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Indirect Determination of Cetirizine Hydrochloride by ICP-AES

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Cetirizine hydrochloride reacted with BiI_4^- in an acidic aqueous solution to form precipitate. After centrifugation, the atomic emission intensity of Bi^{3+} contained in the supernatant solution was measured at the characteristic wavelength of 206.170 nm. The difference between the spectral signal intensity of the blank solution and that of the supernatant, ΔI, was linearly related to the concentration of cetirizine hydrochloride. As a result, a new inductively coupled plasma-atomic emission spectrometric (ICP-AES) method was developed for the analysis of cetirizine hydrochloride. The linear range was from 27.7 to 184.8 $mg \cdot L^{-1}$, with a correlation coefficient (r) of 0.9961 and a detection limit of 9.6 $mg \cdot L^{-1}$. This method is simple and accurate, Without using toxic organic solvents, and is feasible for the quality control of cetirizine hydrochloride tablets and capsules.

Key Words: Cetirizine hydrochloride, ICP-AES, Precipitation, Indirect determination

Introduction

Cetirizine hydrochloride is an efficacious second-generation antihistamine drug with a broad range of applications. It can inhibit histamine not only at the early stage, but also at the later stage as well. It is commonly used for the treatment of allergic rhinitis, allergic skin itching, conjunctivitis, *etc*. Current analytical methods for cetirizine hydrochloride include ultraviolet spectrophotometry,[1,2] high performance liquid chromatography (HPLC),[3-8] head-space-gas chromatography,[9] capillary electrophoresis,[10-12] chemiluminescence method[13] and perchloric acid titration.[14] Each of these methods has its own advantages and disadvantages. To our knowledge, ICP-AES has not been reported as the method for the determination of cetirizine hydrochloride. in this study, cetirizine hydrochloride reacted with BiI_4^- in an acidic solution to form yellow precipitate which was then separated from the liquid phase by centrifugation, and the Bi emission intensity of the supernatant was measured by ICP-AES. On those grounds, a new indirect ICP-AES method for the determination of cetirizine hydrochloride was established. The analytical results were consistent with the labeled amount, and the recovery rate was 96% -103%. This method is simple, rapid, accurate and reliable, without using toxic organic solvents.

Experimental

Instruments and Reagents. An inductively coupled plasma atomic emission spectrometer (Optima 5300DV, PerkinElmer Inc., US) was used, with the operating parameters as in Table 1.

A 800-type centrifuge (Shanghai Surgical Instruments Factory), HH-38 thermostatic water-bath (Changcheng Technology and Business Limited Company, Zhengzhou), Leici pHS-3C pH meter (Shanghai Precision Scientific Instrument Corporation) were used.

Potassium iodide (KI), (AR grade), was purchased from Shanghai Chemical Reagent Co. (Shanghai, China). Bismuth nitrate and glacial acetic acid, (both in AR grade), were purchased from Guangdong Guanghua Chemical Co. (Guangzhou, China). The standard sample of cetirizine hydrochloride was obtained from the National Institute for the Control of Pharmaceutical and Biological Products. Distilled water was used.

Preparation of BiI_4^- Solution.

Bi^{3+} Solution Preparation: A certain amount of solid bismuth nitrate was accurately weighed into a beaker, and then 30 mL of distilled water was added. After the mixture was stirred for a few minutes, the clear upper solution was removed. After the hydrolysis product of Bi^{3+} was washed 5 to 6 times with distilled water to remove the precipitate was dissolved in 40 mL of glacial acetic acid. This solution was then diluted to 250 mL in a volumetric flask with distilled water and was calibrated by an EDTA standard solution in order to obtain the solution concentration of 1.784×10^{-2} $mol \cdot L^{-1}$.

Preparation of KI Solution: 2.861 g of solid potassium iodide was accurately weighed, then dissolved and diluted to 250 mL in a volumetric flask with distilled water. The concentration was 7.136×10^{-2} $mol \cdot L^{-1}$.

