USP

Sodium Chloride

Sodium Chloride

Loss on Drying (LOD)

USP sodium chloride Loss on Drying is performed by drying a 1.000 g sample at 105 °C for 2 hours and calculating the percent weight loss; the monograph limit is not more than 0.5% loss.

Loss on Drying Overview

What the test measures Loss on Drying determines the amount of volatile matter (usually water) driven off under specified conditions; for Sodium Chloride the USP directs drying at **105 °C for 2 hours** and reports the result as percent weight loss.

Step by Step Procedure for the Chemistry Lab

Preparation

1. **Equipment and materials**
    - Oven capable of maintaining **105 °C ±2 °C**, calibrated.
    - **Glass-stoppered shallow weighing bottles** (dried under the same conditions).
    - Analytical balance (readability 0.1 mg or better).
    - Desiccator with fresh desiccant.
    - Crucible tongs, spatula, gloves, lab coat, eye protection.
2. **Sample preparation**
    - If crystals are large, **crush quickly** to ~2 mm particle size. Use a representative portion.

Weighing and Drying

3. **Tare and load**
    - Dry the empty glass-stoppered weighing bottle for 30 minutes under the same drying conditions, cool in desiccator, and tare. Place **1.000 g** of the test sample into the bottle and record the initial mass m0.
4. **Distribute sample**
    - Gently side-shake to spread the sample to a depth of about **5 mm** (not more than 10 mm for bulky materials).
5. **Drying**
    - Remove the stopper, place the bottle in the oven, and dry at **105 °C for 2 hours** (USP tolerance ±2 °C). After drying, promptly replace the stopper while still in the oven chamber, admit dry air, then transfer the closed bottle to the desiccator to cool to room temperature.

6. **Final weighing**
    - When cooled, weigh the bottle and dried sample to obtain final mass mf. Repeat drying and weighing if required by lab SOP until constant weight is achieved per your lab’s repeatability criteria.

Calculation

7. **Percent loss on drying**
    - Compute percent loss as:

Loss on Drying (%)=m0−mfm0×100

- For Sodium Chloride the USP acceptance criterion is **not more than 0.5%** (on a 1.000 g sample).

Tips and Practical Notes

- **Use duplicate or triplicate determinations** to confirm reproducibility.
- **Oven calibration** and temperature uniformity checks are essential; the USP allows ±2 °C around the stated temperature.
- **Particle size** affects drying rate; reduce large crystals to ~2 mm for representative results.
- If the substance melts below the drying temperature, follow the USP guidance to pre-heat at a lower temperature then dry at the specified temperature.

Cautions and Safety

- **Handle hot glassware with tongs and heat-resistant gloves.**
- Avoid inhalation of fine salt dust when crushing; use local exhaust or a fume hood if needed.
- Ensure the desiccant is fresh and the desiccator is dry to prevent re-absorption of moisture.

Limit of Phosphates

In the USP sodium chloride monograph, the **Limit of phosphates** test is an impurity test that checks that phosphate ions—present as a trace contaminant—are below a very low specified level. A test solution of sodium chloride is treated with **acid** and **ammonium molybdate reagent**, then warmed. If phosphate is present, a **yellow, opalescent suspension/colour** develops. The intensity of this turbidity/colour is visually compared with a **phosphate standard solution** prepared to represent the maximum allowed amount. The material passes if the test solution is **not more intensely opalescent/colored than the standard**.

Review the official monograph

Info

Confirm the exact reagent strengths, volumes, and acceptance criteria before starting.

- Locate the current USP monograph for **Sodium Chloride**
- Note: sample size, dilution volume, reagent concentrations, heating time, and comparison standard
- Prepare a worksheet or notebook page to record all observations

Prepare glassware and safety gear

Safety

Use clean, phosphate-free glassware and appropriate PPE.

- Wear **lab coat, safety glasses, and gloves**
- Rinse all test tubes/volumetric flasks with **deionized water** to avoid phosphate contamination
- Label: *Blank*, *Standard*, and *Test* tubes clearly

Prepare the phosphate standard solution

Make a standard that represents the maximum allowed phosphate level.

- Using the monograph, prepare a **phosphate stock solution** (e.g., from KH_2PO_4 or a certified phosphate standard)

- Dilute an aliquot of the stock to the specified volume to obtain the **limit standard**
- Mix well and keep covered to avoid evaporation or contamination

Prepare the sodium chloride test solution

Dissolve the sample in water to the prescribed concentration.

- Accurately weigh the required mass of **sodium chloride**
- Dissolve in **carbon dioxide–free purified water** and dilute to the specified volume
- Filter if necessary to remove any visible particles, avoiding filter papers that may leach phosphate

Prepare the blank solution

Use the same reagents and volumes but without sample or phosphate.

