



# Investigation into structure and dehydration dynamic of gallic acid monohydrate: A Raman spectroscopic study

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## ABSTRACT

The dehydration process of gallic acid monohydrate was carried out by heating method and characterized using Raman spectroscopic technique. Density functional theory calculation with B3LYP function is applied to simulate optimized structures and vibrational frequencies of anhydrous gallic acid and its corresponding monohydrated form. Different vibrational modes are assigned by comparison between experimental and theoretical Raman spectra of above two polymorphs. Raman spectra show that vibrational modes of the monohydrate are distinctively different from those of anhydrous one. Meanwhile, the dynamic information about dehydration process of gallic acid monohydrate could also be observed and monitored directly with the help of Raman spectral analysis. The decay rate of the characteristic band from gallic acid monohydrate and the growth rate of anhydrous one are pretty consistent with each other. It indicates that there is no intermediate present during the dehydration process of gallic acid monohydrate. The results could offer us benchmark works for identifying both anhydrous and hydrated pharmaceutical compounds, characterizing their corresponding molecular conformation within various crystalline forms, and also providing useful information about the process of dehydration dynamic at the microscopic molecular level.

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## 1. Introduction

Gallic acid (3,4,5-trihydroxybenzoic acid, GA, with its molecular structure shown in Fig. 1(a) and also its monohydrate structure shown in Fig. 1(b), as an intermediate component of plant metabolism from the hydrolysis of tannins, is distributed in plants and foods widely. It has been associated with a variety of biological actions including antioxidant, antibacterial, antiviral and antimicrobial [1–5]. GA has been reported to have five monohydrates and three anhydrous forms by Braum et al. [6]. Among them, two kinds of GA monohydrated forms, monohydrated form I (MH-I) and monohydrated form IV (MH-IV), were already reported in the Cambridge Structural Database. MH-I of GA was found to be relatively stable at ambient condition, and it is the commercial crystalline form as well [7,8]. Recently research about monohydrated form II and III (MH-II, MH-III) has also been published, as showing remarkable hydrate polymorphism [9,10]. Monohydrated form V (MH-V), the least stable form, was prepared by evaporating GA from 2-butanol and it would transform to either one of the three anhydrous forms or a hydrate (MH-I, MH-III, MH-IV) [6]. Anhydrous GA is also showing polymorphic effect, though only solvent free structure has been reported as anhydrate form II (AH-II), and the other two

forms (AH-I and AH-III) are metastable polymorphs [6,11]. Various crystalline forms would represent diverse physical properties, such as density, solubility, hardness, melting point, bioavailability *etc.* and consequently can profoundly influence the manufacturing process, long-term stability and performance of drug products [12–14]. The phenomenon of transformation between hydrates and anhydrites of specific pharmaceuticals would contain much valuable information. Knowledge about the extent of hydration is essential for both research and industrial development of pharmaceutical drugs, however it is difficult to completely exclude water or moisture so that the corresponding hydrate formation could not be avoided more or less during the process of drug production and also its storage period [6]. Moreover, it is crucial to understand and control the balance between anhydrate and hydrate ones. Therefore, it is critically important to analyze both structural change and phase transformation between anhydrous and hydrated forms of pharmaceutical compounds.

During analysis, the resulting solid forms of pharmaceuticals must be measured with established techniques. The methods that could be employed are, for example, powder X-ray diffraction, high performance liquid chromatography, nuclear magnetic resonance, differential scanning calorimetry, thermo-gravimetric analysis and vibrational spectroscopy. Compared to vibrational spectroscopy, most of these techniques could not provide any structural information and help to understand polymorphism and also dehydration process at molecular level.

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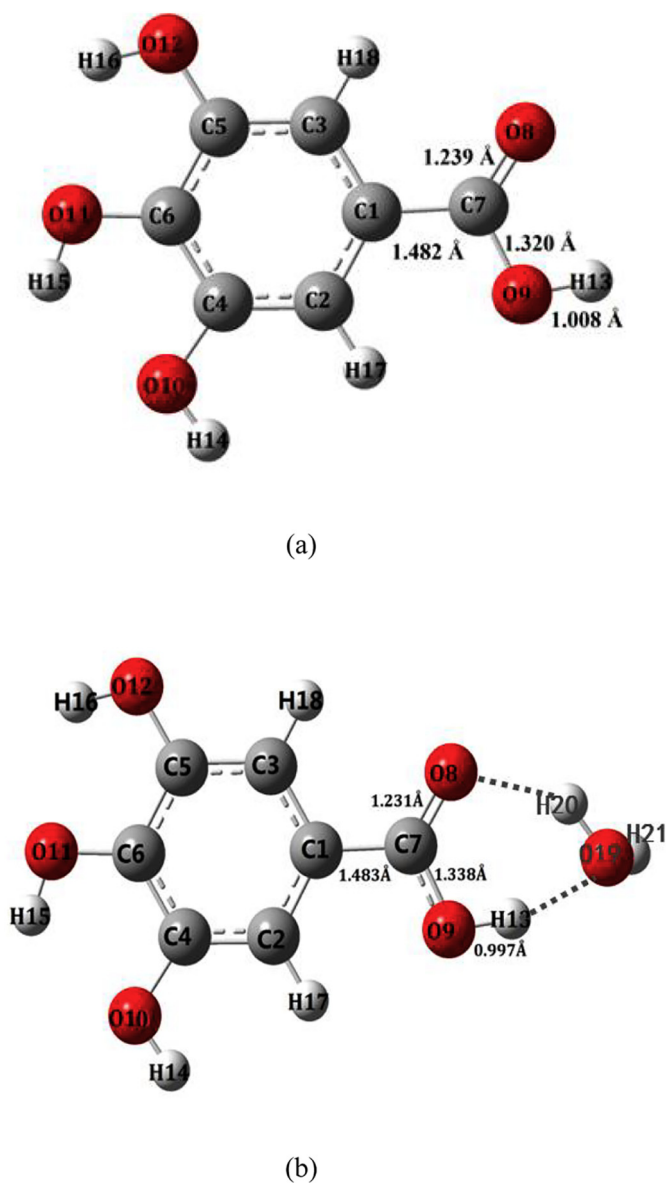


Fig. 1. Molecular structures of GA (a) and its monohydrate one (b).

