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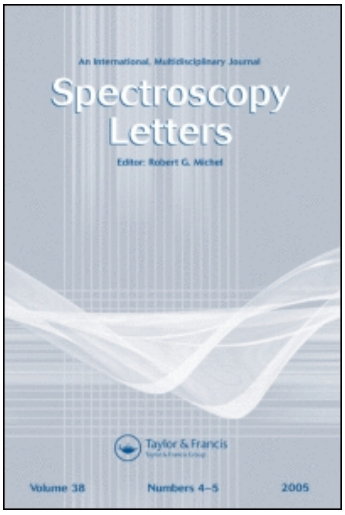

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Platinum Nanoparticle-Based Assay for Proteins by Resonance Light Scattering

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Platinum Nanoparticle–Based Assay for Proteins by Resonance Light Scattering

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ABSTRACT A simple, sensitive, platinum nanoparticle–based assay for trace amounts of protein by resonance light scattering (RLS) was studied. The RLS intensities for bovine serum albumin (BSA) and human serum albumin (HSA) were remarkably enhanced due to the interaction with Pt nanoparticles at pH 3.5 or 4.0, respectively, and the maximum RLS peak appeared at 390 nm. The RLS intensity increased proportionally with Pt concentration below $3.0 \times 10^{-5}\,\mathrm{mol \cdot L^{-1}}$ but declined gradually above $4.0 \times 10^{-5}\,\mathrm{mol \cdot L^{-1}}$. BSA within the range 0.1–3.0 $\mu\mathrm{g \cdot mL^{-1}}$ and HSA of 0.1–2.7 $\mu\mathrm{g \cdot mL^{-1}}$ can be detected with this method, and the detection limits were 4.2 and 10.7 $\mathrm{ng \cdot mL^{-1}}$, respectively. The method was satisfactorily applied to the quantitative determination of total proteins in human serum samples with a maximum relative standard deviation (RSD) lower than 2.8% and recoveries in the range 100.4–102%.

KEYWORDS bovine serum albumin, detection of protein, human serum albumin, platinum nanoparticles, resonance light scattering

INTRODUCTION

The detection of proteins is considered essential in bioanalysis and biodiagnostics because it is often used as a reference for the measurement of other components in biological systems. Many assays for proteins are available such as the Lowry,[1] Coomassie brilliant blue (CBB),[2] bromophenol blue,[3] and bromocresol green[4] methods. However, because of some limitations of these conventional detecting methods in terms of sensitivity, selectivity, stability, and simplicity, a great number of novel assays have been developed, such as spectrophotometric,[5,6] spectrofluorimetric,[7,8] chemiluminescence,[9,10] and electrochemical[11,12] methods. Due to numerous advantages[13,14] compared with conventional detecting methods, the resonance light scattering (RLS) technique has received wide attention after it was developed and introduced to analytical chemistry[15,16] and has been widely used for the determination of trace protein and nucleic acid in solution.[17] This technique is usually based on the enhanced RLS signals resulting from the bioassemblies or aggregation, which can be easily detected by using a common spectrofluorimeter through simultaneously scanning the excitation and emission monochromators with the same wavelength.[15]

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Accordingly, it is desirable to exploit new materials for determination of proteins with RLS.

In recent years, metal nanoparticle–based assays for biomolecules with RLS have attracted tremendous attention due to their unique size-dependent optical and their electronic properties.[18,19] Owing to the specific size effect of nanoparticles, it may especially match the RLS technique in detecting biomolecules. There are some examples of the use of RLS for protein determination employing silver and gold nanoparticles.[20–23] However, there are few reports of protein detection using RLS based on the interaction of platinum nanoparticles with proteins. In this paper, the RLS of the interaction of platinum nanoparticles and proteins was investigated. A novel method for protein determination by RLS based on platinum nanoparticles was developed, and it was applied to the detection of total protein in human serum samples with satisfactory results.

