BP704T · B.Pharm Semester VII · Theory Notes

Modern Analytical Techniques

Unit II — X-Ray Diffraction and Thermal Analysis

Unit II (8 hours)

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit II (8 hours).

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CHAPTER 3: X-Ray Diffraction Methods

3.1 Learning Objectives

After studying this chapter, you will be able to:

1 Explain the origin of X-rays in simple words.

2 Describe the basic aspects of crystals (unit cell, lattice, Miller indices).

3 Explain X-ray crystallography and Bragg's law.

4 Solve a numerical based on Bragg's law ($n\lambda = 2d \sin\theta$).

5 Describe the rotating crystal technique.

6 Compare single crystal diffraction and powder diffraction.

7 Outline the workflow of structural elucidation by X-ray diffraction.

8 List applications of X-ray diffraction in pharmacy.

3.2 Definitions

- **X-rays:** A form of high-energy radiation with very short wavelength (about the same size as the distance between atoms in a crystal).
- **Diffraction:** The bending and spreading of waves when they pass through a regular arrangement of obstacles — here, X-rays scattered by atoms in a crystal.
- **Crystal:** A solid in which atoms, ions, or molecules are arranged in a regular, repeating 3D pattern.
- **Unit cell:** The smallest repeating box of a crystal; the whole crystal is built by repeating it in all directions.
- **Lattice:** The regular 3D arrangement of points representing positions in a crystal.
- **Miller indices (hkl):** Three numbers that name a particular set of parallel planes in a crystal.
- **Bragg's law:** $n\lambda = 2d \sin\theta$ — the equation relating X-ray wavelength, spacing between crystal planes, and the angle at which strong reflection (diffraction) occurs.
- **X-ray crystallography:** The science of determining the arrangement of atoms in a crystal from its X-ray diffraction pattern.
- **Polymorphism:** The ability of a drug to exist in more than one crystal form — very important in pharmacy.

3.3 Terminology Table

Term	Simple Meaning
X-ray tube	The device that produces X-rays

Term	Simple Meaning
Target / Anode	The metal plate (often copper) hit by electrons to produce X-rays
Kα (K-alpha) radiation	The strong, single-wavelength X-rays emitted by the target metal
Interplanar spacing (d)	Distance between two neighbouring crystal planes
Diffraction pattern	The pattern of spots or lines produced by diffracted X-rays
Single crystal	One perfect, unbroken crystal piece
Powder	A sample ground into thousands of tiny randomly-oriented crystals
Rotating crystal technique	Method where a single crystal is rotated in the X-ray beam
Structural elucidation	Finding the exact 3D arrangement of atoms in a molecule

3.4 Simple Explanations

3.4.1 Origin of X-Rays (Simple Idea)

Inside an **X-ray tube**, electrons are boiled off a hot filament (like in an old light bulb) and smashed at high speed into a metal **target** (usually copper). When a fast electron knocks out an inner electron of a copper atom, an outer electron jumps down to fill the gap. This jump releases energy as **X-rays**. The strongest X-rays from copper are called **Kα radiation** — they have one fixed wavelength, which is ideal for diffraction experiments.

Analogy: Like throwing a fast ball (electron) at a stack of boxes (atom) — a box falls out (inner electron ejected) and another box slides down to fill the gap, releasing a "thud" of energy (X-ray).

> **Key takeaway:** Fast electrons hit a metal target → inner electrons ejected → outer electrons fall in → X-rays emitted.

3.4.2 Basic Aspects of Crystals

A **crystal** is a solid with a perfectly repeating arrangement — like a 3D wallpaper pattern. Key ideas:

- **Unit cell:** The smallest repeating "box". Repeat it millions of times in all directions and you get the whole crystal. (Like one tile in a tiled floor.)
- **Lattice:** The framework of points showing where the repeating units sit.
- **Crystal planes:** Imaginary flat sheets passing through the lattice points. X-rays reflect off these planes.
- **Miller indices (hkl):** A naming system for these planes — three small numbers (e.g., 111, 200) that tell which set of planes we mean. You do not need to calculate them; just know they label the planes.

Analogy: A crystal is like a perfectly stacked pile of oranges — the unit cell is one small repeating group of oranges, and Miller indices are like aisle numbers in a supermarket telling you which shelf (plane) you mean.

3.4.3 X-Ray Crystallography and Bragg's Law

Because X-ray wavelengths are about the same size as the gaps between atoms, crystal planes act like mirrors for X-rays — but only at specific angles. **Bragg's law** gives that angle:

```
nλ = 2d sinθ
```

- n = order of reflection (1, 2, 3...; usually 1)
- λ (lambda) = wavelength of the X-rays
- d = distance between neighbouring crystal planes
- θ (theta) = angle between the X-ray beam and the crystal plane (the "Bragg angle")

Simple meaning: Strong diffraction happens only when the extra distance travelled by X-rays reflecting off the deeper plane exactly equals a whole number of wavelengths — then the waves add up (constructive interference) instead of cancelling.

3.4.4 Worked Numerical Example — Bragg's Law

Question: X-rays of wavelength 1.54 Å strike a crystal. First-order (n = 1) diffraction is observed at θ = 15°. Calculate the interplanar spacing d.

Solution — step by step:

Step 1: Write Bragg's law. nλ = 2d sinθ

Step 2: Rearrange for d. d = nλ / (2 sinθ)

Step 3: Insert values. n = 1, λ = 1.54 Å, θ = 15°. sin 15° = 0.2588

Step 4: Calculate. d = (1 × 1.54) / (2 × 0.2588) = 1.54 / 0.5176

Step 5: Divide. d = **2.975 Å ≈ 2.98 Å**

Answer: d ≈ 2.98 Å.

