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Determination of promethazine hydrochloride and its preparations by highly accurate nephelometric titration

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Abstract

A highly accurate nephelometric titration for the determination of promethazine hydrochloride and its preparations was presented. The titration operating conditions were studied and the solubility product constant of promethazine tetraphenylboron precipitation was determined. The result of the titration is comparable to those of control experiments. The proposed method has been found to be accurate, precise, specific and linear.

Keywords: Highly accurate nephelometric titration; Promethazine hydrochloride; Sodium tetraphenylboron; Solubility product constant

1. Introduction

Titrimetry is often applied in analytical chemistry for its superior speed and simplicity with little sacrifice in accuracy and precision. Promethazine hydrochloride forms promethazine tetraphenylboron (PMH-TPB) collosol (in a strongly acidic medium (Chen, 1964)) or precipitation (in a weakly acidic medium (Yu and Meng, 2003)) quantitatively with sodium tetraphenylboron (Na-TPB). However, there is now no accurate method available to determine the titration end-point. So nonaqueous titration (Chinese Pharmacopoeia, 2000; United States Pharmacopoeia, 2000), potentiometric titration (British Pharmacopoeia, 2000; European Pharamacopoeia, 2002) and nonaqueous potentiometric titration (Japanese Pharmacopoeia, XIV) are often used under the circumstance. The instrumental method is generally not as accurate and precise as the titrimetry in macro analyses. Besides, the aprotic solvents are expensive, irritative and pollutional.

In the present paper, an accurate, rapid and simple method, highly accurate nephelometric titration (Zhan et al., 2004) was used for promethazine hydrochloride quantitation. In the titration, an internal nephelometric sensor was immersed in the titrate to monitor the change in the intensity of the scattered light dur-

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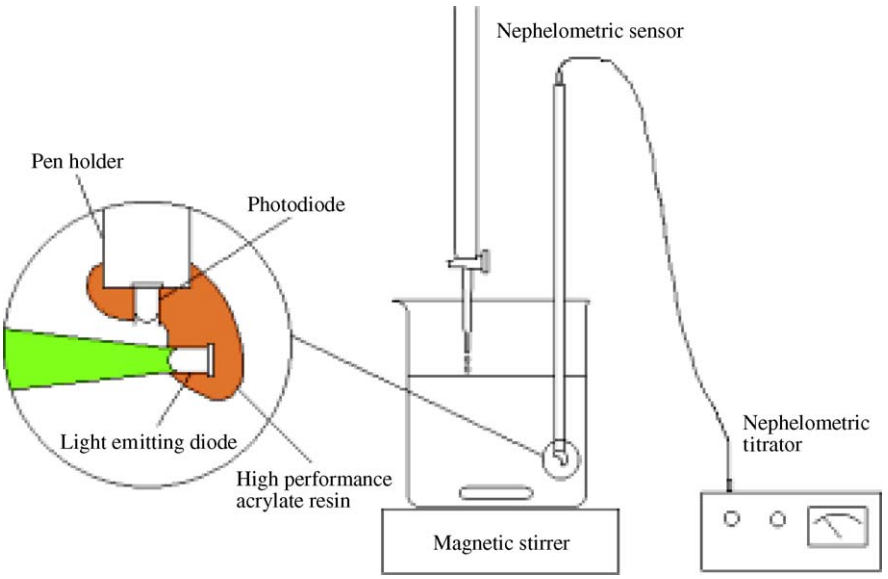


Fig. 1. The nephelometric sensor and the assembly of the nephelometric titrator.

ing the titration. After adding the first drop of the sodium tetraphenylboron solution, the promethazine hydrochloride solution became cloudy, and, as the titration continued, the scattered light detected increased gradually. If the solubility of the colloid were small enough, the scattered light would reach a maximum at the stoichiometric point (Zhan et al., 2004). As more titrant was added after passing the point, the solution would not become cloudier and the scattered light would not increase; on the contrary, the scattered light would decrease in intensity because of the dilution of the solution. A peak would appear at the stoichiometric point in the profile of relative intensity of scattered light versus the volume of titrant and therefore the end-point of the titration could be determined accurately.