Working Solution of BiI_4^-: 11.20 mL of the 1.784×10^{-2} $mol \cdot L^{-1}$ Bi^{3+} solution, 30 mL of glacial acetic acid, 11.20 mL of the 7.136×10^{-2} $mol \cdot L^{-1}$ KI solution and 1 g of solid KI were

Table 1. Equipment operating parameters

element	analytical line/nm	RF power/Wal	pumpspeed/mL/min	plasma gas/L/min	carrier gas/L/min	auxiliary gas/L/min
Bi	206.170	1300	1.5	15	0.8	0.2

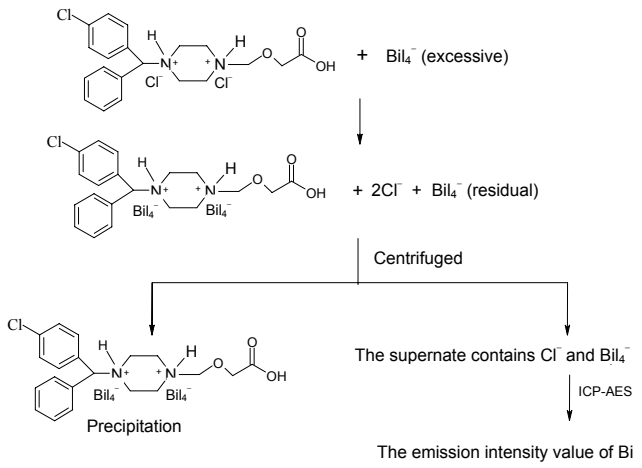

Figure 1. Mechanism and experimental principle of precipitate formation.

added into a 100-mL volumetric flask and diluted to the mark with distilled water, yielding a final concentration of 2.000×10^{-3} mol·L^{-1}.

Procedures. A 4.0 mL of 2.0×10^{-3} mol·L^{-1} BiI_4^- solution and an appropriate amount of cetirizine hydrochloride solution were added to a 10-mL volumetric flask, mixed well, and then diluted to the mark with distilled water. The mixture was shaken and allowed to settle down at 20 °C for 20 min in order to form precipitate. The solution and the precipitates were transferred to a 10-mL marked centrifuge tube and centrifuged at 4000 rpm for 10 min. The characteristic wavelength emission intensity of Bi^{3+} in the supernatant, I_1, at 206.170 nm, was measured by ICP-AES. Under the same conditions, I_0, the emission intensity of Bi^{3+} in a blank solution was measured. ΔI was calculated by the following formula: $\Delta I = I_0 - I_1$.

Experimental Principle. Based on the molecular structure of cetirizine and the experimental results, it is deduced that the reaction mechanism of BiI_4^- and cetirizine hydrochloride is as follows: two Cl^- ions of cetirizine hydrochloride are easily dissociated in aqueous solution and substituted by two BiI_4^- ions giving the neutral salt which precipitates out of solution due to its insolubility in water.

The mechanism and experimental principle leading to precipitate formation is shown in Figure 1.

Results and Discussion

Acidity Effect. As the procedure, the test solutions were adjusted to various pH values with 3 mol·L^{-1} of HCl and 0.1 mol·L^{-1} of NaOH without changing other conditions. It was found that the measured values, ΔI, remained unchanged by the addition of an acid to the test solutions with a pH of ≤ 3.0. However, the measured values, ΔI, increased sharply at pH > 3.5 when an alkaline was added to the test solutions. The above results indicate that the Bi^{3+} of BiI_4^- was strongly hydrolyzed at pH > 3.5 and therefore the analysis was only applicable at pH ≤ 3.0. In the preparation of the BiI_4^- solution, a large volume of glacial acetic acid was added in order to prevent the hydrolysis of Bi^{3+}, resulting in a pH value of approximately 2.0 which

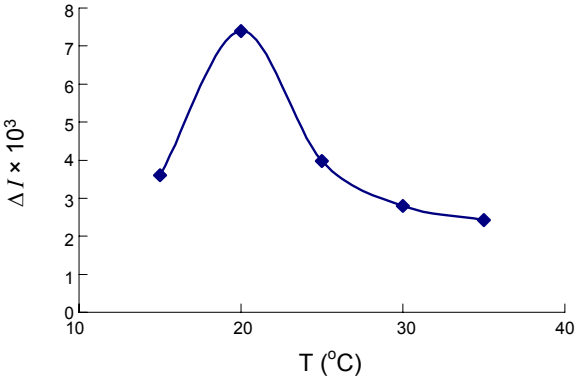

Figure 2. Effect of temperature on ΔI.

