

Unit 1: Preformulation Concepts, Pharmaceutical Dispersions, Parenterals and Optimization Techniques

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Modern Pharmaceutics, subject code MPH103T, is a core Semester 1 subject of M.Pharm Pharmaceutics. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject is about how a pharmaceutical product is developed and manufactured in industry. Before a formulation is made, the drug and its excipients are characterised in preformulation studies and checked for compatibility and stability. The formulation is then improved systematically by optimization techniques and statistical designs instead of trial and error. In the factory, validation proves that facilities, equipment and processes do what they are supposed to do, and current good manufacturing practice (cGMP) with sound industrial management keeps production under control. The last two units deal with the physics of tablet compression, where a powder is consolidated into a compact, and with the parameters and statistics used to judge consolidation, dissolution and drug release profiles. A student who completes this subject should be able to design preformulation studies, interpret stability and dissolution data with the standard models and tests, and explain how an industrial process is qualified and kept in a validated state.

1.1 Preformulation studies: scope and parameters

Preformulation is the stage of development in which the physicochemical properties of a new drug substance are characterised, alone and in combination with excipients, before a dosage form is designed. It is the first step in the rational development of a dosage form. The information generated decides which dosage form is feasible, which excipients are safe to combine with the drug, what processing route to choose, and what stability problems to expect.

The main studies are:

- **Organoleptic and bulk properties:** colour, odour, taste, crystal form and polymorphism, particle size and size distribution, powder flow, density and hygroscopicity.
- **Solubility profile:** solubility in water and in solvents of different pH, pKa and ionisation behaviour, partition coefficient, dissolution behaviour of the solid.
- **Stability profile:** stability of the drug in solid state and in solution, the effect of pH, temperature, light and oxygen, and identification of the main degradation pathways.
- **Compatibility studies:** interaction of the drug with the excipients that are likely to be used, tested before the formulation is finalised (section 1.2).
- **Derived properties for processing:** compressibility, compactibility and flow, which decide between direct compression, granulation and other routes.

Preformulation data save time and money later. A drug that is poorly soluble will need a solubility strategy; a drug that is moisture sensitive will need protective packaging and a dry process; a drug that reacts with lactose cannot be put into a tablet that contains lactose. All of this is cheaper to learn on a few grams of drug than on a production batch.