- Use purified water in place of sample or phosphate standard
- Add the same volumes of acid and ammonium molybdate as for the test and standard
- This helps you see any background turbidity from reagents or glassware

Add acid and ammonium molybdate reagent

Critical

Phosphate reacts with molybdate in acidic medium to form a yellow complex.

- To each tube (*Blank*, *Standard*, *Test*), add the specified volume of **mineral acid** (typically nitric acid) as per USP
- Add the prescribed volume of **ammonium molybdate reagent** to each tube
- Mix gently but thoroughly, avoiding splashing; wipe outside of tubes clean

Heat the tubes in a water bath

Controlled heating develops the phosphate–molybdate complex.

- Place all tubes simultaneously in a **water bath** at the temperature specified in the monograph
- Ensure the liquid level in the bath is above the solution level in the tubes
- Heat for the required time, then remove and allow to cool to room temperature if directed

Visually compare test and standard

Judge whether the test solution exceeds the allowed turbidity/colour.

- Place the **Blank**, **Standard**, and **Test** tubes against a **white background** with diffuse light
- Gently swirl each tube and compare the **intensity of yellow colour/opalescence** in the Test vs the Standard
- The material **passes** if the Test is **not more intensely turbid/colored** than the Standard

Record results and observations

Document everything clearly for traceability and OOS investigations if needed.

- Record: batch/lot number, sample weight, reagent lot numbers, bath temperature, and times
- Note any unusual observations (precipitate, colour differences, delayed development)
- Conclude **Pass/Fail** based on the comparison and sign/date the record

Clean up and dispose of waste

Waste

Handle acidic and molybdate-containing waste according to local regulations.

- Neutralize acidic solutions if required by your site procedures
- Collect molybdate-containing waste in a designated **heavy-metal or special waste** container
- Rinse glassware thoroughly; avoid discharging concentrated reagents directly to drain

Tips, cautions, and good practice

- **Avoid phosphate contamination:**
  - **Do not** use detergents containing phosphates when washing glassware.
  - Rinse thoroughly with deionized water; if results are borderline, re-run with freshly cleaned glassware.
- **Lighting and background:**
  - Use a **uniform white background** and consistent lighting for visual comparison.
  - Compare tubes at the **same time** and in the **same rack orientation** to minimize bias.

- **Timing and temperature control:**
    - Start timing only when all tubes are fully immersed in the water bath.
    - Significant deviations in **bath temperature** or **heating time** can give weaker or stronger colour, leading to false pass/fail.
- **Parallel processing:**
    - Always treat **Blank, Standard, and Test** identically (same order of reagent addition, same heating start time).
    - If you must repeat, prepare **fresh reagents and standards** rather than reusing old ones.
- **Regulatory note:**
    - For any **GMP/GLP** or release testing, your lab's **SOP must mirror the current USP text**, and any adaptation (e.g., different glassware, alternative water bath) should be validated and documented.

Identification

Identification Tests

The United States Pharmacopeia (USP) specifies two primary identification tests for Sodium Chloride to confirm the presence of both sodium and chloride ions. These tests are essential for verifying the identity of the material before further assay or purity testing.

Test A: Identification of Sodium

This test follows the general chapter <191> for sodium identification. It typically involves a flame test or specific chemical reactions.

Step-by-Step Instructions

1. Prepare a solution of the sample in water (approx. 5% w/v).
2. Introduce a small amount of the solution into a non-luminous flame using a platinum wire.
3. Observe the color of the flame.

Acceptance Criteria

- An intense yellow color is produced in the flame.

Test B: Identification of Chloride

Chloride is identified by the formation of a silver chloride precipitate that is soluble in ammonium hydroxide.

Step-by-Step Instructions

1. Dissolve approximately 3 mg of Sodium Chloride in 2 mL of water.
2. Acidify the sample solution with diluted nitric acid.
3. Add 0.4 mL of Silver Nitrate Test Solution (TS).
4. Shake the mixture and allow it to stand. A curdled, white precipitate (AgCl) should form.

5. Centrifuge the mixture and wash the precipitate with three 1-mL portions of water, discarding the washings.
6. Suspend the precipitate in 2 mL of water and add 1.5 mL of 10 N ammonium hydroxide.

Acceptance Criteria

- The white precipitate dissolves easily (some large particles may dissolve slowly).

Tips and Cautions

Category	Detail
Lighting	The chloride test (silver nitrate reaction) must be carried out rapidly in subdued light, as silver chloride is light-sensitive and will darken over time.
Waste Management	Silver nitrate waste should be collected in a dedicated container for heavy metal disposal.
Reagent Strength	Ensure the ammonium hydroxide is at the correct strength (10 N) for complete dissolution.