Because the highly accurate nephelometric titration is based on a quantitative precipitation reaction and the accuracy as well as precision of the titration depends on the solubility of precipitation (Zhan et al., 2004), the composition and the solubility product constant of promethazine tetraphenylboron was determined by Job-Asmus method and the conductivity, respectively, in our experiment. The titration operating conditions were studied. The proposed method has been validated and found to be accurate, precise, specific and linear. This study has not been found in the literature.

2. Apparatus and materials

The nephelometric sensor and the assembly of the nephelometric titrator were self-made (Zhan et al., 2004) and shown in Fig. 1. A pH meter (pHS-3A, Chengdu Instruments Factory), a conductivity meter (DDB-6200, Shanghai Rex Xinjing Instruments Co. Ltd.) and a UV spectrophotometer (UV-2201, Shimadzu Co., Japan) were used.

Promethazine hydrochloride (Changzhou Jiangsu Wujin Pharmaceutical Factory), promethazine hydrochloride injection (50 mg/2ml) (Xi'an Pharmaceutical Co. Ltd.), promethazine hydrochloride tablets (25 mg/tablet) (Shanghai Jiufu Pharmaceutical Co. Ltd.; Changzhou Kangpu Pharmaceutical Co. Ltd.), sodium tetraphenylboron (standardized according to The Pharmacopoeia of the People's Republic of China) were used. The other reagents were all analytical grade.

3. Experiment

3.1. The composition of the promethazine tetraphenylboron (Chen and Zhao, 1993)

Two 0.02 mol l^{-1} stock solutions of promethazine hydrochloride and sodium tetraphenylboron were pre-

Table 1
The relationship between precipitation mass (m) and molar fraction of promethazine hydrochloride (X_{PMH})

V_{PMH} (ml)	0	5	10	15	20	25	30	35	40	45	50
$V_{Na\text{-}TPB}$ (ml)	50	45	40	35	30	25	20	15	10	5	0
X_{PMH}	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
m (g)	0.0000	0.0598	0.1206	0.1803	0.2415	0.3013	0.2405	0.1800	0.1203	0.0595	0.0000

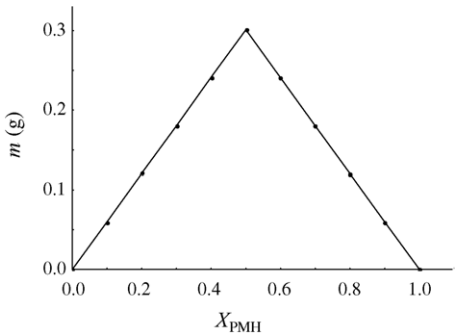


Fig. 2. The relationship between precipitation mass (m) and molar fraction of promethazine hydrochloride (X_{PMH}).

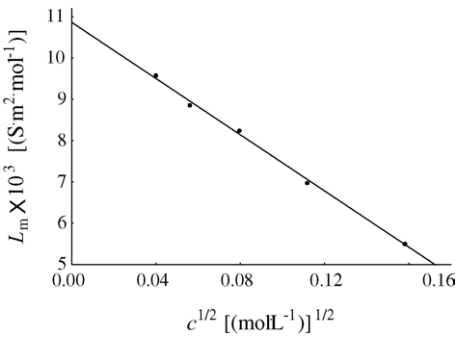
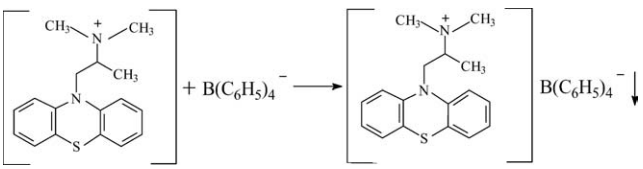


Fig. 3. The linear relationship between Λ_m and $c^{1/2}$ of promethazine hydrochloride solution.

pared. A series of mixtures containing a total volume of 50 ml of above stock solutions in different proportions were made up, and a 20 ml of 0.05 mol l^{-1} HAc-NaAc buffer solution (pH 5.3) was added to each of the mixtures. The precipitations were filtered, washed, dried to constant mass at 110 °C and weighted, respectively. The results are listed in Table 1. A straight line was obtained by plotting the precipitation mass versus molar fraction and is shown in Fig. 2. It is seen from Fig. 2 that the molar ratio of PMH:TPB is 1:1. Therefore, the reaction can be expressed as following:



