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Sensitive determination of 6-mercaptopurine based on the aggregation of phenylalanine-capped gold nanoparticles

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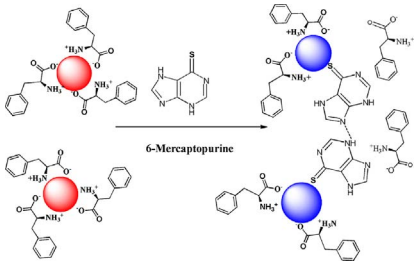
GRAPHICAL ABSTRACT

The aggregation of the gold nanoparticles in the presence of 6-mercaptopurine resulted in a change in the colour of the colloidal solution.



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ABSTRACT

The purpose of the present work was to design a colorimetric method for the determination of 6-mercaptopurine (6-MP). 6-MP is a useful drug for the treatment of leukemia. Gold nanoparticles (NPs) are known to undergo a change in colour upon aggregation. Hence, in the present work phenylalanine-capped gold NPs were used as a colorimetric probe for the determination of 6-MP. Transmission electron microscopy (TEM) measurements revealed that the phenylalanine-capped gold NPs ranged from 6 to 9 nm in size. The UV–vis spectrophotometric measurements showed that the surface plasmon resonance (SPR) band of the metallic NPs was positioned at 516 nm. The effect of 6-MP addition on the SPR band of the gold NPs was investigated at pH 8 and 5. At pH 8, only a slight change in the position and intensity of the SPR band was observed. However, at pH 5, the SPR band of the gold NPs was broadened as well as red shifted in the presence of 6-MP. The colour of the gold NPs changed from red to dark purple. The ratio of the absorbance of the gold NPs at 600 and 516 nm versus the concentration of 6-MP was found to be linear in the range 0.2–1.8 μM. The limit of detection (LOD) of the colorimetric method for the determination of 6-MP was calculated to be 0.647 μM.

1. Introduction

Colloidal solutions of noble metals such as gold and silver are intensely coloured due to their unique surface Plasmon resonance (SPR) absorption [1]. The position of the SPR band is strongly dependent on the shape and size of the colloidal nanoparticles (NPs). The aggregation of the metal nanoparticles results in colour change of the colloidal solution. Therefore, the colour change provides a practical platform for absorption based colorimetric sensing of any molecule that can cause the aggregation of the metal NPs [2–10]. For example, Yuan and coworkers reported thiolated azido derivatives and active functionalized gold NPs for the detection of hydrogen sulfide (H_2S) [9]. Under optimum conditions, 0.2 μM H_2S was detectable using UV–vis spectrophotometry. However, only 4 μM of the analyte could be detected with bare eye. The above mentioned strategy can also be utilized for cation and anion sensing. For example, the colorimetric sensing of Hg^{2+}

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[11,12], Cr^{3+} [13], Cd^{2+} [14], Al^{3+} [15] and pyrophosphate anion [16] have been reported during the past few years using functionalized gold NPs.

An important consequence of the aggregation phenomena is the creation of NP-based assemblies. For example, Mocanu et al. investigated the self-assembly behaviour of the gold NPs in the presence of cysteine [17]. The self-assembly of gold NPs was achieved primarily through the zwitterion-type electrostatic interactions between the charged amine and acid groups of cysteine molecules bound to the NPs by their thiol groups. However, in many of the applications such as drug delivery, suppression of the aggregation of the gold NPs is paramount [18]. As a result, numerous reports have emerged on the aggregation behaviour of the gold NPs in the presence of biological molecules [18–28]. Recently, Blakey et al. reported a novel method for controlling the aggregation of the gold NPs [24]. It was achieved by varying the relative amounts of hydrophobic small molecules, which acted as aggregating agents and end functional hydrophilic polymers which served as steric stabilizing agents.

6-mercaptopurine (6-MP) belongs to the class of purines which are important constituents of DNA. It is an immunosuppressive drug and is used to treat leukemia [29]. The sensing of 6-MP has evoked much interest recently. Several research papers have been published on the detection of 6-MP using colorimetric [30], fluorescence [30,31], voltammetric [29], resonance Rayleigh light scattering [32] and surface enhanced Raman spectroscopic techniques [33]. Compared to the various analytical methods, colorimetry does not require expensive instrumentation since a simple spectrophotometer is sufficient for the experimental work. The colorimetric determination of 6-MP was recently reported using folic acid fabricated silver nanoparticles [30]. However, to the best of our knowledge, there is no previous reported in the literature on the colorimetric determination of 6-MP using gold NPs.

