

Utilization of nanoparticles in microfluidic systems for optical detection

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Abstract An increasing interest has been shown in microfluidic systems due to their properties including low consumption of reagents, short analysis time and easy integration. However, despite of these advantages over conventional methods, some limitations in sensitivity and selectivity still exist in microfluidic systems. Recently advancements in nanotechnology offer some new approaches for the detection of target analytes with high sensitivity and selectivity. As a result, it is an appropriate method to enhance the detection sensitivity through a combination between microfluidic system and nanotechnology. Optical detection is a dominant technique in microfluidics because of its noninvasive nature and easy coupling. Numerous studies that integrate optical microfluidic system with nanotechnology have been reported in recent years. Therefore, optical microfluidic systems in combination with nanomaterials (NMs) are reviewed in our work. We illustrate the functions of different NMs in optical microfluidic systems and the efforts of different researchers to improve the performance of devices. After the introduction of different nanoparticle-based optical detection methods, challenges and future directions in the development of nanoparticle-based optical detection schemes in microfluidics have also been discussed.

1 Introduction

Microfluidic chip is a device with micro-sized channels that can deliver small volume of reagents and samples to reaction

area to achieve analytical purpose. It has several advantages over conventional methods: (1) Rapid analysis can be achieved, since the high ratio of surface area to volume and the short diffusion distance to the reaction areas; (2) Samples and reagents are transferred in channels with micron size, which means a lower consumption; (3) Various processes such as mixing, chemical reaction, separation and detection can be integrated into a microchip to realize integration between different multifunctional units. These features make it suitable for medical diagnostic (Rivet et al. 2011), drug discovery (Dressler et al. 2013; Neuži et al. 2012), point of care testing (Chin et al. 2012; Gervais et al. 2011; Su et al. 2015) and early warning of disease (Jiang et al. 2014). However, despite of these advantages showed in microfluidic system, limitations in sensitivity and selectivity such as low detectable signals and low signal-to-noise ratio are still problems which restrict its further application (Sierra-Rodero et al. 2014).

In recent years, advancements in nanotechnology provide a new approach to sensitively and selectively detect target analytes. Nanomaterials (NMs) exhibit many different properties compared to those materials at macroscopic and microscopic level (Pumera 2011). They can bring a series of advantages in improvement of detection performance when utilized in microfluidic devices, thus resulting in a rapid development of nanoparticle-based microfluidic systems and yielding many different detection schemes using various kinds of nanoparticles (NPs) such as quantum dots (QDs), metal NPs and magnetic NPs to achieve ultra-sensitive detection. Now many studies that integrate nanoparticle-based detection schemes with microfluidic systems have been reported, which can be categorized into optical detection, electrochemical detection and other detections due to the different detection principles.

Optical detection is a dominant technique in microfluidics because of its noninvasive nature and easy coupling

