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Spherical silver nanoparticles as substrates in surface-enhanced Raman spectroscopy for enhanced characterization of ketoconazole

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ABSTRACT

A new method was developed for the characterization and detection of ketoconazole using surface enhanced Raman spectroscopy (SERS) by designing substrates and performing the bands' assignments. Thus, spherical silver nanoparticles (Ag-NPs) were synthesized by a reduction method and designed as substrates for SERS application. The Ag-NPs were characterized using a scanning electron microscope, Fourier transformed infrared spectroscopy and a high-resolution transmission electron microscope. TEM results indicated that the average size of the Ag-NPs was 15 nm. The UV spectrum showed a maximum absorbance of Ag-NPs at about 400 nm. When Ag-NPs were used as substrates in SERS, the Raman spectra of KCZ showed a significant enhancement of the Raman bands. An important finding is a linear relationship between the logarithmical scale of KCZ concentration and the intensity of the SERS bands, for example at 1050 cm^{-1} of KCZ, which is due to the C—N vibration. This was optimized and utilized to develop a calibration curve, which was then used for the detection of the KCZ in real pharmaceutical samples. The method has the advantages of a wide dynamic range with a high coefficient of determination and detection limit calculated based on the signal-to-noise ratio of 3, was 2.6×10^{-10} M and the limit of quantification was 7.8×10^{-10} M. The potential applications that take advantage of the high SERS sensitivity of this method are discussed for practical KCZ analysis where were quantified with this method.

1. Introduction

Ketoconazole (cis-1-acetyl-4-{4-[[2-(2,4-dichloro-phenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl} piperazine,), is a broad-spectrum antifungal agent used as an agent against dermatophytes and yeast. The assaying of ketoconazole in pharmaceutical compounds and formulations is vital. Ketoconazole (KCZ) has been determined in pharmaceutical preparations by spectroscopic, chromatographic and electrochemical methods [1–5]. These methods have the disadvantage of being time and labor intensive and often involves the extraction of solvents, some of which are potentially toxic to humans and the environment. For these reasons, in recent years, the need of alternative methods is a challenge that has been discussed by several researchers [6]. Surface Enhanced Raman Spectroscopy (SERS) is an important technique for the identification and detection of solid, liquid, and gas samples in various applications. SERS is a highly sensitive and selective method when compared with Raman spectroscopy [6,7]. Recently, it has been used in many important research areas such as medical applications, analytical chemistry [8,9]. SERS has been studied both theoretically and experimentally. The first study, by Fleischmann, was performed using pyridine absorbed at the surface of a silver electrode [10].

SERS is a method used to study bounding of the analyte to the substrate, and it is characterized by its high sensitivity and low detection limits [11]. SERS commonly refers to the phenomenon whereby Raman-signals from adsorbates on suitable surfaces are enhanced several times due to the excitation Surface Plasmon Resonance (SPR) on the surface of metals such as silver, gold, and copper [12,13]. The enhancement can be explained by two mechanisms: chemical mechanism and electromagnetic enhancement. The latter is considered the dominant effect due to the SPR [14–16]. This mechanism is sometimes called the Raman reflectance mechanism and it can also arise from modulated overlap between the molecule and surface orbitals.

Metal nanoparticles have been widely used in SERS due to their unique properties, such as their size and shape [17–20]. Silver colloids are the most common type of SERS substrate; they exhibit large enhancement, a strong surface Plasmon polarization mode in the visible light range, and are relatively stable [21,22,23]. There are several methods to synthesize metal nanoparticles, including chemical methods such as chemical reduction and thermal decomposition [24], and physical methods, such as vapor deposition and microwave irradiation [25]. The reduction methods are the most commonly used for the synthesis of nanoparticles. The reduction method requires three main components: (i) a precursor like metal salt, (ii) a reducing agent

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like trisodium citrate, ethylene glycol, and sodium borohydride, and (iii) a stabilizing agent like vinyl pyrrolidone, dodecanoic acid, and oleylamine [26–28]. Silver nanoparticles (Ag-NPs) have been known to be used in the pharmaceutical industry based on their optical, electrical and thermal properties [29,30]. Ag-NPs have been used for treating various human diseases, due to the high surface area resulting from the ability of Ag-NPs to coordinate with legends [31,32].

The computational method is useful to investigate the design of new drugs and materials that are difficult to find or very expensive; further, it is useful to study the properties of molecules and the assignment of IR and Raman bands [33]. This method is based on mathematical algorithms, statistics, and databases to integrate chemical theory [34]. Ab initio, semiempirical and molecular mechanics numerical techniques were used to determine the geometry optimizations, potential energy surface calculations, and frequency calculation, as seen in the calculations [35–37].

The main goal of this study was to develop an efficient SERS method to determine the KCZ in pharmaceutical formulations. Thus, Ag-NPs were prepared, characterized and designed as substrates for SERS measurements. The method was optimized and applied for the detection of KCZ in commercial samples. The DFT calculations were carried out to obtain a detailed interpretation of the SERS spectra and to collect the vibrational assignment.

2. Experimental

2.1. Chemicals and materials

Ketoconazole (KCZ) named as ((±)-*cis*-1-Acetyl-4-(4-[(2-[2, 4-dichlorophenyl]-2-[1H-imidazol-1-ylmethyl]-1,3-dioxolan-4-yl)-methoxy] phenyl) piperazine) ≥98% purity was purchased from Sigma-Aldrich. Silver nitrate ($AgNO_3$), CAS No 7761-88-8, was purchased from BDH ACS. Sodium borohydride ($NaBH_4$) 90% purity and Potassium Bromide (KBr) ≥99% purity were purchased from Sigma-Aldrich. All solutions were prepared with ultrapure water obtained from a water purification system (Ultra Clear™ Lab Water Systems, Siemens Water Technologies USA).

