

Unit 2: Unit Operations

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2.1 Unit operations and unit processes

Chemical engineering divides a manufacturing process into two kinds of step. A **unit operation** is a physical step that changes the state, composition or location of material without changing its chemical identity: extraction, filtration, distillation, evaporation, crystallization, drying, milling. A **unit process** is a chemical step in which bonds are made or broken: the nitration, halogenation, oxidation and reduction of Units 3 and 4. This unit teaches the five unit operations the PCI syllabus names, in the order a work up usually meets them: the reaction mixture is extracted to separate product from water soluble material, filtered to remove solids, distilled and evaporated to exchange and remove solvent, and crystallised to deliver the pure, correctly formed API.

2.2 Extraction: liquid equilibria

Liquid liquid extraction separates components by their unequal distribution between two immiscible liquid phases, most often an aqueous phase and a water immiscible organic solvent. The governing quantity is the **distribution coefficient**, the ratio of a solute's concentration in the organic phase to its concentration in the aqueous phase at equilibrium. A solute with a high coefficient is extracted in few contacts; one near unity needs many. Three practical consequences follow:

- **pH is the process chemist's lever.** For an acidic API, extraction into organic solvent is efficient when the aqueous phase is acidic enough to keep the acid unionised, and back extraction into water is efficient when the phase is made alkaline so the acid ionises and prefers water. Basic compounds are handled in mirror image. Much of API work up design is choosing the pH sequence that walks the product through the phases while leaving impurities behind.
- **Several small extractions beat one large one.** For the same total solvent volume, splitting the extraction into portions removes more solute, a direct consequence of the distribution law; plant practice balances this against time and emulsion risk.
- **Liquid equilibria set the limits.** Phase diagrams for the ternary system (solute plus two solvents) show the region in which two phases exist at all, and mutual solubility of the solvents caps recovery: solvent dissolved in the aqueous raffinate is solvent lost, and product dissolved in it is yield lost.

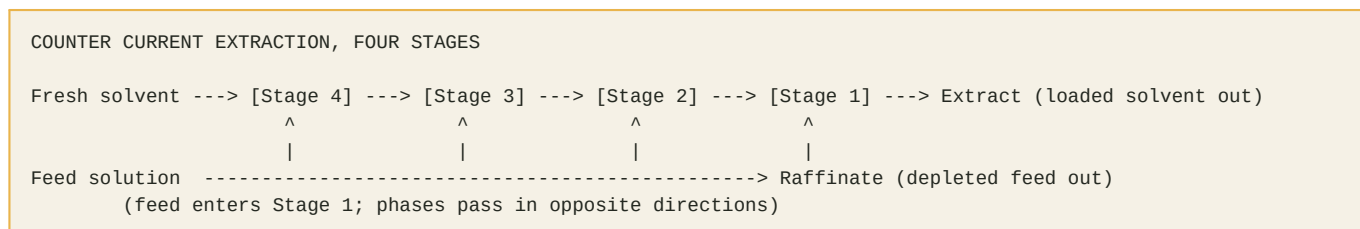
2.3 Extraction with reflux, with agitation, and counter current extraction

The syllabus names three ways of bringing the phases into effective contact.

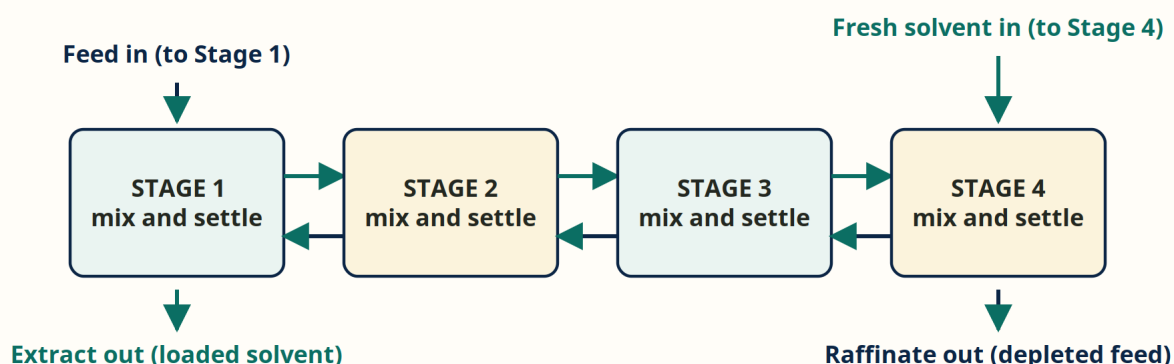
Extraction with agitation is the batch standard: the two phases are stirred together in a vessel until equilibrium is approached, stirring is stopped, the phases are allowed to separate (settle), and the layers are split. Its industrial forms are the stirred extractor and the mixer settler. Agitation creates interfacial area; settling destroys it cleanly. The recurring failure mode is the emulsion, a stable dispersion that will not separate, provoked by over vigorous agitation, fines, surfactant like impurities or a small density difference between phases; remedies include longer settling, brine addition, filtration of the interface, temperature change or centrifugation.