3.2. Determination of the solubility product constant (K_{sp}) of precipitation promethazine tetraphenylboron (Hou and Zhan, 2003)

The conductivity κ depends on the number of charged carriers (ions) present. If the molar concentration is c, the molar conductivity is $\Lambda_m = \kappa/c$. Kohlrausch shows that the molar conductivities of dilute solutions at concentration c obeyed $\Lambda_m = \Lambda_{m,0} - Ac^{1/2}$, A is a coefficient. Promethazine hydrochloride solutions with five concentration levels were prepared directly with the standard substance. Their conductivity, κ was determined and converted to molar conductivity, Λ_m. According to $\Lambda_m = \Lambda_{m,0} - Ac^{1/2}$,a straight line was obtained by plotting Λ_m versus $c^{1/2}$ and is shown in Fig. 3.

The molar conductivity at infinite dilution of promethazine hydrochloride, $\Lambda_{m,0(PMH)} = 108.64 \times 10^{-4}$ S m^2 mol^{-1} was obtained from the intercept of the regression line in Fig. 3, and that of sodium tetraphenylboron, $\Lambda_{m,0(Na\text{-}TPB)} = 70.58 \times 10^{-4}$ S m^2 mol^{-1} by following the aforementioned method. Then those of chloride ion and sodium ion, $\Lambda_{m,0(Cl^-)} = 76.34 \times 10^{-4}$ S m^2 mol^{-1} and $\Lambda_{m,0(Na^+)} = 50.11 \times 10^{-4}$ S m^2 mol^{-1} were found in the literature (Hou and Zhan, 2003).

According to the law of independent migration of ions, the value of the molar conductivity of PMH-TPB

at infinite dilution, $\Lambda_{m,0(PMH\text{-}TPB)}$ was

$$\Lambda_{m,0(PMH-TPB)} = \Lambda_{m,0(PMH)} + \Lambda_{m,0(Na-TPB)} - \Lambda_{m,0(Cl^-)} - \Lambda_{m,0(Na^+)} = 5.277 \times 10^{-3}\,S\,m^2\,mol^{-1}$$

The conductivity of saturated PMH-TPB solution, κ_{sat} was determined to be $2.58 \times 10^{-4}\,S\,m^{-1}$ and that of the water used, $\kappa_{water} = 1.72 \times 10^{-4}\,S\,m^{-1}$. Therefore the solubility of PMH-TPB was

$$c_{sat} = \frac{\kappa_{PMH-TPB}}{\Lambda_{m,0}} = \frac{\kappa_{sat} - \kappa_{water}}{\Lambda_{m,0}} = \frac{2.58 \times 10^{-4} - 1.72 \times 10^{-4}}{5.277 \times 10^{-3}}\,mol/m^3 = 1.63 \times 10^{-5}\,mol\,l^{-1}$$

And so the solubility product constant was

$$K_{sp} = c_{sat}^2 = 2.66 \times 10^{-10}$$

It was reported (Zhan et al., 2004) that the peak would be sharp enough to accurately determine the endpoint when $K_{sp} < 10^{-10}$.

3.3. Optimizing the solvent

Because promethazine hydrochloride forms promethazine tetraphenylboron (PMH-TPB) collosol quantitatively with sodium tetraphenylboron (Na-TPB) in a strongly acidic medium (Chen, 1964), hydrochloric acid solution was used as the solvent in our titration. The influence of the concentration of hydrochloric acid solution on the sharpness of the titration curve was studied.

Table 2
Influence of the concentration of 0.1 mol l^{-1} HCl solution on the titration error

V_{HCl} (ml)	Content of PMH (%)
5	99.28 ± 0.47[a]
10	99.30 ± 0.26
20	99.43 ± 0.12
30	99.55 ± 0.13
50	99.64 ± 0.15
100	99.68 ± 0.18

[a] Average of three determinations ± standard deviation.

Six exact amounts of approximately 0.2 g of promethazine hydrochloride were weighed and transferred into six 100 ml volumetric flasks, and 5 ml, 10 ml, 20 ml, 30 ml, 50 ml and 100 ml of 0.1 mol l^{-1} hydrochloric acid solution were added, respectively. The content was diluted to the mark with water and mixed. From the six volumetric flasks, an exact amount of 25 ml of the solution was transferred into a 100 ml beaker, respectively. Five milliliters of 0.5% polyvinylpyrrolidone (PVP) solution was added as a colloid stabilizer, and then titration was made with 0.01 mol l^{-1} sodium tetraphenylboron solution. The volume of the titrant and the relative intensity of the scattered light both were recorded.

