Düzce University
Journal of Science & Technology

Research Article

Colorimetric Determination of Cu^{2+} by Glycine-Histidine Dipeptide Functionalized-Gold Nanoparticles

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DOI: 10.29130/dubited.884511

ABSTRACT

This study presents the development of a rapid and straightforward Cu^{2+} determination method through the interaction of glycine-histidine dipeptides with gold nanoparticles (AuNPs). Here, it was shown that AuNPs were clustered by the attachment of glycine-histidine dipeptides (GH) to the AuNPs. Accordingly, it was obtained from the UV-Vis spectrum that the $\square_{max}$ of the AuNPs dispersion at 520 nm showed a redshift to a higher energy region. This case was accelerated by adding Cu^{2+} ions to the medium, indicating an interaction between GH coated-AuNPs and Cu^{2+} ions, and the particles come together in a shorter time. This finding demonstrates that the developed-analytical method provides more selectivity to Cu^{2+} when testing in the presence of some other metal ions. The particles and aggregates' sizes were determined by Dynamic Light Scattering (DLS) measurement and Transmission Electron Microscopy (TEM) technique. The determination of Cu^{2+} in the tap water was also tested by spike using the developed method. In the light of the results obtained, it is thought that the developed analytical method can be quite advantageous for the rapid and selective determination of Cu^{2+} in water samples.

Keywords: *AuNPs, Glycine-histidine dipeptide, Copper determination, Analytical method development*

Glisin-Histidin Dipeptidler ile Fonksiyonelleştirilmiş Altın Nanoparçacıklar ile Cu^{2+}'nin Kolorimetrik Tayini

ÖZ

Bu çalışma, glisin-histidin dipeptitlerinin altın nanoparçacıklar (AuNP'ler) ile etkileşimi yoluyla hızlı ve basit bir Cu^{2+} belirleme yönteminin geliştirilmesini sunmaktadır. Burada, AuNP'lerin glisin-histidin dipeptitleri (GH) ile bağlanmasıyla kümelendiği gösterilmiştir. Buna göre, UV-Vis spektrumundan, 520 nm'deki AuNPs dispersiyonunun maksimum absorpsiyon yaptığı dalgaboyunun, daha yüksek bir enerji bölgesine kırmızı bir kayma gösterdiği elde edilmiştir. Bu durum ortama Cu^{2+} iyonları eklendiğinde hızlanmıştır, Bu da GH kaplı AuNP'ler ile Cu^{2+} iyonları arasında bir etkileşim olduğunu ve parçacıkların daha kısa sürede bir araya geldiğini göstermektedir. Bu bulgu, geliştirilen analitik yöntemin bazı diğer metal iyonlarının varlığında test edildiğinde Cu^{2+} 'ya daha fazla seçicilik sağladığını göstermektedir. Parçacıkların ve agregatların boyutları Dinamik Işık Saçılması (DLS) ölçümü ve Transmisyon Elektron Mikroskobu (TEM) tekniği ile belirlenmiştir. Musluk suyundaki Cu^{2+} tayini de geliştirilen yöntem kullanılarak bilinen derişimlerde Cu^{2+} eklenerek test edilmiştir. Elde edilen sonuçlar ışığında, geliştirilen analitik yöntemin su örneklerinde Cu^{2+} 'nın hızlı ve seçici tayini için oldukça avantajlı olabileceği düşünülmektedir.

Anahtar Kelimeler: *Au nanoparçacık, Glisin-histidin dipeptid, Bakır tayini, Analitik yöntem geliştirme*

Geliş: 21/02/2021, Düzeltme: 10/05/2021, Kabul: 17/05/2021

I. INTRODUCTION

Heavy metals are elements that should be considered for human health due to their toxic properties. They may cause severe damage to human metabolism after exposure to particular grizzlies [1]. Besides, they can be quite harmful if taken in small amounts due to their accumulation in the different tissues. In this respect, it is necessary to control the amount of heavy metals, especially in water sources, which are the most crucial resource for life. Different advanced and effective methods such as ICP-MS, AAS, and ICP-OES are used to determine heavy metals. However, alternative methods have been developed for situations such as getting a rapid response due to hindrance of these methods, such as having a suitable device and the extended analysis process [2]-[7]. One of these approaches is the use of plasmonic nanoparticles [8]. With the acceleration of nanoparticles' synthesis and their use in different applications, particles with many different sizes and shapes can be prepared [9]-[11]. Among them, Surface Plasmon Resonance (SPR) is found to quite advantageous by the researchers.

SPR is a unique phenomenon exhibited by plasmonic metal nanoparticles that occur when the co-oscillations of conductive band electrons in the nanoparticle resonate with electromagnetic radiation frequency [12]. It has aroused excitement as a unique feature that has been affected and changed by many changes such as size, shape, surface chemistry [13], [14]. When examined in this respect, the absorbance of these particles in the UV-Vis spectrum has created a potential for use in detection and determination applications [15]. Significantly, this approach is a method used in the determination of AuNPs and many substances such as metal ions and biological molecules [16]-[21]. With this method, many metals and semi-metals such as Arsenic, Mercury, Copper, Lead, Cadmium, Chromium can be determined. Here, the fundamental reason is to use a binder molecule to create the interaction between these metal ions and nanoparticles. Notably, by chemical or physical modifications of the surfaces of AuNPs with very different groups, the affinity of the particles to these metal types is also increased. This can be ensured by the different coordination numbers of many metals, such as the metals listed above and the chelates that are created with organic and biomolecules. One of the most prominent metals that have been frequently researched and method-developed is Cu^{+2} [22], [23]. Copper is an essential trace element used in human metabolism as a metal cation that is frequently used in the enzymatic process as a cofactor. However, as with any substance, high dose copper exposure shows adverse effects on health. Especially for human metabolism, copper accumulation primarily affects the liver like other metals. When taken in large quantities, the copper shows toxic properties for metabolism. The most common of these is oxidative stress and a neurodegenerative Wilson's disease [24], [25]. In this respect, determining the amount of copper in domestic water has been essential. For copper determination, methods such as ICP-MS and AAS are frequently used as in other metal types [3]. However, to get a fast response and reduce the cost of device-based approaches, AuNPs-based colorimetric approaches have been used in recent years.