Extraction with reflux applies when the extracting solvent is volatile and the material tolerates heat: solvent vapour condenses and percolates repeatedly through the material or solution, as in a Soxhlet type arrangement for solids, continually presenting fresh solvent without manual repetition. It suits exhaustive recovery of a solute from a solid matrix or from a solution in a higher boiling medium.

Counter current extraction is the efficient continuous arrangement. The two phases flow in opposite directions through a series of stages, so the freshest solvent meets the most depleted feed and the most loaded solvent meets the freshest feed; the concentration driving force is maintained along the whole cascade, and high recovery is achieved with far less solvent than cross current (repeated batch) extraction.



Counter current extraction: four stage cascade



Feed solution enters Stage 1 and flows right; solvent enters Stage 4 and flows left.
The freshest solvent always meets the most depleted feed, so recovery is high on little solvent.

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Figure: In counter current extraction the phases pass in opposite directions through the stages, keeping the concentration driving force alive along the whole cascade.

Industrial embodiments include cascades of mixer settlers, extraction columns (packed, pulsed or with rotating internals) and centrifugal extractors, which use centrifugal force to separate phases of similar density and give short contact times for unstable products. The penicillin recovery of Unit 4 is the classic pharmaceutical example: extraction of the antibiotic from broth into an organic solvent at low pH, and back into water at higher pH, performed rapidly and cold because the molecule is fragile.

2.4 Filtration: theory

Filtration separates suspended solids from liquid by passing the liquid through a porous medium that retains the solid as a cake. Its process roles are threefold: removing solids that are waste (catalyst, charcoal, salts), collecting solids that are product (the crystallised API), and clarifying solutions before a critical step (polish filtration). The theory of filtration, in the form examinations expect, rests on the idea that flow through the cake and the medium obeys a Darcy type law: the filtration rate is proportional to the driving pressure

difference and inversely proportional to the liquid viscosity and the total resistance, that of the filter medium plus that of the growing cake. As filtration proceeds the cake thickens and the rate falls at constant pressure. The practical lessons are direct:

- **Cake properties dominate.** A crystalline, coarse, incompressible cake filters fast; a fine, gelatinous or compressible cake blinds the medium and slows to a crawl, and squeezing a compressible cake harder can reduce its permeability.
- **Filter aids** (diatomaceous earth, perlite, cellulose) build a porous cake structure and are used as a precoat or body feed when the solids filter badly.
- **Washing the cake** displaces mother liquor and its dissolved impurities; wash efficiency, not just wash volume, decides final purity, and cake cracking during washing short circuits the wash.
- **Temperature and viscosity** matter: hot solutions filter faster but may deposit crystals in the filter if they cool in transit.