The results are listed in Table 2 and the titration curves of 5 ml, 20 ml hydrochloric acid solution are illustrated in Fig. 4. It is seen that when the volume of 0.1 mol l^{-1} hydrochloric acid solution added is ≥20 ml, the peaks in the curves are sharp, and a relative error as well as deviation is within 0.2%. So in the proposed

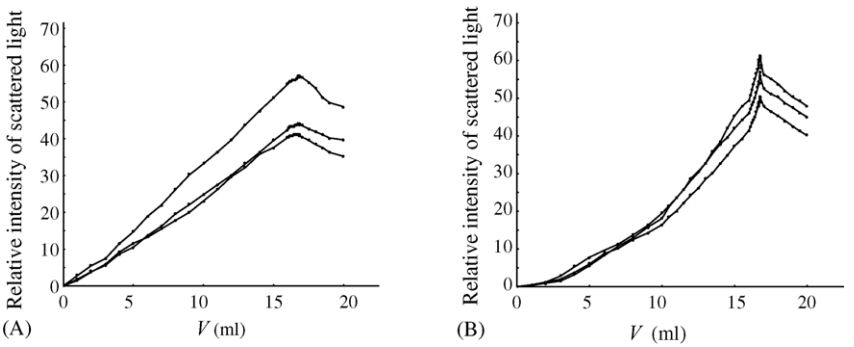


Fig. 4. Influence of the concentration of 0.1 mol l^{-1} HCl solution on the sharpness of the titration curves: (A) 5 ml; (B) 20 ml HCl solution was added in promethazine hydrochloride solution.

Table 3
Capability of the colloid stabilizers to protect PMH-TPB colloid

c (%)	$V_{Dextrin}$ (ml)				V_{PVP} (ml)			
	2	5	10	15	2	5	10	15
0.5	+	+	+	+	+	–	–	–
1	+	+	+	+	–	–	–	–
2	+	+	–	–	–	–	–	–

(+) Colloid coagulated; (–) colloid uncoagulated.

Table 4
Influence of the amount of 0.5% polyvinylpyrrolidone (PVP) on the titration error

V_{PVP} (ml)	Content of PMH (%)
2	99.16 ± 0.50[a]
5	99.51 ± 0.11
10	99.24 ± 0.14
15	99.06 ± 0.14

[a] Average of three determinations ± standard deviation.

procedure, 20 ml of hydrochloric acid solution is added in 100 ml promethazine hydrochloride solution.

3.4. Optimizing the colloid stabilizer

The scattered light detected was unstable for promethazine tetraphenylboron colloid coagulating during the titration, thus a colloid stabilizer was added. To assess the protective capability of the colloid stabilizers, different amounts of polyvinylpyrrolidone and dextrin solutions were added in each 25 ml of 0.0062 mol l^{-1} promethazine hydrochloride solution, and then 0.01 mol l^{-1} sodium tetraphenylboron solution was added slowly, respectively. Table 2 shows the coagulation of the promethazine tetraphenylboron colloid. It is seen that 5 ml of 0.5% or more polyvinylpyrrolidone solution protects the colloid effectively and therefore the polyvinylpyrrolidone solution is used as the colloid stabilizer in our experiment (Table 3).

To study the influence of the amount of polyvinylpyrrolidone on the determined results, 2 ml, 5 ml and 10 ml of 0.5% polyvinylpyrrolidone solution were added in each 25 ml of 0.0062 mol l^{-1} promethazine hydrochloride solution, respectively, the titration was made with 0.01 mol l^{-1} sodium tetraphenylboron solution. The results are summarized in Table 4. It was observed that the amount of polyvinylpyrrolidone solution affected the precision insignificantly. So in the proposed procedure, an amount of 5 ml of 0.5% polyvinylpyrrolidone solution was used.

