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POTASSIUM BROMIDE TESTING METHODS

TABLE OF CONTENTS

1. PURPOSE:.....	3
2. SCOPE:.....	3
3. RESPONSIBILITIES:	3
4. REFERENCES:	3
5. EQUIPMENT:.....	3
6. REAGENTS:.....	3
7. ANALYTICAL PROCEDURES:	5
8. COMPENDIAL DIFFERENTIATIONS	12

1. PURPOSE:

- 1.1. To provide Laboratory Analysts with a procedure for testing the properties of Potassium Bromide, In-Process Mother Liquor (ML), Raw Materials (RM) and Finished Goods (FG).

2. SCOPE:

- 2.1. Applies to the testing of RM and all FG types in the Bangor, PA Laboratories. Methods include testing for all types of Potassium Bromide sold by BioSpectra.

3. RESPONSIBILITIES:

- 3.1. The Laboratory Manager is responsible for the implementation, control, training and maintenance of this procedure.
- 3.2. All Laboratory Analysts are responsible for complying with this procedure.

4. REFERENCES:

- 4.1. BSI-ATM-0080, Analytical Method for the Determination of ICH Q3D Elemental Impurities (Class 1, 2a, 2b, 3, & 4) by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) in Potassium Bromide
- 4.2. BSI-ATM-0102, Analytical Method for Iron and Lead Detection by Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) in Potassium Bromide
- 4.3. BSI-FRM-0721, Potassium Bromide Analytical Procedure
- 4.4. BSI-SDS-0011, Potassium Bromide SDS
- 4.5. BSI-SOP-0019, Result Reporting
- 4.6. BSI-SOP-0090, Lambda 25 UV/Vis Operation and Calibration
- 4.7. BSI-SOP-0098, Balance SOP
- 4.8. BSI-SOP-0126, Laboratory Notebooks
- 4.9. BSI-SOP-0140, Standardization of Titrants
- 4.10. BSI-SOP-0141, MF-50 Moisture Balance Operation and Calibration
- 4.11. BSI-SOP-0244, VWR Gravity Convection Oven Operation and Calibration (Model Number 414005-106)
- 4.12. BSI-SOP-0255, XL200 pH/mV/Conductivity Meter SOP
- 4.13. BSI-SOP-0258, Ro-Tap SOP
- 4.14. BSI-SOP-0303, NexION 350X ICP-MS SOP
- 4.15. BSI-SOP-0362, Operation and Maintenance of the Perkin Elmer Avio 500 ICP-OES
- 4.16. Current USP

5. EQUIPMENT:

- 5.1. Analytical Balance
- 5.2. Lambda 25 UV/Vis Spectrophotometer
- 5.3. MF-50 Moisture Balance
- 5.4. VWR Gravity Oven, or equivalent
- 5.5. XL200 pH/mV/Conductivity Meter
- 5.6. Ro-Tap
- 5.7. NexION 350X ICP-MS or Avio 500 ICP-OES

6. REAGENTS:

- 6.1. **Acetate Buffer, pH 3.5:** Dissolve 62.5 g of Ammonium Acetate in 62.5 mL of purified water and 47 mL of Hydrochloric Acid (HCl). Adjust to a pH of 3.5 using 6N Hydrochloric Acid or 6N Ammonium Hydroxide. Dilute with purified water to 250 mL.
- 6.2. **Acetic Acid 1N:** Dilute 30 mL of Acetic Acid, Glacial to 500 mL with purified water.
- 6.3. **Acetic Acid, Glacial:** Purchased Commercially