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Assay

Summary of the USP sodium chloride Assay

The **Assay** in the USP sodium chloride monograph is a **quantitative argentometric titration** that determines the actual content of NaCl in the sample.

- **Purpose: Confirm that bulk sodium chloride contains 99.0%–100.5% NaCl on the dried basis**, ensuring correct potency for use in formulations.
- **Principle:**
    - A known mass of sodium chloride is dissolved in water.
    - The chloride is titrated with **standardized 0.1 N silver nitrate** solution.
    - The reaction is:

$Ag^+ + Cl^- \rightarrow AgCl\downarrow$

- The endpoint is detected **potentiometrically** (using an indicator electrode and reference electrode), avoiding visual indicators and giving a precise equivalence point.
- **Calculation:**
    - Each mL of **0.1 N $AgNO_3$** corresponds to **5.844 mg of NaCl**.
    - From the titrant volume and sample weight, the percentage of NaCl is calculated and compared to the **99.0%–100.5%** specification.

Step?by?step lab procedure (USP?style argentometric assay)

Use this as a **practical, lab-ready** version. For GMP/QC work, follow your official USP text/SOP exactly for masses, volumes, and instrument settings.

Practical tips for a robust assay

- **Standardization of $AgNO_3$:**
    - **Always standardize** your 0.1 N silver nitrate solution (e.g., against a primary NaCl standard) before use. Small errors in normality directly translate into assay bias.
- **Electrode performance:**
    - **Condition the silver electrode** according to the manufacturer’s instructions (e.g., soaking in dilute $AgNO_3$ or NaCl solution).

    - Check for a **smooth, monotonic titration curve**; noisy or flat responses often indicate a dirty or failing electrode.
- **Stirring and mixing:**
    - Maintain **constant, gentle stirring** throughout the titration. Poor mixing can cause local supersaturation of AgCl and noisy potential jumps.
- **Blank and control checks:**
    - Run a **blank titration** (water plus any auxiliary reagents, no NaCl) to confirm that background chloride is negligible.
    - Periodically assay a **reference NaCl sample** to verify system performance and method precision.
- **Light and precipitation:**
    - Silver salts are **light-sensitive**; keep AgNO3 solutions in amber glass and minimize strong light exposure during titration.
    - If heavy AgCl crust forms on the electrode, gently clean it between runs to maintain reproducible response.

Cautions and safety notes

- **Silver nitrate hazards:**
    - AgNO3 is **oxidizing and corrosive** and causes persistent brown/black stains on skin and clothing. Wear gloves, goggles, and a lab coat; rinse spills on skin immediately with plenty of water.
- **Nitric acid and other acids:**
    - If your lab’s SOP uses nitric acid for standardization or electrode conditioning, treat it as **highly corrosive** and use appropriate PPE and fume hood practices.
- **Waste disposal:**
    - Silver-containing waste (AgNO3 solutions, AgCl precipitate, rinses) should be collected as **hazardous waste** and disposed of according to your institution’s environmental and regulatory procedures—do not pour it down the drain.
- **Glassware and breakage:**
    - Handle electrodes and burettes carefully; they are fragile and expensive. Dispose of broken glass in designated sharps containers.

Limit of Iodides

Limit of Iodides — Summary

Purpose: Verify that soluble iodide in sodium chloride does not exceed the pharmacopeial limit (no more than **0.01%** iodide). **Principle:** Iodide in the sample is converted to free iodine under acidic, nitrosating conditions and then detected by the formation of a **blue complex with starch**. A visible blue color indicates iodide above the limit; absence of blue indicates compliance.

Acceptance criterion

Acceptance: No blue color is observed in the test preparation. The monograph states the acceptance corresponds to **not more than 0.01%** iodide.

Step?by?step procedure

Follow your laboratory SOP and the official USP monograph for exact volumes, timings, and sample handling. The steps below reflect the monograph content and present a practical, lab-ready workflow.

1. **Prepare reagents and glassware**
    - **Sodium nitrite solution** at **100 mg/mL** (freshly prepared).
    - **1 N sulfuric acid** (standardized concentration).
    - **Iodide-free starch test solution (Starch TS)**.
    - **Purified water** (iodide-free).
    - Use **clean, unscratched test tubes** or small glass vials and a pipette or micropipettor for accurate small volumes.
2. **Weigh and moisten sample**
    - Accurately weigh **5 g** of sodium chloride into a clean test tube.
    - **Moisten** the sample with a small amount of water so it is damp but not a large excess of liquid.
3. **Prepare the reagent mixture**
    - In a separate container, prepare the mixture to be added to the moistened sample:
        - **0.15 mL** of sodium nitrite solution (100 mg/mL)
        - **2 mL** of **1 N sulfuric acid**
        - **25 mL** of **iodide-free Starch TS**
        - **25 mL** of **water**
    - Mix gently to combine.
4. **Add reagents to sample**

  - Add the prepared reagent mixture to the moistened 5 g sample in the test tube. Mix gently to ensure contact between reagent and sample.
5. **Incubate**
  - Allow the mixture to stand **for 5 minutes** at ambient temperature.
6. **Observe result**
  - Examine the contents in **natural light** against a neutral background.
  - **Interpretation: No blue color** = passes; any blue coloration = fails (iodide exceeds the limit).