3.5. Optimizing titration concentration

It was reported (Zhan et al., 2004) that the titration error depends on the sharpness of the peak in the titration curve and the sharpness is related to the concentration of the solutions. To study the influence of the concentration on the sharpness of the peak and the titration error, promethazine hydrochloride solutions with six different concentrations (1.3×10^{-2} mol l^{-1}, 6.2×10^{-3} mol l^{-1}, 3.1×10^{-3} mol l^{-1}, 1.6×10^{-3} mol l^{-1}, and 7.8×10^{-4} mol l^{-1}) were prepared and titrated with sodium tetraphenylboron solutions with the approximate concentrations as the promethazine hydrochloride solutions, respectively. The volume of the titrant and the relative intensity of the scattered

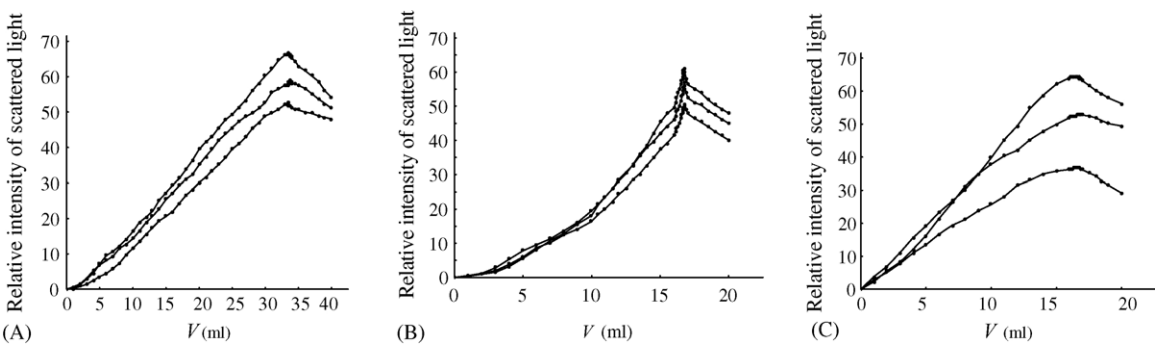


Fig. 5. Effect of the concentration on the sharpness of the peak in titration curve: (A) 2.5×10^{-2} mol l^{-1}; (B) 6.2×10^{-3} mol l^{-1}; (C) 7.8×10^{-4} mol l^{-1}.

Table 5
Influence of the concentration of on the titration error

C_{PMH} (mol l^{-1})	Content of PMH (%)
2.5×10^{-2}	99.31 ± 0.39[a]
1.3×10^{-2}	99.53 ± 0.18
6.2×10^{-3}	99.51 ± 0.12
3.1×10^{-3}	99.35 ± 0.15
1.6×10^{-3}	98.42 ± 0.83
7.8×10^{-4}	98.23 ± 1.08
3.9×10^{-4}	PMH could not be titrated for the unobvious change in turbidity

[a] Average of three determinations ± standard deviation.

light both were recorded. The titration curves are illustrated in Fig. 5 and the results are listed in Table 5. It was seen that the sharpness of the peak in titration curves depends on the concentration of the solutions, and the optimum titration concentration leading to a minimum error was 0.006 mol l^{-1}.

4. The proposed procedure

4.1. Promethazine hydrochloride

4.1.1. Assay

Transfer approximately 0.2 g of promethazine hydrochloride, accurately weighted, to a 100 ml volumetric flask, add 20 ml of 0.1 mol l^{-1} HCl solution and swirl to dissolve, dilute with water to volume, and mix. Transfer accurately 25 ml of the previous promethazine hydrochloride solution to a 50 ml beaker, add 5 ml of 0.5% polyvinylpyrrolidone solution, place the beaker on a magnetic stirrer, immerse the nephelometric sensor in the beaker, and titrate with 0.01 mol l^{-1} sodium tetraphenylboron solution. Record both the volume of the titrant and the relative intensity of the scattered light. Determine the end-point by the peak in the profile of relative intensity of scattered light versus the volume of titrant. Each ml of 0.01 mol l^{-1} sodium tetraphenylboron is equivalent to 3.2089 mg $C_{17}H_{20}N_2S{\cdot}HCl$.