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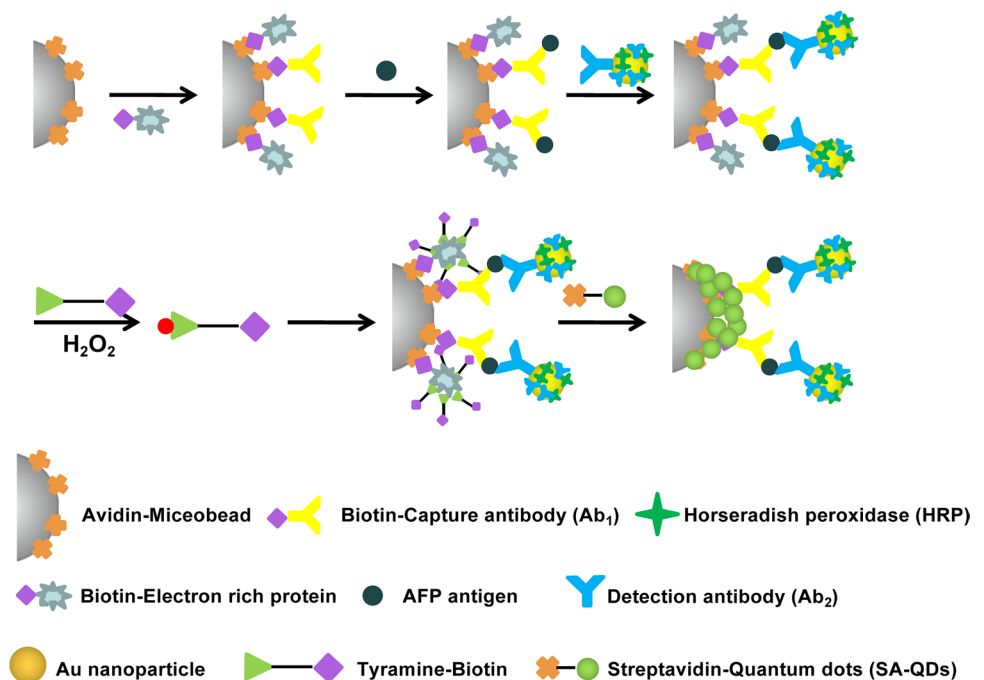
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(Han et al. 2013; Yi et al. 2006). It can enhance the detection sensitivity on chip through a combination with other techniques (Su et al. 2015). With the rapid development of nanotechnology, a variety of schemes utilize NPs to benefit optical methods (colorimetry, fluorescence, surface enhanced Raman scattering, etc.) according to the unique properties of NPs. For instance, semiconductor crystal NPs which are also called quantum dots have high fluorescence efficiency and can be utilized as signaling labels for fluorescence detection. Noble metal NPs such as gold NPs and silver NPs are utilized to enhance SERS signal due to their plasmonic response. In this review, some optical microfluidic systems utilizing NPs have been proposed to see the roles of NPs in these microfluidic systems and the authors' efforts to improve the detection performance. Paper-based microfluidics is a recently developed technology, which is low-cost and simple (Ge et al. 2014; Zhang et al. 2015). Moreover, it can absorb and transport liquids without any additional devices. These features make it a promising analytical method for point of care testing. Among various detection methods used in paper-based microfluidics, optical detection accounts for a large proportion. However, it also shows limitation in sensitivity (Liana et al. 2012). So we introduce some examples that utilizing NPs to improve the detection performance of paper-based microfluidics in some sections. At the end of the review, challenges related to the development of nanoparticle-based optical detection schemes in microfluidics will be discussed, as well as future outlooks.

2 Utilization of nanoparticles in microfluidic systems for fluorescent detection

Fluorescence detection is the most commonly used optical method in microsensing systems. It has shown its usefulness in microfluidic system using nanoparticles such as semiconductor quantum dots (QDs) and metal NPs functionalized with fluorescent dyes. Quantum dots are semiconductor nanocrystals with narrow, size-based emission spectrum and can be excited simultaneously with a single light. Compared with organic fluorescent dyes, QDs have better stability and higher quantum yield (Han et al. 2013), thus overcoming photobleaching and pH sensitivity problems. When integrated into microfluidic devices, QDs can be used to label proteins, nucleic acids, or other targets and amplify the detection signals (Hu et al. 2013; Zhang et al. 2013, 2014a). For instance, Zhang et al. (2013) reported a method that utilized multienzyme-nanoparticle amplification for the detection of α -fetoprotein (AFP)—a biomarker for cancer. As shown in Fig. 1, polystyrene microspheres functionalized with the capture antibody and electron rich proteins were utilized as a sensing platform and HRP-antibody functionalized gold nanoparticles (Au NPs) were utilized as labels. Enzyme-functionalized nanoparticles were introduced onto the surface of microbeads by using “sandwich” immunoreactions and subsequently horseradish peroxidases on the surface of Au NPs could catalyze the oxidation of biotin-tyramines, resulting in the deposition of multiple biotin moieties onto the solid phase. Then streptavidin-labeled quantum dots could bind to the deposited

Fig. 1 Schematic illustration of microbead-based multienzyme-nanoparticle amplification for ultrasensitive detection of α -fetoprotein (Zhang et al. 2013)



biotin moieties and exhibit the fluorescent signal. According to this enzymatic process, multiple signal output could be triggered to achieve signal amplification. The detection limit could reduce to 0.2 pg/ml in 10 μ l calf serum, which was 500 times higher than that of the off-chip test and 50 times higher than that of common beads-based microfluidic immunoassay. Another example was the detection of microRNA due to the enzymatic amplification (Zhang et al. 2014a). The hybrid between target microRNA and immobilized capture probes could be labeled with the biotin-labeled nucleotides by the use of the bound microRNAs, which served as a primer for an enzymatic elongation. At the final step, the streptavidin-labeled quantum dots could bind to the biotin moieties to exhibit the fluorescence signal. This method showed a 200-fold increase in detection limit compared to the off-set chip test. In addition to detecting a single analyte, QDs also show great potential in simultaneous detection of different analytes such as waterborne pathogens (Agrawal et al. 2012) and cancer markers (Jokrest et al. 2009) due to their size-based emission spectrum.