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Preformulation study sequence
Drug substance received
|
v
Characterisation: identity, purity, crystal form, particle size
|
v
Solubility and ionisation profile (pKa, log P, pH solubility)
|
v
Stability in solid state and solution (heat, light, pH, oxygen)
|
v
Excipient compatibility screening
|
v
Report: recommended dosage form, excipients, process and packaging

```

Preformulation Study Sequence

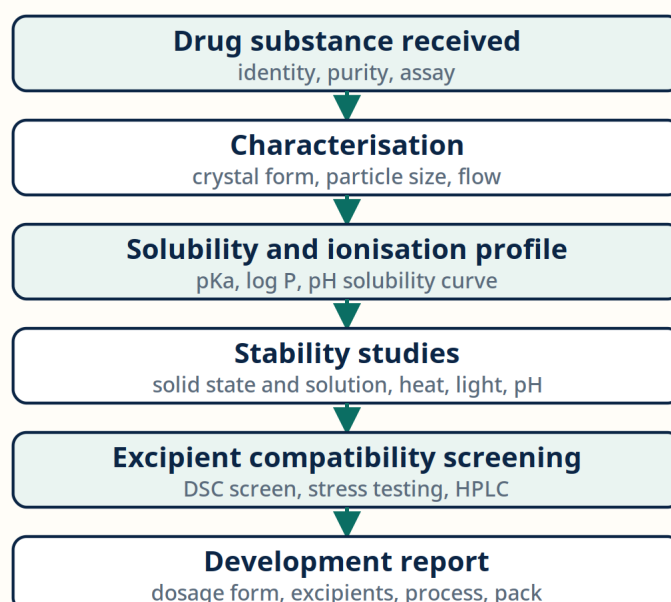


Figure: The preformulation study sequence: each stage produces information the next stage needs, ending in a development report that fixes the dosage form, excipients, process and packaging.

1.2 Drug excipient interactions: types and mechanisms

An interaction between a drug and an excipient is any change in the physical or chemical nature of the drug caused by the excipient, or a change in the excipient caused by the drug, which can alter stability, dissolution, bioavailability or appearance of the product. Some interactions are wanted (for example a solubiliser improving dissolution), but most preformulation work is about detecting unwanted ones early.

Interactions are grouped as:

- **Physical interactions:** no chemical reaction, but the physical state or availability of the drug changes. Examples: adsorption of a drug onto a finely divided excipient, complexation (for example tetracyclines chelating with calcium and magnesium salts), formation of eutectic mixtures that melt or soften during processing, and changes in crystal form induced by an excipient.
- **Chemical interactions:** a true chemical reaction that degrades the drug or forms a new entity. Common mechanisms are hydrolysis promoted by the moisture or pH microenvironment of an excipient, oxidation

catalysed by trace metals or peroxide impurities in polymers, and the Maillard reaction between primary amine drugs and reducing sugars such as lactose, which causes browning and potency loss.

- **Biopharmaceutical interactions:** the excipient changes the release or absorption of the drug without a chemical reaction, for example a lubricant film of magnesium stearate slowing wetting and dissolution, or a surfactant changing membrane permeability.

Interaction	Typical pair	Result if undetected
Maillard reaction	Primary amine drug + lactose	Browning, loss of potency
Chelation	Tetracycline + calcium or magnesium salts	Poor absorption of the antibiotic
Adsorption	Drug + colloidal silicon dioxide or clays	Slow or incomplete release
Hydrolysis promotion	Ester or amide drug + moist alkaline excipient	Degradation on storage
Oxidation catalysis	Oxidation prone drug + peroxide impurities in PEG or povidone	Degradants, discolouration
Eutectic formation	Two low melting solids mixed together	Softening, sticking during compression

1.3 Methods for studying drug excipient interactions

Several methods are used together, because no single technique proves or excludes an interaction.

Thermal methods. Differential scanning calorimetry (DSC) is the most used screening tool. The drug, each excipient and the binary mixtures (often 1:1) are scanned. A shift, broadening or disappearance of the drug melting endotherm, or a new peak, suggests an interaction or a physical change such as dissolution of the drug in a molten excipient. DSC is fast and needs little sample, but a changed thermogram is only an indication: it must be confirmed by another method, because some changes are simple physical effects. Differential thermal analysis (DTA) and thermogravimetric analysis (TGA) support the same conclusions.

Spectroscopic methods. Infrared spectroscopy compares the spectrum of the drug with that of the mixture; disappearance or shifting of characteristic peaks points to interaction. UV spectroscopy, NMR and mass spectrometry are used in solution studies and for identifying degradation products.

Chromatographic methods. Thin layer chromatography and HPLC of stressed mixtures detect new spots or peaks, that is, actual degradation products. HPLC with assay and related substances measurement is the most convincing evidence because it quantifies the loss of drug.

Isothermal stress testing. Mixtures of drug and excipient, often with a small amount of added water, are stored at an elevated temperature (commonly 40 to 50 degrees Celsius) for a fixed period, then examined for physical changes (colour, liquefaction, caking) and analysed chemically. This imitates storage stress in a short time.

Other methods. X-ray powder diffraction detects changes in crystallinity; microscopy shows physical changes such as crystal growth or melting; slurry and solution studies in the presence of the excipient measure pH shifts and degradation rates. A practical programme uses DSC for rapid screening, isothermal stress testing for confirmation, and HPLC to quantify any real degradation.

1.4 Kinetics of stability

Stability kinetics describes how the rate of a degradation reaction depends on concentration, and it is the basis for predicting shelf life. The rate of reaction is the change in concentration of drug with time. For a reaction in which drug A degrades, the order of the reaction states how the rate depends on the concentration of A.

- **Zero order:** the rate is independent of the concentration of the reactant. Rate = k_0 , and concentration falls linearly with time: $C = C_0 - k_0 t$. Suspensions often show apparent zero order behaviour because the dissolved concentration stays constant while solid remains. The half life depends on the starting concentration.
- **First order:** the rate is proportional to the concentration remaining. Log concentration falls linearly with time. Most drug degradation reactions are first order or pseudo first order. The half life, $t_{1/2} = 0.693/k$, is independent of the starting concentration.
- **Second order:** the rate depends on the concentration of two reactants, or on the square of one concentration. Less common for single drug degradation, but seen in bimolecular reactions.

Two derived times are used constantly:

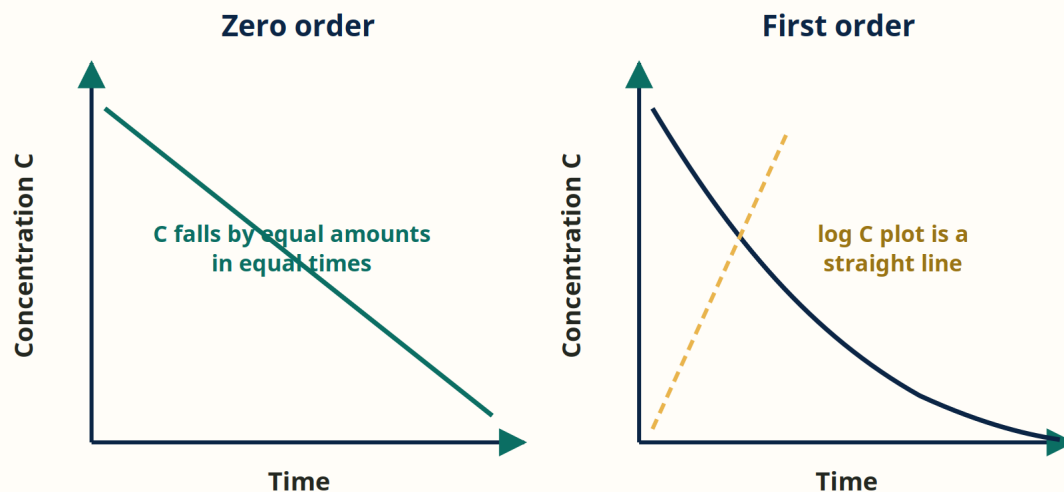
- **$t_{1/2}$ (half life):** time for the concentration to fall to half its initial value.
- **t_{90} (shelf life):** time for the concentration to fall to 90 percent of the initial value, that is, 10 percent degradation, which is the usual limit for acceptable potency. For a first order reaction, $t_{90} = 0.105/k$.

Temperature is the strongest accelerator of degradation. The Arrhenius equation relates the rate constant to temperature: $k = A e^{-E_a/RT}$, where E_a is the activation energy and A is a frequency factor. A plot of $\log k$ against $1/T$ is a straight line, so rate constants measured at several elevated temperatures can be extrapolated to room temperature to predict the shelf life before long term data exist. The Q10 rule is a rough shortcut from the same idea: many reaction rates roughly double or triple for each 10 degree rise in temperature. Other factors that affect the rate are pH (many drugs have a pH of maximum stability), light, oxygen, moisture, ionic strength, and the presence of catalysts such as trace metals.

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Effect of temperature on degradation (Arrhenius approach)
Store samples at 40, 50, 60, 70 degrees Celsius
    |
    v
Assay at intervals, find k at each temperature
    |
    v
Plot log k against 1/T (straight line)
    |
    v
Extrapolate the line to 25 degrees Celsius to get k25
    |
    v
Shelf life  $t_{90} = 0.105 / k_{25}$  (for first order degradation)
  