4.1.2. Accuracy and precision

The accuracy here is the closeness of the measured value of highly accurate nephelometric titration to those of the control experiments for promethazine hydrochloride. The results of promethazine hydrochloride determined by the proposed method and by the control experiments are summarized in Table 6. Statistical analysis of the mean values using the Student's *F*-test and *t*-test (Sun, 2002) at 95% confidence interval was performed. All *F* values were less than the *F* critical ($F_{0.05,5.5} = 5.05$) and all *t* values were less than the *t* critical ($t_{0.05,10} = 2.228$). The results indicate that there was no significant difference in the mean values between highly accurate nephelometric titration and the control experiments.

Table 6
Accuracy and precision of assay methods of the promethazine hydrochloride

Methods	Content of PMH (%)	*F*-test	*t*-test
Highly accurate nephelometric titration	99.50 ± 0.10[a]		
Nonaqueous titration (CHP2000)	99.45 ± 0.11	1.03	0.83
Nonaqueous titration (USP24)	99.48 ± 0.10	1.01	0.34
Potentiometric titration	99.43 ± 0.12	1.38	1.08
Nonaqueous potentiometric titration	99.55 ± 0.11	1.15	0.81

[a] Average of six determinations ± standard deviation.

4.1.3. Linearity

The linearity study verified that the sample solutions were in a concentration range where analyte response was linearly proportional to concentration. The degree of linearity was assessed by the correlation coefficient, intercept and slope. This study was performed by preparing standard Promethazine Hydrochloride solutions at seven concentration levels from 0.0030 to 0.0095 mol l^{-1} (50–150% of assay level) and determined their concentrations by highly accurate nephelometric titration. Each point was analyzed three times. The determined concentration and the actual result were subjected to least-squares linear regression analysis to calculate the regression equation and the correlation coefficient. The linearity regression equation obtained was $c_{\text{determined}} = -0.00012 + 0.9942\ c_{\text{actual}}$, and the correlation coefficient was 0.9999. The regression line is shown in Fig. 6. The result indicates that there was an excellent correlation between the determined and the actual concentration in the range tested.

4.2. Promethazine hydrochloride injection

4.2.1. Assay

Transfer an accurately measured volume of promethazine hydrochloride injection, equivalent to about 500 mg promethazine hydrochloride, to a 250 ml vol-

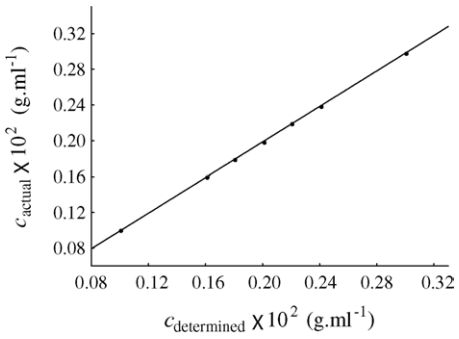


Fig. 6. The regression line of highly accurate nephelometric titration.

umetric flask, add 50 ml of 0.1 mol l^{-1} HCl solution, dilute with water to volume, and mix. Transfer 25.0 ml of the resulting solution to a 50 ml beaker, proceed as directed under Section 4.1.1, beginning with "add 5 ml of 0.5% polyvinylpyrrolidone solution". Caculate the assay of labeled claim of promethazine hydrochloride ($C_{17}H_{20}N_2S{\cdot}HCl$).

The results of promethazine hydrochloride injection determined by the proposed method and by the control experiments are summarized in Table 7.

4.2.2. Recovery

The formulas of the injection (Gu, 1983) are as follows:

Ampoule	
Ingredients	
Promethazine hydrochloride (g)	25
Sodium hydrogen sulfite (g)	1
Anhydrous sodium sulfite (g)	1
Sodium chloride (g)	6
Ascorbic acid (g)	2
Water for injection (ml) q.s.ad	1000

Table 8
The recovery of promethazine hydrochloride in 25.0 ml of the resulting solution

Added (mg)	Found (mg)	Recovery (%)
40.16	39.82 ± 0.08[a]	99.15 ± 0.19[a]
50.02	49.94 ± 0.06	99.84 ± 0.12
60.00	59.54 ± 0.05	99.24 ± 0.08

[a] Average of three determinations ± standard deviation.

Weigh accurately 20 g, 25 g, 30 g of promethazine hydrochloride (80%, 100%, and 120% of the formula amount) and other ingredients of the injection, make up three injection samples. Transfer 25.0 ml of each of the resulting solutions to three 50 ml beakers, respectively, proceed as directed under Section 4.1.1, beginning with "add 5 ml of 0.5% polyvinylpyrrolidone solution". Caculate the recovery. The results are summarized in Table 8.