Vibrational spectroscopic techniques like Raman spectroscopy represent one of the most useful tools for obtaining information about structures and properties of molecules [15–19]. Raman spectroscopy is nowadays steadily gaining in importance for monitoring of chemical reactions, analysis of pharmaceuticals and other materials systems, and increasingly for many other real-world applications. The bands observed in Raman spectra are due to energy transfer between the photons of an excitation source and the molecule, *i.e.*, the inelastic scattering of light. Raman spectroscopy also has several practical features that make it attractive for investigating pharmaceutical solid-state materials, including the fact that most APIs typically contain aromatic or conjugated systems, which show strong Raman activity, while many excipients such as starch are aliphatic and exhibit much weaker Raman signals. Raman spectroscopy has been successfully used for monitoring hydration and dehydration processes of different molecular systems [18,19]. Also simple sample preparation and handling, non-destruction and easily monitoring of phase transformation in real time make Raman spectroscopy suitable for identification and quantification of crystal forms in drug products [20,21].

In this paper, Raman vibrational spectroscopy was performed on analyzing the commercial GA MH-I, AH-II and also the dehydration

process of MH-I. Quantum chemical DFT calculation was used to simulate the vibrational frequencies and optimize structures of different theoretical GA forms in order to help understand the Raman spectroscopic observations and also structural changes due to various inter-molecular interactions within different GA crystalline forms.

## 2. Materials and Methods

GA MH-I was purchased from Sigma-Aldrich Company (Shanghai, China) and GA AH-II was donated by J&K Chemical Company (Shanghai, China). Both samples were used without further purification. The process of dynamic dehydration was performed by heating GA MH-I using electric vacuum drying oven (DZF-6020, Hangzhou, China) at a constant temperature 105 °C. A part of samples were taken out every 5 min for the following Raman spectra analysis.

Raman spectra of all samples were recorded at room temperature in the frequency range 3700–100  $\text{cm}^{-1}$  by using the Fourier Transform Raman (FT-Raman) spectrometer (Nicolet 960, Thermo Nicolet, USA). All the spectra were averaged over 64 scans with 2  $\text{cm}^{-1}$  spectral resolution and a 1064 nm laser excitation with the operating power around 200 mW.

Quantum chemical calculations were performed to simulate the structures of GA single molecule, different GA dimers and different monohydrated forms. The vibrational frequencies and optimized geometries were computed within the density functional theory (DFT) employing the Lee-Yang-Pair correlation functional (B3LYP) [22–24] by using Gaussian 03 software [25] at the basis set of 6-31G(d). The corresponding scaling factor was chosen to be 0.96 [26].

## 3. Results and Discussion

### 3.1. Raman Spectra and Structural Information of Anhydrous and Monohydrated GA

Fig. 2 presents the Raman spectra of GA MH-I and anhydrous GA (which is formed from GA MH-I after completed dehydration procedure). Significant changes in the Raman spectra could be observed for GA MH-I upon dehydration. The most striking difference between the Raman spectrum of GA MH-I and anhydrous GA is the disappearance of the characteristic band at 1691  $\text{cm}^{-1}$  upon dehydration. In addition, GA MH-I just has one band at 1622  $\text{cm}^{-1}$ , however, anhydrous GA has two strong bands in this region, 1597  $\text{cm}^{-1}$  and 1614  $\text{cm}^{-1}$

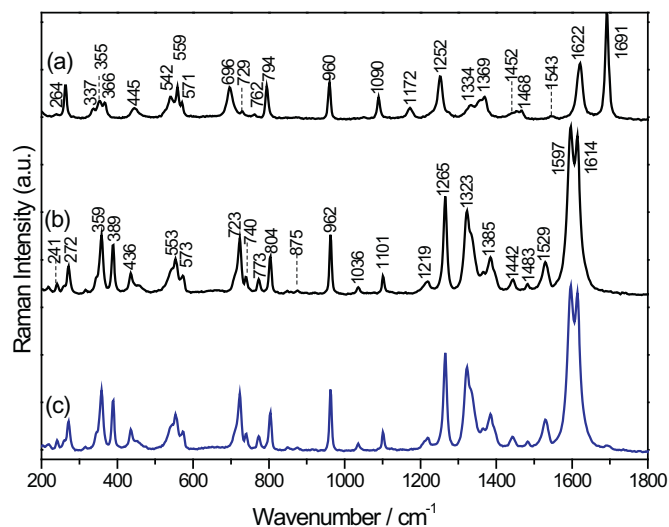


Fig. 2. Raman spectra of GA monohydrate (a), anhydrous GA (b, which was formed from GA monohydrate after completed dehydration) and commercial raw material of anhydrous form (c).

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