```

Zero Order and First Order Degradation



Half life is constant for first order; it depends on starting concentration for zero order.

Figure: Zero order degradation loses equal amounts in equal times, while first order degradation follows an exponential curve whose log plot is a straight line.

1.5 Stability testing

Stability testing is the formal programme of studies that shows how the quality of a drug substance or product varies with time under the influence of temperature, humidity and light, and it establishes the shelf life and storage conditions printed on the label. The ICH guidelines (mainly Q1A) harmonise the design: the world is divided into climatic zones, and long term conditions are set for each zone. India falls in Zone IV, the hot and humid zone, so long term testing of products for the Indian market is commonly done at 30 degrees Celsius and 65 or 75 percent relative humidity.

A standard programme contains:

- **Long term (real time) studies:** storage at the labelled long term condition for the full proposed shelf life, with testing at defined intervals (for example 0, 3, 6, 9, 12, 18, 24 months). These data confirm the shelf life.
- **Accelerated studies:** storage at a stress condition, commonly 40 degrees Celsius and 75 percent relative humidity for 6 months, with testing at 0, 3 and 6 months. Significant change at the accelerated condition triggers intermediate condition studies and can limit the shelf life.
- **Stress testing:** deliberate severe exposure (heat, humidity, oxidation, photolysis, acid and base hydrolysis) done mainly on the drug substance to reveal degradation pathways and validate that the analytical methods are stability indicating.

