B.PHARM SEMESTER III · THEORY

BP307T Pharmaceutical Engineering

Unit II — Filtration, Crystallization & Centrifugation

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Unit II

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CHAPTER 3: Filtration and Crystallization

3.1 Learning objectives

After studying this chapter you will be able to:

1. Define filtration and explain the theory of filtration in simple terms.
2. Classify filter media and explain the role of filter aids.
3. Describe the construction and working of the filter press, pressure leaf filter, rotary drum vacuum filter, meta filter, cartridge filter, and membrane filter.
4. Explain air filtration and the role of HEPA filters.
5. Define crystallization and explain supersaturation and the theories behind it.
6. Explain nucleation and crystal growth in simple words.
7. Describe the construction and working of tank, circulating-magma, Swenson–Walker, Krystal, and evaporating-pan crystallizers.
8. Explain caking of crystals and how to prevent it.
9. Compare filtration and crystallization equipment and state their pharmaceutical applications.

3.2 Definitions

- **Filtration:** Separating solid particles from a liquid (or gas) by passing the mixture through a porous barrier (filter medium) that lets the fluid through but holds back the solids.
- **Filter medium:** The porous barrier itself — cloth, paper, membrane, or metal screen.
- **Filtrate:** The clear liquid that passes through the filter.
- **Filter cake:** The layer of solids collected on the filter medium.
- **Filter aid:** An inert powder (like diatomaceous earth) added to form a porous cake and speed up filtration of slimy solids.
- **Crystallization:** Formation of solid crystals with a regular, ordered structure from a solution, melt, or vapour.
- **Supersaturation:** A solution holding more dissolved solid than it normally can at that temperature — the driving force for crystallization.
- **Nucleation:** The birth of the first tiny crystal seeds in a supersaturated solution.
- **Caking:** Crystals sticking together into hard lumps during storage.

3.3 Terminology you must know first

Term	Simple meaning
Slurry	A pumpable mixture of solid particles suspended in liquid (like thin mud)
Clarification	Filtering to remove tiny unwanted particles and make a liquid clear
Sterile filtration	Filtering through a 0.22 µm membrane to remove all bacteria
HEPA filter	High-Efficiency Particulate Air filter — traps ≥99.97% of 0.3 µm particles from air
Magma	A thick suspension of crystals in their mother liquor inside a crystallizer
Mother liquor	The liquid left behind after crystals are removed
Seeding	Adding small crystals to a supersaturated solution to start crystallization
Porosity	How much empty space a filter medium has — more pores = faster flow

3.4 Introduction — cleaning liquids and growing crystals

Technical concept: Filtration separates by size exclusion through pores; crystallization separates by forming pure ordered solids from solution. Both are purification operations — one removes solids from liquids, the other builds pure solids from liquids.

> **Simple explanation:** Filtration is like straining tea — leaves stay in the strainer, clear tea passes through. Crystallization is like sugar crystals forming in a very sweet syrup left undisturbed — the pure sugar builds itself into neat crystals while impurities stay in the syrup.

Example: Injectable medicines must be completely free of particles and bacteria. They are passed through 0.22 µm membrane filters (sterile filtration) — the liquid drug passes, bacteria (about 1 µm) cannot. And many drugs, like paracetamol, are purified by crystallization — dissolved in hot solvent, then cooled so pure crystals grow.

Key takeaway: Filtration removes unwanted solids from liquids; crystallization builds wanted pure solids from liquids.

3.5 Theory of filtration (in simple words)

Liquid flows through the filter because of a pressure difference — either the slurry is pushed (pressure filtration) or sucked (vacuum filtration) through the medium. Flow is faster when: pressure difference is bigger, the liquid is thinner (low viscosity), the filter area is bigger, and the cake is porous. Flow slows as the cake gets thicker. Filter aids keep the cake porous so flow stays fast.

3.6 Filter media and filter aids

Filter media (classification):

- **Woven:** filter cloth (cotton, nylon), wire mesh — reusable, for coarse filtration.
- **Non-woven:** filter paper, felt — disposable, for clarification.
- **Membranes:** cellulose or polymer films with exact pore sizes (0.22 µm for sterile filtration).
- **Rigid:** sintered glass, sintered metal, ceramic candles — for corrosive liquids.

Filter aids: Inert powders like diatomaceous earth (kieselguhr), perlite, and cellulose. Used in two ways — as a **precoat** (a layer built on the medium before filtration) and as **body feed** (mixed into the slurry). They make a porous, incompressible cake so slimy solids do not blind (block) the filter.

3.7 FILTER PRESS (PLATE AND FRAME)

What it does (one line): A stack of plates and frames squeezes slurry under pressure, trapping solids as cakes between filter cloths.

Principle: Pressure filtration. Slurry is pumped under pressure into chambers; liquid passes through cloth, solids build up as cakes.

Construction (sketch this):

- A heavy frame holding alternating **plates** (solid, with grooved drainage surfaces) and **frames** (hollow rings), pressed tightly together by a screw or hydraulic ram.
- Filter cloth covers each plate; the hollow frames form chambers between plates.
- A slurry inlet channel runs through all frames; filtrate outlet taps on each plate.

Working (numbered steps):

1. Assemble plates and frames with cloths and clamp tightly.
2. Pump slurry under pressure into the chambers through the inlet channel.
3. Liquid passes through the cloth and drains out via plate outlets (filtrate).
4. Solids deposit on the cloth, building cakes that fill the frames.
5. When frames are full (flow nearly stops), stop the pump, open the press, and drop out the cakes.

