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The Precise of The End Point Titration for Determination of Ammonium Chloride by Argentometry Method

Penentuan Titik Akhir Titrasi yang Tepat untuk Penentuan Kadar Amonium Klorida

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ABSTRACT

The end point titration is very important to obtain the accurate analysis. No reference was found related with the end point titration of Mohr's method. In other hand, the quality of drug is important to ensure efficacy and safety. One of requirement is the contain of the drug. Instability of a drug product related with a decreasing in the quality of the drug in term loss of drug efficacy and may be become toxic. Black Cough Syrup is one of famous cough medicine, in Indonesia called Obat Batuk Hitam (OBH). One of the active substances in OBH is ammonium chloride. The determination of titration point in argentometry should be considered appropriately. The study aims were to determine the exact end point of titration and the levels of ammonium chloride in OBH of 3 preparations available in the market and determine the end point titration. NH_4Cl levels were determined using the argentometric titration method. The percentage of ammonium chloride in samples A, B and C were 96.84±1.07, 93.57±1.10, and 97.10±1.10%, respectively. Ammonium chloride levels in all samples fulfill the requirements of official pharmacopeia. The titration point was at once the changing of solution color from pale yellow into reddish brown.

Key words: cough, ammonium chloride, argentometry.

INTRODUCTION

Coughing is a physiological reflex. It is useful for expelling and cleaning the respiratory tract from sputum, dust, inhaled foreign stimulant substances, foreign particles and infectious agents (Tjay & Kirana, 2013). Coughing is defined as an effort to defend the lungs in the face of various stimuli and also as an effort or action of the lungs to clear the respiratory tract. Coughing is a symptom of a disease in or outside the lungs and is sometimes the first symptom of the disease. Cough is the most common symptom of respiratory disease and a problem that doctors often find in daily practice (Tamaweol et al., 2016).

Cough can be treated in various ways, one of which is by administering cough relievers. An example of a cough medicine in syrup form is Black Cough Medicine (BCM). BCM is a cough medicine that is included in the expectorant class for productive coughs which can help expel sputum from the respiratory tract as well as to melt down the sputum (Yazia et al., 2019).

Verifying drug quality is very important to make sure the efficacy and safety of the medicine. According to the Indonesian Pharmacopoeia fifth edition of 2014, the quality requirements for finished drugs should fulfill the levels of efficacious substances and drug stability. Drug stability can be stated from the decrease in the levels of efficacious substances in the dosage form during storage until the expiration date (Gandjar & Rohman, 2012). Instability of a drug product can result in a decrease in the quality of the drug with the loss of medicinal properties and becoming toxic or toxic.

The active pharmaceutical ingredients in BCM are ammonium chloride, succus liquiritiae and SASA (Solutio Ammonia Spirittuosa Anissata). Determination of ammonium chloride content in the BCM dosage form is very important for product quality evaluation before and during the production process, final product to be consumed by the patients. Based on the Indonesian Pharmacopoeia 2014, the determination of ammonium chloride levels can be carried out by argentometric titration (Kuntari et al., 2018).

Khusnu & Dimas (2021) reported that the level of ammonium chloride in the samples of cold and cough syrup determined argentometrically using a potentiometer was 108.56%. The level was fulfilled the Indonesian Pharmacopoeia Edition IV 1995. The amount level of active substance in the dosage form is not less than 90% and not more than 110% (Rosalina, 2018).

Sezey and Adun (2019) had performed a study in term of validation of Mohr's argentometry titration method. But the researchers did not mention the end point titration exactly. It can cause uncertainty in analytical. Uncertainty arises not only from random errors in the analysis such as short-term deviations in temperature, relative humidity and power source variations, from systematic errors such as wrong solvent use, changes in instrumental calibrations but also related with the end point of titration. Endpoint of Mohr's Method titration is accomplished when the reddish brown colour remains stable, does not dissipate with stirring. Chlorine anions are more reactive than CrO42-, cause of that the argentum kations react with Cl– ions firstly to produce a white precipitate before reacting with CrO42–.

Determination of the end point of the Mohr argentometry titration method, based on the reference, is when a pink precipitate and/or the pale red-brown color appears that should remain constant for 30 seconds. The appearance of a precipitate means that there has been an excess of the titer solution and exceeds the solubility product of the compounds resulting from the reaction. It can be explained from the recovery of NaCl added to the distilled water. They found that the recovery of NaCl were salt recoveries from fortified pure water changed from 101 to 121%, an exceed value. To know exactly when the real end point of the titration, it is necessary to study the determination of the end point.

Based on the above information, it is quite interesting for researchers to determine the level the ammonium chloride content in BCM by argentometry and to study the real end point of titration. Argentometric titration is a quantitative analysis based on precipitation reactions. In this study, the argentometric titration method chosen was the Mohr method because it is a simple, fast, and easy method.