Key takeaway: Measuring the angle θ lets us calculate the distance between atomic planes — the first step to mapping the crystal.

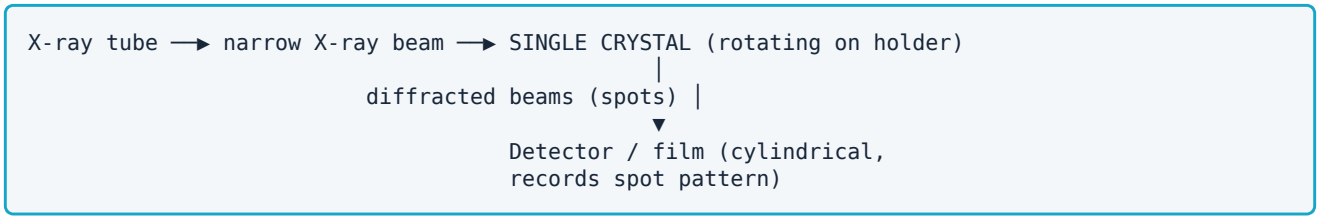
3.5 Rotating Crystal Technique

3.5.1 How It Works

1. A **single crystal** (one perfect piece) is mounted on a holder.
2. A narrow X-ray beam strikes it while the crystal is **slowly rotated**.
3. As it rotates, different sets of crystal planes come into the correct Bragg angle one by one.
4. Each time a set of planes satisfies Bragg's law, a **diffracted spot** appears on the detector or photographic film around the crystal.
5. The pattern of spots is recorded and analyzed to work out the crystal structure.

Why rotate? A stationary crystal only shows a few planes at the Bragg angle. Rotating brings every set of planes into position in turn — like turning a disco ball so each mirror facet flashes in sequence.

3.5.2 Simple Block Diagram



3.6 Single Crystal vs Powder Diffraction

3.6.1 Single Crystal Diffraction

Uses one perfect crystal. Gives a pattern of sharp **spots**. From the positions and intensities of spots, the complete 3D arrangement of atoms can be calculated — the gold standard for structure determination. Limitation: growing a perfect single crystal of a drug can be difficult and slow.

3.6.2 Powder Diffraction

Uses a powder — thousands of tiny crystals in random orientations. Because every orientation is present at once, no rotation is needed. Gives a pattern of **rings/lines** (recorded as intensity vs. angle 2θ). Best for: identifying the crystal form (fingerprint matching), checking crystallinity, and detecting polymorphs. Limitation: less detailed than single crystal data.

3.6.3 Comparison Table

Feature	Single Crystal Diffraction	Powder Diffraction
Sample	One perfect crystal	Powder (many tiny crystals)
Pattern	Spots	Rings / lines (peaks vs 2θ)
Information	Complete 3D atomic structure	Crystal form identification, crystallinity
Sample preparation	Difficult (must grow a good crystal)	Easy (just grind the sample)
Main pharma use	Determining exact structure of a new drug	Polymorph identification, batch comparison

Key takeaway: Single crystal = full structure but hard sample; powder = easy fingerprint for routine identification.

3.7 Structural Elucidation Workflow

3.7.1 Flowchart — From Crystal to Structure

```
Grow / obtain a suitable crystal (or powder)
        |
        ▼
Mount sample; expose to X-ray beam (rotating crystal / powder)
        |
        ▼
Record diffraction pattern (spots or peaks vs angle)
        |
        ▼
Measure spot positions and intensities
        |
        ▼
Calculate unit cell size and plane spacings (using Bragg's law)
        |
        ▼
Solve the structure (work out where atoms sit — done by computer)
        |
        ▼
Refine and verify the 3D molecular structure
```

3.7.2 Simple Explanation

The diffraction pattern is like a shadow of the crystal's atomic arrangement. A computer works backwards from the shadow (spot positions and brightness) to rebuild where each atom sits. The final result is a 3D model of the molecule — bond lengths and angles included.

3.8 Applications of X-Ray Diffraction in Pharmacy

Application	Simple Explanation
Polymorphism identification	Different crystal forms of the same drug give different powder patterns — XRD tells them apart
Crystallinity check	Tells whether a sample is crystalline or amorphous (amorphous gives no sharp peaks)
Crystal structure of APIs	Single crystal XRD gives the exact 3D structure of a new drug molecule
Batch-to-batch comparison	Powder patterns of production batches are matched against a reference pattern
Salt and co-crystal screening	Identifies new solid forms of drugs with better solubility
Excipient characterization	Checks the crystal form of excipients used in tablets

3.9 Infographic Concept Box

INFOGRAPHIC CONCEPT: "XRD in One Picture" — Left: an X-ray tube with electrons smashing into a copper target, lightning-style X-rays coming out labelled "Kα radiation". Centre: a crystal drawn as a neat stack of layers with parallel planes highlighted and labelled "planes (hkl), spacing d"; an incoming X-ray arrow hitting at angle θ and bouncing off, with the formula "nλ = 2d sinθ" in a badge. Right: two panels — "Single crystal → spot pattern → full 3D structure" and "Powder → ring/peak pattern → fingerprint ID". Bottom strip: "Pharma win: finds polymorphs that change drug solubility".

3.10 Tables

Table 1: X-Ray Production Summary

Step	What Happens
1	Filament heated → electrons released
2	Electrons accelerated towards metal target
3	Fast electron knocks out an inner-shell electron of target atom
4	Outer electron falls into the vacancy
5	Energy released as X-rays (Kα radiation)

Table 2: Useful Angles and Terms

Symbol	Name	Meaning
λ	Wavelength	Fixed for a given target (e.g., Cu Kα)
d	Interplanar spacing	Distance between crystal planes
θ	Bragg angle	Angle between beam and crystal plane
n	Order	1, 2, 3... (usually 1)

3.11 Examples

Example 1 — Bragg's law: Cu Kα X-rays (λ = 1.54 Å) show first-order diffraction at θ = 15° → d ≈ 2.98 Å (worked in section 3.4.4).