Advantages vs disadvantages:

Advantages	Disadvantages
Gives very dry cakes with high solids recovery	Batch process — must stop to empty cakes (labour intensive)
Handles large volumes; sturdy and cheap	Cloth changing and cleaning take time
Good for slimy solids with filter aid	Leaks possible at joints under high pressure

Pharmaceutical applications: Filtering antibiotic fermentation broths; clarifying syrups; dewatering precipitated products like calcium carbonate.

Key takeaway: Filter press = clamped plates + frames + pressure → dry cakes, batch operation.

3.8 PRESSURE LEAF FILTER

What it does (one line): Flat filter leaves inside a pressure vessel filter large volumes with easy cake discharge.

Principle: Pressure filtration through flat leaves. Slurry surrounds the leaves; filtrate flows inside the leaf to the outlet.

Construction (sketch this):

- A horizontal cylindrical pressure vessel (tank).
- Inside: several flat, rectangular filter leaves (wire mesh frames covered with cloth), mounted vertically on a central filtrate manifold.
- Slurry inlet, filtrate outlet, and a bottom discharge door for cake.

Working (numbered steps):

1. Pump slurry under pressure into the vessel, submerging the leaves.
2. Liquid passes through the cloth into the hollow leaves and out through the manifold (filtrate).
3. Cake builds on both sides of each leaf.
4. Stop, drain the vessel, open the bottom door, and vibrate or sluice the cake off the leaves.

Advantages vs disadvantages:

Advantages	Disadvantages
Large filter area in a compact vessel	Batch operation
Cake discharge easier than filter press	Higher cost than filter press
Closed system — less exposure	Cloth replacement is fiddly

Pharmaceutical applications: Clarifying large volumes of syrups and elixirs; filtering varnishes and fine chemicals; polishing filtration of liquid products.

Key takeaway: Leaf filter = flat leaves in a pressure tank → large area, easier cake removal than press.

3.9 ROTARY DRUM VACUUM FILTER

What it does (one line): A rotating drum, half-dipped in slurry, filters continuously under vacuum — the only truly continuous filter here.

Principle: Vacuum filtration on a rotating surface. Vacuum inside the drum sucks liquid through the cloth; a knife scrapes off the cake as the drum turns.

Construction (sketch this):

- A large horizontal rotating drum covered with filter cloth, half-submerged in a slurry trough.
- A vacuum system connected through the drum's hollow shaft (divided into zones: filtration, washing, drying, discharge).
- A doctor knife (blade) pressed against the drum to scrape off the cake.

Working (numbered steps):

1. The drum rotates slowly through the slurry trough.
2. Vacuum pulls liquid through the cloth into the drum (filtrate); cake deposits on the outer surface.
3. As the drum rises out of the slurry, wash water sprays the cake (washing zone), then air is sucked through (drying zone).
4. The doctor knife scrapes the dry cake off just before the drum re-enters the slurry — continuous cycle.

Advantages vs disadvantages:

Advantages	Disadvantages
Continuous — no stopping to empty cakes	High initial cost and complex vacuum system
Cake washing and drying in one machine	Not for very fine or slimy solids (cloth blinds)
Large throughput	Vacuum limits the driving pressure

Pharmaceutical applications: Continuous filtration of fermentation broths (antibiotics); dewatering precipitated inorganics; filtering large volumes of crystalline products.

Key takeaway: Rotary drum = rotating cloth drum + vacuum + scraper → continuous filtration, washing, and drying.

3.10 META FILTER (SPARKLER FILTER)

What it does (one line): A stack of metal rings and filter paper discs inside a vessel gives sparkling-clear filtrates.

Principle: Pressure filtration through many thin paper discs — a huge filter area in a small vessel, ideal for polishing (final clarification).

Construction (sketch this):

- A vertical pressure vessel containing a central rod on which alternate metal rings and filter paper discs are stacked tightly (like a pile of coins).
- Slurry enters the vessel outside the stack; filtrate flows inward between discs to the central outlet.

Working (numbered steps):

1. Assemble the ring–paper stack on the central rod and close the vessel.
2. Pump liquid under pressure into the vessel.
3. Liquid passes through the paper discs into the centre and out (bright, clear filtrate).
4. Solids collect on the discs; open and replace discs when flow drops.

Advantages vs disadvantages:

Advantages	Disadvantages
Brilliantly clear filtrate — best for polishing	Discs must be replaced often (consumable cost)
Compact; large area	Not for heavy solids loads
Closed, hygienic system	Assembly is time-consuming

Pharmaceutical applications: Final polishing of syrups, elixirs, and injections; clarifying insulin and fine liquid products; removing the last haze from beverages in allied units.

Key takeaway: Meta filter = stack of paper discs → sparkling-clear polishing filtration.

3.11 CARTRIDGE AND MEMBRANE FILTERS

What they do (one line): Disposable cartridges with exact pore sizes do final purification — down to sterile (bacteria-free) filtration.

Principle: Size exclusion through precise pores. Liquid passes; anything bigger than the pore is retained.

Construction: A cylindrical cartridge (pleated membrane inside a plastic housing) fitted into a stainless steel housing; liquid flows outside-to-inside through the membrane.

Working:

1. Fit a sterile cartridge of the required pore size (0.45 µm for clarification, 0.22 µm for sterile filtration).
2. Pump the liquid through; particles and bacteria larger than the pores are retained.
3. Collect sterile filtrate; discard the disposable cartridge.