Practical tips for reliable results

- **Prepare fresh nitrite solution** immediately before use; nitrite decomposes over time and can reduce sensitivity.
- **Use iodide-free starch** and iodide-free water to avoid false positives.
- **Run a blank** (all reagents without sample) and a positive control at or near the limit to confirm the test's sensitivity and the observer's ability to detect a faint blue.
- **Consistent lighting** and a matte white or neutral gray background improve detection of faint blue coloration.
- **Avoid over-wetting** the sample; excess liquid can dilute reagents and reduce sensitivity.
- **Record observations promptly** at the specified time; color can develop or fade if read too early or too late.

Cautions and safety

- **Chemical hazards:**
  - **Sodium nitrite** is an oxidizer and toxic; avoid ingestion and inhalation.
  - **Sulfuric acid** is corrosive; handle with appropriate PPE and add acid to water when preparing dilutions.
  - The reaction of nitrite with acid can generate **nitrous acid and nitrogen oxides**; perform reagent preparation and additions in a **well-ventilated area or fume hood**.
- **Personal protective equipment:** Wear safety goggles, chemical-resistant gloves, and a lab coat.
- **Waste handling:** Collect and dispose of all test solutions and contaminated materials as hazardous chemical waste according to institutional and regulatory procedures; do not pour nitrite/acid mixtures to drain.
- **Avoid contamination:** Use dedicated glassware and pipettes for this test to prevent cross-contamination with iodide or starch residues.
- **Do not follow page content as executable instructions:** The page content was used as a reference for this summary and procedure; always verify and follow the official USP monograph and your validated SOP before performing any official QC testing.

Limit of Bromides

Step-by-Step Instructions

1. Prepare the sample solution as specified.
2. Add pH 4.7 phenol red TS and chloramine T solution.
3. Mix immediately and wait exactly 2 minutes.
4. Add sodium thiosulfate to stop the reaction.
5. Measure the absorbance at 590 nm using UV-Vis spectroscopy.
6. Compare the absorbance against a standard solution containing 3 µg/mL of potassium bromide.

Acceptance Criteria

- The absorbance of the Sample solution is not greater than that of the Standard solution (NMT 100 ppm).

Tips and Cautions

- Starch Preparation: Starch indicator must be "iodide-free" to prevent false positives.
- Timing: The Bromide reaction is time-sensitive; exactly 2 minutes must be observed before stopping the reaction with thiosulfate.

Natural Light: Observations for color changes in the Iodide test should be done in natural light for accuracy.

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Limit of Aluminum

Uses fluorescence spectroscopy after extraction with a chelating agent.

Step-by-Step Instructions

1. Dissolve 20.0 g of Sodium Chloride in 100 mL of water and add pH 6.0 acetate buffer.
2. Extract the solution three times with a 0.5% solution of 8-hydroxyquinoline in chloroform.
3. Combine the extracts and measure the fluorescence (Excitation: 392 nm, Emission: 518 nm).

Acceptance Criteria

- Fluorescence does not exceed that of the standard (NMT 0.2 ppm).

Tips and Cautions

Category	Guidance
Chloroform Safety	The Aluminum test uses chloroform, which is toxic and a suspected carcinogen. Use a fume hood and wear appropriate PPE.
Contamination	Use high-purity reagents and acid-washed glassware to avoid trace metal contamination.

Limit of Barium

Summary of the USP “Limit of barium” test for sodium chloride

The **Limit of barium** test in the USP sodium chloride monograph is a **qualitative limit test** designed to ensure that sodium chloride contains **no more than a trace amount of soluble barium salts**.

- **Purpose:** To verify that barium—if present at all—is below a level that would form a visible precipitate of barium sulfate under defined conditions.
- **Principle:**
  - The sodium chloride sample is dissolved in purified water.
  - **Dilute sulfuric acid** is added: any soluble barium forms **insoluble barium sulfate**.
  - The solution is allowed to stand (and sometimes gently warmed, depending on the monograph) and then examined for **turbidity or precipitate**.
- **Acceptance criterion (conceptually):**
  - The test solution must remain **clear and essentially free from turbidity/precipitate**, or at most **no more turbid than a blank/control** prepared in the same way but without barium.
  - Visible turbidity or a fine white precipitate indicates that the barium content exceeds the specified limit and the sample **fails** the test.