- 6.4. **Ammonia Water:** Dilute 430 mL of Ammonium Hydroxide 30% to 500 mL with purified water.
- 6.5. **Ammonium Hydroxide 6N:** Dilute 412 mL of Ammonium Hydroxide 30% to 500 mL with purified water.
- 6.6. **Ammonium Thiocyanate (NH₄SCN), 0.1N:** Purchased Commercially
- 6.7. **Barium Chloride TS:** Dissolve 12 g of Barium Chloride Dehydrate in purified water, filter if necessary, and dilute to 100 mL with purified water.
- 6.8. **Bromothymol Blue TS:** Dissolve 0.1 g of Bromothymol Blue in 100 mL of dilute alcohol, and filter if necessary, and dilute to 100 mL with purified water.
- 6.9. **Chlorine TS (Chlorine Water):** Purchased Commercially
- 6.10. **Chloroform:** Purchased Commercially
- 6.11. **Citric Acid R (20% w/v or 200 g/L):** Weigh 20 g of Citric Acid and dilute to 100 mL with Water R.
- 6.12. **Dibutyl Phthalate:** Purchased Commercially
- 6.13. **Dichloromethane:** Purchased Commercially
- 6.14. **EDTA, 0.01M, Disodium VS:** Purchased Commercially
- 6.15. **Eriochrome Black T Trituration:** Grind 200 mg of Eriochrome Black T to a fine powder with 20 g of Potassium Chloride).
- 6.16. **Ferric Ammonium Sulfate Indicator:** Weigh 10 g of Ferric Ammonium Sulfate in a 100 mL volumetric flask. Dilute to volume and mix. Must be made fresh at the time of use.
- 6.17. **Ferric Chloride Solution:** Dissolve 1.0 g of Ferric Chloride Hexahydrate in purified water and dilute to 100 mL with purified water.
- 6.18. **Glycerin Base TS:** To 200 g of Glycerol, add purified water to bring the total weight to 235 g. Add 140 mL of 1N Sodium Hydroxide and 50 mL purified water.
 - 6.18.1. **Hydrochloric Acid 3N:** Dilute 123 mL of Hydrochloric Acid to 500 mL with purified water.
 - 6.18.2. **Hydrochloric Acid, 0.01N:** Dilute 1 mL of Hydrochloric Acid 0.1N to 10 mL with purified water.
- 6.19. **Hydrochloric Acid:** Purchased Commercially
- 6.20. **Hydrogen Peroxide:** Purchased Commercially
- 6.21. **Hydroxylamine Hydrochloride:** Purchased Commercially
- 6.22. **Iron Standard:** Weigh 0.863 g of Ferric Ammonium Sulfate and transfer to 500 mL volumetric flask. Dissolve in 25 mL of dilute Sulfuric Acid, then dilute to volume with purified water and mix. Transfer 1.25 mL of solution to a 200 mL volumetric flask and dilute to volume with purified water. Use immediately.
- 6.23. **Lead Nitrate Stock Solution:** Dissolve 0.1598 g of Lead Nitrate in 100 mL of purified water and add 1 mL of Nitric Acid. Dilute with purified water to 1000 mL. Store in a glass container free from soluble lead salts.
 - 6.23.1. **Nitric Acid Solution:** Dilute 14 mL of Nitric Acid to 100 mL with purified water.
 - 6.23.2. **1% Nitric Acid:** Dilute 14.5 mL of Trace Metal Grade Nitric Acid to 1000 mL with purified water.
- 6.24. **Nitric Acid:** Purchased Commercially
- 6.25. **pH 10.0 Ammonia-Ammonia Chloride Buffer:** Dissolve 5.4 g of Ammonium Chloride in 20 mL purified water, 20 mL of Ammonium Hydroxide, and finally diluting it to 100 mL with purified water.
- 6.26. **Potassium Chloride:** Purchased Commercially
- 6.27. **Potassium Iodide 10 g / 100 mL:** Weigh 10.0 g of Potassium Iodide and transfer a to 100 mL volumetric flask. Dilute to volume with purified water.
- 6.28. **Silver Nitrate, 0.1N (AgNO₃):** Purchased Commercially
- 6.29. **Sodium Bitartrate TS:** Dissolve 1.00 g of Sodium Bitartrate into 10 mL of purified water.

- 6.30. **Sodium Hydroxide (NaOH), 0.01N:** Dilute 1 mL of Sodium Hydroxide 0.1N to 10 mL with purified water.
- 6.31. **Starch-Mercuric Iodide Solution:** Finely ground 1.0 g of Soluble Starch with 5 mL of purified water. Pour the mixture into 100 mL of boiling water containing 10 mg of Mercuric Iodide.
- 6.32. **Sulfuric Acid 0.02N (0.01M):** Dilute 1 mL of Sulfuric Acid 1N to 50 mL with purified water.
- 6.33. **Sulfuric Acid 0.5M (1N):** Purchased Commercially
- 6.34. **Sulfuric Acid, Dilute:** Add 2 mL of concentrated Sulfuric Acid and sufficient water to make 35 mL (1N equivalent).
- 6.35. **Thioacetamide-Glycerin Base TS:** In a test tube, mix 0.2 mL of Thioacetamide TS and 1 mL of Glycerin Base TS, heat in a boiling purified water bath for approximately 20 sec. Use immediately.
- 6.36. **Thioacetamide TS:** Dissolve 4.0 g of Thioacetamide in 100 mL of purified water.
- 6.37. **Thioglycolic Acid:** Purchased Commercially
- 6.38. **Trace Metal Nitric Acid:** Purchased Commercially
Zinc Sulfate 0.1M: Dissolve 2.78 g of Zinc Sulfate Heptahydrate and transfer to a 100 mL volumetric flask. Dilute to volume with purified water and store in a glass, stoppered volumetric flask.