Example 2 — Polymorph check: Two batches of a drug give different powder XRD peak positions. Conclusion: the batches contain different polymorphs — investigate, because solubility and bioavailability may differ.

Example 3 — Amorphous vs crystalline: A spray-dried powder shows only a broad hump with no sharp peaks → the sample is amorphous, not crystalline.

3.12 Analogies

- **X-ray production:** Like a fast ball knocking a box out of a stack, and another box sliding down with a thud (energy = X-ray).
- **Crystal:** Like a perfectly stacked pile of oranges or a tiled floor — the unit cell is one tile.
- **Bragg's law:** Like echoes in a corridor — you hear a strong echo only at certain spots where sound waves add up.
- **Rotating crystal:** Like a disco ball — each mirror flashes as it turns into the light.
- **Powder diffraction:** Like a crowd of people holding mirrors at random angles — some mirror always flashes at you.

3.13 Pharmacy Relevance

- Different polymorphs of a drug can have very different solubility and bioavailability — XRD is the standard tool to identify and control them.

- Regulatory filings for new drugs require solid-state characterization, in which XRD plays a central role.
- In formulation, XRD checks that the drug's crystal form has not changed during processing (milling, compression, coating).

3.14 India Context

- Indian pharmaceutical companies routinely use powder XRD for polymorph screening and batch quality control in solid-dosage manufacturing.
- Single crystal X-ray facilities at Indian national laboratories and universities support structure determination for new drug candidates discovered in India.
- Skill in reading powder diffraction patterns is valued in pharmaceutical solid-state analysis jobs across India's formulation hubs.

3.15 Key Points

1. X-rays are produced when fast electrons hit a metal target; Kα radiation is the useful beam.
2. A crystal is a repeating 3D arrangement; the unit cell is the smallest repeating box.
3. Miller indices (hkl) name sets of crystal planes.
4. Bragg's law: $n\lambda = 2d \sin\theta$ — strong diffraction only at the Bragg angle.
5. Rotating crystal technique: rotate a single crystal so each plane set meets the Bragg angle in turn; spots are recorded.
6. Single crystal diffraction → complete 3D structure (spots); powder diffraction → fingerprint identification (peaks vs 2θ).
7. Structural elucidation: pattern → measure spots → calculate cell → solve atom positions → 3D model.
8. Pharma uses: polymorphism, crystallinity, API structure, batch comparison.

3.16 Common Confusions

- **θ vs 2θ:** θ is the Bragg angle (beam to plane); instruments usually report 2θ (angle between incoming and diffracted beam) — don't mix them in Bragg's law.
- **Single crystal vs powder:** Single crystal gives spots and full structure; powder gives peaks and is for identification — students often swap their uses.
- **XRD vs X-ray imaging:** XRD studies atomic arrangement in crystals; it is not a body scan.
- **Amorphous materials:** They do not give sharp diffraction peaks — a broad hump is normal, not an instrument fault.

3.17 Common Mistakes

1. Using 2θ directly in Bragg's law instead of θ — always halve the instrument's 2θ value first.

2 Forgetting to convert units consistently (λ and d must be in the same units, e.g., both in Å).

3 Assuming every peak shift means a new polymorph — preferred orientation and sample preparation can also shift peaks.

4 Trying powder diffraction for full 3D structure determination — use single crystal for that.

5 Expecting sharp peaks from an amorphous sample.

3.18 Mnemonics

- **Bragg's law — "Never Let Two Dogs Sing": nλ = 2d sinθ** — **N**ever (**n**), **L**et (**λ**), **T**wo (**2**), **D**ogs (**d**), **S**ing (**sinθ**).
- **Crystal basics — "ULM": U**nit cell (smallest box), **L**attice (framework), **M**iller indices (plane names).
- **X-ray origin — "EKE": E**lectrons hit target → **K**nock out inner electron → **E**mit X-rays (Kα).

3.19 Exam Summary

X-rays originate when high-speed electrons strike a metal target, ejecting inner electrons; outer electrons falling in emit Kα radiation. Crystals are repeating 3D arrangements described by the unit cell, lattice, and Miller indices (hkl) for crystal planes. Bragg's law nλ = 2d sinθ gives the angle of strong diffraction; measuring θ lets us calculate interplanar spacing d (e.g., λ = 1.54 Å, θ = 15°, n = 1 → d ≈ 2.98 Å). In the rotating crystal technique, a single crystal is rotated in the X-ray beam so each set of planes meets the Bragg angle in turn, producing a spot pattern. Single crystal diffraction gives complete 3D atomic structure (spots) but needs a perfect crystal; powder diffraction uses randomly oriented tiny crystals giving peaks vs 2θ for fingerprint identification and is easy to prepare. Structural elucidation workflow: obtain crystal → record pattern → measure spots → calculate cell → solve atom positions → 3D model. Applications: polymorphism identification, crystallinity check, API crystal structure, batch comparison, salt/co-crystal screening.

3.20 One-Minute Revision

- X-rays: electrons → metal target → Kα out.
- Crystal = repeating pattern; unit cell = smallest box; (hkl) = plane names.
- nλ = 2d sinθ; use θ, not 2θ.
- Rotating crystal: turn crystal, collect spots.
- Single crystal = full structure; powder = fingerprint.
- Pharma: polymorphs, crystallinity, batch match.

