Pharmaceutical Quantitative

Analysis 1

Unit 7

Definition of Term

Gravimetric Analysis is a quantitative method based on the measurement of the mass of a final product to determine the amount of an original analyte.

If you know the exact weight of a pure precipitate and its chemical formula, you can calculate exactly how much of the drug was in the starting sample using stoichiometric factors

Core Principle

The principle of gravimetric analysis is based on **stoichiometry and conservation of mass**.

If a compound with known composition is formed quantitatively, the amount of analyte can be determined from the mass of that compound.

Instead of measuring volume like titration, gravimetry measures weight of a compound that contains the analyte.

In most pharmaceutical gravimetric procedures, the analyte is:

- Converted into an insoluble compound
- Filtered
- Dried or ignited
- Weighed

The measured mass is then used to calculate the amount of analyte in the original sample.

When a Volumetric assay gives a borderline result, Gravimetry is the "referee." Because it relies on mass which is an absolute SI unit, rather than volume which changes with temperature. Gravimetric is more accurate.

Gravimetric Process

The "Life Cycle of a Precipitate":

1. **Preparation/Precipitation:** Adding a precipitating agent to turn the dissolved drug into a solid.
2. **Digestion "The Aging Process":** Letting the precipitate sit in the mother liquor. To grow larger, purer crystals that are easier to filter.
3. **Filtration & Washing:** Separating the solid from the liquid and washing away "clingy" impurities.
4. **Drying/Ignition to Constant Weight:** Heating the sample until the weight stops changing. This ensures all water is gone.

Main Types of Gravimetric Analysis

There are two main forms.

A. Precipitation Gravimetry

The most common form. The analyte is converted into a sparingly soluble precipitate.

Steps usually include:

1. Dissolution of sample
2. Precipitation of analyte
3. Digestion of precipitate
4. Filtration
5. Washing
6. Drying or ignition
7. Weighing

Example:

Chloride analysis as AgCl.

B. Volatilization Gravimetry

The analyte is converted into a gas and the loss or gain of mass is measured.

Example:

Determining water content by measuring mass lost after heating.

Standard Gravimetric Techniques

1. Ash Content Determination (The "Purity Test")

You are checking a shipment of Ginger or **Gum Arabic** for the production of herbal syrups.

- **The Process:** The sample is ignited in a muffle furnace at high temperatures at around 600°C until all organic matter is burned away. What remains is the "Ash."

If the ash content is higher than the USP limit, it means the sample is "dirty"—it contains sand, soil, or stones added to increase the weight of the raw material. It is a direct measure of **adulteration**.

2. Loss on Drying (LOD) / Moisture Content

Testing Granulated Paracetamol or Excipients like Lactose before they are pressed into tablets.

- **The Process:** A precise weight of the sample is heated in an oven to a constant weight. The mass lost is the water or volatile solvent.

If a tablet mix is too "wet", means high LOD, the tablets will crumble, the active drug may hydrolyze/break down, and bacteria will grow. We weigh the "invisible" water to ensure the drug's shelf-life.

3. Assay of Sulfate (Magnesium Sulfate/Albuterol Sulfate)

The Scenario: Verifying the concentration of Magnesium Sulfate used in IV fluids.

- **The Process:** The sample is reacted with Barium Chloride to form a precipitate of Barium Sulfate. This solid is filtered, washed, dried, and weighed.

$BaSO_4$ is incredibly insoluble. This makes it the most accurate way to verify that an IV solution has the exact electrolyte balance required for a patient's heart and nerve function.

4. Extractives (Crude Drug Analysis)

The Scenario: Determining the potency of a Senna leaf extract for laxative preparations.

- **The Process:** A known weight of the drug is macerated in a solvent like alcohol. The solvent is then evaporated to dryness in a tared evaporating dish. The residue that remains is weighed.

This weight tells us the "yield" of active constituents. If the weight is too low, the extract is "weak" and the medicine won't work. We are weighing the **essence of the drug**.

Analyte / Test	Method Type	Pharmaceutical Importance
Crude Drugs	Ash Determination	Detects inorganic contaminants (soil/sand).
Antibiotics / Granules	Loss on Drying	Prevents degradation and microbial growth.
Sulfate-containing Drugs	Precipitation	Absolute verification of chemical identity.
Botanical Extracts	Extractive Value	Measures the concentration of active principles.

Before modern instruments existed, gravimetric analysis was considered the ***gold standard*** because it is:

- Highly accurate
- Based on mass measurement
- Independent of indicators or titrants

Many atomic weights in early chemistry were determined using gravimetric methods.

Even today, gravimetry is used to validate other analytical methods.

The History: The Alchemy of the Scale

Gravimetry is as old as the balance itself, but its scientific "birth" is tied to the transition from Alchemy to Chemistry.

- **The Age of Lavoisier (Late 18th Century):** Antoine Lavoisier, *the Father of Modern Chemistry*, is the hero of Gravimetry. Before him, chemists focused on color and "spirit." Lavoisier insisted on the **Law of Conservation of Mass**. He proved that matter is neither created nor destroyed by weighing his reactants before and after. This shifted chemistry from a qualitative guessing game to a quantitative counting game.
- **The Determination of Atomic Weights (19th Century):** Scientists like **Jöns Jacob Berzelius** spent decades performing thousands of gravimetric precipitations. By weighing how much Silver Chloride was produced from a known amount of Silver, they calculated the first accurate atomic weights of the elements.
- **T.W. Richards (The Nobel Standard):** Theodore William Richards received the Nobel Prize in 1914 for his "purity" in gravimetric work. He redefined the atomic weights of oxygen and silver with such precision that his values stood for decades.

In the pharmaceutical industry, we call it the "Gold Standard" or the *Primary Method* for three specific, reality-grounded reasons:

A. Absolute vs. Relative (The "No-Standard" Method)

- **The Theory:** Titration is a *relative* method. To know the concentration of your drug, you must first "standardize" your titrant against a "primary standard." If your standard is wrong, your whole assay is wrong.
- **The Reality:** Gravimetry is an **absolute method**. You don't need a "standardized liquid" to tell you the mass. The mass *is* the truth. If you weigh 1.0000g of a pure precipitate, that gram is universally recognized. It is the final referee in any chemical dispute.

B. The "Constant Weight" Reliability

In the lab, we heat the crucible, cool it in a desiccator, and weigh it. We repeat this until the mass stops changing.

This "Constant Weight" ensures that every single molecule of water which fluctuates with humidity, is gone. In pharmacy, we cannot allow *water weight* to be sold as *drug weight*.

Gravimetry is the only way to guarantee that 100% of what you are weighing is the actual substance.

Characteristics of a Good Gravimetric Precipitate

For accurate results, the precipitate must have certain properties:

1. **Low solubility** – to ensure complete precipitation
2. **High purity** – free from contamination
3. **Large particle size** – easier filtration
4. **Stable composition** – should not decompose during drying
5. **Known chemical formula** – required for calculation

Sources of Error in Gravimetric Analysis

Gravimetry can be extremely precise but also sensitive to errors.

Common issues include:

- **Co-precipitation** – impurities trapped in precipitate
- **Post-precipitation** – unwanted compounds forming later
- **Incomplete washing**
- **Loss during filtration**
- **Decomposition during drying**