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Determination of tin in trityl candesartan by flame atomic absorption spectrophotometry (AAS)

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Abstract
Trityl Candesartan, a benzimidazole derivative, is an angiotensin II receptor antagonist. Angiotensin-II is a substance produced in the body that causes blood vessels to tighten. It blocks the action of angiotensin-II and therefore relaxes blood vessels and helps lower blood pressure. One major concern in the preparation process is the usage of tin (Sn) compounds, specifically tributyl tin oxide, which can cause harm to both human and environmental health. In this study, Atomic Absorption Spectrophotometry (AAS) was used for accurate determination of tin in Trityl Candesartan. The study of Sn in Trityl Candesartan found the tin content to be within the limit of 10 mg/Kg, with a correlation coefficient (R^2) of 0.9997, average percent recovery (%R) of 96.5%, and relative percentage difference (%RPD) 0f 3.37%.

Keywords: trityl candesartan, tin, atomic absorption spectrophotometer

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].

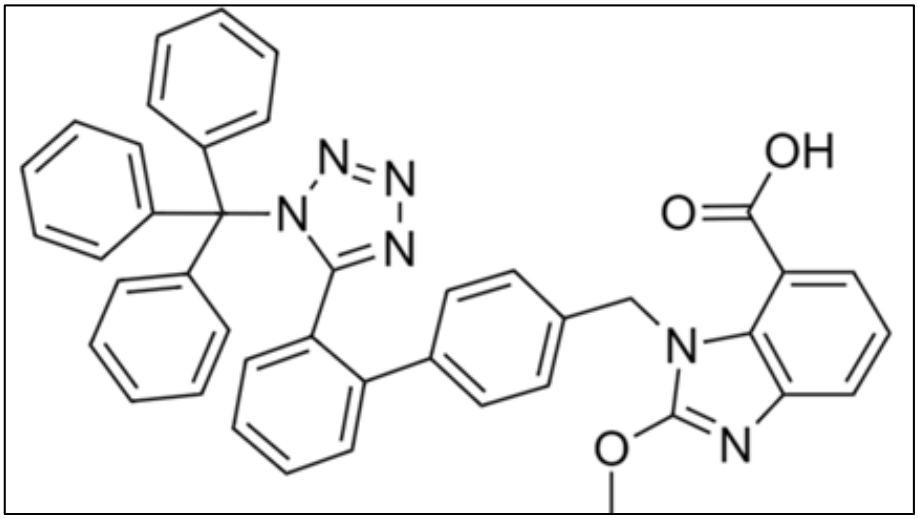

Fig 1: Chemical structure of Trityl Candesartan [2]

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

Due to the versatility of TC and, 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 TC and [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 Perkin Elmer 51000PC Atomic Absorption Spectrophotometer with a Sn (Tin) lamp and 2-inch Nitrous Oxide/ Acetylene burner head. The Spectrophotometer was connected to a computer, loaded with 9 Win Lab 32 for AA Software Assembly, WinLab32 for AA Controller.

Wavelength:	286.3 nm
Slit Width:	0.7
Relative Sensitivity:	1.0 µg/mL
Lamp Energy:	67.0
Lamp Current:	20 mA
Light Source:	Hallow cathode lamp
Oxidant:	Nitrous oxide
Burner Head:	Nitrous Oxide /Acetylene
Type of Flame:	Nitrous Oxide / Acetylene flame
Integration Time:	Reducing 1.5 seconds, 0.5 seconds (for optimizing only)
Color of Flame:	Fuel Rich, Red
Average Readings:	3

2.2 Reagents and Test Solutions

Trityl candesartan: 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, NH_4OH: Sigma-Aldrich, 28.0-30.0% NH_3 basis, Lot# MKBP8461V.

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

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

Distilled water: Alfa Aesar, deionized doubly distilled water.

3. Experiments

3.1 Analytical 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 drop wise 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, 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]

The absorbance of the sample solution and the standard solution were determined according to Atomic Absorption Spectrophotometry, using water as the blank (containing no more than 2 ppm of tin). [9]

3.2 Calibration curve

Several volumes ranging 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 calibration standard solutions for the calibration curve. [Appendix B]

Separately, 5 mL of hydrochloric acid was 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 Atomic Absorption Spectrophotometer at 286.3 nm. These data were plotted on the graph of the calibration curve, standard concentration against absorbance (Table 2, Figure 2).

4. Results and Discussion

Sample was digested with H_2SO_4 and HNO_3 until all solid was consumed. HNO_3 was expelled with addition of water and $HClO_4$, again heating the H_2SO_4 to boiling. The H_2SO_4 was evaporated to dryness and re-suspended residue using HCl and ran on AAS at 286.3 nm. A blank and a tin standard containing 20 µg were carried through the entire digestion and were used to calibrate the AA response.