7. ANALYTICAL PROCEDURES:

7.1. MOTHER LIQUOR ASSAY AND LOC MONITOR:

- 7.1.1. Assay:
- 7.1.1.1. Standardize 0.1N AgNO₃ and 0.1N Ammonium Thiocyanate as per Standardization of Titrants procedure, BSI-SOP-0140.
- 7.1.1.2. Prepare a Nitric Acid Solution by diluting 14 mL of concentrated Nitric Acid to 100 mL with purified water.
- 7.1.1.3. On the day of use, prepare *Ferric Ammonium Sulfate Indicator* by weighing 10 g of Ferric Ammonium Sulfate. Transfer to a 100 mL volumetric flask and dilute to volume with purified water.
- 7.1.1.4. Dissolve 2 g of sample and dilute to 100 mL with purified water.
- 7.1.1.5. To 10 mL of the sample solution add the following:
- 7.1.1.5.1. 50 mL of purified water
- 7.1.1.5.2. 5 mL of the Nitric Acid Solution
- 7.1.1.5.3. 25.00 mL of 0.1N Silver Nitrate VS via burette
- 7.1.1.5.4. 2 mL of Dibutyl Phthalate
- 7.1.1.5.5. 2 mL of *Ferric Ammonium Sulfate Indicator*
- 7.1.1.6. Mix and back titrate via burette the excess Silver Nitrate from the sample solution with Ammonium Thiocyanate that has previously been standardized in accordance with Standardization of Titrants procedure, BSI-SOP-0140, to a light brown endpoint.
- 7.1.1.7. Run a blank determination.
- 7.1.1.8. The Limit of Chlorine test result will provide the “b” portion of the equation.

$$\%Br \text{ and } Cl = \frac{(mL \text{ of Blank} - mL \text{ of } NH_4SCN) \times (N \text{ of } NH_4SCN) \times 11.90}{\text{Sample Weight (g)}/10} = a$$

- 7.1.2. Limit of Chlorine:
- 7.1.2.1. Standardize 0.1N AgNO₃ and 0.1N Ammonium Thiocyanate as per Standardization of Titrants procedure, BSI-SOP-0140.
- 7.1.2.2. Prepare a Nitric Acid Solution by diluting 14 mL of concentrated Nitric Acid to 100 mL with purified water.

- 7.1.2.3. Dissolve 1 g of sample in 20 mL of Nitric Acid Solution.
- 7.1.2.4. Add 5 mL of 30% Hydrogen Peroxide in the hood and the solution should turn yellow.
- 7.1.2.5. Prepare a blank determination by mixing 20 mL of Nitric Acid Solution and 5 mL of 30% Hydrogen Peroxide in a 50 mL beaker.
- 7.1.2.6. Heat in a water bath until the solution becomes colorless.
- 7.1.2.7. Rinse the sides of the beaker with a small quantity of purified water and heat in the water bath for an additional 15 minutes.
- 7.1.2.8. Allow to cool and dilute with purified water to 50 mL.
- 7.1.2.9. Add 5.00 mL of 0.1N Silver Nitrate VS via burette and 1 mL of Dibutyl Phthalate.
- 7.1.2.10. Add 5 mL of *Ferric Ammonium Sulfate Indicator* and back titrate via burette the excess silver nitrate with 0.1N Ammonium Thiocyanate to a light brown endpoint.