2.5 Pressure, vacuum and centrifugal filtration

Equipment	Driving force	Typical process use
Filter press	Pressure from a pump	Bulk solids removal, catalyst and charcoal filtration, filter aid cakes
Nutsche filter (including agitated Nutsche filter dryer, ANFD)	Pressure or vacuum, in a closed vessel	The pharmaceutical workhorse: crystallised API is filtered, washed, reslurried and dried in one contained unit
Vacuum leaf / rotary vacuum filter	Vacuum drawn through the medium	Continuous filtration of fast filtering slurries
Basket and peeler centrifuges	Centrifugal force	Rapid separation and washing of crystalline products; low residual moisture
Pressure leaf filter	Pressure in a closed vessel	Polish filtration of solutions, contained handling of solvent wet cakes

Choice follows the cake and the hazard. A flammable solvent wet, toxic API demands closed, contained equipment (the ANFD earns its place because filtration, washing and vacuum drying happen behind one lid). A hard, coarse, fast crystal suits the centrifuge, which also delivers the driest cake and so shortens drying. Fine catalyst and charcoal are typically removed on a press or leaf filter with filter aid, and the filtrate polish filtered before the next step. Centrifugal filtration is a distinct principle in its own right: the driving force is the centrifugal field, many times gravity, so rates are high and cakes compact and dry, at the price of batch wise operation in most pharmaceutical designs.

2.6 Distillation: azeotropic and steam distillation

Ordinary fractional distillation separates volatile components by boiling point difference and underlies solvent recovery throughout the plant. The syllabus singles out the two special distillations a process chemist reaches for when simple distillation fails.

Azeotropic distillation addresses mixtures that form a constant boiling azeotrope, a composition that distils unchanged so that simple fractionation cannot cross it. The standard pharmaceutical applications are drying and solvent exchange. Water forms azeotropes with many process solvents (toluene carries water over as a low boiling azeotrope, the basis of Dean and Stark water determination and of azeotropic drying of a reaction mass), and ethanol water cannot be dried past its azeotrope by fractionation alone; adding an entrainer that forms a new, separable azeotrope, or switching to molecular sieves or membranes, completes the drying. In process work the commonest use is azeotropic removal of water to drive equilibria

(esterifications and amidations are pushed by distilling water out as it forms) and to prepare the rigorously dry streams that water sensitive steps such as Grignard formation demand.

Steam distillation serves water immiscible, heat sensitive or high boiling organics. Passing steam through the mixture lets the organic component distil at a temperature below 100 degrees Celsius, because the total vapour pressure is the sum of the partial pressures of water and of the organic liquid, and boiling occurs when that sum reaches atmospheric pressure, far below the organic compound's own boiling point. It is used to recover volatile oils and intermediates, to strip residual high boiling solvents and odorous impurities from products, and to separate materials that would decompose at their normal boiling temperatures.

2.7 Evaporation: types of evaporators and factors affecting evaporation

Evaporation concentrates solutions by boiling off solvent, usually under reduced pressure so that heat sensitive APIs are not cooked. It differs from distillation in intent: the liquid concentrate (or the dry residue) is the product, and the vapour is normally condensed only for solvent recovery or disposal.

Evaporator type	Character	Suited to
Open pan / jacketed vessel	Simple batch boiling, often under vacuum in pharma	Small batches, robust materials
Horizontal and vertical tube (calandria) evaporators	Heating tubes inside a body; natural or forced circulation	Large volumes of non fouling solutions
Falling film evaporator	Thin film flows down heated tubes; seconds of contact	Heat sensitive products, low hold up
Forced circulation evaporator	Pumped circulation through an external heater	Viscous liquors, crystallising concentrates, fouling duties
Agitated thin film (wiped film) evaporator	Rotor spreads a thin film on a heated wall	Very heat sensitive and viscous materials, stripping to near dryness

Factors affecting evaporation: the temperature difference between heating medium and boiling liquid (the driving force, raised by vacuum lowering the boiling point but limited by product stability); the heat transfer coefficient, which falls as viscosity rises and as scale and fouling coat the surfaces; the boiling point elevation of concentrated solutions; hydrostatic head in tall liquid columns; foaming, which carries product into the condenser; and the vapour handling capacity of the condenser and vacuum system, which so often turns out to be the real bottleneck when a laboratory evaporation is scaled. Solvent exchanges in API processes, distilling out a reaction solvent while feeding the next one to hold volume constant, are evaporation and distillation doing process work together.