METHOD

Equipment and Materials

The equipment used in this study were analytical balance, pH meter, and glassware that usual used in laboratory.

The materials used were AgNO3, NaCl, NH4Cl and K2CrO4 distilled water, Black Cough Medicine (OBH) brands A, B and C. The batch number and expire date of the BCM brands A, B, and C were IVO1S2/September 2025, 2022004/Jully 2025, and 210209/Oktober 2026, respectively.

Benchmark Test for Determination of End Points

The determination of ammonium chloride was performed for evaluation of the end point of titration following Mohr's Method. 100 mg of ammonium chloride was placed into a 250 mL beaker glass, added with 10 mL of distilled water and stirred until dissolved, added with distilled water up to the mark and homogenized. Five mL of solution was pipetted, poured into a 250 mL Erlenmeyer flask and added with 10 mL of distilled water. 0.5 mL of 5% K2CrO4 solution as

an indicator was added to the solution, and titrated with 0.1 N AgNO3 solution. The volume of 0.1 N AgNO3 needed in the titration was recorded (n=5) (Kuntari et al., 2018).

$NaCl + AgNO_3 \rightarrow NaNO_3 + AgCl$ (↓white) Ksp 1.6 x 10^{-10}.

$2Ag+ + CrO_42- \rightarrow Ag_2CrO_4$ (↓reddish brown) Ksp 1.1 x 10^{-12}.

Evaluation of Accuracy and Precision of Mohr's Titration Method

The data of the determination of ammonium chloride recovery was evaluated for accuracy and precision of method analysis.

Preparation of 0.1 N AgNO3 standard solution

A total of 4.25 grams of AgNO3 was weighed and put into a 250 mL beaker glass, added with 10 mL of distilled water and stirred until dissolved, added with distilled water up to the mark and homogenized (Kuntari et al., 2018).

Standardization of 0.1 N AgNO3 Solution

The standardization of AgNO3 solution was performed using Mohr's Method of Precipitation Titration. A total of 0.292 grams of NaCl was put into a 250 mL beaker glass, added with 10 mL of distilled water, and stirred until dissolved added with distilled water up to the mark and homogenized. 25 mL of the solution was pipetted, placed into a 250 mL Erlenmeyer flask, added with 0.5 mL of 5% K2CrO4 solution. The solution was immediately titrated with standard solution 0.1 N AgNO3, and was stopped if a yellow to reddish brown color changed. The volume of 0.1N AgNO3 solution required for the titration was recorded (n=3) (Kuntari et al., 2018).

Determination of Ammonium Chloride Levels in BCM Samples

Five mL of BCM sample was placed into a 50 mL volumetric flask, added with distilled water up to the mark and homogenized. Five mL of solution was pipetted, put it into a 250 mL Erlenmeyer flask and add 10 mL of distilled water. Then, 0.5 mL of 5% K2CrO4 solution was added and titrated with 0.1 N AgNO3. The volume of 0.1 N AgNO3 needed in the titration was recorded (n=3) (Kuntari et al., 2018).

RESULTS AND DISCUSSION

Benchmark Test for Determination of End Points

The recovery of ammonium chloride obtained from standard solution were 100,05 ± 0,604%. This finding was not in accordance with Sezey and Adun (2015). The researchers reported that the recovery of sodium chloride from fortified pure water changed from 101 to 121%, an exceed value. It can be caused by in-appropriate determination of the end point of titration. To avoid the uncertainty result it is better to very slow titration after precipitation of AgCl occurs. The titration solution was dropped in small amount steeply following by rinsing using distilled water to the point of burette. Once the changing of color solution into reddish brown, wait for 30 seconds and stop the titration soonest.

Chloride ions of ammonium chloride could be determined using the Mohr Argentometric Method. Sodium or potassium chromate (Na2CrO4 or K2CrO4) serves as the indicator, cause of silver ions can react with chromate to form the brick-red silver chromate (Ag_2CrO_4) precipitate at the end point region. The Mohr method should be carried out at pH 7-10. At low pH, the concentration of the chromate ion in the acidic solutions is quite low that it can not form a precipitate with Ag+ at the end point. Because in acidic solutions CrO_42- is transformed to $Cr_2O_72^-$ (chromate ion is conjugated base of chromic acid). At high pH, the silver ions can be reacted with OH- ions to

produced Ag(OH). Ag(OH) is a weak alkaline that can be broken down into Ag_2O precipitate. The titration in this experiment was performed at pH of 7 to 8, the suitable pH for Mohr Method Argentometric Titration. The precipitation of Ag_2CrO_4 is produced and no Ag_2O black precipitate occurred.