At each interval the product is tested for appearance, assay, degradation products, dissolution, moisture content, hardness or other dosage form specific properties. A significant change is defined in the guidelines, for example a 5 percent change in assay from the initial value or failure to meet any acceptance criterion. Shelf life is assigned from the long term data, supported by the accelerated data, using statistical evaluation of the trend of the critical parameters.

1.6 Theories of dispersion

A dispersion is a system in which one substance (the dispersed phase) is distributed as particles, droplets or molecules in another (the continuous phase or dispersion medium). Pharmaceutical dispersions include

suspensions, emulsions, colloids and gels. Their behaviour is governed by what happens at the interface between the phases.

Key ideas:

- **Surface and interfacial tension:** molecules at an interface are in an unbalanced force field, so creating new surface requires work and increases the free energy of the system. A finely divided dispersion has a huge interfacial area and therefore high free energy; it is thermodynamically unstable and the particles or droplets tend to reduce area by aggregating, coalescing or sedimenting. Formulation is the art of slowing these processes.
- **Wetting:** a powder must be wetted by the liquid before it can be dispersed. The contact angle describes wetting: an angle below 90 degrees indicates good wetting. Wetting agents and surfactants lower the interfacial tension and displace air from the particle surface.
- **Adsorption and electrical properties:** ions and polymers adsorb at interfaces and give the particles a surface charge. The zeta potential, the electrical potential at the slipping plane around a moving particle, is a practical measure of this charge. A high zeta potential (commonly above about 30 mV in magnitude) means strong repulsion between particles and a stable dispersion; values near zero allow aggregation.
- **DLVO theory:** the stability of a colloidal dispersion is explained as a balance between van der Waals attraction and electrostatic repulsion between particles. If the repulsive barrier is high, particles stay dispersed; if salts compress the double layer or the charge falls, attraction wins and the particles flocculate or coagulate.
- **Sedimentation:** the rate at which a particle settles follows Stokes law: it increases with particle size and with the density difference between the phases, and decreases with the viscosity of the medium. This one equation drives most suspension formulation choices.

1.7 Emulsions: preparation and stability

An emulsion is a dispersion of one liquid in another immiscible liquid, stabilised by an emulsifying agent that forms a film at the droplet interface. Emulsions are either oil in water (o/w), where oil droplets sit in a water continuous phase, or water in oil (w/o), the reverse. Multiple emulsions (w/o/w and o/w/o) place one emulsion inside another. Emulsions are used for oral oils and vitamins, intravenous fat nutrition, and creams and lotions for the skin.

Preparation. The internal phase is added gradually to the external phase containing the emulsifier, with continuous stirring or homogenisation. Common methods include the dry gum (continental) method and the wet gum (English) method for primary emulsions made with acacia, the bottle method for volatile oils, and mechanical homogenisation or ultrasonication for fine, uniform droplets. Smaller droplets mean slower creaming and a more stable product, so energy input during preparation matters.

Stability problems. An emulsion can fail by:

- **Creaming:** droplets rise or settle because of density difference. It follows Stokes law and is reversible by shaking; it is unsightly but not a break.
- **Flocculation:** droplets group into loose clusters without losing their identity; often a step towards coalescence.
- **Coalescence and breaking:** the interfacial film ruptures, droplets merge, and the emulsion separates into two layers. This is irreversible and the product is finished.
- **Phase inversion:** an o/w emulsion flips to w/o or the reverse, caused by temperature, electrolyte or a change in phase volume.

- **Microbial growth and chemical degradation** of oils and emulsifiers on storage.

Formulators fight these with the right HLB emulsifier or blend, adequate emulsifier concentration, small droplet size, increased viscosity of the continuous phase, and storage away from temperature extremes. Evaluation includes globule size analysis, viscosity, creaming volume, phase separation on centrifugation and stress, and drug content and release.