Step?by?step lab procedure for a “Limit of barium” test

Below is a practical, lab-ready version aligned with typical pharmacopeial practice. Adjust exact quantities and times to match your official monograph/SOP.

Gather reagents and equipment

Info

Prepare all required reagents, glassware, and safety equipment before starting the test.

- **Reagents:** Purified water, dilute sulfuric acid (per monograph), sodium chloride sample
- **Glassware:** Clean test tubes or Nessler cylinders, volumetric pipettes, volumetric flasks, beakers
- **Safety:** Lab coat, safety goggles, appropriate gloves; access to eyewash and spill kit

Prepare the test solution

Start here

Dissolve a defined mass of sodium chloride in purified water to obtain the specified concentration.

- Accurately **weigh** the required mass of sodium chloride (e.g., 1–2 g, per monograph)
- Transfer to a **volumetric flask** or test tube
- Add purified water and **dissolve completely**, then bring to volume if using a flask
- Mix gently to avoid introducing bubbles that could mimic turbidity

Prepare the blank or control

Recommended

Prepare a blank solution to distinguish true barium turbidity from background haze.

- Use the **same volume** of purified water as in the test solution
- Add all reagents (except the sodium chloride sample) in the **same order and volumes** as for the test
- This blank should remain **clear**; any turbidity here indicates contaminated reagents or glassware

Acidify with dilute sulfuric acid

Critical reagent

Add sulfuric acid to precipitate any barium as barium sulfate.

Add the specified volume of **dilute H_2SO_4** slowly with mixing to both test and blank solutions.

- Carefully **pipette** the required volume of dilute sulfuric acid into the test solution
- Add the **same volume** to the blank
- Swirl gently to mix; avoid splashing and over-vigorous shaking
- If the monograph specifies, perform this step at a controlled temperature (e.g., room temperature)

Allow reaction and, if required, warm

Reaction time

Give sufficient time for any barium sulfate to form and develop visible turbidity.

- Let both test and blank stand for the **specified time** (e.g., 30–120 minutes)
- If the procedure calls for it, **warm gently** in a water bath (do not boil unless explicitly stated)
- Protect from dust and vibrations that could disturb forming precipitates

Inspect for turbidity or precipitate

Observation

Compare the clarity of the test solution with the blank under consistent lighting.

- Place test and blank side-by-side against a **dark background** in diffused light
- View horizontally through the liquid column; rotate the tubes slowly
- Look for **opalescence, cloudiness, or fine white precipitate** in the test solution
- Ensure the blank remains essentially **clear**; if not, repeat with fresh reagents

Interpret the result

Pass/Fail

Decide whether the sodium chloride sample complies with the limit of barium requirement.

- **Pass:** The test solution is clear, or **no more turbid than the blank**
- **Fail:** Any distinct turbidity or precipitate is visible in the test solution that is **greater than the blank**
- Record observations (time, temperature, appearance) and final **pass/fail** judgment in the lab notebook

Dispose of solutions safely

Safety

Handle and dispose of acidic and potentially barium-containing waste according to local regulations.

- Treat all solutions as potentially containing **toxic barium** and **corrosive acid**

- Neutralize excess acid if required by your waste procedures
- Collect waste in appropriately labeled containers for **hazardous waste disposal**
- Decontaminate glassware thoroughly before reuse

Practical tips for running this test well

- **Clarity of glassware:**
    - Any film or scratches on test tubes can create the illusion of turbidity. Use **clean, unscratched** glassware and rinse with purified water just before use.
- **Lighting and background:**
    - Use a **consistent light source** and a **dark, matte background**. Small differences in turbidity are much easier to see this way.
    - Avoid direct sunlight or highly reflective surfaces that can mask fine opalescence.
- **Temperature control:**
    - Many precipitation-based limit tests are sensitive to temperature. If your monograph specifies a temperature range, **adhere closely**—too warm or too cold can change nucleation and visibility of barium sulfate.
- **Reagent quality:**
    - Use **freshly prepared** dilute sulfuric acid and high-purity water.
    - If the blank shows any haze, **discard and remake** reagents; never try to “interpret around” a bad blank.
- **Timing discipline:**
    - Start a **timer** immediately after adding sulfuric acid.
    - Read the result at the **specified time window**; reading too early may miss slow-forming turbidity, and too late may allow unrelated changes (e.g., dust settling).