2.8 Crystallization: the purification that defines the product

Crystallization is the most important purification operation in API manufacture, because it is simultaneously a purification (the growing crystal lattice accepts the product and rejects most impurities), an isolation (a filterable solid from a solution) and a definition of the product's physical form (polymorph, particle size and shape, which govern filtration, drying, flow and even dissolution of the final drug). The syllabus structure is: crystallization from aqueous and nonaqueous solutions, the factors affecting crystallization, and nucleation.

A solution becomes capable of crystallising when it is **supersaturated**: it holds more dissolved solute than the equilibrium solubility at that temperature. Supersaturation is generated by cooling (for solutes whose solubility falls with temperature, the commonest case, and the basis of crystallisation from both aqueous and nonaqueous solutions), by evaporating solvent, by adding an antisolvent in which the product is poorly soluble (water into an alcoholic solution, or a hydrocarbon into a polar one), or by reaction (forming a salt in situ). **Aqueous crystallization** suits stable, water tolerant compounds and offers cheap, safe solvent and

easy effluent handling; **nonaqueous crystallization** (alcohols, ethyl acetate, acetone, hydrocarbons and their mixtures) serves water sensitive or water insoluble APIs and gives access to solvates and anhydrous forms water cannot produce.

Factors affecting crystallization: the solvent (sets solubility, the supersaturation profile, which polymorph appears, and crystal habit); the rate at which supersaturation is generated (slow cooling gives growth on few nuclei, hence large pure crystals; crash cooling gives fines that trap mother liquor and filter badly); temperature profile and its control; seeding (see below); agitation (secondary nucleation and breakage versus uniformity); impurities, which can poison growth faces, change habit or be incorporated; and pH and ionic strength for ionisable compounds.

2.9 Nucleation, the metastable zone and seeding

Nucleation is the birth of crystal particles. In **primary nucleation**, new crystals appear spontaneously in a clear supersaturated solution; it needs high supersaturation and is hard to control. In **secondary nucleation**, existing crystals generate new ones by contact with the impeller, vessel walls and each other; it occurs at low supersaturation and is usually the practical source of crystal numbers in a seeded batch. Between the solubility curve and the supersaturation level at which primary nucleation erupts lies the **metastable zone**: a region where a solution will not nucleate on its own but will grow crystals that are introduced into it. The classical description is Miers supersaturation theory, which maps exactly these regions: unsaturated, metastable (growth only) and labile (spontaneous nucleation). Good process design lives in the metastable zone: the batch is brought into it, **seeded** with a small charge of correct form crystals of controlled size and quantity, and then cooled or dosed with antisolvent slowly enough that supersaturation is consumed by growth on the seeds rather than by new nucleation. Seeding is how a plant fixes crystal size distribution and polymorph batch after batch; an unseeded crash crystallisation is how it gets surprises.