MATERIALS AND METHODS

Reagents

Chloroplatinic acid ($H_2PtCl_6 \cdot H_2O$), sodium citrate, and other chemicals were of analytical grade or guaranteed reagents commercially available and used without further purification. Stock solutions of $100\,\mu g \cdot mL^{-1}$ bovine serum albumin (BSA) and human serum albumin (HSA) (Sigma, St. Louis, MO) were stored at 0–4°C. Doubly distilled water was used throughout. Britton–Robinson (BR) buffer was used to control the acidity of the tested solutions. Human serum samples were offered by the People's Hospital of Hubei Province and diluted to 25,000-fold volume with water before use.

Apparatus

Transmission electron microscopy (TEM) was measured with a Tecnai G2 20 electron microscope (FEI Company, Czech-Republic), operating at 300 kV. Samples for TEM measurements were prepared by placing a drop of the metal colloidal dispersion on a copper grid coated with a perforated carbon film, followed by evaporation at room temperature. RLS spectra were recorded on an LS-55 fluorescence spectrometer (PerkinElmer Company, USA). UV-Vis spectra were measured on a Lambda BIO35 spectrophotometer (PerkinElmer Company, USA). The pH values were measured with a model PHS-25 pH meter (Shweiye Com., Shanghai, China).

Procedure

Pt nanoparticles was prepared as follows: 0.5 mL of $41\,mmol \cdot L^{-1}$ H_2PtCl_6 solution was mixed with 8 mL 1% sodium citrate to form a pale-yellowish solution. The resulting solution was then refluxed for 35 min with oil-bath heating, and the color of the solution was changed from pale yellow to brownish black. Particle sizes of Pt colloid were measured by TEM prior to use. The prepared citrate-coated Pt nanoparticles were negatively charged due to the adsorption of citrate with negative charge on the surface of the Pt nanoparticles.

Subsequently, 0.4 mL of $1\,mmol \cdot L^{-1}$ Pt colloid (the concentration was calculated by the precursor), 1.0 mL of 1% NaCl solution, 1.0 mL of $0.05\,mol \cdot L^{-1}$ BR buffer, and 0.1 mL of $100\,\mu g \cdot mL^{-1}$ BSA or HSA was added into a 10-mL volumetric flask successively and then made up to volume with water and mixed thoroughly. TEM was measured, and the RLS spectra were recorded with an LS-55 fluorescence spectrometer by scanning synchronously with the same excitation (λ_{ex}) and emission (λ_{em}) wavelengths ($\Delta\lambda = 0.0$ nm) in the range 200–700 nm; a reagent blank without any protein and Pt nanoparticle as a reference was used. The relative RLS intensities ($\Delta I = I - I_0$, I and I_0 corresponding with that of sample and blank, respectively) were measured with $\lambda_{ex} = \lambda_{em}$ at 390 nm.

RESULTS AND DISCUSSION

UV-Vis Absorption Spectra of Pt Colloid Forming Process

Figure 1 shows the time-dependent UV-Vis absorption spectra for Pt nanoparticles preparation. As shown in Fig. 1, at the beginning the reaction system had two strong characteristic absorption peaks at 215 nm and 265 nm, which are ascribed to that of citrate and $PtCl_6^{2-}$ ion, respectively. In fact, another peak at 400 nm for $PtCl_6^{2-}$ ion was observed but is not given here because it was too weak to identify. As the reaction proceeded, the absorption peaks of citrate and $PtCl_6^{2-}$ ion decreased gradually. When the reaction continued for 35 min, the absorption of $PtCl_6^{2-}$ ion disappeared completely. Meanwhile, the

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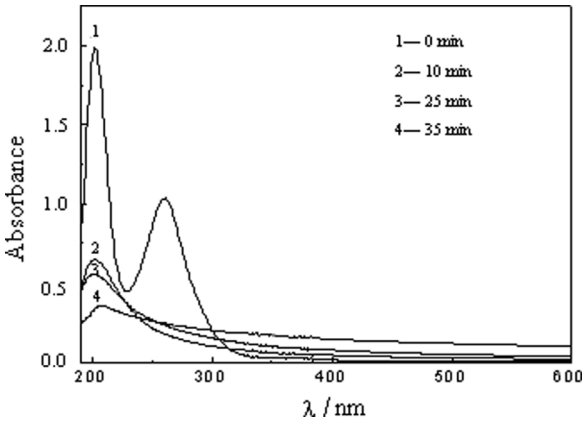