4.3. Promethazine hydrochloride tablets

4.3.1. Assay

Weigh and finely powder not less than 20 tablets. Transfer an accurately weighted portion of the powder, equivalent to about 200 mg of promethazine hydrochloride, to a 100 ml volumetric flask, add 20 ml of 0.1 mol l^{-1} HCl solution and shake for 15 min, dilute with water to volume, and mix, filter the mixture through quantitative slow-filter. Transfer 25.0 ml of the subsequent filtrate to a 50 ml beaker, proceed as directed under Section 4.1.1, beginning with "add 5 ml of 0.5% polyvinylpyrrolidone solution". Caculate the assay of labeled claim of promethazine hydrochloride ($C_{17}H_{20}N_2S{\cdot}HCl$).

The results of promethazine hydrochloride tablets determined by the proposed method and by the control experiments are summarized in Table 9.

Table 7
Accuracy and precision of assay methods of promethazine hydrochloride injection

Sample number	Assay, percent of labeled claim		*F*-test	*t*-test
	Highly accurate nephelometric titration	Ultraviolet spectrophotometric method		
1	100.48 ± 0.09[a]	100.58 ± 0.08	1.13	2.10
2	100.25 ± 0.07	100.22 ± 0.04	3.15	0.91
3	100.43 ± 0.09	100.50 ± 0.10	1.17	1.32
4	100.74 ± 0.13	100.78 ± 0.13	1.12	0.53
5	98.70 ± 0.10	98.73 ± 0.05	3.83	0.62

[a] Average of six determinations ± standard deviation.

Table 9
Accuracy and precision of assay methods of promethazine hydrochloride tablets

Sample number	Assay, percent of labeled claim		*F*-test	*t*-test
	Highly accurate nephelometric titration	Ultraviolet spectrophotometric method		
1	100.94 ± 0.17[a]	101.07 ± 0.16	1.13	1.33
2	93.53 ± 0.18	93.63 ± 0.16	1.25	1.02
3	99.68 ± 0.16	99.84 ± 0.15	1.10	1.79

[a] Average of six determinations ± standard deviation.

Table 10
The recovery of promethazine hydrochloride in 25.0 ml of the subsequent filtrates

Sample number	Added (mg)	Found (mg)	Recovery (%)
1	40.10	40.09 ± 0.12[a]	99.97 ± 0.27[a]
2	49.92	49.58 ± 0.08	99.32 ± 0.15
3	59.97	59.10 ± 0.18	98.55 ± 0.26
4	39.98	40.06 ± 0.16	100.20 ± 0.27
5	49.85	49.55 ± 0.12	99.40 ± 0.24
6	59.93	59.01 ± 0.16	98.46 ± 0.27
7	39.78	39.81 ± 0.14	100.08 ± 0.35
8	50.03	49.69 ± 0.11	99.32 ± 0.22
9	59.80	58.99 ± 0.18	98.64 ± 0.21

[a] Average of three determinations ± standard deviation.

4.3.2. Recovery

Weigh and finely powder not less than 20 tablets. Transfer three accurately weighted portions of the powder, each equivalent to about 200 mg of promethazine hydrochloride, to three 100 ml volumetric flasks, respectively. Add accurately 160 mg, 200 mg, and 240 mg of promethazine hydrochloride to each flask, respectively. Then add 20 ml of 0.1 mol l^{-1} HCl solution, shake for 15 min, dilute with water to volume, mix, and filter the mixtures through quantitative slow-filter. Transfer 25.0 ml of each of the subsequent filtrates to three 50 ml beakers, respectively, proceed as directed under Section 4.1.1, beginning with "add 5 ml of 0.5% polyvinylpyrrolidone solution". Caculate the recovery. The results are summarized in Table 10.

5. Conclusion

An accurate, rapid and simple method, highly accurate nephelometric titration has been described and validated for quantitative determination of promethazine hydrochloride. Acceptable assay precision and accuracy were obtained at the analytical concentration, and excellent linearity was achieved over a range of 0.003–0.0095 mol l^{-1}. In addition, specificity result indicated that there was no interference from the degradation products.

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