Guo et al. developed a colorimetric system to detect Hg^{2+} and Pb^{2+} with Cu^{2+} using papain-coated AuNPs. Here, papain easily binds directly to the surface of AuNPs. These metal ions interact with the functional groups in the papain protein, and as a result, the particles undergo aggregation. Thus, thanks to the particles coming together, the plasmonic peak makes a redshift. This case is evident from the color change of the AuNPs solution from red to blue [19]. Liu and Li developed a colorimetric method to detect copper using gold nanorods directly in their study. Here, a sulfate group was added on the gold bar's surface in ammonium/ammonia buffer solution. Afterward, the color change was achieved with the copper added to the medium, and thus, determinations could be carried out by UV-Vis spectroscopy method [26]. Weng et al. developed a method for determining copper using a simple amino acid 1-Cysteine. In the method, after l-cysteine is attached to the AuNPs surface, the redshift feature, which is formed as a result of the particles clustering, is bonded with metal ions. Another aspect of the study is the AuNPs solution is not monodisperse and contains large and small nanoparticles. Thus, an arrangement in the form of aggregates similar to core-satellite was achieved with the approach [27]. Another colorimetric approach used in determining Cu^{2+} ions is click-chemistry [28].

Another approach used in the determination of copper ions in the literature is biomolecular approaches. However, a limited number of these approaches have been implemented [27]-[29]. Remarkably, the use of peptide materials in district-release tissue engineering, electronic applications, and catalysis has attracted the attention of researchers in recent years [30]-[32]. Another peptide structure frequently used in the literature is dipeptides. Dipeptides formed by bonding two amino acids with peptide bonds rather than the large molecular mass structures of polypeptide structures are frequently preferred due to their superior properties. It is well known that dipeptides can be processed in different ways, using bottom-up or top-down approaches, to produce a product of different arrangements. From this point of view, they are used in the preparation of bioinspired materials. However, no approach has been made to use dipeptide structures in the colorimetric determination of metal ions with AuNPs or other plasmonic particles. The self-assembly properties that affect the bio-nano interface resulting from the interaction of dipeptides with plasmonic nanoparticles have also been examined in the literature [12]. It is seen that there is an interaction between dipeptides and plasmonic nanoparticles. Here, the type of amino acids the dipeptide structures will contain is a separate issue.

In this work, a selective colorimetric method has been developed for the determination of Cu^{2+}. In the method, different types of metal cations were added into the AuNPs solutions with a diameter of 20 nm, which gave plasmon peak at 520 nm, and then added in GH solution. Thus, the change in the red color of the solutions containing AuNPs was investigated. An approach has been developed for the colorimetric determination of Cu^{2+} from the changes in colors. The obtained findings show that the method can be used to determine different biological or organic species for future applications.

II. MATERIALS&METHODS

A. MATERIALS

All reagents were of analytical grade reagents unless otherwise stated. Aqueous solutions were prepared in ultrapure water (18.3 μΩ cm). H-Gly-His-OH was purchased from Bachem (Bachem AG Switzerland). $HAuCl_4.2H_2O$, Ethanol, Trisodiumcitrate dihydrate was purchased from Sigma-Aldrich. $Cu(Cl)_2$, $Hg(NO_3)_2$, $Zn(NO_3)_2$, $Mg(NO_3)_2$, $Ni(NO_3)_2$, $Pb(NO_3)_2$, $AlCl_3$, $Fe(NO_3)_2$ was purchased from Merck.

B. METHODS

B. 1. Synthesis of AuNPs

For AuNPs synthesis, 1 mL of 12.5 mM $HAuCl_4$ was added to 49 mL of deionized water first. This solution was then heated and boiled on a magnetic stirrer. After it started to boil, 0.94 mL 38.8 mM sodium citrate was added. When the solution turned red after about 5 min, it was allowed to cool [9].

B. 2. Colorimetric Detection of the Metal Ions

To determine the metal ions concentration, a suitable vial with a volume of 0.920 mL of AuNPs solution with a diameter of about 20 nm is taken first. Then 80 µL of GH solution is added. 1 mL of cation solution is added to this prepared solution. After adding the cation solution, waited for 1 minute and the UV-Vis spectrum is taken for mg/L level analysis. However, the waiting time was realized as 5 minutes for analyzes at µg/L level.

B. 3. Analysis of Real Samples

To perform Cu^{2+} real sample, 1 mL of AuNPs solution with a diameter of about 20 nm was added to tap water to perform real sample analysis. Then 80 µL of GH was added to the medium. After that,

Cu^{2+} standard solutions were added to tap water at the final concentration of 1 mg/L and 2 mg/L. The percentage recovery value was calculated as a result of the values found after the addition.

