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Determination of Tin in Trityl Candesartan by UV-VIS Spectrophotometer Using Phenylfluorone

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Abstract: Trityl Candesartan (TCand), a benzimidazole derivative, is widely used in the preparation of Candesartan Cilexitil, a pharmaceutical prodrug created to treat hypertension and to help lower blood pressure. One major concern in the preparation process is the usage of tin compounds, specifically tributyl tin oxide, which can cause harm to both human and environmental health. In this study, UV-VIS Spectrophotometry was used for the simple and accurate determination of tin (Sn) in Trityl Candesartan. The study of Sn in Trityl Candesartan found the Sn content to be within the limit of 10 mg/Kg, with a correlation coefficient (R^2) of 0.9929, average percent recovery (%R) of 96.0%, and relative percentage difference (%RPD) of 0.35%.

Keywords: Trityl Candesartan, Tin, UV-VIS Spectrophotometer, Phenylflourone

1. Introduction

Candesartan is an angiotensin II receptor antagonist which works by relaxing blood vessels so that blood can flow easily. It is used as a first line agent to treat uncomplicated hypertension. Using this chemical hormone, the pharmaceutical industry has synthesized Trityl Candesartan (TCand), a benzimidazole derivative used either alone or in combination with other antihypertensive agents to help lower blood pressure [1]. The molecular structure of Trityl Candesartan is shown in figure 1, and chemical details are displayed in Table 1 [2, 3]. TCand is able to be more than 99% bound to plasma proteins in the blood; since it is well-known for its high purity, optimum quality and reliability, TCand is a key intermediate in the synthesis of the prodrug Candesartan Cilexetil [4].

Table 1. *Details of Trityl Candesartan [3].*

Chemical name:	2-ethoxy-1-((2'-(1-trityl-1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl) methyl)-1H-benzo[d]imidazole-7-carboxylic acid
Molecular formula:	$C_{43}H_{34}N_6O_3$
Appearance:	White or off-white crystalline pharmaceutical chemical powder
Molecular weight:	628.77 g/mol
Density:	1.26 g/cm^3
Flash point:	503.3°C
Boiling point:	908.6°C at 760 mmHg
Melting point:	162-165°C
Solubility:	Slightly soluble in alcohol and methylene chloride; partially insoluble in water

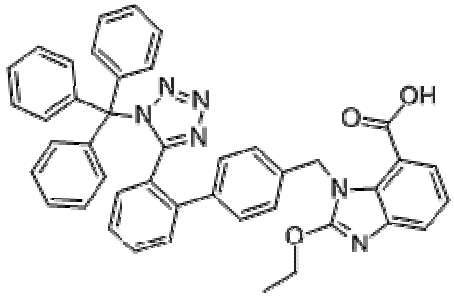

Figure 1. *Chemical structure of Trityl Candesartan [2].*

Due to the versatility of TCand, it is becoming increasingly important to monitor the effects on public health

and safety. One concern is the use of tin, or specifically tributyl tin oxide in the synthesis of TCand [5]. Tin and organotin compounds can interfere with neurotransmitters in the body, causing neurological problems, as well as affecting the gastrointestinal, respiratory, and immune systems [6]. Furthermore, tin absorbed from the stomach may interfere with the absorption of other minerals and nutrients, such as zinc [7]. Tin and tin compounds pose a threat not only to human health, but to environmental health as well. Due to their physico-chemical properties, tributyl tin compounds are especially toxic even at low concentrations in the water. Tin compounds can accumulate on the surface and in sediments, which causes harm to aquatic organisms and animal populations [8]. For these reasons, the content of tin must comply within the limits of 10 mg/Kg in order to preserve public and environmental health and safety.

2. Materials and Method

2.1. Instrumentation

The absorbance spectra for all measurements were carried out using a Shimadzu 1601 PC double beam UV-VIS Spectrophotometer, with 1 cm quartz cells and 2.0 nm fixed slit width. The spectrophotometer was connected to a computer, loaded with Shimadzu UVPC software, and equipped with an Epson LQ-850 printer.

2.2. Reagents and Test Solutions

Trityl candesartan: samples were obtained from Gensynth Fine Chemicals (P) Ltd. Andhra Pradesh India.