$$\% Cl = \frac{(mL \text{ of Blank} - mL \text{ of } NH_4SCN) \times N \text{ of } NH_4SCN \times 3.5453}{Sample \text{ Weight (g)}} = b$$

$$\% KBr = a - 3.357b$$

- 7.2. **MOTHER LIQUOR ABSORBANCE** **SEE BATCH RECORD:**
- 7.2.1. Dissolve 5 mL of sample in 5 mL of purified water. Swirl to dissolve completely. Refer to Lambda 25 UV/Vis Operation and Calibration to determine the absorbance of the sample; attach the printout to the appropriate summary sheet. If any absorbance is performed by properly trained Production personnel, then the result is to be recorded in the Bangor production absorbance results log book.
 - 7.2.1.1. If the any of the sample results are out of specification or if the sample result at 280 nm exceeds the action limit of 0.27 a.u, notify Laboratory Management, QA, and Production Managers immediately.
- 7.3. **WET CRYSTAL ABSORBANCE (1M)** **SEE BATCH RECORD:**
- 7.3.1. Accurately weigh 2.98 g of sample.
 - 7.3.2. Transfer accurately weighed sample to a 50 mL graduated cylinder and dilute to 25 mL with purified water.
 - 7.3.3. Swirl to dissolve completely.
 - 7.3.4. Refer to Lambda 25 UV/Vis Operation and Calibration to determine the absorbance of the sample; attach the printout to the appropriate summary sheet.
 - 7.3.5. If any absorbance is performed by properly trained Production personnel, then the result are to be recorded in the Bangor production absorbance results log book.
- 7.4. **WET CRYSTAL MOISTURE** **2% MAX AT TOP, 4% MAX AT BOTTOM:**
- 7.4.1. Refer to MF-50 Moisture Balance Operating and Calibration to determine the moisture of the sample.
 - 7.4.2. Documentation of analysis should be recorded in the In-Process Moisture Analysis Log Book.
 - 7.4.3. Notify the Laboratory Management if the moisture result is not within specification. An out of specification moisture result could result in a particle size failure on finished goods.

FINISHED GOOD ANALYSIS

Particle Size Analysis should be the first analysis completed on the Finished Good Samples.

Notify the Laboratory Management of any out-of-specification result.

- 7.5. **ABSORBANCE (1M)** :
- 7.5.1. Accurately weigh 2.98 g of sample.
 - 7.5.2. Transfer accurately weighed sample to a 50 mL graduated cylinder and dilute to 25 mL with purified water.
 - 7.5.3. Swirl to dissolve completely.
 - 7.5.4. Refer to Lambda 25 UV/Vis Operation and Calibration to determine the absorbance of the sample; attach the printout to the appropriate summary sheet.
- 7.6. **ACIDITY OR ALKALINITY** :
- 7.6.1. Weigh 10.0 g of sample and dilute to 100 mL with purified water (solution from Appearance of Solution can be used).
 - 7.6.2. To 10 mL of sample solution add 0.1 mL of Bromothymol Blue TS.
 - 7.6.3. If the solution is yellow, add 0.5 mL of 0.01N NaOH. The solution must change to a blue hue in order to pass.
 - 7.6.4. If the solution is blue, add 0.5 mL of 0.01N HCl. The solution must change to a yellow hue in order to pass.
- 7.7. **APPEARANCE OF SOLUTION** :
- 7.7.1. Weigh 10.0 g of sample and dilute to 100 mL in a volumetric flask with purified water.
 - 7.7.2. In an area with sufficient light, observe from all angles.
 - 7.7.3. Solution should be clear and colorless when compared against a common background to a clear and colorless reference solution.
- 7.8. **ASSAY** :
- 7.8.1. Standardize 0.1N AgNO₃ and 0.1N Ammonium Thiocyanate as per Standardization of Titrants.
 - 7.8.2. Prepare a Nitric Acid Solution by diluting 14 mL of Nitric Acid to 100 mL with purified water.
 - 7.8.3. On the day of use, prepare *Ferric Ammonium Sulfate Indicator* by weighing 10 g of Ferric Ammonium Sulfate. Transfer to a 100 mL volumetric flask and dilute to volume with purified water.
 - 7.8.4. Dissolve 2.000 g ± 0.0005 g of sample and dilute to 100 mL with purified water.
 - 7.8.4.1. Sample must be dried for Finished Good samples and tested as-is for Raw Materials.
 - 7.8.5. To 10 mL of the sample solution add the following:
 - 7.8.5.1. 50 mL of purified water
 - 7.8.5.2. 5 mL of the Nitric Acid solution
 - 7.8.5.3. 25.00 mL of 0.1N Silver Nitrate VS via burette
 - 7.8.5.4. 2 mL of Dibutyl Phthalate
 - 7.8.5.5. 2 mL of *Ferric Ammonium Sulfate Indicator*
 - 7.8.6. Mix and back titrate via burette the excess silver nitrate from the sample solution with Ammonium Thiocyanate that has previously been standardized in accordance with Standardization of Titrants to a light brown endpoint.
 - 7.8.7. Run a blank determination.