B. 4. Characterization

All UV-Vis spectra were recorded by Cintra GBC 303 model UV-Vis spectrophotometer. AuNPs and Cu^{2+} added GH functionalized-AuNPs structures were characterized by a Fei Transmission Electron Microscopy with an acceleration voltage of 120 kV.

III. RESULTS&DISCUSSION

In the study, firstly, the interaction of metal ions with GH-AuNPs was investigated. The optical properties of AuNPs are realized due to a distinctive phenomenon called surface plasmon resonance (SPR). The difference or change in any of the particles' size, shape, or geometry changes the local electron confinement, which alters the SPR absorption maxima. The change of SPR maxima also changes the color of the solution of colloidal AuNPs. Here, when the particles increase in size, they show a redshift. The redshift is due to a blue-to-blue color change in the solution's color and the shift of the SPR wavelength of the solution to a longer wavelength. With this starting point, if the particles' size can be changed with the metal ions to be determined, the concentrations of metal ions can be determined indirectly. There may be a redshift here either due to the interaction between the added metal ions and the AuNPs. However, generally at this stage, an auxiliary substance will be required to establish a bond between AuNPs and metal. In our study, the GH structure was used to functionalize Au nanoparticles, especially with a biomolecule-based approach that has potential for use in this interaction. Looking at the GH structure, it is possible to see the use of the amino acids formed in the structure in the determination of different types of metal and biomolecular structures with AuNPs or other plasmonic nanoparticles. At this stage, the potential use of dipeptides, which are the smallest peptide structures, in the determination of metal ions with plasmonic nanoparticles was investigated.

Firstly, UV-Vis spectra of synthesized AuNPs and GH functionalized Au nanoparticles were taken to examine the interactions between AuNPs and GHs. As can be seen in Figure 1, the concentration of GH increases, the absorption maxima of AuNPs shows a redshift and change depending on the concentration towards around 600 nm. This situation can be seen visually from the colors of AuNPs dispersion with different amounts of GH added. This case shows that there is an interaction between the GH and AuNPs. Here, as the amount increases, AuNPs come together due to the interaction, and the plasmon peak maximums of AuNPs with a diameter of 20 nm at 520 nm increase linearly according to the added amount and change up to 650 nm. Here, the lowest concentration was taken at which the plasmon peaks of the particles shifted to around 650 nm while determining the sufficient amount for the determination. Also, the amount of GH to be used in the study is tried to be determined. As the amount of GH increases, the particles affinity increases, so the AuNPs come together, and the redshift increases. Such that, after the addition of about 80 µL concentration, more aggregates are formed, and the color of the solution turns blue. Thus, by keeping the aggregate formation at a certain level with the basic approach GH, it was ensured that the redshift was predominantly with the metal cation concentration. As seen in the photographs given in Figure 1, with the increase in the GH amount, around 80 µL of color now changes from red / pink to purple. As the amount of GH increases, the color clearly shows a purple/blue change. Here, the AuNPs surface interacts with GH and aggregates into aggregates due to the bound GH molecules' affinity to each other.