Advantages	Disadvantages
Exact, validated pore sizes — regulatory acceptance	Disposable — recurring cost
Sterile filtration without heat (for thermolabile injections)	Clogs fast with dirty liquids — needs pre-filtration
Compact and easy to validate	Low solids capacity

Pharmaceutical applications: Sterile filtration of injections, eye drops, and vaccines that cannot be heat-sterilized; final filtration of WFI (water for injection); vent filtration on tanks.

Key takeaway: Membrane cartridge = exact pores → sterile filtration of heat-sensitive liquids.

3.12 AIR FILTRATION AND HEPA FILTERS

What they do (one line): Clean the air itself — removing dust and microbes from the air entering sterile manufacturing areas.

Principle: Air is passed through progressively finer filters; HEPA filters trap particles by interception, impaction, and diffusion in a dense glass-fibre mat.

Construction: Deep-pleated glass-fibre paper in a rigid frame, sealed into air-handling ducts; usually the last stage after pre-filters and fine filters.

Working:

1. Room air is drawn through pre-filters (catch coarse dust), then fine filters.
2. Finally it passes through the HEPA filter, which retains ≥99.97% of 0.3 µm particles — including bacteria-carrying droplets.
3. Clean, nearly sterile air enters the manufacturing room (used with laminar air flow).

Advantages	Disadvantages
Near-sterile air for aseptic areas	Expensive; must be integrity-tested regularly
Protects both product and workers	High resistance — needs powerful fans

Pharmaceutical applications: Sterile manufacturing rooms, laminar air flow workstations, and clean corridors in injection plants; powder containment areas.

Key takeaway: HEPA = final air-cleaning stage → near-sterile air for injection manufacturing.

3.13 Comparison table — filtration equipment

Equipment	Driving force	Batch/continuous	Best for
Filter press	Pressure	Batch	Dry cakes, large volumes
Leaf filter	Pressure	Batch	Large-area clarification
Rotary drum	Vacuum	Continuous	Continuous broth filtration
Meta filter	Pressure	Batch	Polishing, sparkling clarity
Membrane cartridge	Pressure	Batch/disposable	Sterile filtration
HEPA	Fan pressure	Continuous	Clean air

3.14 CRYSTALLIZATION — SUPERSATURATION, NUCLEATION, GROWTH

Technical concept: A hot solution can dissolve more solid than a cold one. Cool it, and the extra solid must come out — it does so by building orderly crystals.

> **Simple explanation:** Dissolve lots of sugar in hot water, then let it cool without disturbing. The water cannot hold all the sugar anymore (supersaturation), so sugar molecules start joining together into neat crystals — first tiny seeds appear (nucleation), then the seeds grow bigger (crystal growth).

Supersaturation methods: cooling a hot saturated solution; evaporating the solvent; adding a liquid in which the drug is less soluble; chemical reaction forming an insoluble product.

Miers' supersaturation theory (simple): There are three zones — stable (no crystals), metastable (crystals grow only if seeds are added), and labile/unstable (crystals form by themselves). Good crystallization stays in the metastable zone with seeding — controlled growth, uniform crystals.

Nucleation vs crystal growth: Nucleation = birth of new tiny crystals (many small crystals if too fast). Crystal growth = existing crystals getting bigger (few large crystals if slow). For uniform product: few nuclei + steady growth.

Key takeaway: Supersaturation drives it; nucleation starts it; controlled growth perfects it — stay in the metastable zone with seeding.

3.15 TANK CRYSTALLIZER

What it does (one line): A simple jacketed tank where a hot solution cools slowly and crystals grow — the simplest batch crystallizer.

Principle: Cooling crystallization. Lowering temperature creates supersaturation; crystals nucleate and grow on slow cooling with gentle stirring.

Construction (sketch this):

- A cylindrical tank with a cooling jacket (cold water circulates in the jacket).
- A slow-speed agitator (paddle) to keep crystals suspended.
- A bottom outlet to discharge the crystal magma.

Working (numbered steps):

1. Fill the tank with hot saturated solution.
2. Circulate cold water in the jacket; stir slowly.
3. As temperature falls, supersaturation develops; seed crystals may be added.
4. Crystals grow; when growth is complete, discharge the magma and separate crystals by filtration/centrifugation.

Advantages vs disadvantages:

Advantages	Disadvantages
Simplest and cheapest crystallizer	Slow — large batches take hours
Easy to operate and clean	Wide crystal-size range (poor uniformity)
Good for small batches	Crystals can stick to walls and agitator

Pharmaceutical applications: Small-batch crystallization of drug salts; laboratory and pilot-plant crystallization; crystallizing heat-stable organics.

Key takeaway: Tank crystallizer = cooled stirred tank → simplest batch crystallization.

3.16 CIRCULATING-MAGMA CRYSTALLIZER

What it does (one line): Circulates the crystal slurry through a heater/cooler loop for controlled, continuous crystal growth.

Principle: A pump keeps magma circulating between the crystallizer body and a heat exchanger; controlled supersaturation gives uniform crystal growth.

Construction (sketch this):

- A conical-bottomed vessel with a circulating pump and an external heat exchanger (cooler) in the loop.
- A fines-dissolving loop may redissolve tiny crystals so only large ones survive.

Working (numbered steps):

1. Magma is pumped continuously through the cooler, generating mild supersaturation.
2. It returns to the vessel where crystals grow on existing seeds.
3. Fine crystals are selectively redissolved (fines destruction) for uniform size.
4. Product magma is withdrawn continuously; mother liquor is recycled.

Advantages vs disadvantages:

Advantages	Disadvantages
Uniform crystal size (fines control)	Complex; higher cost
Continuous operation	Needs careful control of circulation

Pharmaceutical applications: Continuous crystallization of bulk drugs requiring uniform crystal size (for consistent dissolution); large-scale salt crystallization.