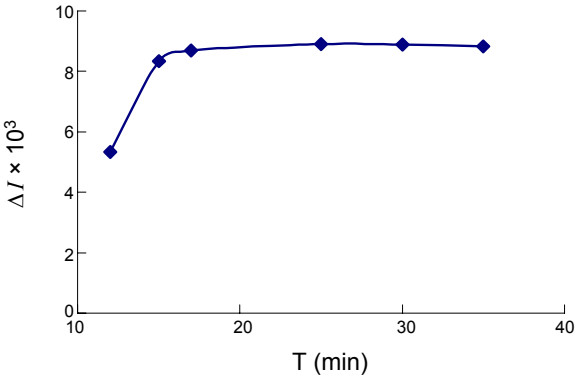

Figure 3. Effect of reaction time on ΔI.

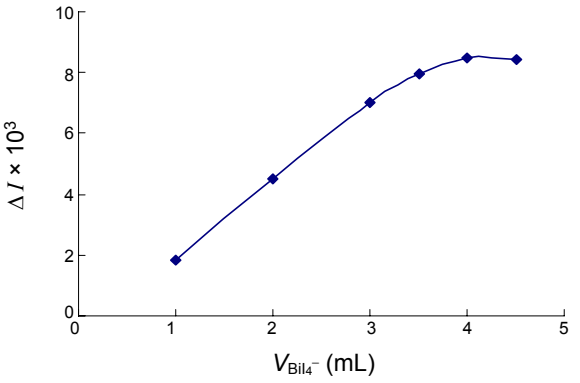

Figure 4. Effect of precipitant amount on ΔI.

was in line with the necessary conditions for the reaction. Therefore, the pH value of the reaction system was not adjusted.

Influence of Reaction Temperature. The effect of temperature (15 - 40 °C) on the reaction of BiI_4^- and cetirizine hydrochloride are shown in Figure 2. ΔI reached the maximum value at 20 °C. The ΔI values fell as the reaction temperature was increased above 20 °C indicating that the reaction was completed at 20 °C and The decrease in ΔI above 20 °C was probably caused by decomposition of the product.

Influence of Reaction Time. Figure 3 shows that the reaction is quite rapid with the ΔI values remaining constant after 7 min.

Unless otherwise stated, a 20 min reaction time was selected in the following study.

Reagent Consumption. 2.00 mL of 2.00×10^{-3} mol·L^{-1} cetirizine hydrochloride was added to various amounts of BiI_4^- solutions respectively under the same other conditions. The data shown in Figure 4 indicate that the reaction is basically complete when the volume ratio of BiI_4^- solution to cetirizine hydrochloride solution was 2:1. Therefore, the volume of BiI_4^- solution must be as twice as that of the cetirizine hydrochloride standard solution.

Linear Range. The working curve was obtained by plotting the ΔI values for various concentrations of cetirizine hydrochloride standard solutions. The results establish that the ΔI values were proportional to the cetirizine hydrochloride concentration in the range of 27.7 - 184.8 mg· L^{-1}. Regression analysis yields the equation $\Delta I = 0.0353C_{drug} + 0.0926$, with a correlation coefficient of 0.9961. The detection limit (3σ) as calculated by the IUPAC method was 9.63 mg·L^{-1}.

Precision. 2.00 mL of 2.00×10^{-3} mol·L^{-1} cetirizine hydrochloride and 4 mL of 2.00×10^{-3} mol·L^{-1} BiI_4^- solutions were mixed in eleven 10-mL volumetric flasks, and the eleven ΔI values were subsequently determined and calculated to a RSD of 1.4%.