Emulsion Types: o/w and w/o

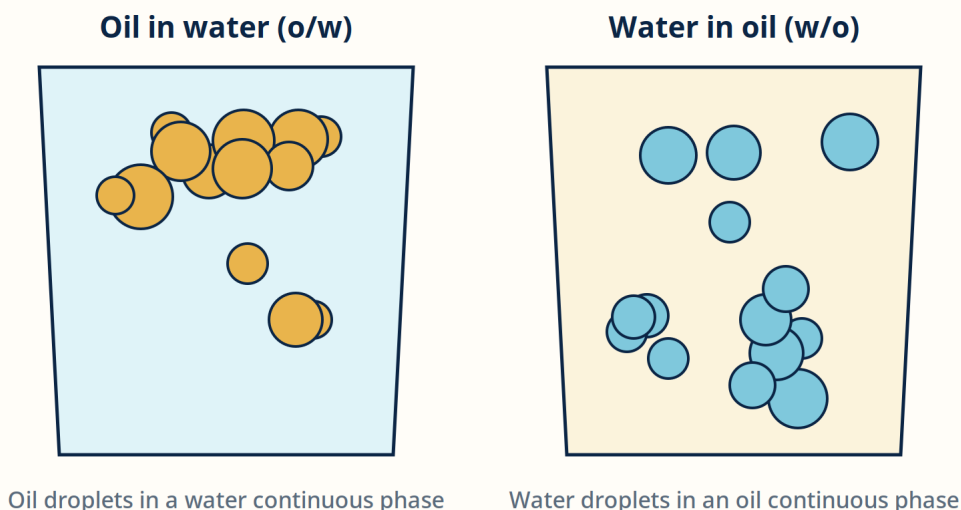


Figure: The two simple emulsion types. In an o/w emulsion the oil is the dispersed phase; in a w/o emulsion the water is dispersed in oil.

1.8 Suspensions: preparation and stability

A pharmaceutical suspension is a dispersion of insoluble solid particles in a liquid medium, used when the drug is insoluble, unstable in solution, or needed as a depot or a palatable liquid for children. Particle size is usually in the range of about 0.5 to 10 micrometres for oral products.

Preparation. The drug is first reduced to the required size and wetted with a wetting agent, then dispersed in a vehicle containing suspending agents that build viscosity and structure (for example methylcellulose, tragacanth, bentonite or carbomers). Flocculating agents, buffers, preservatives, sweeteners and flavours are added, and the product is homogenised or milled to a uniform dispersion.

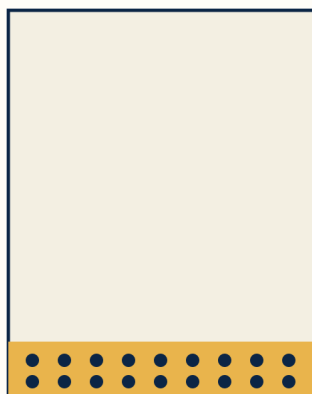
Stability and the two sedimentation behaviours. Particles settle by Stokes law. What matters is how they settle:

- **Deflocculated system:** particles are individually dispersed and repel each other. They settle slowly, but the sediment packs tightly into a hard cake that cannot be redispersed (caking). Supernatant stays clear for long.
- **Flocculated system:** particles are linked in loose flocs (controlled flocculation is produced by electrolytes, surfactants or polymers that reduce the zeta potential to a chosen range). Flocs settle fast and form a loose, voluminous sediment that redisperses easily on shaking.

Controlled flocculation is therefore the preferred strategy for most suspensions: slightly less elegant settling, but the patient can always resuspend the dose uniformly. Evaluation includes sedimentation volume (the ratio of sediment height to total height, F), redispersibility, particle size, viscosity and rheology, zeta potential and drug content uniformity.

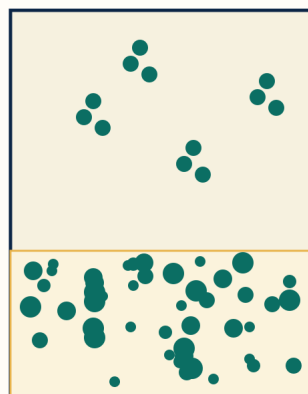
Deflocculated and Flocculated Suspensions

Deflocculated



Slow settling, hard cake,
difficult to redisperse

Flocculated



Fast settling, loose sediment,
redisperses easily on shaking

Figure: Deflocculated particles settle slowly but cake hard; flocculated particles settle fast into a loose sediment that shakes back into a uniform suspension.