Key takeaway: Circulating magma = pumped loop + fines control → uniform crystals, continuous.

3.17 SWENSON–WALKER CRYSTALLIZER

What it does (one line): A long open trough with a slow spiral scraper cools solution continuously while moving crystals along.

Principle: Cooling crystallization in a continuous trough; a spiral agitator gently moves the growing crystals forward while scraping walls clean.

Construction (sketch this):

- A long, U-shaped open trough with a cooling jacket divided into sections.
- A slow-rotating spiral (helical) scraper running the length of the trough.
- Feed inlet at one end, magma outlet at the other.

Working (numbered steps):

1. Hot solution enters at one end of the trough.
2. Jacket cooling creates supersaturation progressively along the trough.
3. The spiral scraper moves crystals forward and scrapes the wall (prevents encrustation).
4. Crystal magma discharges continuously at the far end.

Advantages vs disadvantages:

Advantages	Disadvantages
Continuous; self-cleaning walls (scraper)	Open trough — not for sterile or volatile solvents
Simple and robust	Large floor space needed

Pharmaceutical applications: Continuous crystallization of inorganic salts and intermediates; large-scale crystallization of bulk chemicals.

Key takeaway: Swenson–Walker = jacketed trough + spiral scraper → continuous cooling crystallization.

3.18 KRYSTAL CRYSTALLIZER

What it does (one line): A draft-tube crystallizer with internal circulation that grows large, uniform crystals.

Principle: Gentle internal circulation suspends crystals in a mildly supersaturated zone; classified product removal takes out only the large crystals.

Construction (sketch this):

- A tall vessel with an internal draft tube (central pipe) and a propeller/agitator inside it.
- A conical settling zone at the bottom for classifying crystals by size.

Working (numbered steps):

1. The agitator in the draft tube circulates magma gently upward inside the tube and downward outside it.
2. Supersaturation is kept low and uniform — crystals grow steadily without excess nucleation.
3. Large crystals settle into the bottom classifying zone and are withdrawn as product.
4. Fines stay suspended and keep growing.

Advantages vs disadvantages:

Advantages	Disadvantages
Large, uniform crystals	Tall vessel; higher cost
Low supersaturation — minimal fines	Needs skilled operation

Pharmaceutical applications: Crystallizing drugs where large uniform crystals are needed for easy filtration and consistent dissolution (e.g., purified drug substances).

Key takeaway: Krystal = draft-tube circulation → large uniform crystals.

3.19 EVAPORATING-PAN / EVAPORATIVE CRYSTALLIZER

What it does (one line): Boils off solvent in an open or jacketed pan so crystals form as the solution concentrates.

Principle: Evaporative crystallization — removing solvent (not cooling) creates supersaturation.

Construction: A shallow open pan or jacketed vessel with steam heating; sometimes with an agitator.

Working:

1. Fill with solution and heat (steam jacket).
2. Solvent evaporates; concentration rises past saturation.
3. Crystals form and grow; stir to keep them suspended.
4. Discharge the magma when the desired yield is reached.

Advantages	Disadvantages
Simple; works when solubility hardly changes with temperature	Not for heat-sensitive drugs
Good for salts like sodium chloride	Open pan — contamination and solvent loss

Pharmaceutical applications: Crystallizing inorganic salts and excipients whose solubility changes little with cooling; traditional salt crystallization.

Key takeaway: Evaporative crystallizer = boil off solvent → crystals when cooling alone will not work.

3.20 CAKING OF CRYSTALS

What it is: Dry crystals sticking together into hard lumps during storage — caused by moisture absorption, temperature cycling (dissolve–recrystallize bridges between crystals), or impurities.

Prevention: Dry crystals thoroughly; pack in moisture-proof containers with desiccants; store at stable temperature; add approved anti-caking agents for excipients; keep crystal size uniform.

Pharmaceutical relevance: Caked crystals do not flow or dissolve uniformly — they ruin tablet weight uniformity and dissolution. That is why proper drying and packing follow crystallization.

3.21 Comparison table — crystallizers

Crystallizer	Supersaturation by	Batch/continuous	Crystal character
Tank	Cooling	Batch	Mixed sizes
Circulating magma	Cooling (loop)	Continuous	Uniform
Swenson–Walker	Cooling (trough)	Continuous	Medium, robust
Krystal	Cooling (draft tube)	Continuous	Large, uniform
Evaporating pan	Evaporation	Batch	Coarse salts

3.22 Flowchart — from reaction mixture to pure crystals

```
Hot saturated solution
        │
        ▼
 CREATE SUPERSATURATION (cool / evaporate / add antisolvent)
        │
        ▼
 NUCLEATION (seeds form or seeding added) → stay in metastable zone
        │
        ▼
 CRYSTAL GROWTH (slow, controlled)
        │
        ▼
 SEPARATE (filter / centrifuge) → WASH → DRY → PACK (prevent caking)
```

3.23 INFOGRAPHIC CONCEPT BOX — Unit II, Chapter 3

"Two Ways to Purify a Liquid" (one-page visual): split page. Left side "FILTRATION": a funnel/tea-strainer icon with slurry going in, cake staying on top, clear filtrate dripping below; small icons of filter press, drum filter, membrane (0.22 µm) with captions. Right side "CRYSTALLIZATION": a beaker of hot clear solution → snowflake/crystal icons growing → pure crystals; labels "supersaturation → nucleation → growth". Bottom banner: "Filtration removes solids from liquids; crystallization builds pure solids from liquids."