Besides QDs, noble metal NPs can act as carriers to load fluorescent dyes or as quenchers functionalized with fluorescent molecules for fluorescent detection (Lafleur et al. 2012; Peng et al. 2012; Zhu et al. 2014). Zhu et al. (2014) utilized Au NPs to enhance the fluorescence signal for the detection of DNA. The Au NPs aggregated a large number of fluorescent molecules on its large surface area, thus enhancing the fluorescence intensity. What's more, when the spectrum of emitted fluorescence was consistent with the spectrum adsorption peak of Au NPs, fluorescence signal would be amplified due to the plasmon resonance phenomenon (Lakowicz et al. 2008; Wang et al. 2010b). Peng et al. (2012) utilized fluorophore-labelled DNA hairpin probes immobilized on the Ag NPs surface for DNA detection. As shown in Fig. 2, Ag NPs served as quenchers for a close proximity to the fluorophore when target DNA was absent. As target DNA presented, complementary interaction between target DNA and probe unfolded the hairpin

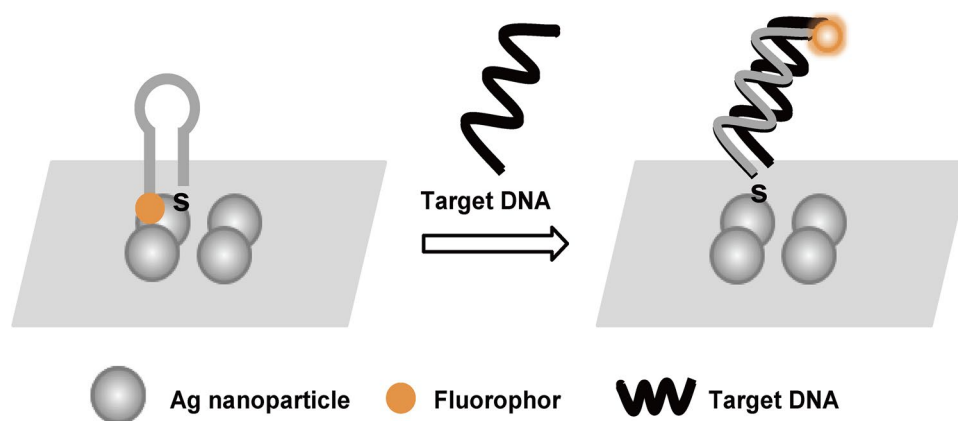
structure, thus preventing the quenching by moving the fluorophore away. The fluorescence intensity increased accordingly. Based on the high affinity of mercury for gold, Lafleur et al. (2012) reported two detection schemes named “turn-off” and “turn-on” methods for the detection of Hg^{2+} . The fluorescent BSA-AuNCs and non-fluorescent rhodamine R6G-AuNPs were utilized as Hg sensing probes. The appearance of Hg^{2+} could lead to fluorescence quenching of BSA-AuNCs in the “turn-off” method while R6G-AuNPs recovered fluorescence intensity in the “turn-on” method.

3 Utilization of nanoparticles in microfluidic systems for SPR

As a powerful platform for many binding assays, Surface Plasmon Resonance (SPR) can investigate biomolecular interactions by measuring the adsorption of molecules on a thin metal surface without labels (Su et al. 2015). The common used platform for SPR consists of a polarised light source, a prism, a thin metallic film and a detector. SPR detection is based on the measurement of a change in the refractive index near the surface of metal layer which is sensitive to the dielectric environment. When a binding assay occurs on the metal surface, dielectric properties at the metal layer can be changed. It can influence the angle of the reflected light, which has a direct relationship to the concentration of target analyte. Therefore, SPR signals can be used to detect many analytes by monitoring the change in reflectivity.