FIGURE 1 **UV-Vis absorption spectra of Pt colloid forming process: (1) 0 min; (2) 10 min; (3) 25 min; (4) 35 min. [H_2PtCl_6], 2.4×10^{-3} mol · L^{-1}.**

color of the solution turned to brownish black and the curve shifted up due to the enhancement of the plasmon scattering, indicating a complete reduction of Pt^{4+} to Pt^0 and the formation of Pt colloid.

TEM Images of Pt Nanoparticles

Figure 2a, b demonstrate typical TEM images of the Pt colloids without and with BSA, respectively, showing well-dispersed Pt nanoparticles. The average diameters of Pt nanoparticles were 1.3 nm for neat Pt colloid and 2.6 nm for the Pt–BSA complex, respectively, with relatively narrow particle size distributions as shown in Fig. 2c, d, in which standard deviation was 0.3 nm from counting about 300 particles in the TEM images. A slightly larger particle diameter as well as wider size distribution for Pt colloid after mixing with BSA indicated a binding of Pt nanoparticles with BSA.

RLS Spectral Characteristics

Figure 3 shows the RLS spectra of the reagent blank, Pt colloids, and the Pt–BSA complex under optimum conditions. As shown in Fig. 3, the light scattering of Pt colloid is very weak in the range 200–700 nm as well as that of BSA solution. However, when BSA was added into Pt colloids, the scattering intensity enhanced remarkably and the RLS peak reached the maximum at 390 nm, which demonstrated minimum UV-Vis absorption for Pt colloid, as shown in Fig. 1, and was chosen as the excitation and emission wavelengths for the measurement of RLS intensity. In addition, the RLS intensity increased linearly with the increase of the concentration of BSA. These mean that an interaction has occurred between Pt colloid and BSA molecules. The enhanced light-scattering spectra suggested that Pt–BSA complex was formed for the interaction of

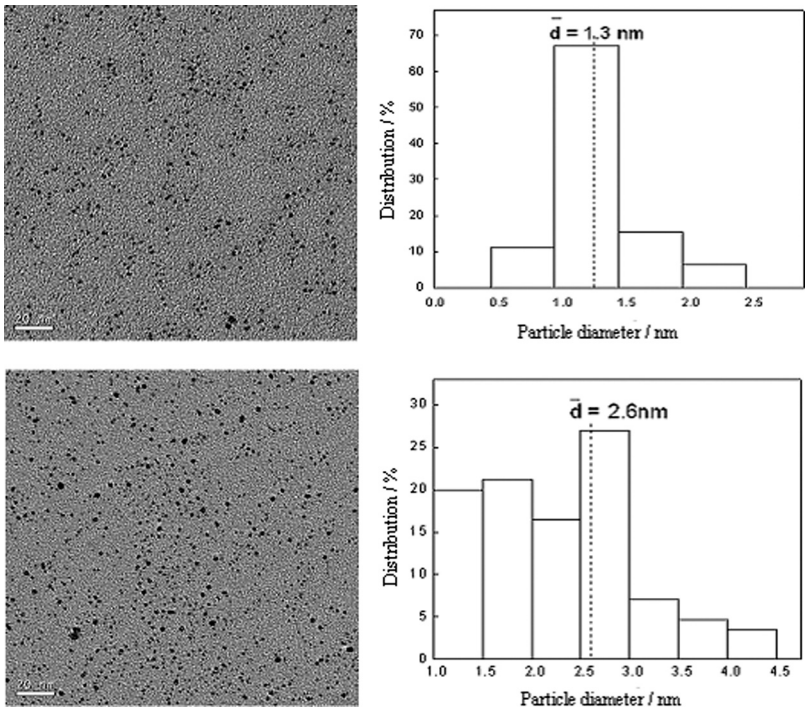

FIGURE 2 **TEM images of Pt colloids (a) without and (b) with BSA, and the corresponding particle size distribution histograms, respectively.**