Perkin-Elmer 5100PC Atomic Absorption Spectrophotometer was used with a short part burner and nitrous oxide/acetylene flame optimized with hollow cathode lamp and a single element was measured. The background correction was selectable on an element by element basis. Water had been run between each reading; AA measurements were thus performed [10].

Determined the concentration (ppm) of tin (Sn) in the working samples using a curve of absorbance vs. concentration (mg/L). The working sample concentration had been calculated by Excel in mg/Kg (Table 3). The results of a single method for the detection of tin in the trityl candesartan were obtained (Figure 2, Table 2 and 3). The calibration curve matched the standards, and sample's single absorbance data point was interpreted in terms of the standards' slope and intercept. The blank subtraction was done automatically.

The analysis showed good linearity (R^2= 0.9997) (Table 2), precision, accuracy (RSD < 0.5%), and recovery for spiked and spiked duplicate (R= 95.6% and 97.4% respectively) (Table 3); method detection limit was 0.03mg/L (ppm) and results met the requirements.

Table 2: Tin (Sn) Calibration Curve Data

[Sn] (mg/L)	Abs	m	0.0012
0	0.0000	b	0.0002
1	0.0014	R^2	0.9997
5	0.0063		
10	0.0119		
15	0.0177		
20	0.0238		

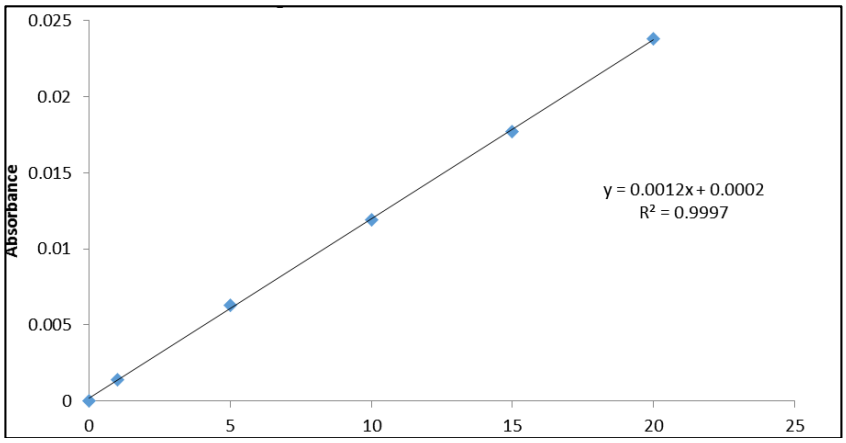

Fig 2: Calibration Curve

Table 3: Absorbance of Sample and QA/QC Study Tin in trityl candesartan using AAC flame with particular attention to wavelength and slit width. Linear Calibration- Calculated in Excel

Sample	Abs.	Blank-corr. Abs.	[Sn] mg/L	W (g)	V (mL)	ppm
Water	-0.0002					
1 mg/L	-0.0008	0.0005	0.09			
5 mg/L	0.0050	0.0063	5.10			
10 mg/L	0.0085	0.0110	9.15			
15 mg/L	0.0170	0.0177	14.93			
Sample 1	0.0022	0.0039	3.07	5.0008	10	6.14
Sample 2	0.0024	0.0038	2.98	5.0002	10	5.96
Sample 3	0.0026	0.0044	3.46	5.0010	10	6.91
Sample 4	0.0025	0.0041	3.24	5.0012	10	6.48
Sample 5	0.0023	0.0043	3.41	5.0009	10	6.83
Sample 6	0.0025	0.0042	3.28	5.0011	10	6.57
Sample 6 Dup.	0.0025	0.0043	3.41	5.0011	10	6.82
Sample Spiked	0.0068	0.0070	5.74	5.0011	10	11.48
Spiked Duplicate	0.0068	0.0071	5.79	5.0011	10	11.57
Digestion Blank	0.0059	0.0062	5.01			

Average sample result: 6.70 mg/L — spiked amount: 5.0 mg/L
Concentration of spiking solution: 1000 mg/L — % R MS:95.6%
RPD: 3.73% — % R MSD:97.4%

mL of spiking solution: 0.05 mL
Sample Volume: 10 mL

Average percent recovery: 96.5%

5. Conclusion

Atomic Absorption spectrophotometric determination of tin was found to be adequately sensitive in terms of linearity, repeatability, and accuracy. The correlation coefficient (R^2) was found to be 0.9997, average percent recovery (%R) was 96.0%, and relative percentage difference (%RPD) was 0.35%. The percent recovery was found to be 95.6% for spiked sample, and 97.4% 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 6.70 mg/Kg.