1.9 SMEDDS: self-microemulsifying drug delivery systems

Many new drugs are poorly water soluble, and their oral absorption is limited by dissolution. SMEDDS are a formulation answer to this problem. A SMEDDS is an isotropic mixture of an oil, a surfactant, and usually a cosurfactant or cosolvent, with the drug dissolved in it. The mixture is filled into a soft or hard capsule as a liquid or semisolid. On contact with gastrointestinal fluid and gentle agitation, it spontaneously forms a fine oil in water microemulsion with droplets commonly below about 200 nanometres, presenting the drug in a solubilised form over a very large surface area.

Components are selected from solubility studies and phase diagrams: the oil dissolves the drug and forms the droplet core; the surfactant (often a high HLB nonionic surfactant) stabilises the droplets; the cosurfactant improves flexibility of the interfacial film and widens the self-emulsifying region. Advantages are improved dissolution and oral bioavailability of lipophilic drugs, more reproducible absorption with smaller food effects in many cases, and a simple capsule presentation. Limitations are a high surfactant load (possible gastrointestinal irritation), drug precipitation risk on dispersion or digestion, and limited drug loading. Evaluation includes self-emulsification time, droplet size and zeta potential after dispersion, robustness to dilution, precipitation studies, dissolution testing and stability of the filled capsules.

How a SMEDDS Works After Swallowing



Drug stays solubilised over a very large surface area, so absorption improves

Figure: A SMEDDS capsule disperses spontaneously in gastrointestinal fluid to a fine microemulsion, keeping the drug solubilised for absorption.

1.10 Large and small volume parenterals

Parenteral products are sterile preparations given by injection or infusion. Small volume parenterals (SVP) are injections of 100 mL or less, typically ampoules, vials and prefilled syringes. Large volume parenterals (LVP) are infusions above 100 mL, typically 250 to 1000 mL of intravenous fluids, nutrition or dialysis solutions.

Physiological considerations. The product enters the body past all protective barriers, so the formulation must respect physiology: tonicity close to that of blood (isotonic, adjusted with sodium chloride, dextrose or mannitol) to avoid pain and haemolysis; pH as near physiological as buffers and drug stability allow; freedom from pyrogens (bacterial endotoxins), controlled by a strict endotoxin limit; sterility, an absolute requirement; and freedom from visible and sub-visible particulate matter, which can embolise in small vessels.

Formulation components. The vehicle is almost always Water for Injection (for LVP and for reconstitution) or a non-aqueous vehicle for a few injections. Added substances include antimicrobial preservatives (only in multidose SVP, never in LVP), antioxidants, buffers, tonicity adjusters, solubilisers and stabilisers, each justified and controlled.

Manufacturing. Production takes place in classified cleanrooms with a sterile core. In outline: preparation of Water for Injection, compounding, filtration (including sterilising grade membrane filtration at 0.22 micrometres where used), filling into washed and depyrogenated containers, sealing, terminal sterilisation by moist heat where the product allows it, or aseptic processing where it does not, then inspection for particles and container integrity. LVP in plastic containers add container forming and sealing steps.

Evaluation. Sterility testing, bacterial endotoxin testing, particulate matter counts, assay and pH, container closure integrity, extractables and leachables for plastic systems, and for LVP also volume, osmolality and clarity checks. The combination of sterility and endotoxin control is why parenterals are the most demanding products in this subject.

1.11 Optimization techniques: concept and parameters

Optimization in formulation means finding the best combination of the variables that control a product, so that the product meets all its quality targets at the same time. The classical approach, changing one factor

at a time and keeping the others fixed, is slow, uses many experiments, and misses interactions between factors. Modern optimization uses planned statistical experiments to map the effect of several factors together, with far fewer runs.

The vocabulary of optimization:

- **Independent variables (factors):** the inputs the formulator can set, for example binder concentration, lubricant level, compression force, or the ratio of oil to surfactant in an emulsion. They are studied at chosen levels (low, middle, high).
- **Dependent variables (responses):** the measured outputs, for example hardness, disintegration time, dissolution at 30 minutes, viscosity or droplet size.
- **Constraints:** the acceptable limits on responses (for example disintegration not more than 15 minutes). A formulation is only acceptable inside its constraints.
- **Optimum:** the combination of factor levels that gives the most desirable set of responses within the constraints.

