrum as shown in Fig. 1.

Dispersed AuNPs have a red colour and maximum absorption around 520 nm, whereas aggregated AuNPs have a blue or purple colour, and the absorption intensity at higher wavelengths is increased. Therefore, it is critical in colorimetric detection to achieve selective interaction between the analyte and AuNPs for the aggregation to occur. There are several mechanisms underlying the colour change of AuNPs. Fig. 2 summarizes a few examples reported in literature.

Two basic strategies have been employed in such detection, namely, aggregation and anti-aggregation induced by the analyte as discussed below. Nucleic acid and peptide/protein functionalised AuNPs for colorimetric detection are discussed separately due to their special characteristics.

3.1.1. Aggregation

In this strategy, the analyte can interact with bare or functionalised AuNPs and cause their aggregation and colour change. In the case of bare AuNPs, the analyte interacts with AuNPs *via* chemical bonding. In the use of functionalised AuNPs, the analyte