6. References

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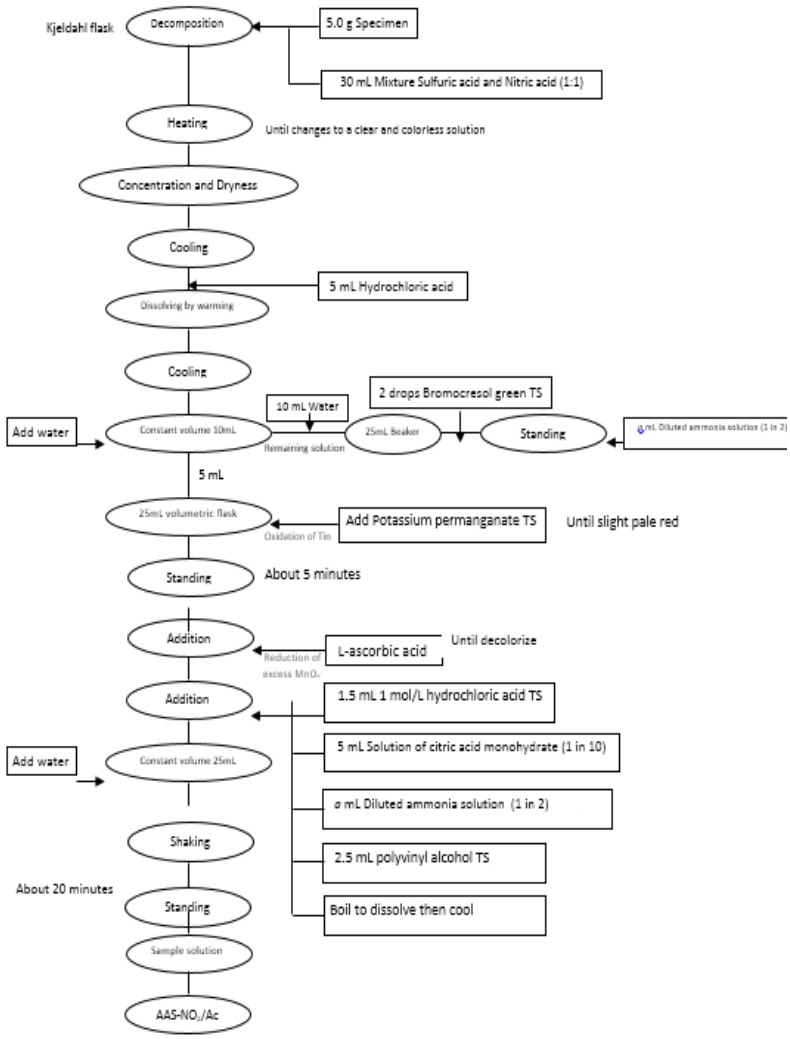
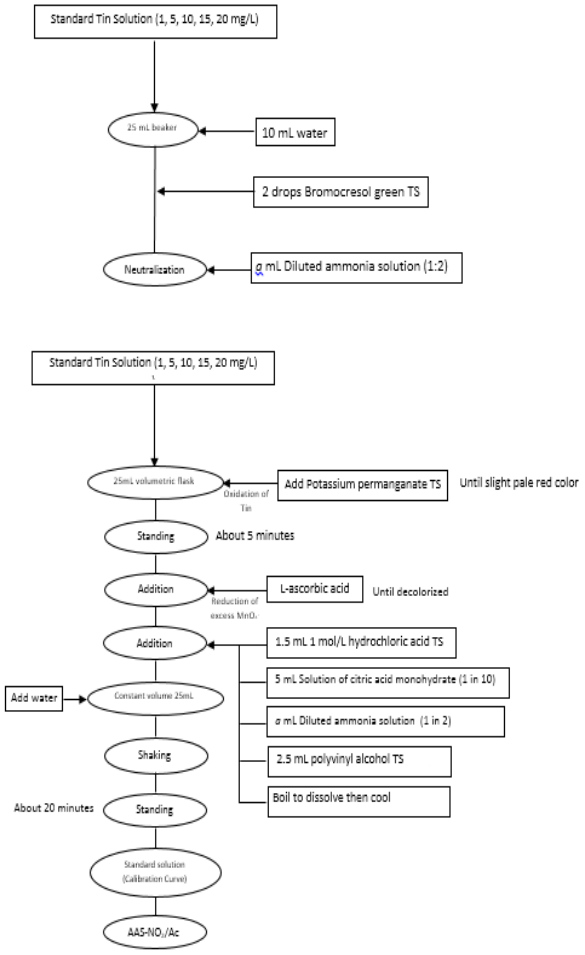
Appendix

A - Process flow of sample solution



B - Process flow of standard solution for calibration curve



C - Process flow of blank for calibration curve