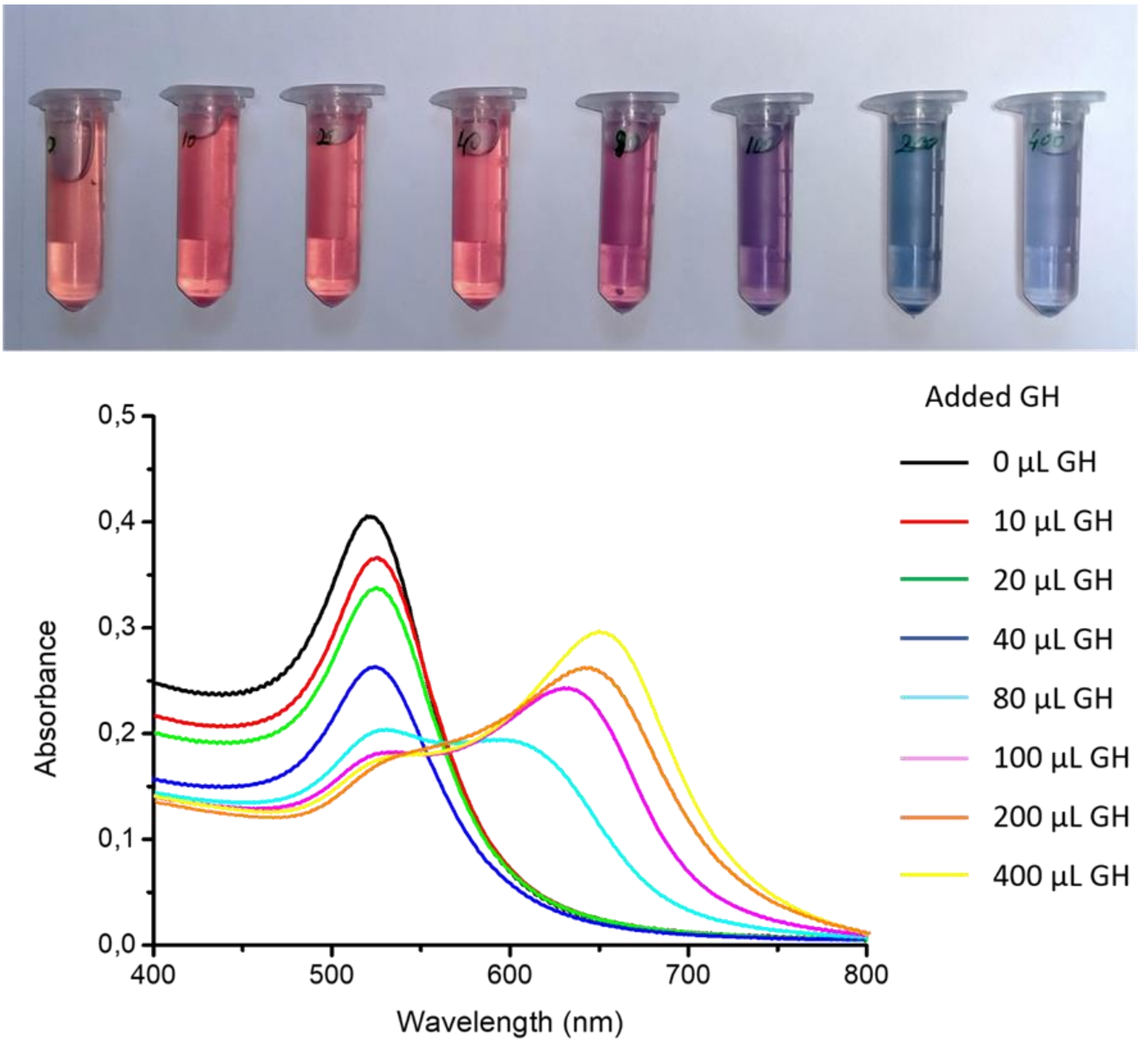

Figure 1. *GH concentration effect on surface plasmon resonance AuNPs*

When determining nanoparticles using the colorimetric approach, one of the issues to be examined is the cations to be used for the determination. In the present approach, some metal salts that are commonly available and exhibit toxic properties were prepared. Anionic effects have not been investigated because of anions such as NO_3^- and Cl^- in the salts prepared. These ions are not thought to interact with AuNPs since the surface charges of AuNPs are generally negative due to citrate ions.

Cu^{2+}, Hg^{2+}, Ni^{2+}, Al^{3+}, Pb^{2+}, Zn^{2+}, and Fe^{2+} cations were added at a concentration of approximately 5 mg/L to examine GH functionalized-AuNPs interaction with different metal cations, and their UV-Vis spectra and the behavior of the peak were examined. Besides, the physical condition of the AuNPs solution after the GH additions was photographed. As seen in the Figure 2, the color of the solution shifted towards blue in the presence of Cu^{2+}. This finding indicates that the GH functionalized AuNPs in the presence of Cu^{2+} are strongly linked together and organized into aggregates. Thus, it was obtained that Cu^{2+} determination can be made at the determining stage of the metal ions concentration aimed in the study.