3.21 Short Answer Questions

1 How are X-rays produced in an X-ray tube?

2 What is Kα radiation?

3 Define unit cell, lattice, and Miller indices.

4 State Bragg's law and explain each term.

5 Describe the rotating crystal technique briefly.

6 Differentiate single crystal and powder diffraction (any two points).

7 What information does a powder diffraction pattern give?

8 How does XRD help in identifying polymorphs?

9 What does a broad hump with no sharp peaks indicate?

10 Give two pharmaceutical applications of XRD.

3.22 Long Answer Questions

1 Explain the origin of X-rays with a neat labelled description of the X-ray tube. What is Kα radiation and why is it useful?

2 Describe the basic aspects of crystals: unit cell, lattice, crystal planes, and Miller indices, with simple diagrams described in words.

3 State and explain Bragg's law. Solve: X-rays of wavelength 1.54 Å give first-order diffraction at θ = 15°. Calculate d showing all steps.

4 Describe the rotating crystal technique with a block diagram. How is the diffraction pattern used for structural elucidation?

5 Compare single crystal diffraction and powder diffraction under the heads: sample, pattern obtained, information, sample preparation, and pharmaceutical use.

6 Write a note on the applications of X-ray diffraction in pharmacy, with emphasis on polymorphism.

3.23 MCQs with Answer Keys

Q1. X-rays are produced when: a) Slow neutrons hit water b) High-speed electrons strike a metal target c) Light passes through glass d) Sound waves reflect **Answer: b) High-speed electrons strike a metal target**

Q2. Bragg's law is: a) $n\lambda = 2d \sin\theta$ b) $\lambda = d \sin\theta$ c) $n\lambda = d\theta$ d) $E = mc^2$ **Answer: a) $n\lambda = 2d \sin\theta$**

Q3. In Bragg's law, 'd' represents: a) Detector distance b) Interplanar spacing c) Tube diameter d) Film thickness **Answer: b) Interplanar spacing**

Q4. Miller indices are used to: a) Count electrons b) Name sets of crystal planes c) Measure temperature d) Weigh samples **Answer: b) Name sets of crystal planes**

Q5. The smallest repeating unit of a crystal is called the: a) Atom b) Unit cell c) Molecule d) Ion **Answer: b) Unit cell**

Q6. In the rotating crystal technique, the crystal is rotated to: a) Cool it down b) Bring each set of planes to the Bragg angle in turn c) Mix the sample d) Increase X-ray intensity **Answer: b) Bring each set of planes to the Bragg angle in turn**

Q7. A powder diffraction pattern is best used for: a) Full 3D structure determination b) Fingerprint identification of crystal forms c) Measuring melting point d) Counting atoms **Answer: b) Fingerprint**

identification of crystal forms

Q8. An amorphous sample in XRD shows: a) Sharp spots b) Sharp peaks c) A broad hump with no sharp peaks d) Nothing at all **Answer: c) A broad hump with no sharp peaks**

Q9. Different polymorphs of a drug can be distinguished by XRD because they give: a) The same pattern b) Different diffraction patterns c) No pattern d) Coloured patterns **Answer: b) Different diffraction patterns**

Q10. For λ = 1.54 Å, n = 1, θ = 15° (sin15° = 0.2588), the interplanar spacing d is approximately: a) 1.54 Å b) 2.98 Å c) 5.96 Å d) 0.52 Å **Answer: b) 2.98 Å**

3.24 Viva Questions

1 How are X-rays generated?

2 What is the target material commonly used in X-ray tubes?

3 Define diffraction.

4 What is a unit cell?

5 State Bragg's law.

6 What is the difference between θ and 2θ?

7 What does the rotating crystal technique record — spots or rings?

8 Which is easier to prepare: a single crystal or a powder sample?

9 What is polymorphism and why does it matter in pharmacy?

10 Name two applications of powder XRD.

3.25 Application-Based Questions

1 Two production batches of a tablet show different powder XRD patterns although the chemical assay is identical. What is the likely cause, and why should the QC manager be concerned?

2 A researcher cannot grow a good single crystal of a new drug. Which XRD method can still be used, and what information will it give?

3 Calculate the interplanar spacing d if second-order (n = 2) diffraction is observed at θ = 20° with λ = 1.54 Å (sin20° = 0.342). Show steps.

4 A spray-dried formulation intermediate shows no sharp XRD peaks. Is the instrument faulty? Explain.

3.26 References

- Cullity & Stock
- Skoog / Holler / Crouch

CHAPTER 4: Thermal Analysis

4.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define thermal analysis in simple words.

2 Explain TGA (thermogravimetry): principle, TG curve parts, applications.

3 Explain DTA (differential thermal analysis): principle and the ΔT concept.

4 Explain DSC (differential scanning calorimetry): principle, heat flow concept, and its two types.

5 Compare TGA, DTA, and DSC in a table.

6 List factors affecting thermal analysis measurements.

7 Draw simple block diagrams of TGA, DTA, and DSC instruments.

8 List pharmaceutical applications of thermal analysis.

4.2 Definitions

- **Thermal analysis:** A group of techniques that study how a material's properties change as its temperature is increased (or decreased) in a controlled way.
- **TGA (Thermogravimetric Analysis):** Measures the change in mass of a sample as temperature rises — answers "does it lose weight on heating, and when?"
- **DTA (Differential Thermal Analysis):** Measures the temperature difference (ΔT) between the sample and an inert reference as both are heated — detects heat absorbed or released.
- **DSC (Differential Scanning Calorimetry):** Measures the heat flow into or out of the sample compared to a reference — precisely quantifies melting, crystallization, and decomposition energies.
- **TG curve:** The graph from TGA: mass (y-axis) vs temperature (x-axis).
- **Inert reference:** A material (like alumina) that shows no thermal changes in the experiment's temperature range, used for comparison in DTA/DSC.
- **Heating rate:** How fast the temperature rises, e.g., 10 °C per minute.
- **Polymorphism:** Same drug, different crystal forms — thermal analysis detects the differences.