3.24 Pharmacy relevance

Filtration purifies every liquid medicine — syrups are clarified, injections are sterile-filtered. Crystallization purifies nearly every solid drug — the purity of paracetamol, aspirin, and most antibiotics depends on controlled crystallization. Both operations decide the safety and quality of the final product.

3.25 India context

Indian bulk-drug (API) plants — in Hyderabad, Visakhapatnam, Ahmedabad, and Ankleshwar — run crystallization as the final purification step for most drug substances made for the world market. Sterile filtration (0.22 µm membranes) is standard in India's large injectable-manufacturing plants. HEPA-filtered clean rooms are mandatory in every Indian sterile facility.

3.26 Key points

1. Filtration: pressure difference drives liquid through a porous medium; cake builds up; filter aids keep cakes porous.
2. Filter press (batch, dry cakes), leaf filter (large area), rotary drum (continuous + washing + drying), meta filter (polishing), membrane cartridge (sterile filtration), HEPA (clean air).
3. Crystallization needs supersaturation (cooling, evaporation, antisolvent).
4. Miers' zones: stable, metastable (seed and grow — the working zone), labile (uncontrolled nucleation).
5. Nucleation starts crystals; growth enlarges them — control both for uniformity.
6. Crystallizers: tank (simple batch), circulating magma (uniform, continuous), Swenson–Walker (trough, continuous), Krystal (large uniform crystals), evaporating pan (solvent removal).
7. Caking = lumps on storage; prevent by drying, moisture-proof packing, stable temperature.

3.27 Common confusions

- **Filtrate vs filter cake:** Filtrate = clear liquid passing through; cake = solids left behind. Do not swap them.
- **Nucleation vs crystal growth:** Nucleation = new tiny crystals born; growth = existing crystals getting bigger.
- **Metastable vs labile zone:** Metastable = crystals grow only on seeds (controlled — we want this); labile = spontaneous shower of tiny crystals (uncontrolled).
- **Sterile filtration vs sterilization by heat:** Membrane filtration removes bacteria without heat — for thermolabile injections that cannot be autoclaved.
- **HEPA filter vs membrane filter:** HEPA cleans AIR; membrane cartridge cleans LIQUIDS.

3.28 Common mistakes

- Writing that the rotary drum filter is batch (it is continuous).
- Forgetting filter aids when explaining filtration of slimy solids.
- Drawing the cyclone separator in the filtration chapter (it is a size-separation/air-classification device from Chapter 1).
- Saying crystallization purifies by filtration (it purifies by ordered crystal building; filtration only separates the crystals afterward).

3.29 Mnemonic

"Please Let Me Make Happy Crystals" — filtration equipment: **P**ress, **L**eaf, **M**eta, **M**embrane, **H**EPA (+ rotary drum **R**: "...Press, Leaf, Rotary-drum, Meta, Membrane, HEPA"). Crystallizers: **"Tall Cats Sit Kindly Everywhere"** — **T**ank, **C**irculating-magma, **S**wenson–Walker, **K**rystal, **E**vaporating pan.

3.30 Exam summary

Filtration separates solids from liquids through a porous medium driven by pressure difference; filter aids (diatomaceous earth) keep cakes porous. Equipment: filter press (batch, dry cakes), leaf filter (large area), rotary drum vacuum filter (continuous + wash + dry), meta filter (polishing), membrane cartridge (0.22 µm sterile filtration), HEPA (clean air). Crystallization: supersaturation (Miers' stable/metastable/labile zones) → nucleation → crystal growth. Crystallizers: tank, circulating magma, Swenson–Walker, Krystal, evaporating pan. Caking prevented by drying and moisture-proof packing.

3.31 One-minute revision

Slurry → pressure/vacuum → medium → cake + filtrate → filter aids help → press (batch) → drum (continuous) → membrane (sterile) → HEPA (air) → supersaturation → nucleation → growth → tank/magma/SW/Krystal/pan → dry well, prevent caking.

3.32 Practice questions

Long answers (10 marks):

1. Describe the construction and working of the rotary drum vacuum filter with a neat labelled diagram. Give advantages, disadvantages, and applications.
2. What is supersaturation? Explain Miers' supersaturation theory. Describe any two crystallizers with diagrams.
3. Describe the filter press and the meta filter with diagrams. When is each preferred?

Short answers (2–5 marks):

1. Define filtrate, filter cake, and filter aid.
2. What is the pore size used for sterile filtration? Why?
3. Differentiate between nucleation and crystal growth.
4. What is caking? How is it prevented?
5. Why are filter aids used? Name two.

MCQs:

1. Sterile filtration uses a membrane of pore size:

a) 0.45 µm b) 0.22 µm c) 5 µm d) 10 µm — **Answer: b**

1. The only continuous filter among these is:

a) Filter press b) Leaf filter c) Rotary drum vacuum filter d) Meta filter — **Answer: c**

1. The metastable zone is the zone where:

a) No crystals can ever form b) Crystals grow only on added seeds c) Spontaneous nucleation occurs d) Solution is unsaturated — **Answer: b**

1. HEPA filters are used for:

a) Filtering syrups b) Cleaning air c) Filtering injections d) Drying crystals — **Answer: b**

1. Caking of crystals is caused by:

a) Over-drying b) Moisture absorption and temperature cycling c) Seeding d) Fast cooling — **Answer: b**

Viva questions:

1. Why can't a thermolabile injection be autoclaved? How is it sterilized?
2. What is the difference between a filter aid used as precoat and as body feed?
3. Why do we seed a supersaturated solution?