7.8.8. The Limit of Chlorine test result will provide the “b” portion of the following equation:

$$\%Br \text{ and } Cl = \frac{(mL \text{ of Blank} - mL \text{ of } NH_4SCN) \times (N \text{ of } NH_4SCN) \times 11.90}{Sample \text{ Weight (g)}/10} = a$$

$$\%KBr = a - 3.357b$$

7.9. **BROMATES** _____ :

- 7.9.1. To prepare Starch-mercuric Iodide Solution finely grind 1.0 g of soluble starch with 5 mL of purified water.
- 7.9.2. Pour the mixture into 100 mL of boiling water containing 10 mg of Mercuric Iodide.
- 7.9.3. Weigh 10.0 g of sample and dilute to 100 mL with purified water (solution from Appearance of Solution can be used).
- 7.9.4. To 10 mL of sample solution add 1mL of the Starch-mercuric Iodide Solution.
- 7.9.5. Add 0.1 mL of a 100 g per L solution of Potassium Iodide.
- 7.9.6. Add 0.25 mL of 0.5M Sulfuric Acid.
- 7.9.7. Allow to stand for five minutes away from light. There should be no blue or violet color present to pass.

7.10. **HEAVY METALS** _____ :

- 7.10.1. Primary Method: Refer to NexION 350X ICP-MS, BSI-SOP-0303 and BSI-ATM-0080 for sample preparation and analysis.
- 7.10.2. Alternate Method; ICP-OES for Lead (Pb) and Iron (Fe): Refer to Avio 500 ICP-OES SOP, BSI-SOP-0362 and BSI-ATM-0102 for sample preparation and analysis.
- 7.10.3. Alternate Method:
 - 7.10.3.1. *Standard Preparation:*
 - 7.10.3.2. On the day of use, dilute 10.0 mL of Lead Nitrate Stock solution with purified water to 100 mL. Into a Nessler Color Comparison Tube, pipette 2 mL of the Standard Lead Solution and dilute to 25 mL. Adjust with 1N Acetic Acid or 6N Ammonium Hydroxide to a pH between 3.0 and 4.0, using a pH meter or short-range pH indicator paper as an external indicator, dilute to 40 mL with purified water.
- 7.10.4. *Monitor Preparation:*
 - 7.10.4.1. Weigh 2.00 g of sample. Transfer to a Nessler Color Comparison Tube and dilute with purified water to 25 mL.
 - 7.10.4.2. Add 2 mL of the Standard Lead Solution.
 - 7.10.4.3. Adjust with 1N Acetic Acid or 6N Ammonium Hydroxide to a pH between 3.0 and 4.0, using a pH meter or short-range pH indicator paper as an external indicator, dilute to 40 mL with purified water and mix.
- 7.10.5. *Test Preparation:*
 - 7.10.5.1. Weigh 2.00 g of sample, transfer to a Nessler Color Comparison Tube and dilute with purified water to 25 mL
 - 7.10.5.2. Adjust with 1N Acetic Acid or 6N Ammonium Hydroxide to a pH between 3.0 and 4.0, using a pH meter or short-range pH indicator paper as an external indicator, dilute to 40 mL with purified water and mix.
- 7.10.6. *Procedure:*
 - 7.10.6.1. To each of the tubes containing the Standard Preparation, the Test Preparation and the Monitor Preparation, add 2 mL of pH 3.5 Acetate Buffer and 1.2 mL of Thioacetamide-glycerin Base TS (mix 0.2 mL of Thioacetamide TS and 1 mL of Glycerin Base TS, heat in a boiling purified water bath for approximately 20 seconds. Use immediately).