4.3 Terminology Table

Term	Simple Meaning
Furnace	The heated chamber holding the sample
Crucible / Pan	The tiny container holding the sample (platinum, alumina, aluminium)
Thermocouple	A sensor that measures temperature

Term	Simple Meaning
Microbalance	An extremely sensitive weighing balance used in TGA
Endothermic	A change that absorbs heat (e.g., melting)
Exothermic	A change that releases heat (e.g., crystallization, decomposition)
Baseline	The flat part of the curve where nothing is happening
Onset temperature	The temperature at which a change begins
Purge gas / Atmosphere	The gas (e.g., nitrogen) flowing around the sample during heating
Heat flux DSC	DSC type measuring temperature difference, converted to heat flow
Power-compensated DSC	DSC type keeping sample and reference at the same temperature by adjusting heater power

4.4 Simple Explanations

4.4.1 What is Thermal Analysis? (Simple Idea)

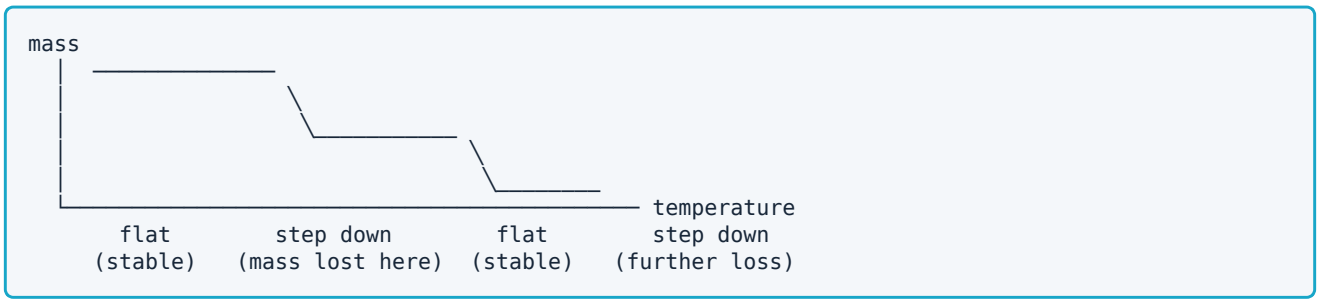
Thermal analysis means heating a small sample in a controlled way and watching what happens to it — does it lose weight? melt? absorb heat? release heat? Different materials behave differently on heating, so the "heating behaviour" works like a fingerprint for identification and quality checking.

Analogy: Like watching ice, butter, and chocolate melt on a warm pan — each melts at its own temperature and behaves differently. Thermal analysis does this scientifically, with precise measurement.

4.4.2 TGA — Thermogravimetric Analysis

Principle: The sample sits on a super-sensitive balance inside a furnace. As temperature rises at a steady rate, the balance continuously records the sample's mass. If the sample decomposes, loses water, or burns, its mass drops — and the TG curve shows steps.

The TG curve (mass vs temperature):



Parts of the curve:

- **Flat regions (plateaus):** Sample is stable, no mass change.
- **Steps (mass loss):** Sample loses something — water, solvent, or decomposition products.
- Each step's size tells **how much** mass was lost; its position tells **at what temperature**.

Applications of TGA:

- Moisture / water content determination in drugs and excipients.
- Decomposition temperature — how hot a drug can get before breaking down.
- Checking hydrates and solvates (water/solvent trapped in crystals).
- Purity assessment via decomposition behaviour.

4.4.3 DTA — Differential Thermal Analysis

Principle: The sample and an **inert reference** (a material that does nothing on heating, e.g., alumina) are heated side by side in the same furnace. Thermocouples measure both temperatures. The instrument plots **ΔT = T(sample) − T(reference)** against temperature.

- If the sample **absorbs heat** (melting — endothermic), it becomes cooler than the reference → ΔT goes negative (a dip).
- If the sample **releases heat** (crystallization — exothermic), it becomes hotter than the reference → ΔT goes positive (a peak).

Simple idea: Two cups heated together — one with water, one with sand. The water cup lags behind while the water evaporates (absorbing heat). DTA watches this "lag" precisely.

4.4.4 DSC — Differential Scanning Calorimetry

Principle: Like DTA, sample and reference are heated together — but DSC measures the **heat flow** (energy per second) needed to keep them changing temperature together. It precisely measures **how much heat** each change absorbs or releases, so we can find melting points, purity, and energies of transitions.

Types of DSC:

Type	How It Works (Simply)
Heat-flux DSC	One furnace heats both sample and reference; the temperature difference between them is measured and converted into heat flow
Power-compensated DSC	Sample and reference have separate tiny heaters; the instrument adjusts power to keep both at exactly the same temperature — the extra power used IS the heat flow signal

What DSC shows: Melting appears as an endothermic dip (heat absorbed); crystallization as an exothermic peak. The **area** of the peak gives the energy involved. A sharp, single melting peak suggests a pure, single crystal form; extra peaks suggest impurities or polymorphs.