Interference Test. Drugs often contain additives such as glucose, dextrin, starch, magnesium stearate, calcium ions and other metal cations. Therefore, interference experiments on these substances for drug determination were conducted. The volume of cetirizine hydrochloride and BiI_4^- solutions were fixed at 2.00 mL and 4.00 mL, respectively, and then varying amounts of the interfering substances listed above were added. The mixture was diluted to 10 mL with distilled water, and then the concentration of cetirizine hydrochloride was determined under the optimized conditions. With a measurement error of ± 5%, the amount of allowable interfering substances is given in Table 2.

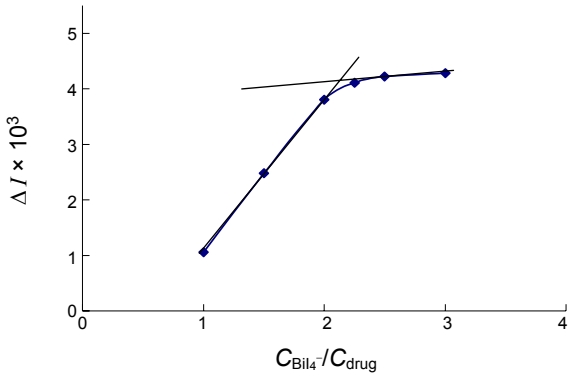

Figure 5. The ratio of Associating precipitation.

The data in Table 2 suggest that starch, Ca^{2+} and Mg^{2+} effect determining the concentration of cetirizine hydrochloride. For starch, the reason is that it has poor water solubility and forms a suspension in water which affects the formation of associated complexes. However, the starch excipient in drugs can be removed by filtration when the sample solution is processed, and therefore, it has little effect on the sample measurement. Unfortunately, Ca^{2+} and Mg^{2+} can interfere with the measurement of the ΔI values. This phenomenon is deduced that because these ions can inhibit the ionization of Bi^{3+} in plasma flame. The result led to decrease emission spectra intensity of Bi^{3+}, the ΔI values between the blank solution and the supernatant of the centrifuged test solution was increased. However, Ca^{2+}, Mg^{2+} interference eliminated by adding $H_2C_2O_4$.[15]

Ion-association Ratio. Figure5 shows the plot of the ΔI values versus $C_{BiI_4^-}/C_{drug}$. The association ratio of BiI_4^- and cetirizine hydrochloride is approximately 2:1.

Measurement of the Solubility Product Constant and K_{sp} of the Precipitate. The working curve for Bi^{3+} was obtained by using a series of BiI_4^- standard solutions and then the linear regression analysis was conducted to generate the equation of the line. The resulting equation gives $I = 0.3143C_{Bi} - 1.5525$, $r = 0.9988$. Cetirizine hydrochloride and the BiI_4^- standard solutions were added to a beaker at a 2:1 ratio of $C_{BiI_4^-}/C_{drug}$, allowing to form the precipitate. The precipitate was washed six times by aqueous solution of acetic acid (pH = 3). After the final wash, centrifuged and the clear upper liquid was removed for measuring emission spectra intensity, I, under the spectral line of Bi^{3+}, the concentration of BiI_4^- in the supernatant was cal-

Table 2. Data for interfering substances

interference	starch	glucose	stearic acid	dextrin	Ca^{2+}	Mg^{2+}	$C_2O_4^{2-}$
allowed maximum multiple	10	400	200	250	15	5	300

Table 3. Average measured concentration and % recovery of cetirizine hydrochloride samples (n = 5)

Sample	Labeled/mg	Measured/mg	Equivalent to the labeled amount /% ± S.D.	Added/mg	Measured/mg	Recovery/% ± S.D.
1[a]	1.00	1.02	102.0 ± 0.64	0.185	1.212	101.0 ± 0.33
2[b]	1.00	0.999	99.9 ± 0.55	0.185	1.182	99.1 ± 1.43
3[c]	1.00	0.992	99.2 ± 0.21	0.185	1.170	97.4 ± 0.024
4[d]	1.00	0.992	99.2 ± 0.38	0.185	1.177	97.5 ± 3.2