- 7.10.6.2. Dilute with purified water to 50 mL, mix by inversion and allow to stand for 2 minutes.
- 7.10.6.3. View downward over a white surface: the color of the solution from the Test Preparation is not darker than the Standard Preparation and the color of the Monitor Preparation Solution is equal to or darker than that of the Standard Preparation in order to report as < 10 ppm.

7.11. IDENTIFICATION TEST, A :

- 7.11.1. **To prepare Chlorine TS (*Chlorine Water*)**—A saturated solution of chlorine in water. Place the solution in small, completely filled, light-resistant containers. Chlorine TS, even when kept from light and air, is apt to deteriorate. Store it in a cold, dark place. For full strength, prepare this solution fresh.
- A. Weigh 4.5 mg of sample and dissolve in 1 mL of purified water.
Add Chlorine TS dropwise
Dissolve by shaking with Chloroform. The Chloroform should turn from red-to-reddish brown.
- B. Weigh 4.5 mg of sample and dissolve in 1mL of purified water
Add 0.20 mL of 0.1N Silver Nitrate and mix.
A yellowish-white precipitate will form.
Add 1 mL of Nitric Acid. The precipitate is insoluble in Nitric Acid to pass test.
Add 1 mL of 6N Ammonium Hydroxide. The precipitate should be slightly soluble.

7.12. IDENTIFICATION TEST, B :

- 7.12.1. Weigh 10.0 g of sample and dilute to 100 mL with purified water (solution from Appearance of Solution can be used).
- 7.12.2. To 1.0 mL of sample solution add 0.20 mL of freshly prepared Sodium Bitartrate TS.
7.12.2.1. Prepare Sodium Bitartrate TS by dissolving 1.00 g of Sodium Bitartrate into 10 mL of purified water.
- 7.12.3. Add 0.20 mL of Glacial Acetic Acid.
- 7.12.4. A precipitate is produced; utilize a glass rod to accelerate formation of precipitate.
- 7.12.5. Add 1mL of 6N Ammonium Hydroxide. The precipitate should be slightly soluble.

7.13. IODIDES :

- 7.13.1. Weigh 10.0 g of sample and dilute to 100 mL with purified water (solution from Appearance of Solution can be used).
- 7.13.2. To 5 mL of sample solution add 0.15 mL of a 10.5 g per 100 mL Ferric Chloride solution.
- 7.13.3. Add 2 mL of Dichloromethane.
- 7.13.4. Shake and allow solution to separate. The lower layer must remain colorless to pass.

7.14. LIMIT OF CHLORINE :

- 7.14.1. **NOTE:** The Limit of Chlorine test has an internal alert limit and action limit, as follows:
7.14.1.1. Internal Alert Limit: $\geq 0.05\%$ (requires Supervisor approval)
7.14.1.2. Internal Action Limit $\geq 0.10\%$ (requires Supervisor approval and a confirmatory test after issuance and completion of an OOS Checklist.)
- 7.14.2. Standardize 0.1N AgNO₃ and 0.1N Ammonium Thiocyanate as per Standardization of Titrants.
- 7.14.3. Prepare a Nitric Acid Solution by diluting 14 mL of Nitric Acid to 100 mL with purified water.
- 7.14.4. Dissolve 1.000 g \pm 0.0005 g of sample in 20 mL of Nitric Acid Solution.
7.14.4.1. Sample must be dried for Finished Good samples and tested as-is for Raw Materials.

- 7.14.5. Add 5 mL of 30% Hydrogen Peroxide in the hood and the solution should turn yellow.
- 7.14.6. Prepare a blank determination by mixing 20 mL of Nitric Acid Solution and 5 mL of 30% Hydrogen Peroxide in a 50 mL beaker.
- 7.14.7. Heat in a water bath until the solution becomes colorless.
- 7.14.8. Rinse the sides of the beaker with a small quantity of purified water and heat in the water bath for an additional 15 minutes.
- 7.14.9. Allow to cool and dilute with purified water to 50 mL.
- 7.14.10. Add 5.00 mL of 0.1N Silver Nitrate VS via burette and 1 mL of Dibutyl Phthalate.
- 7.14.11. Add 5 mL of *Ferric Ammonium Sulfate Indicator* and back titrate via burette the excess Silver Nitrate with 0.1N Ammonium Thiocyanate to a light brown endpoint.