4.4.5 Comparison Table — TGA vs DTA vs DSC

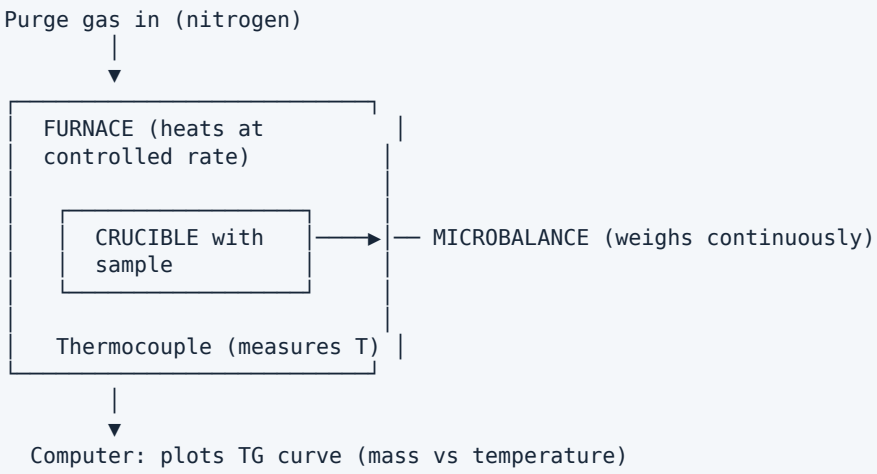
Feature	TGA	DTA	DSC
Full name	Thermogravimetric Analysis	Differential Thermal Analysis	Differential Scanning Calorimetry
Measures	Mass change	Temperature difference (ΔT)	Heat flow
Y-axis	Mass (mg or %)	ΔT	Heat flow (mW)
X-axis	Temperature	Temperature	Temperature

Feature	TGA	DTA	DSC
Detects melting?	No (no mass change on melting)	Yes	Yes (quantitatively)
Quantifies energy?	No	Approximately	Yes, precisely
Main pharma uses	Moisture, decomposition, hydrates	Quick screening of thermal events	Purity, polymorphism, compatibility

Key takeaway: TGA weighs the sample; DTA compares temperatures; DSC measures heat flow precisely.

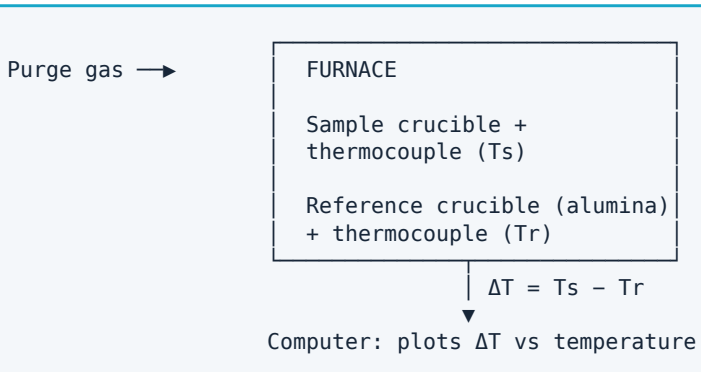
4.5 Instrumentation — Block Diagrams (Plain Text)

4.5.1 TGA Instrument

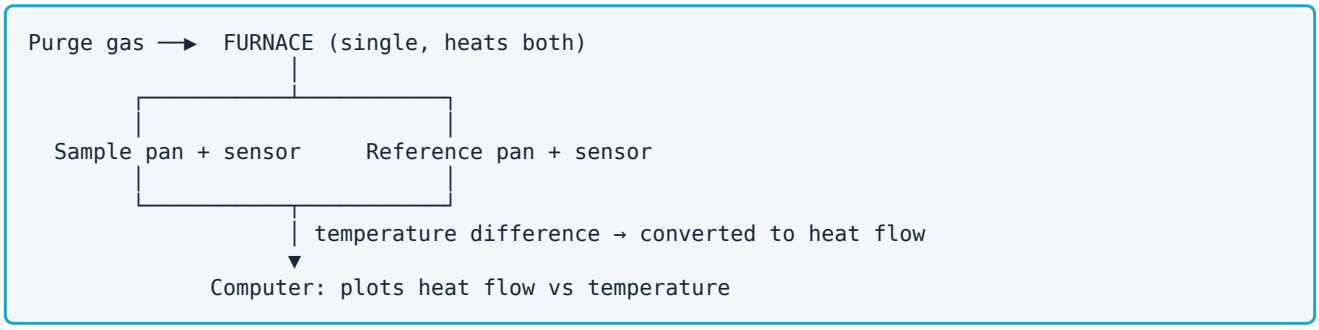


Parts: furnace, crucible, microbalance, thermocouple, purge gas supply, computer/recorder.

4.5.2 DTA Instrument



4.5.3 DSC Instrument (Heat-Flux Type)



(Power-compensated DSC: same idea, but with two separate micro-heaters and a power-difference signal.)

4.6 Factors Affecting Measurements

Factor	Effect (Simply)
Heating rate	Faster heating shifts events to higher temperatures and makes peaks broader; slow heating gives sharper, better-separated peaks
Sample size / mass	Large samples give bigger signals but broader peaks and temperature lag inside the sample; small samples give sharper peaks
Atmosphere (purge gas)	Nitrogen (inert) prevents oxidation; air/oxygen allows combustion studies; the gas changes decomposition behaviour
Crucible / pan material	Must not react with the sample; platinum, alumina, or aluminium pans are chosen to suit the temperature range
Sample packing	Loosely packed powder heats unevenly; consistent packing gives reproducible curves
Particle size	Fine particles react/decompose faster and more uniformly than coarse ones

Key takeaway: Same sample can give different curves if heating rate, sample size, or atmosphere differ — so methods must fix these conditions.