Surface Plasmon resonance imaging (SPRI) which has the same fundamental principles with conventional SPR is a well-established technology that can be used for the detection of many analytes such as RNA (Li et al. 2007), protein (Chandra and Srivastava 2010) and many other analytes. The intensity of light reflected from the surface of metal layer is directly related to the number of targets, so

Fig. 2 Schematic illustration of the plasmonic-enabled DNA biosensor (Peng et al. 2012)



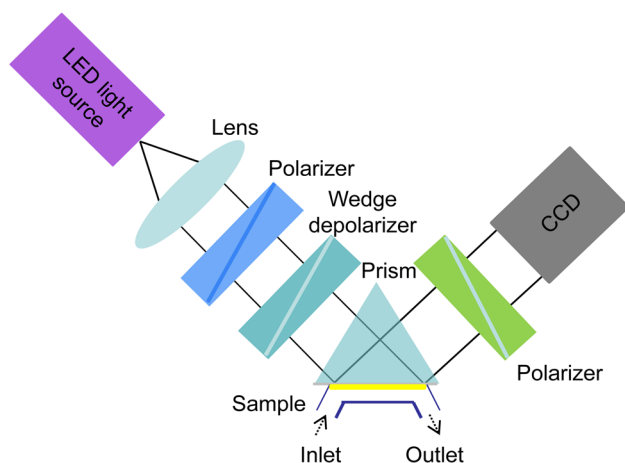


Fig. 3 Schematic illustration of the near infrared SPR-PI optical setup. Copyright (2012) American Chemical Society

it was detected by a CCD camera to measure the concentration of targets. Recently, an ultrasensitive detection method named nanoparticle-enhanced surface plasmon resonance-phase imaging (SPR-PI) was used for multiplexed hybridization DNA assays, which showed 20 times more sensitive than nanoparticle-enhanced SPRI (Zhou et al. 2012). As shown in Fig. 3, a near-IR light emitting diode (LED) light source was used as light source and a CCD camera was used to collect the reflected light to image the intensity. It measured the phase shift from light incident at a fixed angle onto the surface of a gold thin-film. Silica NPs which replaced gold or silver NPs could enhance the SPR-PI signal due to the optical effect that greatly increased the interfacial refractive index.

Localized surface plasmon resonance (LSPR) is an active method that utilizes noble metal NPs (Au and Ag NPs) as LSPR sensing platform to improve sensitivity. The testing principle relies on the spectral shifts caused by the change of surrounding dielectric environment in an interfacial binding event. However, problems such as how to constitute a self-assembled monolayer are still challenges for the combination of a microfluidic system and LSPR-based biosensor.

4 Utilization of nanoparticles in microfluidic systems for SERS

Raman spectroscopy which can provide a label-free format has been used in many fields. Multiple analytes can be detected according to the relatively narrow peaks in spectrum (Rivet et al. 2011; Yazdi and White 2013). However, the weak signal limits its sensitivity (Han et al. 2013; Prado et al. 2014; Zhou et al. 2011), thus methods that can enhance the signal are necessary to achieve ultrasensitive

detection. In the past decades, surface-enhanced Raman spectroscopy (SERS) based on surface plasma resonance has been proved to be powerful to improve detection performance. SERS signals can be enhanced at SERS hot spots which are usually rough metal surfaces or nanostructured metallic surfaces. Among various nanoparticles, noble metal NPs such as Ag NPs and Au NPs are commonly used in microfluidic systems for signal amplification according to various kinds of methods to form hot spots. For instance, a sensitive method for the simultaneous detection of three fungicides was described using an opto-fluidic SERS microsystem (Yazdi and White 2013). The SERS signal could be improved by utilizing silica microbeads packed in the detection area to aggregate Ag NPs and adsorbed analyte molecules. Compared with the SERS in an open microfluidic channel, the SERS signal obtained a fourfold increase. Prado et al. (2014) utilized SERS method for the detection of specific RNA sequences instead of utilizing fluorescence labels. In order to produce SERS hot spots as enhancing surface, $MgCl_2$ was utilized to aggregate silver nanoparticles inside the microfluidic devices. Besides, combined with a droplet microfluidic system, this microfluidic device could benefit for the SERS detection by avoiding the large clusters and the formation of clogging.