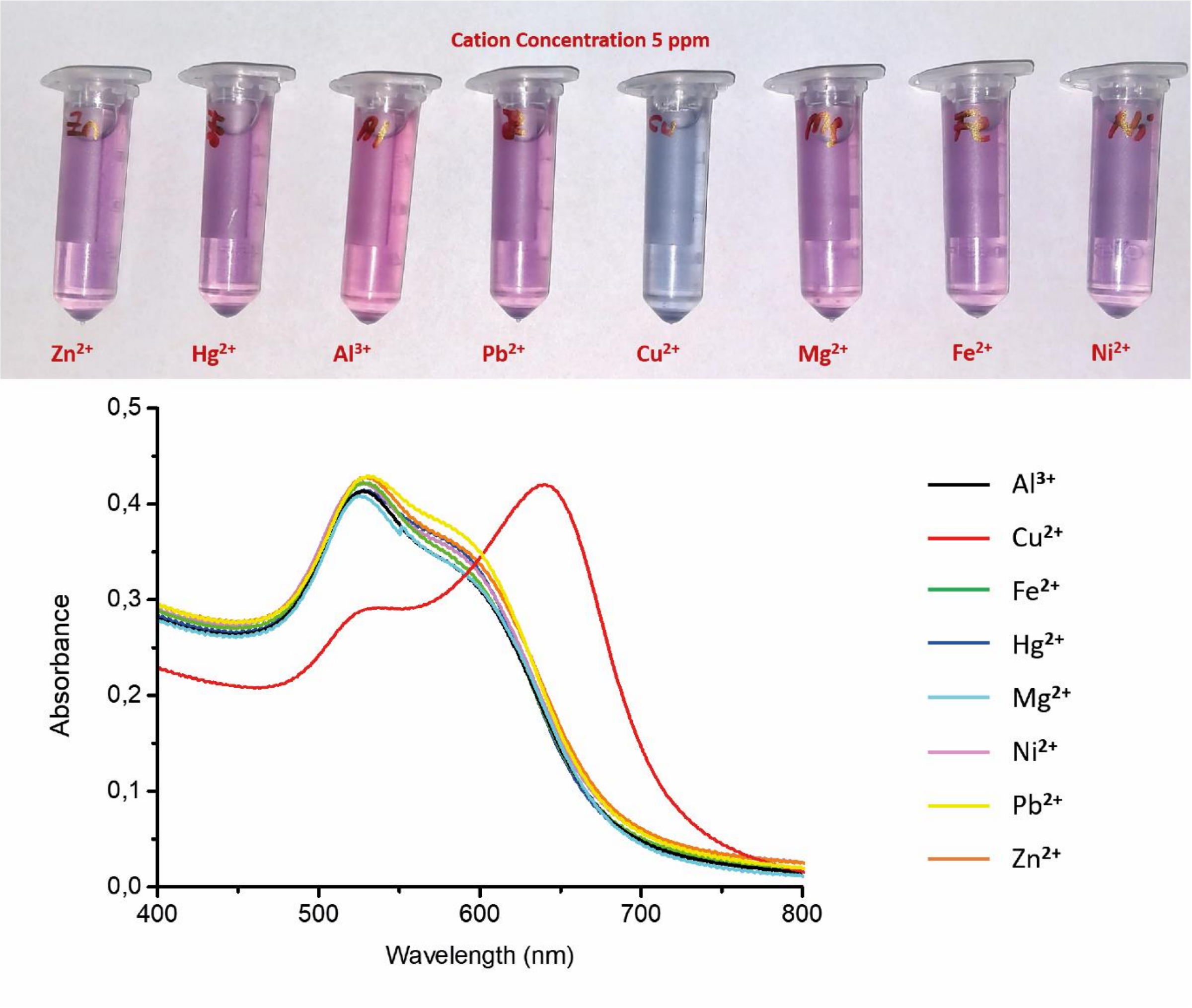

Figure 2. *UV-Vis spectra obtained after Cu^{2+}, Hg^{2+}, Mg^{2+}, Ni^{2+} Al^{3+}, Pb^{2+}, Zn^{2+}, Fe^{2+} cations at a concentration of 5 mg/L added to AuNPs medium functionalized with GH and color changes of the solutions*

A little redshift is observed in other cations as well. However, this situation does not provide the critical difference for determination. However, since this interaction is not as strong as the interaction seen in Cu^{2+}, the redshift amount remains specific. The highest interaction was obtained with Cu^{2+} in the examined cation group.

As seen in Figure 3a, the plasmon maximum of AuNPs at approximately 520 nm showed a redshift with 1 mg/L GH added to the medium. This may be an indication that GHs are attached to the gold surface. When Cu^{2+} is added to the environment, the particles are arranged in aggregates due to the interaction between Cu^{2+} and GH. As can be understood from the DLS analysis conducted to examine the aggregates condition with the addition of Cu^{2+} at different concentrations, as the amount of Cu^{2+} increases, the size of the aggregates increases. As can be understood from the spectrum (Figure 3a), the accumulation of AuNPs in the form of aggregates was due to the interaction between GH molecules attached to the particles surface in the presence of GH. In this case, when examined with the graph given in Figure 3b, it shows linearity with TEM images. Figure 3c shows that non-functionalized AuNPs are about 20 nm in diameter. As seen in the TEM images, it is understood that the particles are arranged in small aggregate groups by adding GH to the medium containing a small number of AuNPs together (Figure 3d). The Cu^{2+} ions added to the environment interact with the GH structures, causing more AuNPs to come together, and thus particles come together in the form of larger aggregates (Figure 3e). After increasing linearly up to about 100 nm, it increased rapidly and formed aggregates around 2000 nm in the presence of about 12.5 mg/L Cu^{2+}. To support this situation with TEM analysis, images of AuNPs, GH functionalized Au NPs, and 1 mg/L Cu^{2+} added GH-AuNPs structures were taken. As seen from the images, a strong bridge is established between the particles in the presence of $Cu^{2+,}$ and the structures come together.