4.7 Infographic Concept Box

INFOGRAPHIC CONCEPT: "Thermal Analysis Trio" — Three panels side by side, each with a mini curve sketch: (1) "TGA — The Weigher": a balance icon over a furnace, TG curve with steps labelled "water lost here", "decomposes here"; (2) "DTA — The Comparator": two cups (sample vs reference) with a thermometer showing ΔT, curve with dip labelled "melts (absorbs heat)" and peak "crystallizes (releases heat)"; (3) "DSC — The Accountant": a calculator/heat icon, sharp melting peak with shaded area labelled "area = energy". Bottom strip: "Remember: TGA = mass, DTA = ΔT, DSC = heat flow. Pharma uses: purity, polymorphs, moisture, compatibility".

4.8 Flowchart — Choosing the Right Thermal Technique

```
What do you want to know?
        |
        ├── Does it lose weight on heating? (moisture, decomposition)
        |         → Use TGA
        |
        ├── At what temperature does something happen? (quick screen)
        |         → Use DTA
        |
        └── How pure is it? Which polymorph? Is it compatible?
            (needs precise heat measurement)
                  → Use DSC
```

4.9 Tables

Table 1: Thermal Events — Endothermic or Exothermic?

Event	Endo / Exo	Seen in
Melting	Endothermic (absorbs heat)	DTA, DSC
Crystallization	Exothermic (releases heat)	DTA, DSC
Decomposition with mass loss	Usually endothermic	TGA, DTA, DSC
Water evaporation	Endothermic	TGA (mass loss), DSC
Oxidation	Exothermic	DTA, DSC

Table 2: DSC Types at a Glance

Feature	Heat-Flux DSC	Power-Compensated DSC
Furnaces	One (heats both)	Two separate micro-furnaces
Signal	Temperature difference → heat flow	Power difference = heat flow directly
Design	Simpler, robust	More sensitive, faster response

4.10 Examples

Example 1 — Moisture by TGA: A drug sample shows a 5% mass loss between 80–120 °C on the TG curve → surface/absorbed moisture evaporating. The QC limit might be "not more than 5%".

Example 2 — Purity by DSC: Pure drug X melts sharply at 168 °C. A batch shows melting at 164 °C with a broader peak → impurity present (impurities lower and broaden the melting point).

Example 3 — Polymorphs by DSC: Two crystal forms of the same drug melt at 150 °C and 162 °C respectively — DSC distinguishes them in minutes.

Example 4 — Compatibility study: Drug + excipient mixture is run on DSC. If the drug's melting peak disappears or shifts greatly compared to the drug alone, a drug–excipient interaction is suspected.

4.11 Analogies

- **Thermal analysis:** Like watching ice, butter, and chocolate on a warm pan — each responds to heat in its own way.

- **TGA:** Like weighing yourself before and after a workout — the difference tells you what was lost (sweat ≈ moisture).
- **DTA:** Like a race between two runners where one carries a heavy backpack (absorbs energy) and lags behind.
- **DSC:** Like an accountant precisely counting every rupee of heat entering or leaving.
- **Heating rate effect:** Like driving fast past signboards — you miss details; slow driving lets you read each one.

4.12 Pharmacy Relevance

- **Purity testing:** DSC melting behaviour is a standard purity check for drug substances.
- **Polymorphism:** Different polymorphs melt differently — DSC and TGA identify and control them.
- **Compatibility studies:** DSC screens drug–excipient interactions during preformulation.
- **Moisture content:** TGA quantifies water in hygroscopic drugs and excipients.
- **Stability:** Decomposition temperatures from TGA guide storage and processing conditions.

4.13 India Context

- Indian pharmaceutical QC and R&D laboratories routinely use DSC for purity and polymorph checks and TGA for moisture and decomposition studies of drug substances.
- Thermal analysis is part of preformulation and compatibility screening workflows in Indian formulation development centres.
- Familiarity with TGA/DSC/DTA operation and curve interpretation is commonly expected in pharmaceutical analytical roles in India.

4.14 Key Points

1. Thermal analysis studies property changes vs temperature.
2. TGA measures mass vs temperature — moisture, decomposition, hydrates.
3. DTA measures ΔT (sample − reference) — detects endothermic/exothermic events.
4. DSC measures heat flow precisely — purity, polymorphism, compatibility.
5. DSC types: heat-flux (one furnace, ΔT → heat flow) and power-compensated (two heaters, power difference).
6. Melting = endothermic dip; crystallization = exothermic peak.
7. Factors: heating rate, sample size, atmosphere, crucible, packing, particle size.
8. Fix experimental conditions for reproducible, comparable curves.

4.15 Common Confusions

- **DTA vs DSC:** Both compare sample and reference, but DTA plots temperature difference (ΔT) while DSC measures heat flow quantitatively — DSC gives energies, DTA is more qualitative.
- **TGA and melting:** Melting involves no mass change, so TGA cannot detect melting — use DSC/DTA.
- **Endothermic vs exothermic:** Endothermic absorbs heat (melting — dip in DSC); exothermic releases heat (crystallization — peak). Students often swap them.
- **Reference material:** The reference must be inert (no thermal events) in the studied range — it is not a second sample.

4.16 Common Mistakes

1 Using TGA to find a melting point — TGA sees no mass change on melting.

2 Comparing curves recorded at different heating rates as if conditions were identical.

3 Using too large a sample — broad peaks and temperature lag hide close events.

4 Running an oxidation-sensitive drug in air instead of nitrogen and misreading the curve.

5 Calling every DSC peak shift a new polymorph — impurities and poor packing also shift peaks.

4.17 Mnemonics

- **Trio — "Weigh, Compare, Count":** **T**GA **weighs** (mass), **D**TA **compares** (ΔT), DS**C counts** heat (calorimetry).
- **Endo/Exo — "Melt Eats, Crystal Creates":** **Melt**ing **eats** heat (endothermic); **crystal**lization **creates** (releases) heat (exothermic).
- **Factors — "H SAP P":** **H**eating rate, **S**ample size, **A**tmosphere, **P**an (crucible), **P**acking/particle size.