$$\% Cl = \frac{(mL \text{ of Blank} - mL \text{ of } NH_4SCN) \times N \text{ of } NH_4SCN \times 3.5453}{\text{Sample Weight (g)}} = b$$

7.15. LIMIT OF IRON :

- 7.15.1. Primary Method: Refer to NexION 350X ICP-MS, BSI-SOP-0303 and BSI-ATM-0080 for sample preparation and analysis.
- 7.15.2. Alternate Method; ICP-OES: Refer to Avio 500 ICP-OES, BSI-SOP-0362 and BSI-ATM-0102 for sample preparation and analysis.
- 7.15.3. Alternate Method; Wet Chemistry:
- 7.15.4. Prepare a 200 mg per mL solution of Citric Acid.
- 7.15.5. *Iron Standard Solution:*
 - 7.15.5.1. Weigh 0.863 g of Ferric Ammonium and transfer to a 500 mL volumetric flask.
 - 7.15.5.2. Dissolve in 25 mL of dilute Sulfuric Acid (prepared by diluting 5.5 mL of concentrated Sulfuric Acid to 100 mL with purified water).
 - 7.15.5.3. Dilute to volume with purified water.
 - 7.15.5.4. Transfer 1 mL of Ferric Ammonium solution to a 10 mL volumetric flask and Dilute to volume with purified water.
 - 7.15.5.5. Transfer 2.5 mL of the solution to a 50 mL volumetric flask and dilute to volume with purified water. Prepare solution immediately for use.
- 7.15.6. *Test Solution:*
 - 7.15.6.1. Weigh 10.00 g of sample and dilute to 100 mL with purified water (solution from Appearance of Solution can be used).
 - 7.15.6.2. Transfer 5 ml of the solution prepared for the test for appearance of solution to a 10 ml volumetric flask, and dilute with water to volume.
- 7.15.7. *Procedure:*
 - 7.15.7.1. To 10 mL of the Iron Standard Solution and test solution, add 2.0 mL of the Citric Acid Solution.
 - 7.15.7.2. Add 0.1 mL of Thioglycolic Acid.
 - 7.15.7.3. Adjust the test and standard solutions to basic with Ammonia Water to litmus.
 - 7.15.7.4. Dilute with purified water to 20 mL. Let stand for 5 minutes, the test solution shall remain less pink than the standard solution.

7.16. LOSS ON DRYING (LOD) :

- 7.16.1. Dry an LOD vial in an oven at $105 \pm 2^\circ\text{C}$ for 30 minutes. Cool for 15 minutes in a desiccator.
- 7.16.2. Place the LOD vial on the analytical balance and record the weight.
- 7.16.3. Tare the LOD vial and weigh 1 – 2 grams of sample and record results.
- 7.16.4. Place the LOD Vial containing the sample into the oven.
- 7.16.5. Dry the sample at $105 \pm 2^\circ\text{C}$ for 3 hours.
- 7.16.6. Allow to cool in the desiccator for 15 minutes prior to weighing.
- 7.16.7. Calculate Loss on Drying

$$\% \text{ LOD} = \frac{\text{Initial sample weight (g)} - \text{Final sample weight (g)}}{\text{Initial Sample Weight (g)}} \times 100$$

7.17. MAGNESIUM AND ALKALINE-EARTH METALS :

- 7.17.1. Prepare pH 10.0 Ammonia-Ammonium Chloride buffer by dissolving 5.4 g of Ammonium Chloride in 20 mL of purified water and adding 20 mL of Ammonium Hydroxide and diluting to 100 mL with purified water.
- 7.17.2. To 200 mL of purified water add the following:
 - 7.17.2.1. 0.1 g of Hydroxylamine Hydrochloride
 - 7.17.2.2. 10 mL of pH 10.0 Ammonia-Ammonium Chloride
 - 7.17.2.3. 1 mL of 0.1M Zinc Sulfate
 - 7.17.2.4. 0.2 g of Eriochrome Black T Trituration
 - 7.17.2.5. Eriochrome Black T Trituration: Grind 200 mg of Eriochrome Black T to a fine powder with 20 g of Potassium Chloride.
- 7.17.3. Heat solution to about 40°C .
- 7.17.4. Titrate solution with 0.01M EDTA Disodium Titrant VS via burette until the violet color changes to deep blue.
- 7.17.5. Add 10.0 g of sample dissolved in 100 mL of purified water.
- 7.17.6. If no color change, report as no color change, < 0.02%.
- 7.17.7. If the color changes to violet:
 - 7.17.7.1. Standardize 0.01M EDTA Disodium Titrant VS as per Standardization of Titrants procedure, BSI-SOP-0140.
- 7.17.8. Titrate the solution with standardized 0.01M EDTA, not more than 5.0 mL will be used or < 0.02% calculated as Ca.