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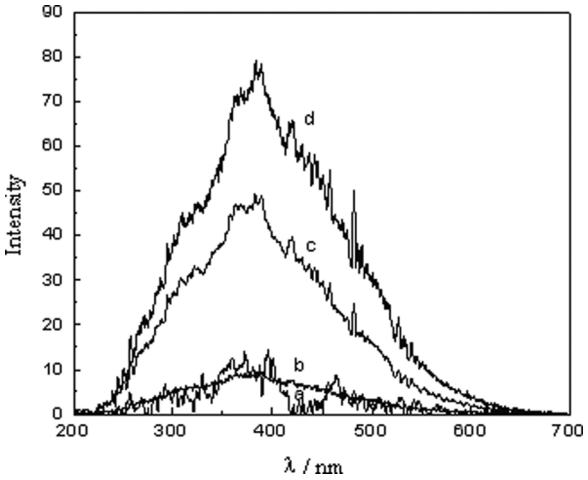

FIGURE 3 **RLS spectra under the optimal conditions. (a) BSA solution only; (b) Pt colloids only; (c) and (d) Pt colloids with $1\,\mu g \cdot mL^{-1}$ and $2\,\mu g \cdot mL^{-1}$ BSA, respectively. Pt concentration is $4.0 \times 10^{-5}\ mol \cdot L^{-1}$.**

Pt nanoparticles with BSA. A similar characteristic was also observed for HSA at the same condition. Based on these results, a method of quantitative determination of protein can be proposed.

Effect of pH Value on RLS Intensity

The effect of pH on the RLS intensities of the complexes is shown in Fig. 4. It can be seen that pH has a great influence on the scattering intensity of Pt–BSA and Pt–HSA in the pH range 2.0–8.0. The optimum pH for the determination of BSA and HSA is 3.50 and 4.00, respectively, at which the signal of the corresponding complex reached the maximum. At the optimum pH value, which is lower than the isoelectric point of BSA or HSA (pI = 4.7 to 4.9),

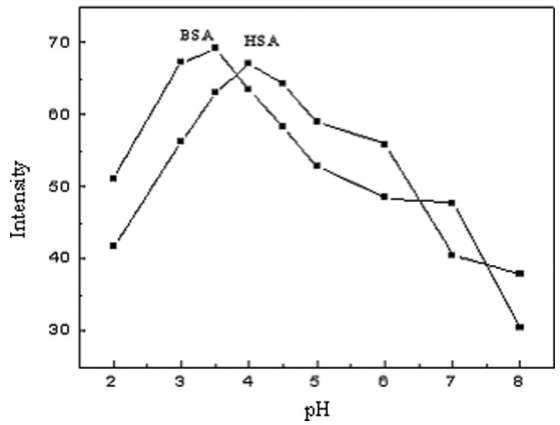

FIGURE 4 **Effect of pH values on RLS intensities. (a) Pt–BSA complex; (b) Pt–HSA complex; Pt concentration is $4.0 \times 10^{-5}\ mol \cdot L^{-1}$; protein concentration is $2.0\,\mu g \cdot mL^{-1}$.**

the surface of the peptide molecules held positive charges because of the protonation of the amino groups of the basic amino acids of BSA or HSA. When protein was added into the Pt colloid, the interaction between Pt nanoparticles with negative charges and protein molecules with positive charges occurred as a result of electrostatic attraction. The interaction made Pt nanoparticles aggregate on the protein molecules to produce Pt–protein complex and enhance the intensity of RLS. As shown in Fig. 4, RLS intensity decreased sharply when the pH was higher than the optimum pH value, especially the pI. This phenomenon may be ascribed to the decrease of the electrostatic attraction between Pt nanoparticles and protein molecules because of the decrease of the surface positive charges of protein, or the increase of repulsion due to negative charges on protein surface at higher pH than pI. In addition, the solutions were buffered at the optimum pH with 0.5–1.5 mL BR buffer, and it gave good sensitivity as well as high stability. Because the volume of the added buffer had little influence on the RLS intensity, 1.0 mL BR buffer was used in all subsequent experiments.