Application-based:

1. An antibiotic fermentation broth must be filtered continuously at large scale. Which filter will you choose and why?
2. A batch of drug crystals formed a shower of tiny crystals instead of uniform large ones. Which zone did the process enter, and how would you correct it?

3.33 References

1. Banker, G. S. Pharmaceutical Engineering. Marcel Dekker.
2. Sambamurthy, K. Introduction to Pharmaceutical Engineering. New Age International.
3. Banker, G. S. and Rhodes, C. T. Modern Pharmaceutics. CRC Press.
4. Cole, G. C. Pharmaceutical Facilities: Design, Layouts and Validation. CRC Press.

CHAPTER 4: Centrifugation

4.1 Learning objectives

After studying this chapter you will be able to:

1. Define centrifugation and explain the principle of centrifugal force in simple words.
2. Explain the difference between filtration centrifuges and sedimentation centrifuges.
3. Describe the construction and working of the perforated basket centrifuge.
4. Describe the construction and working of the non-perforated basket (tubular bowl) centrifuge.
5. Describe the construction and working of the supercentrifuge and ultracentrifuge.
6. Compare centrifuges using advantages–disadvantages tables.
7. State the pharmaceutical applications of each centrifuge.

4.2 Definitions

- **Centrifugation:** Separating materials using centrifugal force generated by rapid rotation — heavier parts move outward, lighter parts stay near the centre.
- **Centrifugal force:** The outward-pushing effect felt by a mass in a rotating system (like clothes pressed to the wall of a spinning washing-machine drum).
- **Sedimentation:** Settling of particles under gravity or centrifugal force because they are denser than the liquid.
- **Filtration centrifuge:** A centrifuge with a perforated (holed) wall — liquid passes through, solids stay (like a spinning strainer).
- **Sedimentation centrifuge:** A centrifuge with a solid (non-perforated) wall — solids settle against the wall, liquid stays in the centre (like spinning muddy water).
- **RCF (relative centrifugal force):** How many times stronger than gravity the centrifugal force is (e.g., 10,000 × g).

4.3 Terminology you must know first

Term	Simple meaning
Perforated basket	Drum with holes, lined with filter cloth — liquid escapes through holes
Non-perforated (solid) bowl	Drum with no holes — separation by settling only
Supernatant	The clear liquid layer left above settled solids
Weir / dam	An adjustable ring that sets the liquid level inside a solid-bowl centrifuge
Tubular bowl	A long, narrow, solid-wall bowl spinning at very high speed
Critical speed (centrifuge)	A vibration-prone speed to pass through quickly during start/stop

4.4 Introduction — why spin instead of just filtering?

Technical concept: Gravity settles particles slowly; spinning multiplies the settling force thousands of times, so separation that takes hours by gravity takes minutes in a centrifuge.

Simple explanation: A washing machine spins wet clothes at high speed and water flies out — the same idea separates crystals from liquid or cream from milk in seconds instead of hours. When particles are too fine to filter easily, or when you want a continuous fast separation, you centrifuge.

Example: After crystallization, drug crystals sit in mother liquor. Pouring through a filter is slow for fine crystals; a basket centrifuge spins the magma and throws the liquid out through the cloth in minutes, leaving a clean crystal cake that can be washed while spinning.

Key takeaway: Centrifugation = gravity multiplied thousands of times → fast separation of fine or delicate materials.

4.5 Classification of centrifuges

```
Centrifuges
├── Filtration (perforated wall — liquid passes through)
│   └── Perforated basket centrifuge (batch; also semi-continuous types)
└── Sedimentation (solid wall — solids settle on wall)
    ├── Non-perforated basket / tubular bowl centrifuge
    ├── Supercentrifuge (very high speed, small particles)
    └── Ultracentrifuge (highest speed — proteins, viruses, nanoparticles)
```

Mnemonic: "Filter has holes, settler is solid" — perforated = filtration; non-perforated = sedimentation.

4.6 PERFORATED BASKET CENTRIFUGE

What it does (one line): A spinning holed basket lined with cloth throws liquid out through the holes while crystals stay inside as a cake.

Principle: Centrifugal filtration. Centrifugal force (thousands of × g) drives the liquid through the filter cloth and basket holes; solids cannot pass and form a cake on the cloth.

Construction (sketch this):

- A vertical cylindrical basket with perforated (holed) walls, lined inside with filter cloth.
- The basket is mounted on a vertical shaft driven by a motor from below or above.
- An outer casing collects the thrown-out liquid (filtrate) and leads it to an outlet.
- A feed pipe at the top; a brake and a lid for safety.

Working (numbered steps):

1. Start the motor and bring the basket to full speed.
2. Feed the crystal slurry (magma) into the spinning basket through the feed pipe.
3. Centrifugal force flings the liquid through the cloth and holes into the casing (filtrate outlet); crystals deposit as a cake on the cloth.
4. Spray wash liquid on the spinning cake to wash it.
5. Stop the machine (or slow it) and scrape out the cake manually or with a scraper.

Advantages vs disadvantages:

Advantages	Disadvantages
Very fast separation and washing of crystals	Batch process — loading/unloading downtime
Gives a clean, well-washed cake	Manual cake discharge is labour intensive
Simple and sturdy	Not for very fine particles (they pass through cloth)
Handles large crystal loads	Vibration if loaded unevenly

Pharmaceutical applications: Separating drug crystals from mother liquor after crystallization (e.g., paracetamol, aspirin); washing antibiotic crystals; dewatering precipitated products.