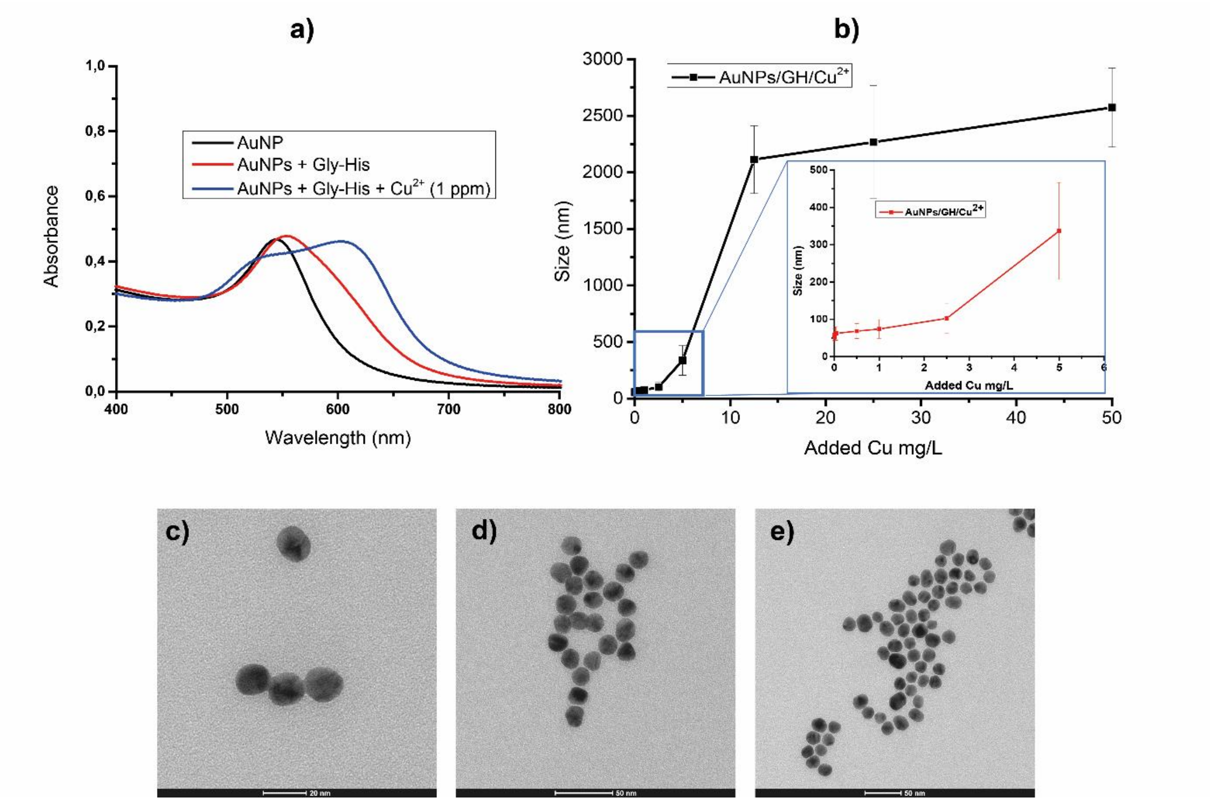

Figure 3. *a) UV-Vis spectra of Au NPs, GH functionalized AuNPs and GH functionalized AuNPs in the presence of 1 mg/L* Cu^{2+}*, b) aggregate sizes obtained as a result of DLS measurements of GH-AuNPs formed in the presence of increasing* Cu^{2+} *concentration, c) TEM image of non-functionalized Au NPs, d) TEM images of GH functionalized AuNPs e) TEM images of GH functionalized AuNPs in the presence of 1 mg/L* Cu^{2+}

In the study, to examine the changes in AuNPs peaks in the presence of Cu^{2+} at different concentrations, the UV-Vis spectra of GH functionalized AuNPs containing Cu^{2+} at mg/L and µg/L levels were taken. Calibration curves were created using the relationship between cation concentration and maximum wavelength. In the photo given in Figure 4a, the color changes that occur after adding the Cu^{2+} samples prepared at different concentrations at mg/L level to the GH functionalized AuNPs solution are shown. As can be seen here, depending on the Cu^{2+} concentration, the solution colors show a transition from violet to blue. This is an indication that colorimetric determination is possible. With the addition of Cu^{2+} at mg/L level in Figure 4b, AuNPs decrease plasmon maxima at 520 nm by showing redshift. Simultaneously, a shouldering of a new plasmon peak occurs around 650 nm, where the shouldering shows both redshift and shifts to higher wavelengths as the concentration increases. With the addition of Cu^{2+} at mg/L level, peak enlargements and redshifts are observed. To obtain a calibration graph from the obtained spectra, the method of plotting the value obtained by comparing the absorbance values of the old peak with the new peak formed by the red shifting of the AuNPs solution, which is frequently used in the literature, against the concentration [12]. For this, first, the absorbance maxima of the solutions were determined. The value obtained by comparing the absorbance values of the plasmon peak formed around 650 nm with the addition of Cu^{2+} and the AuNPs peaks formed around 520 nm was plotted. As can be seen in Figure 4c, the linear increase at a particular concentration progressed at a constant value after the concentration value of 5 mg/L. This shows that AuNPs, GH used in the designed method can be analyzed up to 5 mg/L. For this purpose, the values obtained by the method mentioned above in solutions containing Cu^{2+} between 0.5-5 mg/L values were plotted (Figure 4d). Thus, a calibration graph was obtained for the determination of Cu^{2+} at mg/L level in the study.