Although the utilization of NPs can benefit the detection, SERS signals are hard to reproduce due to the difficulty in controlling the aggregation of NPs. Therefore, it is essential to develop different strategies to control the aggregation state in microfluidics for SERS detection. Recently Liberman et al. (2015) reported a novel method that controlled aggregation of Ag NPs by laser irradiation to monitor the products of organophosphate breakdown. The Ag clusters could be formed at any desired area inside the channel to act as hot spots to enhance the Raman spectroscopic signal. Wang et al. (2014) utilized silica-coated, highly purified SERS clusters in microfluidic systems for the sensitive detection of two pathogen antigens—EHI_115350 and EHI_182030. In order to reproduce the SERS signal, continuous density gradient centrifugation was used to purify the SERS clusters. In addition, the silica-coating could make the particles stable in different buffer systems. In this microfluidic system, nanoyeast single-chain variable fragment (NYscFv) was first used as an affinity reagent, which was cost-effective, stable and specific. The detection limits of two pathogen antigens were 1 pg/ml (EHI_115350) and 10 pg/ml (EHI_182030). A simple method for the aggregation of nanoparticles was reported by using a pneumatic valve and nanorod arrays at the end of the microchannel (Zhou et al. 2011). As shown in Fig. 4, when reaching the area that contained the valve and nanorod arrays, Au NPs were trapped in the microchannel by pressing the PDMS membrane of the valve against the nanorods to create SERS hot spots for SERS detection. This method is

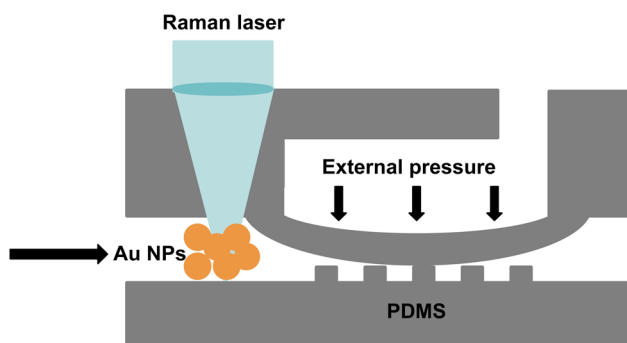


Fig. 4 Schematic illustration of trapping of gold nanoparticles utilizing a pneumatic microvalve for SERS detection (Zhou et al. 2011)

convenient to aggregate nanoparticles more conveniently and according detection limit can reach to picomolar level (Pan et al. 2007). In addition to these methods, some novel methods have also been reported in paper-based microfluidics to ensure the reproducibility. Zhang et al. (2014b) utilized a painting brush to fabricate SERS active microfluidic paper chips, which were utilized to detect Rhodamine 6G and malachite green. Ag NPs were deposited on the surface of the filter paper substrate which contained abundant wrinkles and fibrils to form SERS hot spots. This method achieves good reproducibility due to similar depositing effects obtained from the relatively light brushing force and soft bristles. Saha and Jana (2015) utilized silver coated gold nanoparticles (Ag@Au NP) functionalized with 4-mercaptopyridine and affinity molecules as SERS nanoprobe for the detection of proteins. 4-mercaptopyridine acted as Raman reporter molecules to produce characteristic Raman signals. In this paper-based microfluidic system, both nanoparticles and analytes were used in the mobile phase. When target proteins and functionalized Ag@Au nanoparticles reached the reaction area through two separate channels, affinity molecule such as glucose and biotin could interact with the proteins, which induced aggregation of Ag@Au particles and generation of hot spot inside the microchannel. Then the enhanced SERS signal was detected by a Raman spectrometer. This approach overcomes poor reproducibility of SERS which limits its detection applications and other biomolecules can also be detected in this microfluidic system.

As is well known, the ultimate goal of microfluidic technology is real world application. However, few studies have been reported using real samples. Recently Torul et al. (2015) utilized SERS method to detect glucose in blood samples without any pretreatment procedure, which may provide a direction for microfluidic analysis systems. In this paper-based microfluidic system, a nitrocellulose membrane was used as substrate paper and patterned with a wax printing. SERS platform was constructed by dropping

gold nanoparticles on cellulose-based papers to form SERS active substrate. Gold nanoparticles were modified with 4-mercaptophenylboronic acid (4-MBA) and 1-decanethiol (1-DT) molecules to entrap the proteins and blood cells. With the contribution of Au NPs, this paper membrane-based SERS platform exhibited a good linear relationship in the range of 0.5–10 mM and observed limit of detection (LOD) value was 0.1 mM.