Key takeaway: Perforated basket = spinning strainer → fast crystal separation and washing, batch operation.

4.7 NON-PERFORATED BASKET / TUBULAR BOWL CENTRIFUGE

What it does (one line): A spinning solid-wall bowl separates fine particles or two liquids by settling them against the wall — no filter cloth.

Principle: Centrifugal sedimentation. In a solid bowl, denser solids (or the denser liquid) move to the wall; the lighter liquid stays near the centre and overflows.

Construction (sketch this):

- A long, narrow cylindrical (tubular) solid-wall bowl, vertical, spinning at very high speed.
- Feed enters at the bottom centre; inside, an adjustable weir (dam ring) at the top sets the liquid level.
- Two outlets at the top: one for the light liquid overflowing the weir, and (for liquid–liquid) one for the heavy liquid.

Working (numbered steps):

1. Spin the bowl up to very high speed.
2. Feed the suspension at the bottom; centrifugal force throws solids to the bowl wall where they form a compact layer.
3. Clear liquid (supernatant) stays near the centre and overflows the weir at the top — collected continuously.
4. Stop periodically to scrape out the accumulated solids from the wall (batch solids removal).

Advantages vs disadvantages:

Advantages	Disadvantages
Separates very fine particles that filters cannot catch	Solids removal is batch (machine must stop)
Also separates two immiscible liquids	High speed = high maintenance, careful balancing
No filter medium to replace	Lower solids capacity than basket

Pharmaceutical applications: Clarifying fine suspensions and colloidal products; separating emulsions; recovering fine precipitates (e.g., in vaccine and biological processing); dewatering starch.

Key takeaway: Tubular bowl = solid wall, very high speed → catches fines and separates liquids by settling.

4.8 SUPER CENTRIFUGE

What it does (one line): An extra-long, extra-fast tubular bowl that separates extremely fine particles and emulsions.

Principle: Same as the tubular bowl (centrifugal sedimentation) but at much higher speed and with a longer bowl — giving far higher RCF for sub-micron particles.

Construction (sketch this):

- Essentially a taller, slimmer version of the tubular bowl centrifuge with a more powerful drive and stronger bowl material to withstand the higher speed.
- Feed at the bottom, weir-controlled liquid outlets at the top, as in the tubular bowl.

Working:

1. Operate exactly like the tubular bowl centrifuge, but at much higher rotational speed.
2. Even colloidal-size particles and stable emulsion droplets are thrown to the wall.
3. Clarified liquid overflows continuously; solids are removed batch-wise after stopping.

Advantages	Disadvantages
Separates colloids and stable emulsions nothing else can	Very expensive; precision engineering
Continuous liquid flow	Batch solids discharge; skilled operation needed

Pharmaceutical applications: Separating fine biological products; clarifying fermentation broths with colloidal solids; breaking stable emulsions in processing.

Key takeaway: Supercentrifuge = tubular bowl pushed to extreme speed → for colloids and stubborn emulsions.

4.9 ULTRA CENTRIFUGE

What it does (one line): The fastest centrifuge of all — spins so fast it can separate proteins, viruses, and nanoparticles.

Principle: Centrifugal sedimentation at up to hundreds of thousands of × g, often under vacuum (to avoid air friction heating) and with refrigeration.

Construction (sketch this):

- A small, thick-walled titanium rotor holding sample tubes, spinning inside a vacuum chamber.
- Vacuum pump removes air; refrigeration keeps samples cold; precise electronic speed control.
- Two types: **preparative** (separates and collects material) and **analytical** (has optics to watch sedimentation and measure molecular properties).

Working:

1. Load sample tubes symmetrically into the rotor (balance is critical).
2. Evacuate the chamber and start refrigeration.
3. Accelerate to the set ultra-high speed; particles settle strictly by size and density — largest/densest first.
4. Decelerate gently; collect separated layers (preparative) or read the optical data (analytical).

Advantages vs disadvantages:

Advantages	Disadvantages
Separates molecules — proteins, viruses, nanoparticles	Extremely expensive; research/pilot scale
Analytical type measures molecular weight and purity	Tiny sample volumes; not a production machine

Pharmaceutical applications: Purifying vaccines and viral products; separating liposomes and nanoparticles for drug delivery; analytical ultracentrifugation for protein characterization in biopharmaceutical QC.

Key takeaway: Ultracentrifuge = hundreds of thousands of × g in vacuum → separates molecules, mainly for biologics and research.

4.10 Comparison table — centrifuges

Centrifuge	Wall	Principle	Batch/continuous	Best for
Perforated basket	Holed + cloth	Filtration	Batch	Crystals from mother liquor
Tubular bowl	Solid	Sedimentation	Semi-continuous	Fine particles, two liquids
Supercentrifuge	Solid, long	Sedimentation (extreme)	Semi-continuous	Colloids, stable emulsions
Ultracentrifuge	Rotor + tubes	Sedimentation (ultra)	Batch (small)	Proteins, viruses, nanoparticles

4.11 Flowchart — choosing the separation method

```
Slurry to separate
        |
   Are particles coarse crystals?
   YES → PERFORATED BASKET (fast cake + wash)
   NO ↓
   Are particles very fine / colloidal, or two liquids?
   YES → TUBULAR BOWL / SUPERCENTRIFUGE (sedimentation)
   NO ↓
   Molecules / nanoparticles?
   YES → ULTRACENTRIFUGE
```

4.12 INFOGRAPHIC CONCEPT BOX — Unit II, Chapter 4

"Spin It to Separate It" (one-page visual): a washing-machine drum icon at the centre labelled "centrifugal force = gravity × thousands". Four quadrant icons: perforated basket (holes + cake), tubular bowl (solid wall + layers), supercentrifuge (tall thin bowl, "extreme speed"), ultracentrifuge (tiny rotor, "molecules"). A speed ladder on the side: basket → bowl → super → ultra, with particle sizes caught: crystals → fines → colloids → proteins/viruses. Bottom banner: "Holes filter, solid walls settle."