The synthesis of gold NPs with controlled size may be useful from the point of view of their applications for catalytic studies. Li et al. have reported the synthesis of concentrated gold NPs with low size distribution by modifying the classical citrate reduction method [34]. They used a tenfold concentrated precursor (2.5 mM $HAuCl_4$) by the addition of sodium hydroxide and controlling the temperature. Recently, tartrate was used as a substitute of citrate for the synthesis of gold NPs with controlled size [35]. Among all sizes, highly monodisperse and functionalizable sub–10 nm gold NPs with tunable surfaces are appealing materials [36]. Such NPs are especially attractive for biomedical applications and nanomedicine. The synthesis of sub-10 nm gold NPs has been reported recently by two research groups [36,37]. In the present work, we have synthesized colloidal gold NPs using the amino acid, phenylalanine, as a capping agent. The synthesized gold NPs have a narrow size distribution and are sub–10 nm in size. The phenylalanine-capped gold NPs have be used as a colorimetric probe for the determination of 6-MP.

2. Material and methods

2.1. Materials

Au (III) chloride trihydrate, sodium borohydride and L-Phenylalanine were obtained from Sigma Aldrich. Glutathione and methionine were obtained from Himedia Private limited Mumbai. All other chemicals were of analytical grade. All reagents were used without further purification. The glassware was cleaned with aqua-regia before use.

2.2. Instrumentation

TEM measurements were carried out using a JEOL 100 CX transmission electron microscope operating at 100 kV. A drop of the gold NP solution was placed on a copper grid and air dried before the measurement. The UV–vis absorption spectra were obtained using a PerkinElmer Lambda 25 spectrophotometer. The spectra were acquired using a 1 cm length quartz cell. The dynamic light scattering (DLS) measurements were carried out using a Zetasizer Nano ZS90 system manufactured by Malvern Instruments Limited. The scattering angle was 90° and the scattering intensity data were processed by the software supplied with the instrument to obtain the hydrodynamic diameter.

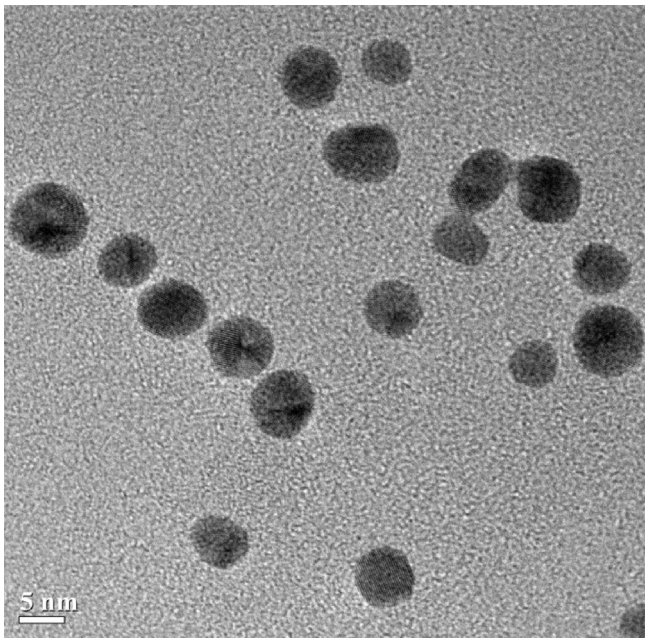

Fig. 1. TEM image of the phenylalanine-capped gold NPs.

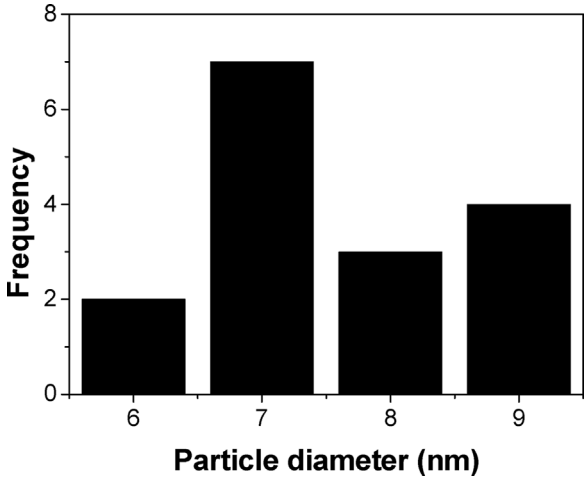

Fig. 2. Size distribution of the phenylalanine capped gold NPs.

2.3. Preparation of phenylalanine-capped gold nanoparticles

100 ml of 2×10^{-4} M gold chloride solution ($HAuCl_4$) was reduced by 0.01 g of sodium borohydride at room temperature. A brownish colloidal solution was obtained which changed to red. Then 0.2 ml of various concentrations (0.1 M–0.1 mM) of the stock solutions of L-Phenylalanine were added to the 100 ml gold solution and stirred for 10 min. Varying the concentration of the capping agent leads to the formation of different size of the gold NPs as shown by the DLS measurements and supported by UV–vis spectrophotometric measurements (Fig. S1 and S2, Supplementary data). The red colloidal gold solution was kept overnight for ageing and could be used for studies thereafter. The pH of the synthesized phenylalanine-capped gold NPs was 8.0. The