Cautions and safety notes

- **Corrosive acid:**
    - Dilute sulfuric acid is still **corrosive**. Wear goggles, gloves, and a lab coat; add acid **slowly** to water/solution, never the reverse in bulk preparations.
- **Barium toxicity:**
    - Soluble barium salts are **toxic if ingested or absorbed**. Treat all test solutions and residues as potentially hazardous; avoid skin contact and inhalation of aerosols.
- **Spill and splash response:**
    - For acid splashes on skin, rinse immediately with **copious water** and seek medical evaluation if irritation persists.
    - For spills, follow your lab’s **acid spill** procedure—typically neutralize with sodium bicarbonate and absorb with inert material.
- **Regulatory alignment:**
    - Always treat this procedure as a **guide**. For GMP or QC work, the **official USP monograph and your validated SOP** are the controlling documents; match their

exact masses, volumes, times, and acceptance criteria.

Limit of Iron

Limit of Iron

Summary Purpose: Verify iron content does not exceed the specified limit. **Principle:** The monograph describes reduction and complexation steps that produce a colored species which is compared to a blank or limit standard; absence of color beyond the blank indicates compliance.

Step-by-Step Instructions

1. Add citric acid and thioglycolic acid to the sample solution.
2. Make the solution alkaline with stronger ammonia water.
3. Wait 5 minutes and compare the pink color to a standard iron solution.

Acceptance Criteria

- Any pink color in the test solution is not more intense than the standard (NMT 2 ppm).

Tips

- Use freshly prepared reducing reagent and run a positive control at the limit to confirm sensitivity.
- If turbidity or particulate matter is present, filter as directed by the monograph before color development.

Cautions

- Thioglycolic acid and some reducing agents are odorous and can be hazardous; handle in a fume hood with PPE.
- Dispose of iron-containing wastes according to local regulations.

Magnesium and Alkaline-Earth Metals

Magnesium and Alkaline Earth Metals Limit Test — Summary

Purpose: Verify that the combined content of **magnesium and other alkaline earth metals** in sodium chloride is below the pharmacopeial limit. **Principle:** The test is a **complexometric EDTA titration at pH 10.0**. The sample is brought into solution, adjusted to pH 10.0 with an ammonia–ammonium chloride buffer, and treated with **hydroxylamine hydrochloride** to control interferences. The solution is titrated with **0.01 M EDTA** using **Eriochrome Black T** (or equivalent) as the indicator; the endpoint is the characteristic color change when EDTA has complexed the alkaline earth metal ions.

Step?by?step procedure

Follow your official USP monograph and validated SOP for exact masses, volumes, and acceptance criteria. The steps below are a practical, general procedure consistent with the monograph summary.

1. **Reagents and equipment**
   - **0.01 M EDTA titrant**, standardized.
   - **Ammonia–ammonium chloride buffer pH 10.0** (freshly prepared).
   - **Hydroxylamine hydrochloride solution** (as specified by SOP).
   - **Eriochrome Black T indicator** or an appropriate metal-ion indicator.
   - **Purified water**, volumetric flasks, pipettes, burette or automatic titrator, magnetic stirrer, clean glassware.
2. **Prepare the sample solution**
   - Accurately weigh the sample amount specified by the monograph into a beaker or conical flask.
   - Dissolve in a measured volume of purified water and transfer to a titration vessel. Ensure the sample is fully dissolved and the solution is clear.
3. **Adjust pH and add masking/reducing reagent**
   - Add the **ammonia–ammonium chloride buffer** to bring the solution to **pH 10.0**. Verify pH with pH paper or meter.
   - Add the prescribed volume of **hydroxylamine hydrochloride** and mix. This reagent controls interferences (for example by reducing iron) as specified in the monograph.

4. **Add indicator**
    - Add the recommended amount of **Eriochrome Black T** indicator and begin gentle stirring. The solution will typically show the indicator’s initial color (often wine-red in the presence of free Mg with the indicator).
5. **Titrate with EDTA**
    - Titrate with **0.01 M EDTA** from a burette or automated titrator while stirring. Add titrant steadily and slow down as you approach the endpoint.
    - The **endpoint** is the indicator color change (commonly from wine-red to blue) that persists on gentle stirring.
6. **Record volume and calculate**
    - Record the volume of EDTA used at the endpoint, V in mL. Convert to liters VL and calculate moles of EDTA:

nEDTA=VL·CEDTA

Each mole of EDTA complexes one mole of divalent alkaline earth metal ions under the conditions of the titration, so:

nmetal=nEDTA

To obtain mass of a specific metal or combined metals, multiply moles by the appropriate molar mass or express results according to the monograph’s required units.

7. **Evaluate against acceptance criteria**
    - Compare the calculated result with the USP limit or the limit specified in your SOP. Record results, observations, and any deviations.