4.18 Exam Summary

Thermal analysis studies how material properties change with temperature. TGA measures mass vs temperature on a microbalance — TG curves show plateaus (stable) and steps (mass loss); used for moisture, decomposition temperature, and hydrates/solvates. DTA heats sample and inert reference together and plots ΔT = T(sample) − T(reference); endothermic events (melting) give dips, exothermic events (crystallization) give peaks. DSC measures heat flow precisely for quantitative purity, polymorphism, and compatibility studies; two types — heat-flux (one furnace, ΔT converted to heat flow) and power-compensated (separate heaters, power difference is the signal). Comparison: TGA = mass, DTA = ΔT, DSC = heat flow; TGA cannot detect melting. Factors affecting measurements: heating rate, sample size, atmosphere (nitrogen vs air), crucible material, sample packing, and particle size — conditions must be fixed for comparable results.

4.19 One-Minute Revision

- Thermal analysis = heat it, watch what changes.
- TGA = mass vs T (moisture, decomposition).

- DTA = ΔT vs T (endo dips, exo peaks).
- DSC = heat flow vs T; types: heat-flux, power-compensated.
- Melting = endothermic; crystallization = exothermic.
- Factors: heating rate, sample size, atmosphere, crucible, packing.
- Uses: purity, polymorphs, compatibility, moisture.

4.20 Short Answer Questions

1 Define thermal analysis.

2 What does TGA measure? Draw a labelled TG curve.

3 What is ΔT in DTA? What do a dip and a peak signify?

4 Differentiate DTA and DSC.

5 Name and briefly explain the two types of DSC.

6 Why can't TGA detect melting?

7 List four factors affecting thermal analysis measurements.

8 How does heating rate affect a DSC curve?

9 Why is nitrogen used as purge gas in TGA?

10 Give two pharmaceutical applications each of TGA and DSC.

4.21 Long Answer Questions

1 Define thermal analysis. Explain the principle of TGA with a labelled block diagram, describe the parts of a TG curve, and discuss its pharmaceutical applications.

2 Explain the principle of DTA with a block diagram. How are endothermic and exothermic events identified? Give examples.

3 Explain the principle of DSC and describe its two types (heat-flux and power-compensated) with block diagrams.

4 Compare TGA, DTA, and DSC under the heads: quantity measured, axes of the curve, ability to detect melting, quantitative capability, and pharmaceutical uses.

5 Discuss the factors affecting thermal analysis measurements and explain why experimental conditions must be standardized.

6 Write a note on the applications of thermal analysis (TGA, DSC, DTA) in pharmacy: purity, polymorphism, compatibility studies, and moisture determination.

4.22 MCQs with Answer Keys

Q1. TGA measures: a) Heat flow b) Mass change vs temperature c) Temperature difference d) pH change **Answer: b) Mass change vs temperature**

Q2. In DTA, the plotted quantity is: a) Mass b) ΔT (sample − reference) c) Heat flow in mW d) Volume **Answer: b) ΔT (sample − reference)**

Q3. DSC quantitatively measures: a) Mass b) Colour c) Heat flow d) Particle size **Answer: c) Heat flow**

Q4. Melting is a: a) Exothermic process b) Endothermic process c) Isothermal process d) Athermal process **Answer: b) Endothermic process**

Q5. Which technique CANNOT detect melting? a) DSC b) DTA c) TGA d) All can detect it **Answer: c) TGA**

Q6. The two types of DSC are: a) Hot and cold DSC b) Heat-flux and power-compensated c) Open and closed DSC d) Fast and slow DSC **Answer: b) Heat-flux and power-compensated**

Q7. A faster heating rate generally: a) Sharpens peaks b) Shifts events to higher temperatures and broadens peaks c) Has no effect d) Cools the sample **Answer: b) Shifts events to higher temperatures and broadens peaks**

Q8. Nitrogen is used as purge gas in TGA mainly to: a) Oxidize the sample b) Provide an inert atmosphere c) Increase mass d) Cool the furnace **Answer: b) Provide an inert atmosphere**

Q9. In a TG curve, a flat plateau indicates: a) Rapid decomposition b) The sample is thermally stable (no mass change) c) Instrument error d) Melting **Answer: b) The sample is thermally stable (no mass change)**

Q10. DSC is widely used in pharmacy for: a) Purity and polymorphism studies b) Measuring blood pressure c) Counting tablets d) Testing dissolution only **Answer: a) Purity and polymorphism studies**

4.23 Viva Questions

1 What is thermal analysis?

2 What does TGA measure?

3 What is plotted in DTA?

4 What are the two types of DSC?

5 Is melting endothermic or exothermic?

6 Why can't TGA detect a melting point?

7 Name two factors affecting thermal measurements.

8 What is an inert reference? Give an example.

9 How does DSC help in detecting polymorphs?

10 What is a drug–excipient compatibility study?

4.24 Application-Based Questions

1 A hygroscopic drug shows 4.8% mass loss between 70–130 °C on TGA. How would you interpret and report this in QC?

2 A formulation scientist mixes a drug with a new excipient and the drug's sharp DSC melting peak disappears. What does this suggest, and what should be done next?

3 Two suppliers send the "same" drug; DSC shows melting at 150 °C for one and 162 °C for the other. What is the likely explanation, and why does it matter?

4 You must choose between TGA and DSC to check whether a drying process has removed all solvent from a drug. Which do you choose and why?

4.25 References

- Brown
- Skoog / Holler / Crouch