1.12 Statistical designs: factorial, response surface and contour methods

Factorial designs study two or more factors at two or more levels in all combinations. A 2 level factorial design with 3 factors needs 8 experiments and gives the main effect of each factor and the interactions between them, which the one factor at a time method cannot detect. Fractional factorial designs use a carefully chosen fraction of the runs for screening many factors. Factorial designs are the workhorse of formulation optimization: typical responses studied are tablet hardness and dissolution against binder and lubricant levels, or emulsion droplet size against oil and surfactant levels.

Response surface methodology (RSM) fits a mathematical model (usually a polynomial) relating the responses to the factors, using designs such as the central composite design or the Box-Behnken design, which add centre and star points to a factorial core. The fitted surface shows how the response changes across the whole experimental region, not only at the tested points, and the optimum can be read or computed from the model.

Contour designs and contour plots present the fitted surface in two dimensions: lines on the plot join factor combinations that give the same response value, like contours on a map. Overlaying the contour plots of several responses shows the region, sometimes called the design space or sweet spot, where all responses meet their constraints at once. Any formulation chosen inside that region is expected to pass.

Applications in formulation and processing. Optimization is applied to tablet formulations (binder, disintegrant and lubricant levels against hardness, friability and dissolution), granulation and compression parameters, emulsion and suspension compositions, coating processes, and analytical method development. The practical gain is a formulation that is understood, not just found: the formulator knows which factors matter, how they interact, and how much room exists before the product fails.

Optimization workflow

List factors (independent variables) and responses (dependent variables)

|
v

Choose a design: screening design, then factorial design

|
v

Prepare and test the experimental runs in random order

|
v

Fit models, check interactions and significance (ANOVA)

|
v

Draw response surfaces and contour overlays

|
v

Pick the optimum inside the design space, confirm with fresh batches

Contour Plot of a Response Surface

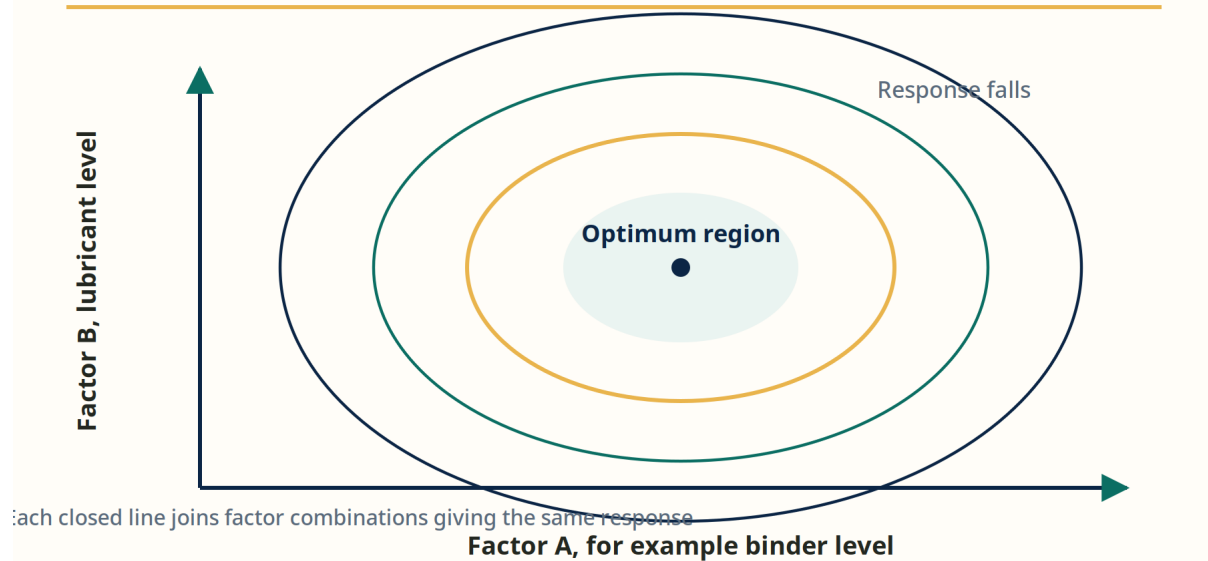


Figure: A contour plot of a fitted response surface. Overlaying such plots for several responses reveals the design space in which all responses pass.