5 Utilization of nanoparticles in microfluidic systems for absorbance (colorimetric) detection

Colorimetry is a technology usually used in macroscale analytical chemistry. The color change can be measured by using a spectrophotometer or can even be seen by naked eyes. Compared with other optical methods in microfluidics, the sensitivity of colorimetry is relatively poor. However, its advantages such as low cost, portability and ease of use make it available for practical or even personal use and cause researchers' attention (Han et al. 2013; Lin et al. 2010). In recent years, the rapid development of nanotechnology provides the opportunity to improve the performance of colorimetric detection in microfluidic systems (Chen et al. 2014; Evans et al. 2014; Lin et al. 2005; Song et al. 2011; Xu et al. 2009). For instance, colorimetric detection is the most common used method in paper-based microfluidics due to the simplicity of the final response. However, the uneven color distribution in the detection areas can influence the detection performance (Evans et al. 2014; Hu et al. 2014; Yetisen et al. 2013). In order to overcome this problem, nanoparticles have been utilized in microfluidic paper-based analytical devices (μ PADs) for colorimetric detection (Evans et al. 2014). In addition, the utilization of NPs can also improve the sensitivity. Chen et al. (2014) combined colorimetric gold nanoparticles with microfluidic paper-based analytical devices to detect mercury ions. Au NPs were used as colorimetric sensors, the surface charge of which was negative. Different concentrations of Hg^{2+} could cause different degrees of Au NPs aggregation by sheltering the surface charge. According to the surface plasmon resonance, the color of Au NPs could be changed. The results of this colorimetric assay were quantified by instruments. A detection limit of 50 nM was achieved.

Recently some studies reported a simple and low-cost method based on the aggregation of nanoparticles (Chin et al. 2011; Date et al. 2012; Luo et al. 2005). The concentrations of analytes could be easily detected according to the absorbance value by using some commonly used optical instruments. For instance, the gold nanoparticle-labeled antibodies could act as tracers of metal ions and were captured in the detection area (Date et al. 2012). As shown in

Fig. 5 Schematic illustration of the absorbance detection utilizing gold nanoparticles (Date et al. 2012)

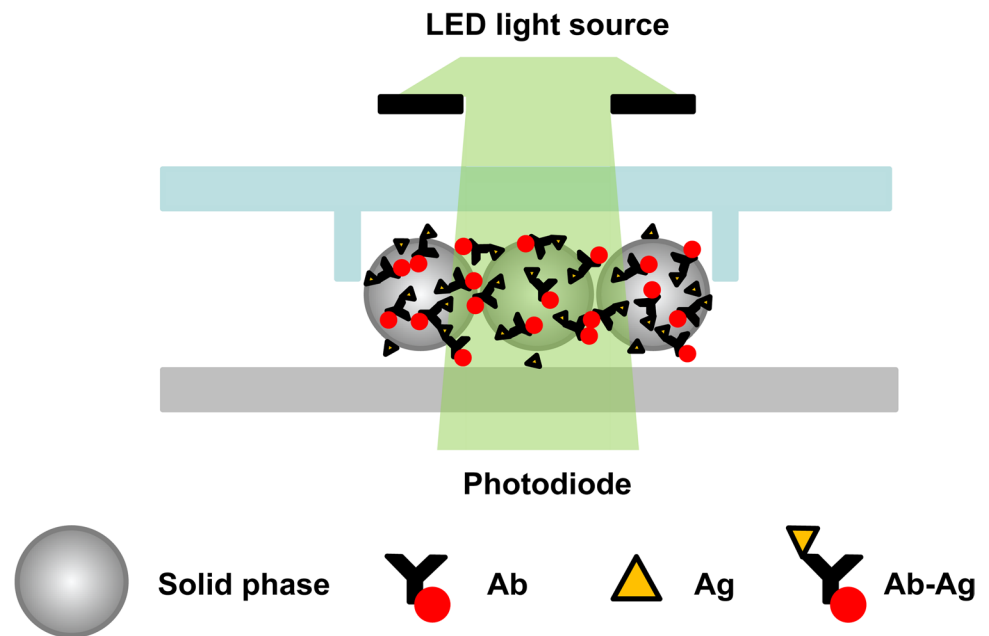


Fig. 5, the metal concentration was proportional to the gold label and thus could be obtained by detecting the absorbance of Au NPs. This low-cost and sensitive device could be utilized for the detection of cadmium, chromium and lead.