Effect of Pt Nanoparticle Concentration on RLS Intensity

The effect of Pt concentration on the RLS intensity was shown in Fig. 5. It was found that the most appropriate concentration of Pt nanoparticles was 3.0×10^{-5} to $4.0 \times 10^{-5}\ mol \cdot L^{-1}$ (the concentration of Pt nanoparticles was calculated according to the precursor, which was regarded to be reducted completely) when the concentration of BSA was $2.0\,\mu g \cdot mL^{-1}$ at pH 3.50. When Pt concentration was less than $3.0 \times 10^{-5}\ mol \cdot L^{-1}$, the RLS intensity and sensitivity became lower. This may be because the incomplete interaction of Pt with protein generated a lower aggregation number and smaller aggregates, resulting in less enhancement of the scattering. The RLS intensity increased due to the enhancement of aggregation with increasing the concentration of Pt nanoparticles up to $3.0 \times 10^{-5}\ mol \cdot L^{-1}$ but declined gradually when Pt concentration was more than $4.0 \times 10^{-5}\ mol \cdot L^{-1}$. The reason may be that a higher concentration or large excess of Pt particles means relatively less protein molecules adsorbed on Pt nanoparticles, thus the aggregation number

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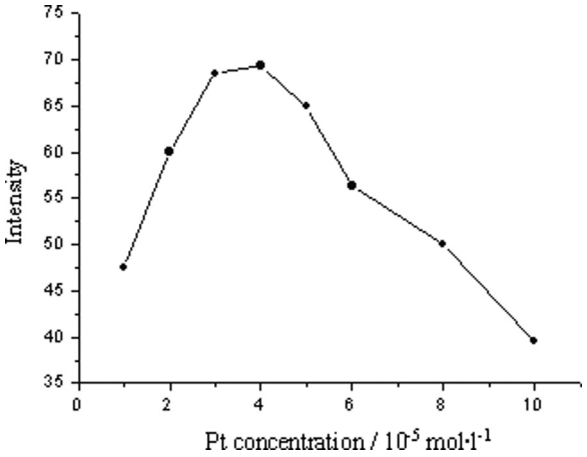

FIGURE 5 **Effect of Pt concentration on enhancement of RLS intensities. The concentration of BSA is 2.0 μg · mL^{-1}; pH = 3.50.**

of protein with Pt particles reduced greatly, resulting in a decrease of RLS intensity.

Effect of Ionic Strength

Ionic strength had a little effect on the interaction of Pt nanoparticles and protein molecules. The experiments showed that the RLS remained at high sensitivity and intensity below 0.3% NaCl of ionic strength, and an obvious decrease in the RLS signal was observed above 0.3% NaCl of ionic strength. Thus only 0.1% NaCl was used in the system.

Mixing Sequence of Reagents

The influence of the mixing sequence of Pt colloids, protein, NaCl, and BR buffer on RLS intensity were also investigated. Though Pt nanoparticles interacted with protein rapidly at room temperature, the mixing sequence is very important. It was found that the favorable formation of Pt–protein complex was accomplished with the adding sequence of Pt, BR buffer, NaCl solution, and protein. It is necessary for the interaction of Pt nanoparticles with protein to control the optimum pH and appropriate ionic strength, so the buffer and NaCl should be mixed with Pt nanoparticles before adding protein.

Effect of Coexisting Substances on RLS

The possible interferences of some ions and amino acids were investigated at 2.0 μg · mL^{-1} of BSA under the optimal conditions (allowable deviation ±5%). The data are presented in Table 1. The results demonstrated that few metal ions and amino acids interfered with protein determination except for several ions such as Cu^{2+}, Pb^{2+}, and Ag^{+}. Possibly, the heavy metal ions can strongly complex with the amino groups and then interfere with the detection to some extent. In fact, the experimental concentrations of all these substances were much higher than the concentrations presented in biological fluids. Furthermore, dilution with water can minimize all interferences in the detection of biological fluids such as human serum samples.