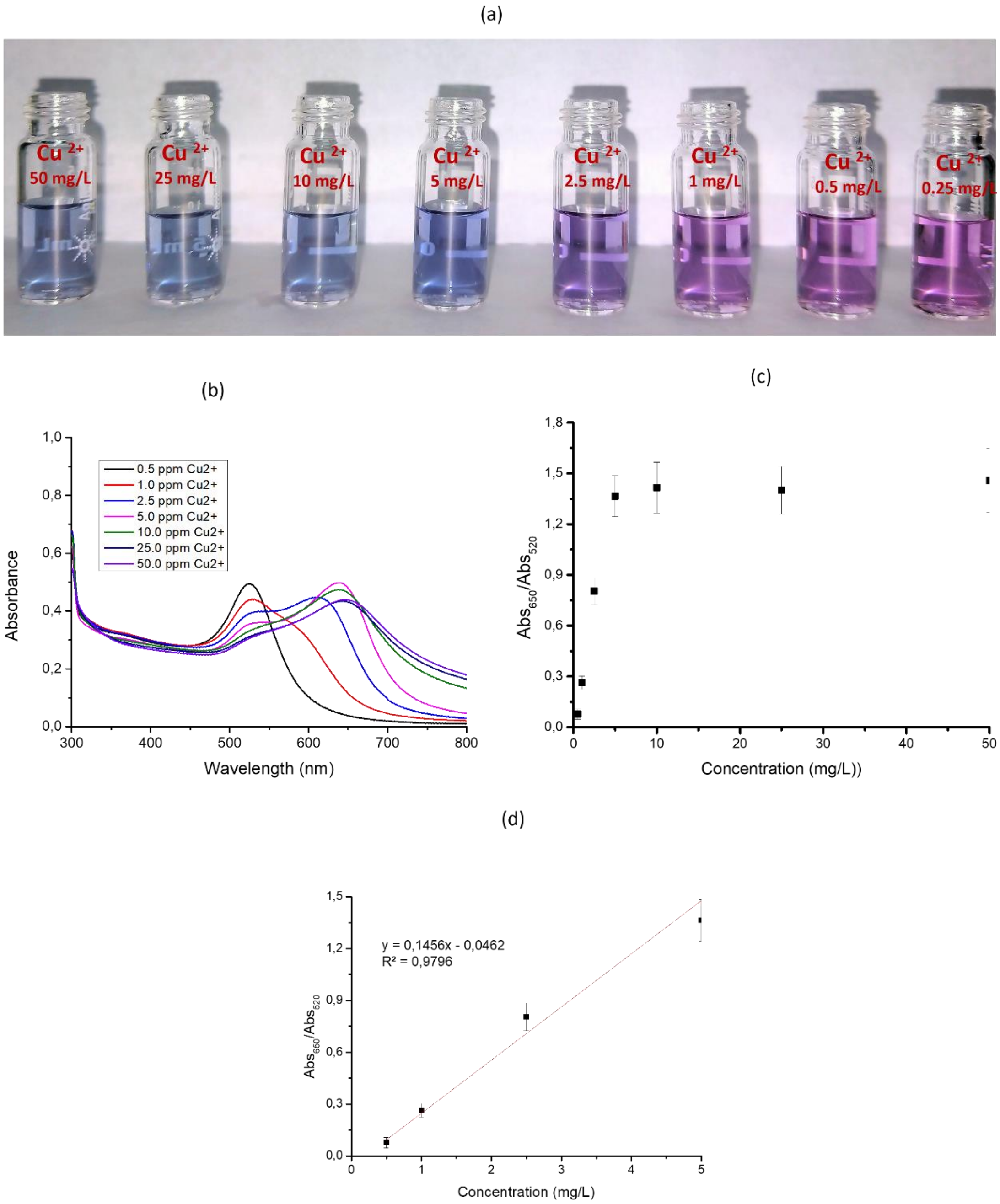

Figure 4. *a) Images of solutions obtained in the presence of Cu^{2+} in different concentrations of mg/L, b) UV-Vis spectra of solutions containing Cu^{2+} at various concentrations, c) curve obtained by plotting Abs650/Abs520 value against concentration, d) linear range graph*

Color change in solutions containing 0.5, 1, 2.5, 5.0, and 10 µg/L Cu^{2+} was investigated to examine whether Cu^{2+} determination can be made at µg/L level with the method developed in the study. The critical situation here is the waiting time after Cu^{2+} addition. Due to the low concentration of Cu^{2+} added to the medium, the color change, in other words, redshift is not intense. In the image in Figure

5a, the color change with concentration is seen, albeit a little. However, whether there is a change or not was determined by the UV spectrum. When the UV spectra of the solutions prepared at this concentration are taken, redshift occurs with the increase of Cu^{2+} concentration, and a secondary peak occurs at 600 nm (Figure 5b). With an approach similar to the method performed at mg/L level, when the number obtained by proportioning the absorbance value of the plasmon peak at 600 nm to the absorbance value of the peak at 520 nm is plotted against the concentration, a linear increase is observed in the range of 0.5-10 μg/L value (Figure 5c). When the graph was rearranged for these concentrations, a linear calibration graph could be obtained (Figure 5d).