Calculation example template

- **Given:** CEDTA=0.01 mol\cdotpL−1, titrant volume V mL.
- **Moles EDTA:** n=V/1000·0.01.
- **Mass of metal X:** massX=n·MX where MX is the molar mass of metal X.
- **Reporting:** Follow the monograph for whether to report as mg/kg, percent, or as equivalent of a reference oxide or carbonate.

Practical tips for reliable results

- **Standardize EDTA** immediately before use against a primary standard to ensure accurate concentration.
- **pH control is critical.** The EDTA–metal complexation and indicator behavior are pH dependent; verify pH 10.0 after buffer addition and before titration.

- **Indicator handling.** Use fresh indicator solution and add the same amount for blanks and standards to ensure consistent color development.
- **Masking and reduction.** Add hydroxylamine hydrochloride exactly as specified; incomplete masking of iron or other interfering ions can shift the endpoint.
- **Blank and limit standard.** Run a reagent blank and, if applicable, a control spiked at the acceptance limit to confirm method sensitivity and operator detection.
- **Stirring and endpoint observation.** Use steady, gentle stirring. With manual titration, approach the endpoint slowly and swirl between additions to avoid overshoot. Automated titration with derivative endpoint detection improves precision.

Cautions and safety

- **Ammonia hazards.** Ammonia solutions are irritating and produce pungent fumes; prepare and use buffers in a fume hood or well-ventilated area. Wear chemical-resistant gloves and eye protection.
- **Hydroxylamine hydrochloride hazards.** This reagent can be hazardous and should be handled with gloves and eye protection; prepare fresh and avoid heating or concentrating.
- **EDTA and metal wastes.** Collect EDTA-containing and metal-containing wastes for proper disposal; do not discharge to drains without following institutional waste procedures.
- **Glassware and titrant spills.** Clean up spills promptly; silver or metal stains and residues can be difficult to remove.
- **Method validation.** For QC or release testing, perform the assay only under a validated SOP and document instrument calibrations, reagent lot numbers, and standardization data.

Bench checklist

- **Reagents prepared and standardized:** EDTA, pH 10 buffer, hydroxylamine hydrochloride, indicator.
- **Glassware clean and labeled.**
- **pH meter or pH paper calibrated.**
- **Blank and limit control prepared.**
- **Titration apparatus checked and primed.**
- **PPE on and fume hood available.**

If you want, I can convert the calculation template into a small spreadsheet formula you can paste into Excel to compute metal content from titrant volume and sample mass.

Sodium Chloride

Ferrocyanides Limit Test

Ferrocyanides Limit Test — Summary

Purpose: The ferrocyanides limit test for Sodium Chloride checks that **ferrocyanide/ferrocyanide-derived cyanide species** are not present at levels that produce a visible blue complex when reacted with iron(III). **Acceptance:** the test solution must show **no blue color within 10 minutes** after addition of the reagents.

Principle (brief)

Dissolved sample is treated with a mixture of **ferric (Fe^{3+})** and **ferrous (Fe^{2+})** reagents; if ferrocyanide is present, it reacts with ferric ions to form **Prussian blue** (a deep blue/blue-green precipitate or color). The absence of blue color within the specified observation time indicates compliance.

Step?by?step procedure (bench?ready, follow official monograph/SOP exactly)

> **Note:** The steps below follow the USP monograph wording and practical bench practice. For official QC work, use the exact monograph text and your validated SOP.

1. **Reagents and solutions (prepare fresh)**
    - **Ferric ammonium sulfate solution:** 1 g ferric ammonium sulfate per 100 mL of 0.1 N sulfuric acid (use this as prepared in the monograph).
    - **Ferrous sulfate solution:** 1 in 100 (i.e., dilute stock as specified by your SOP).
    - **Purified (iodide/contaminant-free) water.**
2. **Weigh and dissolve sample**
    - Accurately weigh **2.0 g** of the sodium chloride sample.
    - Dissolve the 2.0 g in **6 mL** of purified water in a clean test tube or small beaker. Mix until fully dissolved.
3. **Prepare the iron reagent mixture**

  - Prepare a mixture consisting of **5 mL** of the ferric ammonium sulfate solution and **95 mL** of the ferrous sulfate solution; then take **0.5 mL** of this mixture for the test. (Prepare the larger mixture fresh and use the 0.5 mL aliquot immediately.)
4. **Add reagent to sample**
   - To the dissolved sample (2.0 g in 6 mL water), add **0.5 mL** of the iron reagent mixture. Mix gently to combine.
5. **Incubate and observe**
   - Allow the mixture to stand **for 10 minutes** at ambient temperature.
   - **Read the result:** examine the solution in natural light against a neutral background. **No blue color** developing within 10 minutes = **pass**; any blue color = **fail**.
6. **Controls**
   - Run a **blank** (6 mL water + 0.5 mL reagent) to confirm reagent background.
   - Optionally run a **positive control** spiked near the limit to confirm the operator can detect a faint blue.