2.2. Synthesis of Ag-NPs

Ag-NPs were prepared by the chemical reduction method. First, 50 ml of aqueous 0.001 M of $AgNO_3$ solution was prepared as a precursor of Ag-NPs. Then, 150 ml aqueous solution 0.0020 M $NaBH_4$ was prepared as a stabilizing and reducing agent (the $NaBH_4$ solution was prepared fresh), by dissolving 11.34 mg in distilled water. The sodium borohydride was placed on ice for 20 min to cool; then the $AgNO_3$ solution was added to the $NaBH_4$ solution at a rate of 1 drop/s under continuous stirring. When the silver nitrate was added the color of the mixture turned to dark yellow; this color indicates the formation of the neutral Ag-NPs. The chemical equation of Ag-NPs formation is:

$$AgNO_3+NaBH_4 \rightarrow Ag+1/2H_2+1/2B_2H_6+NaNO_3$$

2.3. Characterization

The Ag-NPs were characterized by using Ultraviolet–visible spectroscopy to determine the surface Plasmon band λ_{max} of the Ag-NPs, the UV spectrum was recorded in 200–800 nm range. Two milliliters of Ag-NPs were placed into a quartz cuvette and placed in the sample holder of Beckman DU640 UV/Vis spectrophotometer. The smaller Ag-NPs showed a surface Plasmon band λ_{max} of 400 nm. TEM and SEM techniques were used for the determination of the morphology, particle size, and particle distributions of Ag-NPs. FT-IR spectra of KCZ was obtained by Perkin-Elmer FT-IR spectrophotometer using potassium bromide (KBr) pellets. The pellet was prepared by mixing the sample and KBr with a ratio (1:100) [38]. FT-IR measurement was scanned at a range of wavelength from (400 to 4000) cm^{-1}. He-Ne laser source operating at 0.5 W was utilized for sample excitation.

2.4. Surface-enhanced Raman spectroscopy (SERS)

The SERS spectra of KCZ were obtained by a using Raman spectroscopy system, namely a Lab Ram HP Evolution Raman spectrometer equipped with an internal He-Ne 17 mW laser at a 633 nm excitation wavelength. SERS samples were prepared by using a 3:1 volume ratio of the KCZ solutions to the colloid in a cuvette. The parameters of the

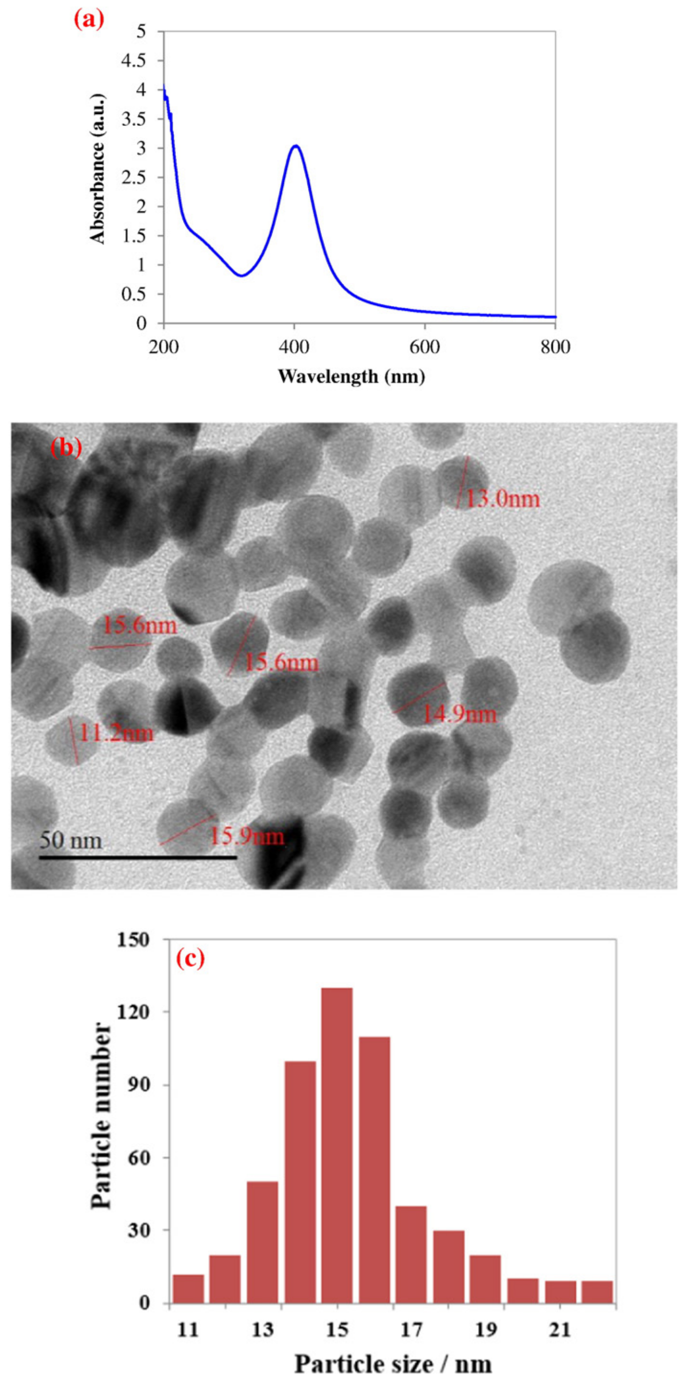

Fig. 1. (a) UV–Vis absorption spectra and (b) TEM image of Ag-NPs; (c) particle size distribution histogram; where a.u. stands for an arbitrary unit.