4.13 Pharmacy relevance

Centrifuges recover the pure drug after crystallization — the step that turns a reaction mixture into a sellable API. They also clarify biological products and separate emulsions. Without centrifugation, fine crystals and colloidal products could not be recovered economically.

4.14 India context

Indian API plants use perforated basket centrifuges after almost every crystallization step — rows of basket centrifuges are a familiar sight in Hyderabad and Visakhapatnam bulk-drug units. Tubular bowl and supercentrifuges serve India's growing biologics and vaccine industry.

4.15 Key points

1. Centrifugation multiplies gravity thousands of times (RCF).
2. Perforated wall = filtration centrifuge (basket) — batch, crystals + washing.
3. Solid wall = sedimentation centrifuge (tubular bowl) — fines and two liquids.
4. Supercentrifuge = extreme-speed tubular bowl — colloids, stubborn emulsions.
5. Ultracentrifuge = hundreds of thousands of × g in vacuum — proteins, viruses, nanoparticles; preparative vs analytical.
6. Balance the load — uneven loading causes dangerous vibration.

4.16 Common confusions

- **Perforated vs non-perforated basket:** Perforated has holes + cloth and filters; non-perforated (tubular bowl) has a solid wall and settles. Do not draw holes in a sedimentation centrifuge.
- **Supercentrifuge vs ultracentrifuge:** Supercentrifuge is a production-scale tall tubular bowl; ultracentrifuge is a small, vacuum, refrigerated rotor for molecules.
- **Centrifuge vs cyclone separator:** Cyclone has no motor and no spinning parts — air spins by itself. A centrifuge is motor-driven.

4.17 Common mistakes

- Calling the basket centrifuge continuous (it is batch — loading and unloading need stops).
- Writing that the tubular bowl has a filter cloth (it has none — solid wall).
- Forgetting the weir/dam that controls liquid level in the tubular bowl.
- Ignoring balancing — an unbalanced high-speed rotor is dangerous.

4.18 Mnemonic

"Baskets have holes, Bowls are solid, Super is taller, Ultra is smallest-but-fastest." Or by speed ladder: **B–B–S–U** (Basket → Bowl → Super → Ultra), each step faster and catching smaller particles.

4.19 Exam summary

Centrifugation uses centrifugal force (RCF = multiples of gravity) for fast separation. Filtration centrifuges (perforated basket: holed wall + cloth, batch, crystal separation and washing). Sedimentation centrifuges (tubular bowl: solid wall, fines and liquid–liquid; supercentrifuge: extreme speed for colloids; ultracentrifuge: vacuum, refrigerated, hundreds of thousands of × g for proteins/viruses/nanoparticles — preparative vs analytical).

4.20 One-minute revision

Spin = gravity × thousands → perforated basket (holes, batch, crystals) → tubular bowl (solid wall, fines) → supercentrifuge (taller, faster, colloids) → ultracentrifuge (vacuum, molecules). Holes filter; solid walls settle.

4.21 Practice questions

Long answers (10 marks):

1. Describe the construction and working of the perforated basket centrifuge with a neat labelled diagram. Give advantages, disadvantages, and applications.
2. Explain the principle of centrifugation. Describe the tubular bowl centrifuge with diagram and compare it with the basket centrifuge.
3. Write notes on the supercentrifuge and ultracentrifuge with their pharmaceutical applications.

Short answers (2–5 marks):

1. Define centrifugation and RCF.
2. Differentiate between filtration and sedimentation centrifuges.
3. What is a weir? What is its function?
4. Why is the ultracentrifuge operated under vacuum?
5. Name the two types of ultracentrifuge and their uses.

MCQs:

1. A perforated basket centrifuge works on the principle of:

a) Sedimentation b) Centrifugal filtration c) Gravity settling d) Evaporation — **Answer: b**

1. The tubular bowl centrifuge has:

a) A perforated wall b) A solid wall c) A filter cloth d) A membrane — **Answer: b**

1. The ultracentrifuge is mainly used for:

a) Crystals b) Proteins and viruses c) Syrups d) Tablets — **Answer: b**

1. In a tubular bowl, the liquid level is controlled by the:

a) Brake b) Weir/dam c) Knife d) Hopper — **Answer: b**

1. Which gives the highest RCF?

a) Basket b) Tubular bowl c) Supercentrifuge d) Ultracentrifuge — **Answer: d**

Viva questions:

1. Why must a centrifuge load be balanced?
2. Basket or tubular bowl — which would you use to separate fine colloidal particles? Why?
3. What is the difference between preparative and analytical ultracentrifugation?

Application-based:

1. After crystallization, you have paracetamol crystals in mother liquor that must be washed clean. Which centrifuge and what operating sequence?
2. A vaccine process needs to separate virus particles from cell debris. Which centrifuge is appropriate?

4.22 References

1. Banker, G. S. Pharmaceutical Engineering. Marcel Dekker.
2. Sambamurthy, K. Introduction to Pharmaceutical Engineering. New Age International.
3. Hickey, A. J. Pharmaceutical Process Engineering. CRC Press.
4. Banker, G. S. and Rhodes, C. T. Modern Pharmaceutics. CRC Press.