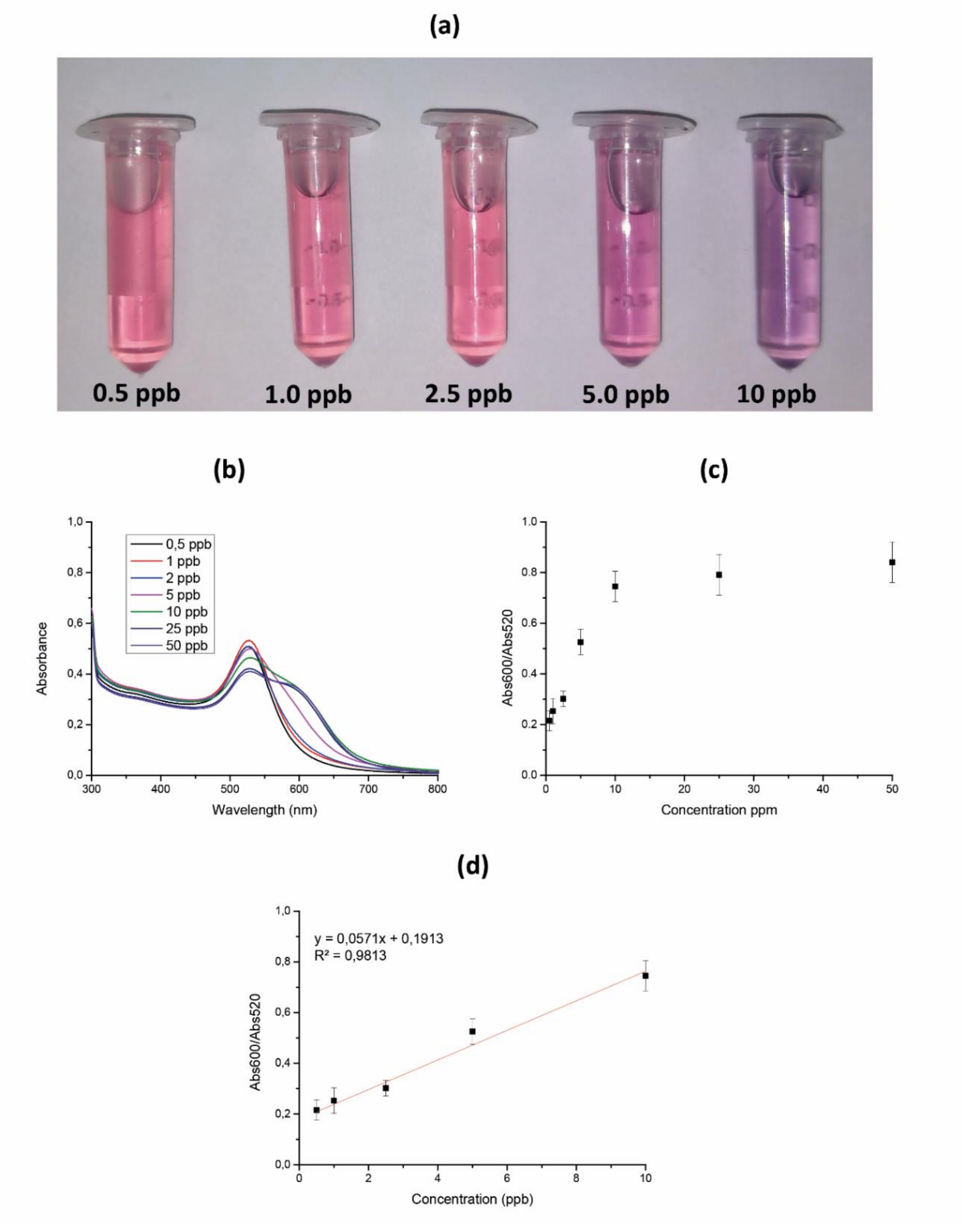

Figure 5. *a) Images of solutions obtained in the presence of Cu^{2+} in different concentrations of µg/L, b) UV-Vis spectra of solutions containing Cu^{2+} at various concentrations, c) curve obtained by plotting Abs600 / Abs520 value against concentration, d) linear range graph*

The limit of detection (LOD) value was determined by dividing the standard deviation of the Abs650 / Abs520 for mg/L and Abs600/Abs520 for µg/L values for obtained from the blank solutions by the calibration graph's slope obtained from the method. The LOD value was found to be 0.08 mg/L in the Cu^{2+} determination performed at mg/L level by the method. In the determination of the µg/L level LOD by the method, the value was determined as 0.04 µg/L. Considering the calibration graphs obtained by the method, the correlation coefficient values were found to be 0.98. This value indicates that there is an increase close to linear within the specified working range. In the study, the determination of Cu^{2+} in 1643e NIST water-certified reference material was also performed. The certified value is given as 22.76 µg/L. The result of the determination was found as 21.54 µg/L with the adjustment of the dilution factors. With this result, 94% recovery was achieved at a 95% confidence level. This shows that the developed method can be used to determine ppb levels within acceptable limits.

Table 1. *The calibration curve, detection, and quantification limits of elements measured by the developed method*

Level	Parameters	Found
mg/L	Calibration curve	A=0.1456C-0.0462
	R^2	0.98
	Linear Range (mg/L)	0.5-5.0
	LOD (mg/L)	0.08
	LOQ (mg/L)	0.24
µg/L	Calibration curve	A=0.0571C+0.1913
	R^2	0.98
	Linear Range (µg/L)	0.5-10
	LOD (µg/L)	0.04
	LOQ (µg/L)	0.13

In the last stage of the study, the use of the concept developed on real examples was examined. For this purpose, Cu^{2+} determination is carried out in the sample of tap water. First of all, the method developed was first applied only to the tap water sample. As a result of this application, a readable value could not be reached. Then, spiking was applied to tap water to contain 1.0 mg/L and 2.0 mg/L Cu^{2+}. The absorbance values obtained were converted into concentrations by using the calibration curve values given in Table 1, and the results obtained are given in Table 2.

Table 2. *The use of the developed method in the determination of Cu^{2+} in real sample*

Sample	Added Cu^{2+} (mg/L)	Found* (mg/L)	Recovery (%)	RSD%
Tap water	-	ND**	-	-
Tap water	1.00	1.04± 0.07	104	+5
Tap water	2.00	2.03±0.12	102	+4

* Mean of three replicates at % 95 confidence level

** Not Detected

Comparing the data obtained in the study with the Cu^{2+} determination studies that were previously performed colorimetrically with AuNPs is given in Table 3. Accordingly, when the results are compared with the studies employing different functional structures with a wide range of minimum determination limits, it was observed that the GH-AuNPs particles responded at both ppb and ppm level in specific concentration ranges, which reveals the positive aspect of the study.

Table 3. *Literature comparison table of the colorimetric Cu^{2+} determination via functionalized Au NPs*

Detected Metal	**Functionalized Group**	**SPR***	**MDL****	**Cited**
Cu^{2+}	L-cystein	522 nm	10 µM	[33]
Cu^{2+}	Citrate	520 nm	2500 µM	[34]
Cu^{2+}, Hg^{2+}, Pb^{2+}	Papain	626 nm and 524 nm	200 nM	[19]
Cu^{2+}	GH	650 nm and 520 nm	0.08 mg/L	This Study
Cu^{2+}	GH	600 nm and 520 nm	0.04 µg/L	This Study

* Surface Plasmon Resonance
**Minimum Detection Limit

IV. CONCLUSIONS

In this study, the potential for use in the colorimetric determination of metals after the interaction of AuNPs with dipeptide-based GH molecule was investigated. In this respect, it is understood that the colorimetric determination of Cu^{2+} ions can be performed among some toxic metal types. Here, with increasing Cu^{2+} amount, it is seen that the color change occurs as a result of the shift of AuNPs plasmon peaks towards the region with higher energy. The color change occurs as a result of aggregation in particles in the presence of GH and Cu^{2+}. The proposed method shows that the potential for use in determining some more toxic species can be made with dipeptide-based molecules. It is presented as an innovative application for the use of dipeptide-based materials, especially in the literature.

ACKNOWLEDGEMENTS: This work is supported by University of Health Sciences Turkey Scientific Research Project (Project no: 2020/10).

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