The determination of captopril in Solution by Raman spectroscopy

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Abstract. Captopril, 1-[(2S)-3-mercapto-2-methyl propionyl]-Lproline, is an angiotensin converting enzyme (ACE) inhibitor, which reduces peripheral resistance and lowers blood pressure. It is widely used in the hypertensive ailments and congestive heart failure treatment. Due to such crucial pharmacological importance, development of simple and accurate methods for the determination of captopril is desired. In this work, the normal Raman spectra of the captopril in different concentrations were studied, and the relationship between the Raman intensity and the concentrations of the captopril was quantificationally analysed. By selecting appropriate characteristic Raman bands of the captopril, the solution of some captopril purchased in a local pharmacy was quantificationally determined. A quantificationallinear relationship between the Raman intensity and the concentrations of captopril was obtained, and it is little affected by other compounds in the solution of captopril. This study provides an effective technique for the quantification determination of captopril in solutions, and it has a potential application in the analysis of medicament.

Keywords: Raman spectroscopy; Captopril; Quantitative determination

1. introduction
Captopril, 1-[(2S)-3-mercapto-2-methyl propionyl]-Lproline, is an angiotensin converting enzyme (ACE) inhibitor. This medication work to block an enzyme system, which causes artery walls to relax, reducing blood pressure. It is widely used in the treatment of hypertension. Other uses of captopril have also been reported, such as decreasing high blood pressure caused by blood vessels in the kidneys, decreasing symptoms of cystinuria, reducing rheumatoid arthritis symptoms, treating Raynaud’s phenomena and progression of kidney disease in peoples with diabetes [1,2]. Due to such crucial pharmacological importance, development of simple and accurate methods for the

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determination of captopril is desired. Determination of captopril has previously been reported by capillary electrophoresis, flow injection analysis[3], high performance liquid chromatography, kinetic spectrophotometry[4], FT-Raman spectroscopy[5], voltammetry[6], gas chromatography–mass spectrometry etc[7]. But these methods require many special sample preparation. Raman spectroscopy, as a scattering technique, is well known for the minimum of sample handling and preparation that is required [8]. Compared with many other common analytical methods, this technique does not require any special sample preparation, so analysed drugs are usually in their unmodified forms. In spite of these advantages, application of Raman spectroscopy to captopril quantification is not widespread. In this paper, we have studied the normal Raman spectra of the captopril in different concentrations from 0.67% to 3.33%. the solution of some captopril purchased in a local pharmacy was quantificationally determined. A quantificational linear relationship between the Raman intensity and the concentrations of captopril was obtained.

2. experimental

2.1. sample
Captopril, with a mass fraction purity of 0.99, was purchased from Sigma Aldrich. The samples were used without further purifications. The solutions were prepared by dissolving the sample into doubly distilled water. The Concrete steps were as follows: first, we accurately weighed 5g of the captopril powder, and the powder was dissolved in 150 ml doubly distilled water. The volumes of doubly distilled water, 10 ml, 20 ml, 40 ml, 80 ml, were prepared. Then the solution of the captopril (40 ml) were added to these doubly distilled water, respectively. The final concentrations of captopril were 3.33%, 1.67%, 1.11%, 0.83% and 0.67% respectively. The captopril tablets (12.5 mg/tablet) were purchased from the local pharmacy. The solution of the captopril tablets were prepared by dissolving eight tablets into the 9ml doubly distilled water, and the concentration is 1.11%.

2.2. Instruments
A 514.5 nm argon ion laser was used as Raman excitation. The spectral line width of laser was further spectrally purified with an interference type laser line band-pass filter, and a notch filter (HSPF-514.5-1.0, Kaiser Optical Systems Inc., USA) was used to reject the excitation light while allow Raman signal entering the spectrometer system.

The Raman system was equipped with a BX-41 Olympus microscope and 45× objectives. Spectrometer system (Acton spectro@2300i, Princeton Acton, USA) was used with a 1200 g/mm holographic grating. An air cooled CCD detector (Pixis 256, Princeton Acton, USA) was used for measuring the Raman signal by an integration method. Exposure time of CCD was 50 s and 1 scan. The laser power at the samples was 8 mW.

3. Results and discussion

3.1. Raman spectrum of captopril in different concentrations
In Fig. 1 Raman spectra of the captopril in the concentration 3.33% are presented. The range is from
3560 to 230 cm\(^{-1}\). The Raman peaks at 2997, 2947, 2895, 2583, 1606 and 1458 cm\(^{-1}\) are very obvious. In the quantitative determination of the captopril, in order to ensure accuracy, the Raman bands with high intensity should be selected as the quantitative band. Thus, we will focus on analysis of these bands and the vibration mode of these bands. The peaks at 2997 and 2947 cm\(^{-1}\) should be assigned to the asymmetric CH\(_3\) and CH\(_2\) stretching vibration, and the peak at 2895 cm\(^{-1}\) should be due to the symmetric CH\(_3\) stretching mode. The peak at 2583 cm\(^{-1}\) corresponds to the SH stretching vibration. The peaks at 1606 cm\(^{-1}\) should be assigned to the amide band. The peaks at 1482 and 1458 cm\(^{-1}\) are due to the asymmetric and symmetric CH\(_3\) bending vibrations, respectively, and the peak at 1340 cm\(^{-1}\) should be assigned to the OH bending vibration\(^{[9,10]}\). In addition, the wide band in the range 3100–3500 cm\(^{-1}\) is assigned to the liquid water, and the peaks are at 3273 and 3421 cm\(^{-1}\). The Raman peak of the liquid water will be chosen as the internal standard peak. It not only simplify the sample preparation process, but also avoid effect of other substances on the determination of captopril.

