Plasmonic nanoparticles: Towards the fabrication of biosensors

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Abstract. Au and Ag nanoparticles are mainly employed in the fabrication of biosensors owing to their unique optical properties compared to other noble metal nanoparticles. Many biosensors are fabricated for the rapid detection of different analytes such as organic and inorganic molecules, biomolecules like DNA, proteins, biotoxins and pathogens. In this mini review we mainly discuss on the usage of Au and Ag nanoparticles for the fabrication of colorimetric, SERS and two photon based photoluminescence biosensors.

1. Introduction
In recent years much attention is paid towards the synthesis of plasmonic nanoparticles owing to their unique optical, electronic and catalytic properties compared to their bulk counterparts [1-7]. A strong localized surface plasmon resonance (LSPR) phenomenon can be seen in Au and Ag nanoparticles due to collective oscillations of conduction electrons induced by the interaction of electromagnetic radiations [8]. LSPR frequencies of Au and Ag nanoparticles (NP) are mainly depending upon on size, shape, inter particle distance and composition [8, 9]. A strong electromagnetic enhancement can be attained through the excitation of their LSPR and this peculiar property attracted for the usage of these NP in the fabrication of biosensors [9]. The fabrication of biosensors becomes crucial for the improvement of health and environmental sectors for the early rapid detection of analytes and diseases. In recent years several biosensors such as colorimetric [10-12], SERS [13], two photon based photoluminescence [14], electrochemical and refractive index based sensors are fabricated for the real time monitoring of different analytes and biotoxins present in water and food samples. It is still a challenging task to fabricate low-cost based biosensors [1]. In this report, we mainly summarize on the usage of Au and Ag nanoparticles in fabrication of colorimetric, SERS and two photon based photoluminescence biosensors towards the detection of analytes related to biological, environmental and clinical sectors.

2. Colorimetric based sensors
In colorimetric based sensors the analytes are mainly detected based on the colour change in NP solution. In presence of specific analytes the NP aggregate to give different colour intensity and measuring the change in colour can quantify the presence of analytes in the given samples [15]. The detection method is very simple, selective, portable and instrumentation free which even can judge color change based on the naked eye [1]. For the first time Mirkin et al. developed a colorimetric assay
for the detection of DNA by using Au Nps [16]. In their method two different batches of gold nanoparticles of size 13 nm were attached with thiol modified DNA and the other batch with its complimentary DNA molecules. On mixing these two batches of Au Nps aggregate with each other due to binding affinity between the DNA molecules and developed a color change from red to blue. The binding interaction between DNA molecules can be controlled by its thermal denaturation [16]. After this work several similar strategies were developed for the analysis of RNA [17], proteins [18] cancerous cells [19], organic [20] and inorganic molecules [21]. Xia, et al. developed a label free detection of DNA, proteins and ions molecules by using unmodified Au Nps in presence of positive electrolytes [15]. In their approach, single stranded DNA molecules in the presence of positive electrolytes got aggregated and color change from red to blue whereas double stranded DNA molecules are stabilized without aggregation and thus no color change. This approach can be used for the detection of different DNA molecules by simply changing the probe DNA. Lu et al. developed a low cost biosensor for the detection of melamine in raw milk. In their approach 1-(2-mercaptoethyl)-1,3,5-triazinane-2,4,6-trione (MTT) stabilized gold nanoparticles were synthesized and in the presence of melamine, MTT shows affinity with melamine due to hydrogen bonding and thus aggregation of gold nanoparticles takes place to give different color as shown in figure 1 [20].

Figure 1. (A) Visual color transition of the MTT-stabilized gold nanoparticles from red to blue upon addition of melamine (from left to right: 0, 1.5 μM) [20].

3. Surface-enhanced Raman scattering (SERS) based biosensors

Raman scattering spectroscopy, the powerful technique which can provide information about molecules based on their vibrations. Raman spectrum is unique and act as fingerprint for the analysis of molecules. But this technique is based on inelastic scattering which is week compared to elastic scattering and thus generates very low Raman signal [1]. For the enhanced Raman signals Au and Ag nanoparticles were used and this technique is known as Surface-enhanced Raman scattering (SERS) [22, 23]. Several strategies were developed for SERS activity and this mainly depends upon size, shape, inter-particle distance and composition of NPs [24, 25]. Aggregation of NPs can improve SERS activity compared to individual NPs. Gary Braun et al. developed a label free DNA detection approach using Ag nanoparticles as shown in figure 2 [26]. In their method, hot spots were created by self-assembly tethering of Ag nanoparticles on a thin Ag film which gives an enhanced Raman signal for the detection of DNA molecules.
Feng shao, et al. reported a similar strategy for the detection of animal viruses as shown in figure 3 [27]. In their method 3D SERS substrates were synthesized by depositing Ag islands on a biomimetic scaffold chitin with sputtering technique. After deposition of Ag islands developed a hierarchical structure with hot spots and this can be used as SERS for label free detection of animal viruses. Several similar strategies were developed for the detection of biomolecules, metal ions and organic molecules.

Figure 3. Schematic representation of the fabrication process for Ag-decorated CNAs as the 3D biomimetic substrate applied in label-free animal virus detection. By using sputtering technique, Ag-NIs and Ag-NFs are formed simultaneously on the side surfaces and top ends of chitin nanopillars with hierarchical nanogaps, respectively [27].
Figure 4. Schematic representation of two-photon sensing of thrombin using Ag NPs and TBA15 [29].

TBA_{15}: 5’-GGTTGGTGGTGGTTGG-3’

Figure 5. Schematic illustration of assembly mechanism of gold nanocubes (Au NCs) induced in the presence of Cysteine/Glutathione aminoacids [30].
4. Two-photon photo luminescence based biosensors (TPPL)
The two photon photo excitation has better advantages compared to single photon excitation such as quenching of auto-fluorescence, high penetration depth and reduced photo bleaching. Au and Ag nanoparticles show enhanced TTPL and strongly depend on LSPR frequencies and surrounding medium. For an example a Au nanoparticle shows nearly 58 times enhanced TPPL compared to conventional single organic dye (Rhodamine) [14]. TPPL intensity mainly depends on the size of Au and Ag nanoparticles [28]. As compared to SERS technique which requires an additional Raman tags as probe molecules may not require in TPPL technique since the plasmonic nanostructures itself act as TPPL probe molecules. Several biosensors were fabricated based on this strategy. For example Cuifeng Jiang et al. developed TPPL based biosensor using Ag nanoparticles for the detection of thrombin protein as shown in figure 4 [29].

Zhenping Guan, et al. followed a similar strategy and developed a biosensor for the detection of cysteine/glutathione amino acid using Au nanocubes as shown in figure 5 [28]. The developed method has good potential to be used for in vivo biosensing and imaging. This approach can also be applied for the detection of metal ions.

5. Conclusion
In this report we briefly describe about the usage of plasmonic nanostructures such as Au and Ag nanoparticles for the fabrication of biosensors for the detection of different analytes based on colorimetric, SERS and TPPL techniques. Though several biosensors were developed using nanoparticles but the real challenge lies in the fabrication of portable low cost based label free biosensors for the error free real time detection of different analytes.

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