TABLE 1 **Effect of Interfering Substances on the Determination of BSA**

Substances	Content (μg · mL^{-1})	Deviation (%)	Substances	Content (μg · mL^{-1})	Deviation (%)
Cr^{3+}	10	0.7	Ag^{+}	5	7.9
Fe^{3+}	10	0.8	Urea	20	0.2
Ca^{2+}	2	0.15	Glucose	40	1.2
Zn^{2+}	5	0.5	Vitamin C	40	1.9
Ni^{2+}	1	0.7	Lys	20	1.6
Cu^{2+}	5	6.1	Glu	20	2.5
Sn^{2+}	5	2.9	Phe	20	0.9
Co^{2+}	10	1.4	Pro	20	3.2
Pb^{2+}	2	4.8	Cys	20	−0.5
Mn^{2+}	10	0.6	His	20	3.3

The concentration of Pt nanoparticles is 4.0×10^{-5} mol · L^{-1} and the concentration of BSA is 2.0 μg · mL^{-1}.

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TABLE 2 The Calibration Curves of Two Kinds of Serum Albumins

Protein	Linear range ($\mu g \cdot mL^{-1}$)	Linear regression equation ($c, \mu g \cdot mL^{-1}$)	Detection limit ($ng \cdot mL^{-1}$)	Correlation coefficient (R)
BSA	0.1∼3.0	$\Delta I = 12.0 + 27.9\ C$	4.2	0.997
HSA	0.1∼2.7	$\Delta I = 27.6 + 19.6\ C$	10.7	0.999

The concentration of Pt nanoparticles is $4.0 \times 10^{-5}\ mol \cdot L^{-1}$ and the concentration of BSA or HSA is $2.0\ \mu g \cdot mL^{-1}$. Each result was the average of five measurements. ''C'' refers to the concentration of protein.

Calibration Curves and Detection Limit

The relation between the relative RLS intensity (ΔI) and the content of proteins was investigated under the optimal experimental conditions described above. A good linear relationship between ΔI and the concentration of protein was obtained. The correlation coefficient, linear regression equation, linear range, and detection limit are given in Table 2. The results demonstrated that this assay had a higher sensitivity and can be applicable in protein detection.

Detection of the Total Protein in Human Serum Samples

According to the general procedure described above, the total protein contents in human serum samples were assayed by using the current method, and HSA was chosen as the standard. The assaying data are presented in Table 3. The maximum relative standard deviation (RSD) was 2.8%, and the recovery yields were about 100.4–102%. The total protein content measured by the proposed method was in excellent agreement with those obtained by CBB method, indicating that the current method can be used in total protein content in human serum samples.

TABLE 3 Total Content of Proteins in Human Serum Samples

Samples	RLS method ($mg \cdot mL^{-1}$)	CBB G-250 method ($mg \cdot mL^{-1}$)	Recovery yield (%)	RSD (%)
1	74.3	75.8	102.0	2.8
2	73.6	73.9	100.4	1.7
3	75.1	75.9	101.1	1.3

The concentration of Pt nanoparticles is $4.0 \times 10^{-5}\ mol \cdot L^{-1}$. Each result was the average of five measurements.

CONCLUSIONS

The method proposed here is based on the interaction of Pt colloid with BSA by use of RLS. The interaction of Pt nanoparticles and BSA demonstrated much stronger RLS intensity in contrast with the weak RLS signals of Pt colloid or BSA alone at the optimal conditions. The enhanced light-scattering intensity suggested the formation of Pt–BSA complex due to this interaction. Based on the experimental results, a highly sensitive assay for proteins with platinum-nanoparticles RLS was proposed. The current method was applied to the detection of total protein content in human serum samples with high sensitivity, selectivity, and reproducibility, and the results were in excellent agreement with those obtained by conventional method. Therefore, the colloidal Pt nanoparticle–based assay with RLS may have potential applications in protein detection.

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