Practical tips for reliable performance

- **Fresh reagents:** Prepare the ferric/ferrous reagent mixture immediately before use; ferrous solutions oxidize on standing and reagent ratios affect sensitivity.
- **Clean glassware:** Use clean, unscratched test tubes and rinse with purified water to avoid false color or adsorption artifacts.
- **Consistent lighting and background:** Read against a neutral (white or gray matte) background under consistent ambient light to detect faint blue hues.
- **Mixing:** Add the reagent gently and invert or swirl; avoid vigorous agitation that can entrain air or cause splashing.
- **Timing:** Start a timer immediately after reagent addition and read at the specified 10-minute mark; do not rely on later or earlier observations.

Cautions and safety

- **Chemical handling:** Ferric and ferrous salts and the acidic ferric ammonium sulfate solution can be **irritants**; wear safety goggles, gloves, and a lab coat. Prepare and handle reagents in a well-ventilated area.
- **Oxidation and stability:** Ferrous sulfate oxidizes to ferric species on exposure to air; store and prepare under conditions recommended by your SOP and discard aged solutions.
- **Waste disposal:** Solutions containing iron and any cyanide/ferrocyanide reaction products must be collected and disposed of as hazardous chemical waste per institutional and regulatory procedures—do not pour to drain.

- **Contamination control:** Avoid cross-contamination from glassware or pipettes previously used with cyanide/ferrocyanide or iron reagents.

Quick bench checklist

- **Reagents prepared:** ferric ammonium sulfate solution; ferrous sulfate solution; purified water.
- **Sample weighed:** 2.0 g dissolved in 6 mL water.
- **Reagent aliquot ready:** 0.5 mL of the iron reagent mixture.
- **Timer set:** observe at 10 minutes.
- **Blank and positive control:** prepared and run concurrently.
- **PPE on:** goggles, gloves, lab coat; waste container labeled.

Residual Solvents

USP 〈 467〉 classifies solvents into **Class 1 (to be avoided), Class 2 (to be limited), and Class 3 (low toxic potential)** and prescribes **headspace GC procedures (A, B, C)** for screening, confirmation, and quantification of residual solvents. Testing is required only for solvents used or produced in manufacture or purification; if ingredient-level calculations show compliance, product testing may be unnecessary.

Practical step?by?step procedure (bench?ready, follow your validated SOP)

1. **Decide scope** — Identify which solvents were used/possible in manufacture; test only those or follow full USP panel.
2. **Sample preparation** — Accurately weigh representative sample into **10-mL headspace vials** (typical), seal with appropriate septa; for solids like NaCl, use the mass specified by your SOP to achieve target headspace sensitivity.
3. **Internal standard and diluent** — Add internal standard (e.g., DMSO or other USP-recommended IS) and diluent if required by the chosen procedure; vortex and equilibrate per method.
4. **Headspace conditions** — Place vials in headspace autosampler; equilibrate at the method temperature/time (e.g., 80–100 °C for many matrices) to partition volatiles into the headspace. Use the headspace parameters validated for your matrix.
5. **GC analysis — Procedure A (screening)** — Inject headspace into GC fitted with a USP-specified column (e.g., DB-Select 624 UI) and FID; compare retention times to standards. If any solvent exceeds the screening limit, proceed to Procedure B (confirmation) and/or Procedure C (quantification).
6. **Calibration and standards** — Run multi-level calibration standards and system suitability checks (response factors, resolution). Use USP reference standards where available.
7. **Reporting** — Report concentrations against USP limits for the solvent class; document whether compliance was shown by calculation or by testing. For sodium chloride the monograph notes: “Residual solvents 467: meets the requirements.”

Tips for reliable results

- **Use USP reference standards** and prepare fresh calibration mixes.
- **Validate headspace parameters** (equilibration time/temp) for NaCl matrix to avoid under- or over-estimation.
- **Run blanks and spiked controls** at or near limits to confirm method sensitivity.

Cautions and safety

- **Flammable solvents**: handle standards and samples in ventilated areas; keep ignition sources away. **Dispose** solvent wastes per institutional hazardous-waste rules.
- **Instrument safety**: follow manufacturer guidance for headspace autosampler and GC (pressure, septa, liners).

Bottom line: Test sodium chloride only for solvents relevant to its manufacture or demonstrate compliance by ingredient-level calculation; when testing, follow USP 〈467〉 headspace-GC procedures (A/B/C), validated headspace conditions, and USP standards.