[a]Tablets from Suzhou Dawnrays Pharmaceutical Co., Ltd. Labeled amount, 10 mg/tablet. [b]Tablets from Kunshan Dragon Reddy Pharmaceutical Co., Ltd. Labeled amount, 10 mg/tablet. [c]Tablets from Chongqing Winbond Pharmaceutical Co., Ltd. Labeled amount, 5 mg/tablet. [d]Capsules from Zhuhai Phoenix Pharmaceutical Co., Ltd. Labeled amount, 10 mg/grain.

Table 4. Comparison of methods

method	Linear range/ug/mL	Recovery/%	RSD%	Reference
ICP-AES	27.7 - 184.8	98.8	0.30	This method
HPLC	5.1 - 102.4	99.9	0.80	[16]
RP-HPLC	1.25 - 10	98.4	0.53	[7]

culated against the working curve equation shown above. Finally, the K_{sp} value was calculated as 5.73×10^{-13} according to the formula $K_{sp} = [BiI_4^-]^2$ [drug] ([drug] = 1/2 [BiI_4^-]). The results indicate that the association complex is stable.

Analysis of Samples.

Pre-treatment of Sample: It is known from the specifications that the tablets of cetirizine hydrochloride contain magnesium stearate. The previous interference tests revealed that

Mg^{2+} had a significant influence on the determination of the cetirizine hydrochloride. Therefore, some $H_2C_2O_4$ must be added to eliminate the interference of Mg^{2+} during sample preparation.

Twenty tablets of cetirizine hydrochloride were accurately weighed and ground into powder. An amount of powder equivalent to 50 mg of cetirizine hydrochloride was weighed and added to a small beaker, added 0.2 g $H_2C_2O_4$, and some water, stirred well, then transferred to 100 mL volumetric flask with distilled water diluted to volume 100 mL. The solution was filtered to yield the filtrate for the following test.

Sample Concentration and Percentage of Recovery: 2.00 mL of sample solution and 4.00 mL of 2.00×10^{-3} mol·L^{-1} of BiI_4^- solution were added to a 10-mL volumetric flask, mixed and measured five times individually using the method. The concentration of cetirizine hydrochloride in the tablets and the percent recovery of a known quantity of cetirizine hydrochloride were determined. The concentration of cetirizine hydrochloride determined by the experimental method was compared to the given concentration stated by the manufacturer as determined by the methods in the pharmacopoeia. The experimental results are shown in Table 3.

Method' Comparison. This method compared with already known technique high performance liquid chromatography as shown in Table 4.

Table 4 shows that the reproducibility and accuracy of ICP-AES, HPLC and RP-HPLC is same, but HPLC and RP-HPLC more sensitive. Although high performance liquid chromatography is better sensitive, but this method is complex and determination of high cost. When cetirizine hydrochloride tablets was determined, because content is not too low, ICP-AES can be used instead of HPLC and RP-HPLC.

Conclusions

In this paper, based on the precipitation reaction of BiI_4^- anion and cetirizine hydrochloride, the concentration of cetirizine hydrochloride in real samples was determined indirectly by inductively coupled plasma atomic emission spectrometry. The optimal conditions for this method were developed experimentally as follows: pH of the solution to be ≤ 3.0, a reaction temperature of 20 °C, reaction time of 20 min, and the ratio of $C_{BiI_4^-}/C_{drug} = 2:1$.

The method used in these experiments has the following characteristics: an obvious reaction phenomenon, simple steps, low-cost, accurate results and the elimination of toxic solvents in the detection process. It is therefore safer and more environment-friendly compared to the current methods for analyzing cetirizine hydrochloride content. Most importantly, this method has extended the scope of applications for ICP-AES which has mainly been used for metallic, non-metallic element analysis only.

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