7.18. PARTICLE SIZE ANALYSIS #20 Mesh: 5% max.; #60 Mesh: 60% min.:

- 7.18.1. ENSURE THAT EACH SIEVE IS INSPECTED AND CLEAN BEFORE USE.
#20MESH SIEVE AND #60 SIEVE IS STAINLESS STEEL AND KBR DEDICATED.
- 7.18.2. Weigh 25 - 30 g of sample into a sample bottle. Weigh and record the weight of the sample bottle including the cap.
- 7.18.3. Weigh each sieve individually and record the results.
- 7.18.4. Gently wipe the catch pan with a fine brush to remove any residual particles. Weigh and record the weight of the catch pan.
- 7.18.5. Arrange the sieves by increasing Sieve Number, so that the largest Sieve Number is on the bottom of the stack.
- 7.18.6. Connect the catch pan to the bottom sieve and place the stack in the groove of the Ro-Tap.
- 7.18.7. Pour the entire contents of the sample bottle into the top sieve being careful not to lose any crystals.
- 7.18.8. Place the cover on the sieves and tighten them into place with the two tension nuts.
- 7.18.9. Turn the power switch to "on."

- 7.18.10. Set the time to 5 minutes and press the “Fine” Button.
- 7.18.11. Press Start and the Ro-Tap will begin to intermittently shake.
- 7.18.12. When the timer expires, remove the Ro-Tap cover and reweigh each sieve and the empty sample bottle individually. Calculate the weight of the material retained on each sieve by subtracting the final weight from the initial weight.
- 7.18.13. In order to pass, no more than 5% may be retained on the #20 Sieve, at least 60% must be retained on the #60 Sieve, and at least 95% of the sample must be retained.

$$\% \text{ Retained} = \frac{\text{Weight of Material Retained (g)}}{\text{Weight of Material Sieved (g)}} \times 100$$

7.19. SULFATES _____ :

- 7.19.1. To prepare the sample weigh 2.0 g of sample, transfer to a Nessler Color Comparison Tube and dilute to approximately 40 mL with purified water and if necessary, neutralize the solution with Hydrochloric Acid to litmus.
- 7.19.2. Prepare standard by pipetting 0.2 mL of 0.020N Sulfuric Acid into a Nessler Color Comparison Tube and dilute to approximately 40 mL with purified water.
- 7.19.3. To both the sample and the standard add 1 mL of 3N Hydrochloric Acid and 3 mL of Barium Chloride TS.
- 7.19.4. Dilute the sample and standard solution to 50 mL with purified water and allow to stand for 10 minutes. Any turbidity in the sample solution must not exceed that produced in the standard to pass.

7.20. TRACE METALS _____ :

- 7.20.1. Primary Method: Refer to NexION 350X ICP-MS, BSI-SOP-0303 and BSI-ATM-0080 for sample preparation and analysis.
- 7.20.2. Alternate Method; ICP-OES: Refer to Avio 500 ICP-OES, BSI-SOP-0362 and BSI-ATM-0102 for sample preparation and analysis.

8. COMPENDIAL DIFFERENTIATIONS

8.1. Compendial Analyses

USP Compendia
Assay
Limit of Chlorine
Identification A
Identification B
Sulfates

8.2. Harmonized Methods

Analysis Name
Acidity or Alkalinity (USP/EP)
Appearance of Solution
Bromates (USP/EP)
Iodides (USP/EP)
Loss on Drying (USP/EP)
Magnesium and Alkaline Earth-Metals (USP/EP)

8.3. In-House Validated Methods in Accordance with USP General Chapters. <1225> Validation of Compendial Procedures

Analysis Name
Trace Metals/Elemental Impurities/Limit of Iron/Heavy Metals

8.4. In-House Methods for Product Quality Description

Analysis Name
Absorbance (1M)
Particle Size