6 Challenges for nanoparticle-based optical detections in microfluidics

In recent years, various nanoparticles have been utilized in optical microfluidic systems to improve the performance of microdevices. QDs which have narrow, size-based emission spectrum can serve as fluorescent labels in the microfluidic systems. It can be used to detect one or more analytes on a chip according to the properties of these semiconductor nanocrystals. Noble metal NPs such as Ag NPs and Au NPs can be aggregated by various methods to form SERS active area to enhance the SERS signal. What's more, the highly specific and narrow band SERS signal makes it possible to detect multiple analytes at the same time. The other applications of NPs in SPR and colorimetric detection can also bring a lot of benefits. However, although different nanoparticle-based optical schemes are available in microfluidics, there are still challenges in the development of these technologies. Firstly, it should be pointed out that many researches stay on the level of developing sensors for the detection of pure samples or synthetic samples. Up to now, most nanoparticle-based optical detection schemes in microfluidic systems have not been used for real application. Without verification of their applicability under real-world conditions,

their applicability is still in question (Monošík and Angnes 2015). Secondly, as is well-known, the optical properties of NPs partly depend on their size and shape. However, the synthesis of NPs with good control of size and shape is difficult (Wang et al. 2010a). Deviations are accumulated during the synthesis process, which can influence the reproducibility of microfluidic systems. Thus, it is essential to design and develop new strategies for easy synthesis of NPs with controllable size and shape. In addition, while many NPs are utilized for highly sensitive detection, they still have their own drawbacks. For instance, QDs which can be utilized as nanoprobe suffer from a limited shelf life (Vannoy et al. 2011) and show blinking characteristics when excited with high intensity laser. The varied response of QDs to various substances under different conditions such as H^+ , Fe^{3+} , and H_2O_2 makes it hard to achieve real sample detection (Hu et al. 2010; Wang et al. 2008). Metal NPs can be used as enhancers in surface enhanced Raman scattering detection. However, their aggregation state which can influence the SERS activity remains difficult to be controlled. The large surface area of NPs can absorb endogenous macromolecules, resulting in inactive surface and reduction of surface enhanced Raman scattering ability (Wang et al. 2013). Besides, the toxicity of NPs should also be considered while utilizing them in (bio) sensing systems (Pan et al. 2007; Wang and Chen 2011; Zhang et al. 2014c). In the future, great efforts should be made to solve these problems and take these systems from lab to real. Finally, the usage of conventional equipments negates the purpose of portability. To cope with this challenge, it is essential to develop portable versions of relevant equipments.

7 Conclusion and future outlooks

This review focused on recent strategies of nanoparticle-based optical detections in microfluidic devices. On the one hand, nanoparticles exhibit many different properties compared to those materials at macroscopic and microscopic level, which can develop various detection schemes to improve the performance of the analysis. On the other hand, various advantages offered by microfluidic technologies such as low consumption of reagents, short analysis time and easy integration are beneficial to develop a miniaturized platform. The synergism between nanotechnology and microfluidic technology can bring new analytical devices for sensitive detection of various analytes.

Future aim should take these systems from lab to real world. However, some problems still need to be solved. Firstly, compared with most samples utilized in laboratory studies, real samples such as blood and seawater are complex. Therefore, the verification of on-chip detection for real samples is essential in order to adopt these microfluidic systems for real world application. Secondly, problems related to nanoparticles such as the stability, size variation, uncontrollable aggregation, and toxicity should also be carefully considered while integrating nanoparticles with microfluidic systems. Such drawbacks should be overcome by developing novel nanomaterials and proper technologies. Moreover, in order to meet future demand, it is essential to develop portable devices. The integration of microfluidic devices with smart phones can be a future trend. Finally, more effective interdisciplinary collaborations are needed to bridge the gap in technology.

In conclusion, the integration of nanoparticles with optical microfluidic systems is an active area of research due to its various advantages. It shows great potential for various applications such as point of care testing, medical diagnostic, drug discovery and early warning of disease. As many researchers are making great efforts to overcome the drawbacks of these microfluidic systems, the realization of the real world application is only a question of time.

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