Evaluation of Accuracy and Precision of Mohr's Titration Method

Table 1. The Recovery, Accuracy and Precision of Ammonium Chloride Titration

Titration	Volume of 0.1N $AgNO_3$ (mL)	Contents of NH_4Cl (mg)	Mean ± SD	% RSD
1	1.900	100.63		
2	1.900	100.63		
3	1.890	100.10	100,05± 0,604	0,604
4	1.880	99.57		
5	1.875	99.31		

Standardization of 0.1N AgNO3

The real normality of the 0,1N AgNO3 solution after standardization were 0,099 N ± 0,0005 (RSD = 0.505). The end point of titration wase stated based on the observation of benchmark test for its determination. The 0.1 N AgNO3 standard solution was freshly prepared using the substance weighed accurately. AgNO3 solution is a secondary standard solution whose concentration in term of purity and stability cannot be directly determined in the process of weighing, dissolving and storage. Therefore, the concentration was determined by standardization. Standardization is a process when the concentration of a secondary standard solution is determined precisely by titration using a primary standard solution. Standardization of the AgNO3 solution in this study used NaCl. NaCl is a salt that can react with AgNO3 to form AgCl precipitate which is difficult to dissolve and has a high degree of purity, is stable in heating and dissolves easily in water cause of that NaCl can be used for standardizing of AgNO3 solutions.

Sezey and Adun (2019) found the mean recoveries for three samples were 105±4.0, 106±4.0, and 111±5%, respectively. Their results were different with our finding (see Table 1). The end point occurs or the precipitate will be available after the more silver nitrate solution added. In other hand, at the real end titration no precipitation occurs, but only the changing of solution color from yellow (Fig 1A) into white pale yellow (Fig. 1B), and following the reddish-brown color (Fig. 1C). The precipitation occurs after centrifugation of the solution. It will take time and the results trend to be over titration. The end of titration stated as the color stable after 30 seconds only also may invite the error because if the reddish-brown color is unstable, and the titration should be continued. In this condition, the silver nitrate solution will also more used. Base on this discussion, it was proposed that after yellow pail color occurs the titration will continue slowly using small amount of silver nitrate solution at the tip of burette and rinse with distilled water. The end point titration is stated, once the reddish-brown color occurred (Fig. 1D).

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(A) (B) (C) (D)

Figure 1. (A) The initial color of sample solution, before titration, (B) The color was changed to white pale yellow before reaching the end point, (C) Once the color of solution was changed to reddish brown color stable for 30 seconds stated as end point of titration because of Ag_2CrO_4 precipitate formed. (D) The exceed of silver chromate occurred.

Table 2. Standardization of 0.1 N AgNO3 Solution

Standardization of 0.1 N $AgNO_3$ Solution				
Titration	Volume $AgNO_3$ 0.1 N (mL)	Concentration of $AgNO_3$ Solution (N)	Mean	% RSD
1	12.70	0.0984	0.099 ± 0.0005	0.505
2	12.68	0.0986		
3	12.65	0.0988		

AgNO3 solution is a secondary standard solution. The real concentration of the solution will be changed time to time. The solution is unstable. Therefore, the concentration should be determined by standardization. Standardization is a process when the concentration of a secondary standard solution is determined precisely by titration using a primary standard solution. At alkaline environment, AgNO3 can be precipitated to form Ag_2CO_3. At neutral pH AgNO3 can be reacted with H_2CO_3 to form the precipitate of Ag_2CO3. H2CO3 is a weak acid produced from CO2 in the air react with water. The $AgNO_3$ solution was standardized using NaCl solution as a primary standard. NaCl can react with AgNO3 to form AgCl precipitate which is difficult to dissolve. In other hand, it is high purity, stable, and dissolves in water easily, so that NaCl can be used to standardize AgNO3 solution.

Table 2. The Concentration of Ammonium Chloride in Black Cough Medicine

Sample	Concentration of NH4Cl (%)			Mean	% RSD
	Titration 1	Titration 2	Titration 3		
A	97.985	96.661	95.867	96.84±1.070	1,105
B	94.807	93.218	92.689	93.57±1.102	1,178
C	97.985	97.456	95.867	97.10±1.102	1,135

The concentration of ammonium chloride in Black Cough Medicine produced by pharmaceutical industries A, B, and C were 96.84±1.070, 93.57±1.102, and 97.10±1.102%, respectively. the requirements for nutritious substance levels of 90-110%. These findings were fulfilled the requirement of Pharmacopeia Indonesia. The concentration of ammonium chloride in BCM should be at range of 90-110%. The percentage of RSD results for samples A, B and C were 1.105, 1.178, and 1.135%, respectively. The permitted RSD value is less than 2% (Rivai et al., 2018). So it can be stated that the results have met the acceptance requirements.

CONCLUSION

It can be concluded that, the end point of the Mohr's Argentometry titration stated once the reddish-brown color changing from white pale yellow occurs after the slowly titration. The concentration of Black Cough Syrup A, B, and C were 96.84±1.070, 93.57±1.102, and 97.10±1.102, respectively. Its were full filled the requirement of Pharmacopeia of Indonesia.

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