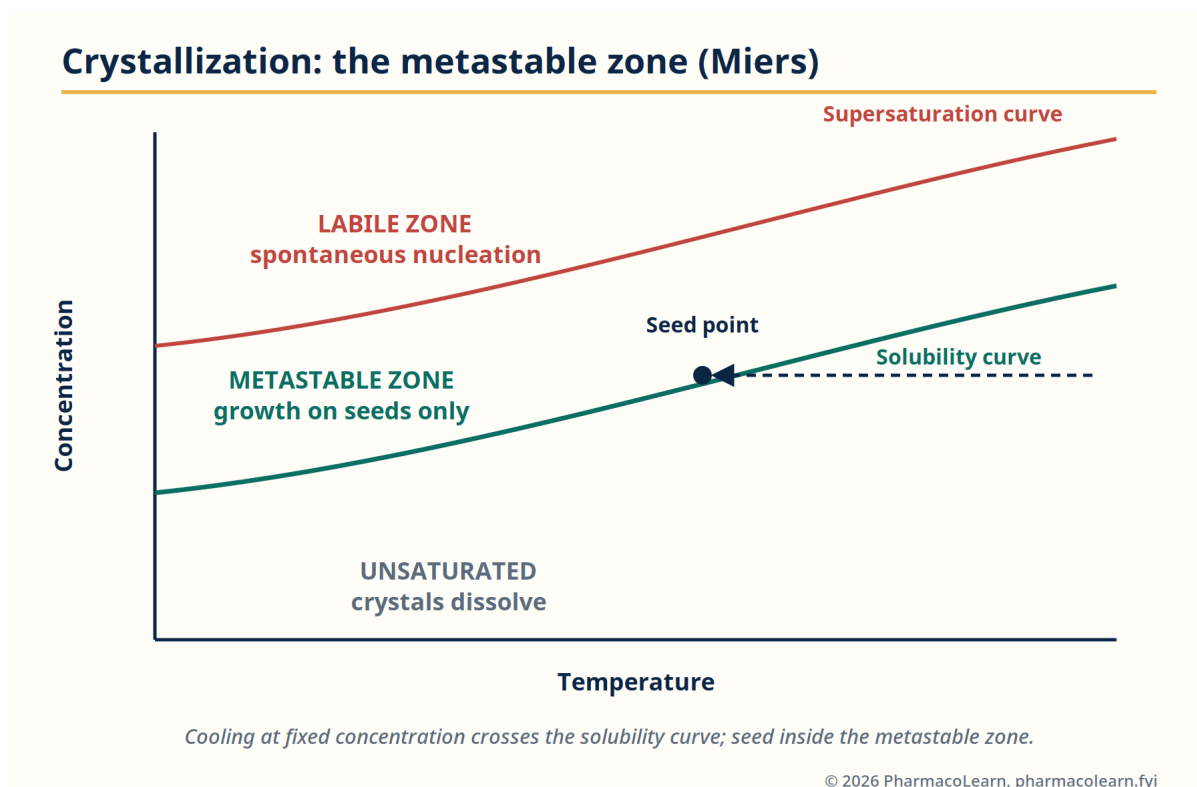


Figure: The Miers picture of crystallization: work in the metastable zone, between the solubility and supersaturation curves, where introduced seeds grow but new nuclei do not form.

2.10 Polymorphs, hydrates, solvates and amorphous APIs

The same molecule can pack into different solid forms, and the forms differ in solubility, stability, melting point, hygroscopicity and mechanical behaviour, all of which reach the patient through the performance of the dosage form.

- **Polymorphs** are different crystal structures of the same chemical composition. The thermodynamically stable form is the least soluble; metastable forms dissolve faster but risk converting to the stable form during processing or storage. The ritonavir episode is the standard cautionary tale taught with this topic: a more stable, less soluble polymorph appeared in the marketed product two years after launch, forced withdrawal and reformulation, and permanently changed how thoroughly industry screens for polymorphs.
- **Hydrates** incorporate water into the lattice, **solvates** incorporate solvent. They form when crystallising from water or the solvent concerned, may be more or less stable than the anhydrate depending on humidity and temperature, and must be controlled because drying can strip the lattice solvent and collapse or convert the form.
- **Amorphous APIs** lack a lattice entirely: they are higher in energy, dissolve faster (a strategy for poorly soluble drugs), and are correspondingly less stable, liable to crystallise on storage and often hygroscopic.

Principle and general methods of preparation, as the syllabus phrases it: polymorphs are prepared by crystallising under different conditions of solvent, temperature, supersaturation and cooling rate, and by techniques such as solvent evaporation, slurry conversion (stirring a form in a solvent until it converts to the form stable in that medium), melt crystallisation and grinding; hydrates and solvates by crystallising from water or the chosen solvent, or by exposing the solid to the vapour; amorphous material by removing the solvent or the melt state faster than crystals can organise, by spray drying, freeze drying, melt quenching or co precipitation with a stabilising polymer. The process point closes the unit: the form is not an analytical afterthought. It is decided at the crystallisation step, in this unit's core operation, and controlled by solvent, seeding and profile choices made there.

2.11 Unit 2 summary

Operation	What it separates or achieves	The variable that decides success
Extraction	Product from aqueous or organic impurities	Distribution coefficient, pH, phase behaviour
Filtration	Solid from liquid	Cake permeability, medium, washing
Distillation	Volatile components; water removal	Azeotrope behaviour, partial pressures
Evaporation	Concentration, solvent removal	Heat transfer, vacuum, residence time
Crystallization	Purification plus physical form	Supersaturation profile, nucleation, seeding

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