Sulfuric acid, H_2SO_4: Fisher Chemicals, Trade metal grade, Lot# 3112052

Nitric acid, HNO_3: J. T. Baker ACS reagent, Lot# EO2056, concentration: 69-70%.

Hydrochloric acid, HCl: Pharmco-Aaper, ACS reagent grade, Lot# PB006406HAG

Potassium permanganate, $KMnO_4$: Fisher Chemical certified ACS, 99.4%. Lot # 1660888

Bromocresol green: Sigma-Aldrich, ACS reagent, dry content: 95.0%, Lot# MKBX0150V

Citric acid monohydrate, $C_6H_8O_7 \cdot H_2O$: Sigma-Aldrich, ACS reagent, 99.0%, CAS# 5949- 29-1

L-Ascorbic acid, $C_6H_8O_6$: Sigma-Aldrich, ACS reagent, ≥99%, Vitamin C

Polyvinyl alcohol: Sigma-Aldrich, 99.0%, CAS# 9002-89-5

Standard Tin Solution: VHG-AASNH-500, Tin AA Standard Sn @ 1000 µg/mL in 20% HCl. CAS# 7440-31-5

Bromocresol green TS: Dissolved 0.05 g of bromocresol green in 100 mL of ethanol (95%) and filtered when necessary.

Ammonia solution, NH4OH: Sigma-Aldrich, 28.0-30.0% NH3 basis, Lot# MKBP8461V

Potassium permanganate TS: Dissolved 3.3 g of potassium permanganate in water to make 1000mL (0.02 mol/L).

1 mol/L Hydrochloric acid TS: Diluted 90 mL of hydrochloric acid with water to make 1000 mL.

Polyvinyl alcohol TS: Weight exactly 0.50 g of polyvinyl alcohol, and add water to make exactly 100 mL.

Phenylfluorone, C19H12O5: MP Biomedical, CAS# 975-17-7.

Phenylfluorone-ethanol TS: Dissolved 50 mg of phenylfluorone (C19H12O5) in 10 mL of mixture of ethanol (95%) and diluted hydrochloric acid (1:3), and added ethanol (95%) to make exactly 500 mL.

2.3. Procedure

In a Kjeldahl flask, 30 mL of a mixture of sulfuric acid and nitric acid (1:1) was added to 5.0 g of the Trityl Candesartan sample. The content was decomposed by gentle heating in a muffle furnace, and a mixture of sulfuric acid and nitric acid (1:1) was occasionally added dropwise until the content changed to a clear, light brown solution. The solution was then heated until the color changed to a clear, colorless solution, and heated to be slowly concentrated to practical dryness. After cooling, the residue was dissolved in 5 mL of hydrochloric acid by warming, and after cooling, water was added to make exactly 10 mL. 5 mL of this solution was pipetted into a 25 mL volumetric flask (A). The remaining solution was transferred to a 25 mL beaker (B) by being washed out with 10 mL of water and 2 drops of bromocresol green TS were added. The beaker solution was neutralized with diluted ammonia solution (1:2), and the volume consumed for neutralization was measured and recorded as *a* mL. To the volumetric flask (A), potassium permanganate TS was added dropwise until a slight pale red color developed, then allowed to stand for about 5 minutes, and a small amount of L-ascorbic acid was added to decolorize the solution. 1.5 mL of 1 mol/L hydrochloric acid TS, 5 mL of a solution of citric acid monohydrate (1 in 10), *a* mL of diluted ammonia solution (1:2), 2.5 mL of polyvinyl alcohol TS, 5.0 mL of phenylfluorone-ethanol TS and water were added to the solution to make 25 mL total volume. After being shaken well, and then allowed to stand for about 20 minutes, this solution was used as the sample solution. [Appendix A]

Separately, to 1.0 mL of Standard Tin Solution, 5 mL of water and potassium permanganate TS were added until a slight pale red color developed, proceeding in the same manner as for the sample solution; this solution was used as the standard solution.