In the direct quantitative determination of the captopril, some uncontrollable factors, such as the different concentration of samples causing changes in refractive index, and the background noise will bring the Raman spectra the unpredictable impact. Therefore, it’s difficult to determinate the concentration of captopril by directly comparing the intensity of Raman spectra of different samples, and it requires adding the appropriate internal standard to eliminate the impact. In this paper, the Raman peak of the liquid water at 3421 cm\(^{-1}\) was chosen as the internal standard peak\(^{[11]}\). It not only simplify the sample preparation process, but also solve the quantitative problems. It is a convenient internal standard in quantitative analysis of aqueous samples.

In the experiment, the acquisition time of each Raman spectrum is 50s.

Figure 1. Raman spectrum of 3.33% captopril

3.2. the selection of the internal standard substances and the quantitative peak

In the direct quantitative determination of the captopril, some uncontrollable factors, such as the different concentration of samples causing changes in refractive index, and the background noise will bring the Raman spectra the unpredictable impact. Therefore, it’s difficult to determinate the concentration of captopril by directly comparing the intensity of Raman spectra of different samples, and it requires adding the appropriate internal standard to eliminate the impact. In this paper, the Raman peak of the liquid water at 3421 cm\(^{-1}\) was chosen as the internal standard peak\(^{[11]}\), it not only simplify the sample preparation process, but also solve the quantitative problems. It is a convenient internal standard in quantitative analysis of aqueous samples.

In the experiment, the acquisition time of each Raman spectrum is 50s. Because the Raman
spectroscopy divided into two section scan, we should choose the Raman bands closing to the Raman peaks of water as the quantitative peak. After testing, as the concentration of the captopril decreases, the intensity of the several peaks closing to the peaks of water decrease, the SH stretching vibration is characteristic Raman bands of the captopril. In this study, we chose the Raman peak of the captopril at 2854 cm$^{-1}$ closing the internal standard as the the quantitative peak of the captopril, and chose the relative peak intensity ratio between 2854 cm$^{-1}$ and 3422 cm$^{-1}$ as the response of the determination of captopril.

3.3. the standard curve and the linear range

In Fig. 2 Raman spectra of the captopril in different concentrations are presented. As can be seen from Fig.2, as the concentration of the captopril increases, the relative intensity of Raman spectra of captopril in solution increases, and the peak intensity of the water remains basically unchanged. The ratio of the intensity of the characteristic peak of the captopril(Ic) at 2584 cm$^{-1}$ and the water(Iw) at 3422 cm$^{-1}$ constitute the relative intensity ratio(R=Ic/Iw). The measured results can be seen in Table 1. The intensity data of the characteristic peak can be directly read out by the software origin 7.5. In Fig. 2, a quantificational linear relationship between the relative intensity ratio R and the concentrations of captopril is shown. The linear working range is from 0.67% to 3.33%. The linear regression equation is $R=0.13085+0.03504C$. The linear correlation coefficient is $r=0.99359$. The result is very satisfactory for the quantitative analysis and the linear regression equation is very useful. The relative intensity ratio(0.67~3.33%) can be predicted.

![Figure 2. Raman spectra in different concentrations of captopril](image-url)
3.4. The determination of captopril tablets in Solution

The captopril tablets (12.5mg/tablet) were purchased from the local pharmacy. The solution of the captopril tablets were prepared by dissolving eight tablets into the 9ml doubly distilled water. First, we crushed eight captopril tablets and dissolved the powder into the 9ml doubly distilled water, gently shaked, then the solution was placed for an hour. When the captopril fully dissolved in water we can found a small amount of material sinking to the bottom. A droplet (50µl) of supernatant was dropped on a clean glass slide and was measured on Raman Spectrometer. In Fig. 4 Raman spectra of solution of the captopril tablets in the concentration 1.11% are presented. The relative intensity ratio \( R_t = 0.171217 \). From the linear regression equation, we can conclude that the relative intensity ratio of the captopril in the concentration 1.11% is \( R = 0.174941 \). The two are very close, and it indicate that the experiment result is satisfactory. This shows that the fitted quantificational linear relationship can be

### Table 1. Intensity and ratio of characteristic peak

| Captopril (%) | \( I_c \) (2584 cm\(^{-1}\)) | \( I_w \) (3422 cm\(^{-1}\)) | \( R \)   |
|---------------|----------------|----------------|------|
| 3.33%         | 2836           | 11462          | 0.247426 |
| 2.67%         | 2208           | 9765           | 0.226114 |
| 2.22%         | 2069           | 9961           | 0.20771 |
| 1.67%         | 1987           | 10760          | 0.184665 |
| 1.11%         | 1783           | 10192          | 0.174941 |
| 0.83%         | 1677           | 10234          | 0.163866 |
| 0.67%         | 1419           | 9513           | 0.149164 |

**Figure 3.** Calibration curves errors for captopril in different concentrations

![Calibration curves errors for captopril in different concentrations](image)
applied to the determination of captopril tablets. By selecting appropriate characteristic Raman bands of the captopril, the impurities contained in the tablets will not affect the determination of the captopril tablets in the liquid water.

![Raman spectrum of 1.11% captopril tablets](image)

**Figure 4.** Raman spectrum of 1.11% captopril tablets

### 4. Conclusion

This study confirms the Raman spectroscopy can be used to determine the captopril in solution, and a quantificational linear relationship between the Raman intensity and the concentrations of captopril was obtained. The proposed method has the advantages of simplicity and rapidity for the determination of the captopril. The determination of captopril tablets purchased from local market in solution has verified this result and shows the possibility of further application in the business.

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