The absorbance of the sample solution and the standard solution were determined according to Ultraviolet-Visible Spectrophotometry at 510 nm, using water as the blank (containing no more than 2 ppm of tin). [9]

2.4. Calibration Curve

Several volumes ranging from 0.3-4 mL (e.g. 0.5, 1, 2, 3, 4 mL) of Standard Tin Solution were pipetted into a 25 mL volumetric flask (A) and 25 mL beaker (B). Preparation proceeded in the same manner as for the sample solution; these solutions were used as standard solutions for the calibration curve. [Appendix B]

Separately, 5 mL of hydrochloric acid were taken and water was added to make exactly 10 mL. 5 mL of this solution was pipetted into a 25 mL volumetric flask (A). Preparation proceeded in the same manner as for the sample solution; this solution was used as the blank solution for the calibration curve. [Appendix C]

The absorbance of the sample solution and the standard solution (calibration curve) against the blank were determined using the Ultraviolet-Visible Spectrophotometer at 510 nm. These data were plotted on the graph of the calibration curve, standard concentration against absorbance.

3. Results and Discussion

The absorbance of five different concentrations of tin (Sn) standards, blank, Trityl Candesartan sample solutions in duplicate, and sample spiked solutions were measured on a UV-VIS Spectrophotometer at 510 nm. The standard solutions were made from a Standard Tin Solution of 5.0 mg/L by pipetting 0.5, 1, 2, 3, 4 mL and proceeding as in Section 2.4 and Appendix B. To calculate the average percent recovery, spiked sample solutions were made by adding Spiking Solution to the sample. To 5.0 g of sample, 5 mL of 5 mg/L spiking solution was added in a 25 mL volumetric flask and diluted to volume with deionized water. The spiked sample solution thus had a spiked tin amount of 1.0 mg/L, a true value of 0.025 mg Sn.

Raw data obtained from the UV-Vis Spectrophotometer is shown in Table 1, with the blank-corrected absorbance values calculated using Equation (1). The calibration curve was obtained for a series of standard concentrations in the range of 0.10 mg/L to 0.80 mg/L, the data for which is shown in Table 2. The correlation was found to be linear, as shown in the graph in Figure 2. The correlation coefficient, slope, and intercept were found to be 0.9929, 0.4111, and 0.0142, respectively. The equation for this line of best fit was used to calculate the concentration of tin in the sample solutions from the blank-corrected absorbances, as shown in Table 3, Equation (2), and Equation (3). The results obtained were within acceptable limits of 10 mg/Kg maximum.

Equation (1): Blank-corrected absorbance = observed absorbance – Blank absorbance.

Table 2. *Absorbances of Standards.*

Standard Concentration (mg/L)	DF	Absorbance	Blank-corrected Absorbance
Air		0.0000	
Water	1	0.0406	
Blank	1	0.1062	
0.1	1	0.1650	0.0588
0.2	1	0.2106	0.1044
0.4	1	0.2904	0.1842
0.6	1	0.3772	0.2710
0.8	1	0.4366	0.3304

Table 3. *Calibration Curve Data.*

[Sn] (mg/L)	Abs	Slope	0.4111
0.00	0.0000	Intercept	0.0142
0.10	0.0588	R^2	0.9929
0.20	0.1044		
0.40	0.1842		
0.60	0.2710		
0.80	0.3304		

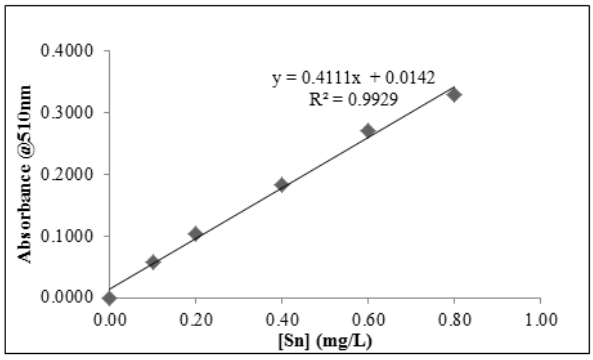

Figure 2. *Calibration Curve.*

Table 4. *Absorbance of Samples.*

Sample	DF	Absorbance	Blank-corrected Absorbance	[Sn] (mg/L)	Sample weight (g)	Final volume (mL)	[Sn] (mg/kg)
Air	1	0					
Water	1	0.0406					
Blank	1	0.1062					
0.2 ppm Check Std	1	0.2108	0.1046	0.2198			
Sample	1	0.3530	0.2468	0.5657	5.0022	25.0	2.83
Sample dup	1	0.3542	0.2480	0.5686	5.0112	25.0	2.84
Spiked Sample	1	0.4325	0.3263	0.7590	5.0094	25.0	3.79
Spiked Sample dup	1	0.4329	0.3267	0.7600	5.0006	25.0	3.80

Table 3. Data of absorbances of sample solutions and spiked sample solutions, each analyzed in duplicate; concentration of Sn calculated using Equations (2) and (3).

Equation (2): [Sn] (mg/L) = (Blank-corrected Absorbance – 0.0142) / 0.4111

Equation (3): [Sn] (mg/kg) = [Sn] (mg/L) * Final volume (mL) / Sample weight (g)

4. Conclusion

UV-Vis spectrophotometric determination of tin with phenylfluorone was found to be adequately sensitive in terms of linearity, repeatability, and accuracy. The correlation coefficient (R^2) was found to be 0.9929, average percent recovery (%R) was 96.0%, and relative percentage difference

(%RPD) was 0.35%. The percent recovery was found to be 95.5% for spiked sample, and 96.5% for the duplicate. The results were within the specification of 10 mg/Kg maximum, with the average concentration of tin in sample found to be 2.635 mg/Kg.

Appendix

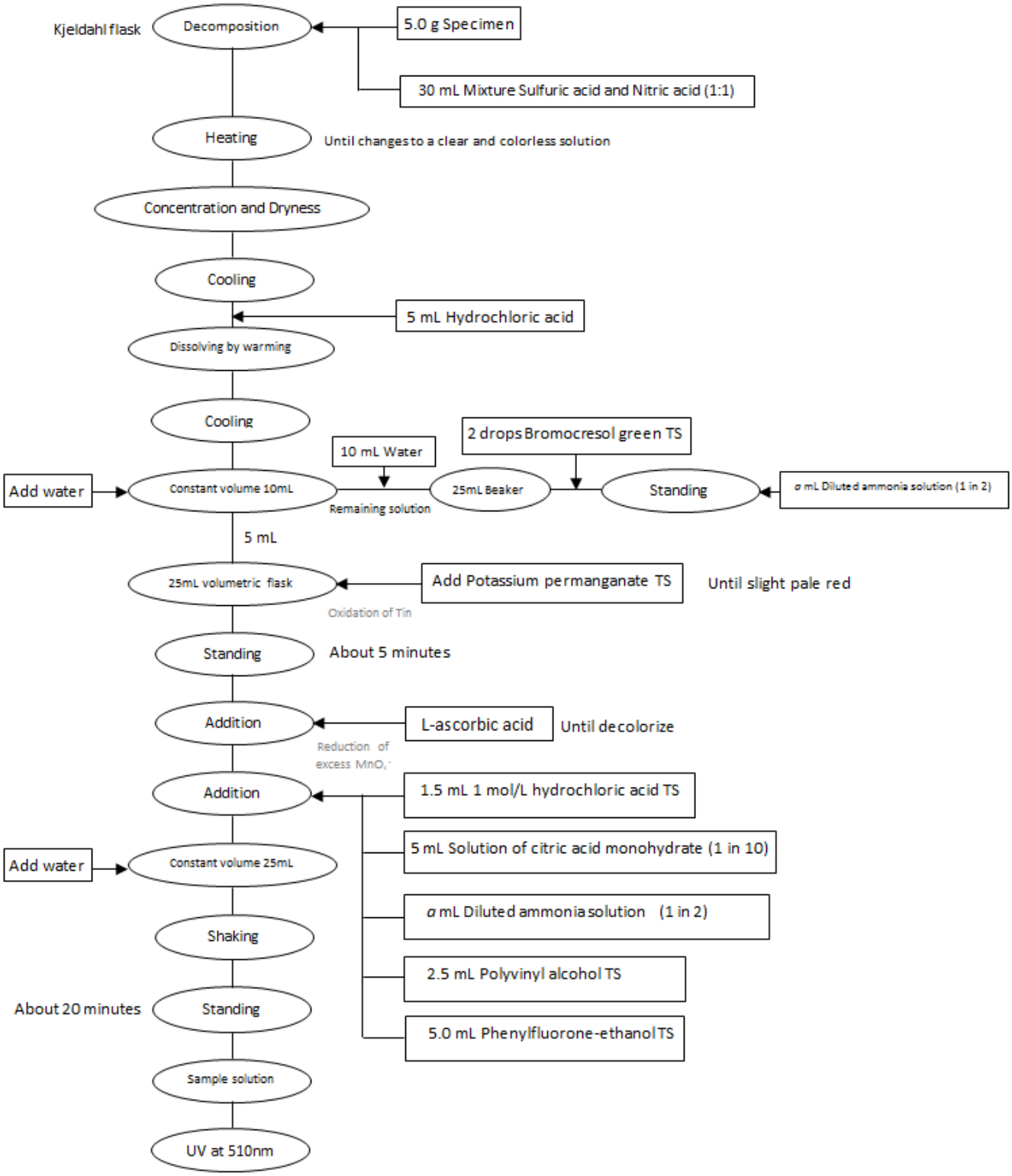

Figure 3. *Process flow of sample solution.*

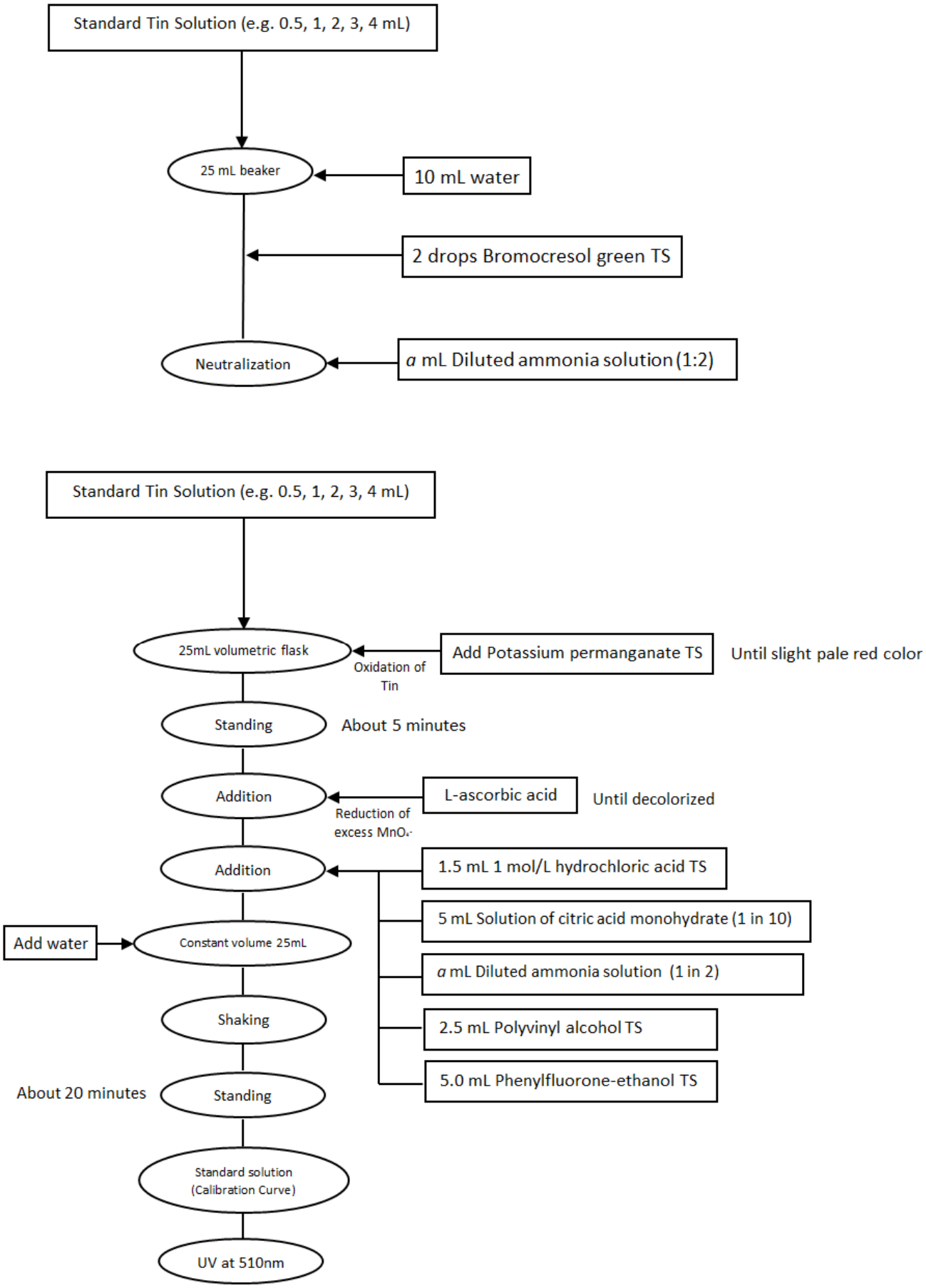

Figure 4. *Process flow of standard solution for calibration curve.*

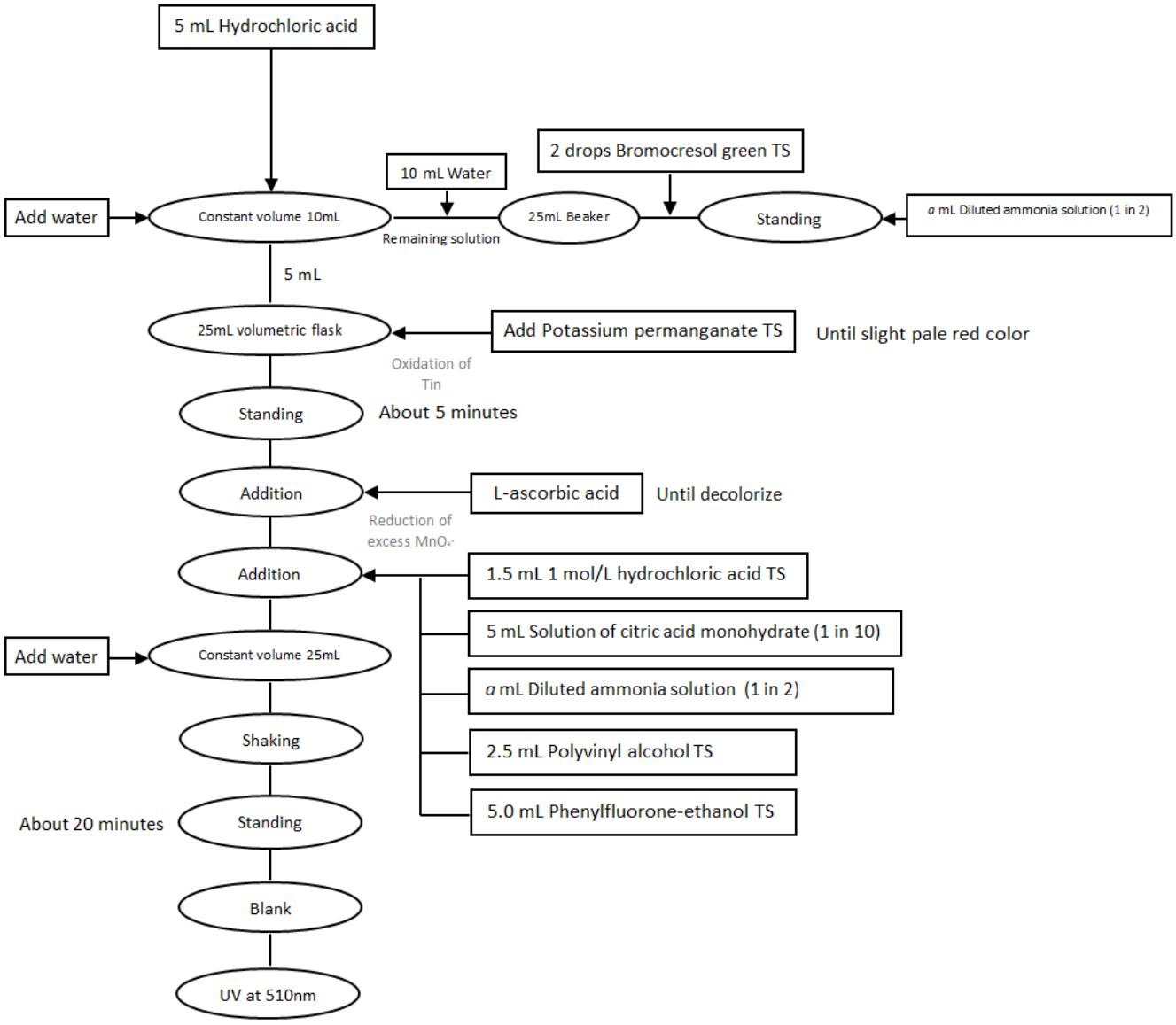

Figure 5. *Process flow of blank for calibration curve.*

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