

Unit 3: Computer Aided Formulation Development

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3.1 The concept of optimization

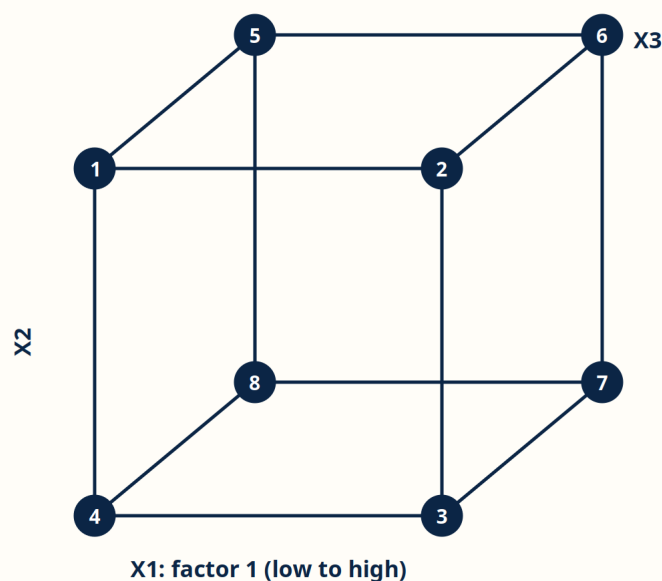
Optimization, in formulation work, means finding the combination of variables that gives the best product, where "best" is defined in advance by measurable targets. The traditional method, vary one factor at a time while holding the rest fixed, is slow, uses many experiments, and systematically misleads: it cannot detect interactions, in which the effect of one variable depends on the level of another, and interactions are the rule in formulations, where a binder's effect depends on moisture and a lubricant's harm depends on blending time. Computer aided optimization replaces that habit with designed experiments: the variables are changed together in planned patterns, a statistical model is fitted to the results, and the model, not intuition, locates the optimum and maps the region around it. The word optimization carries a discipline with it: first define the responses and their targets, then choose variables and ranges worth studying, then run a design matched to the question, then fit and check the model, then predict the optimum and confirm it experimentally. This is the same machinery that Unit 1 placed inside Quality by Design; here it is studied as the formulator's everyday tool, under the heads the syllabus gives: optimization parameters, factorial design, screening design and optimization technology.

3.2 Optimization parameters: variables and responses

An optimization study is defined by its parameters, in the statistician's sense of the things chosen before the runs begin. The **independent variables** (factors) are what the experimenter sets, and they fall in two groups. Formulation variables are the recipe: amounts and grades of binder, disintegrant, lubricant, surfactant, polymer, the drug's particle size, the solvent ratio of a coating. Process variables are the method: mixing time and speed, granulation fluid volume, drying temperature, compression force, curing conditions. Each variable is studied over a **range** divided into **levels**, coded for analysis as minus 1 (low), 0 (centre) and plus 1 (high), coding that puts variables of different units on one scale. The **responses** (dependent variables) are what is measured on each experimental batch: hardness, friability, disintegration time, dissolution at a stated time, assay, content uniformity, viscosity, globule size, stability indicators. Responses carry the targets: some are to be maximised, some minimised, some held in a window, and constraints (a response that must not cross a limit, such as friability below 1 percent) bound the acceptable region. Choosing the wrong variables or ranges is the commonest cause of a useless study: too narrow a range finds no effects, too wide a range leaves the region where a workable product exists.

3.3 Factorial design

The 2³ Factorial Design: Eight Runs



a 2 level, 3 factor design: 8 runs, every combination of low and high

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Figure: The 2 to the power 3 factorial design. Eight runs at the cube's corners measure every main effect and every interaction, which no one factor at a time programme can do.

The factorial design is the workhorse of optimization: every combination of the chosen levels of the factors is run, so each factor's effect is measured at every setting of the others. For k factors at two levels the design has 2 to the power k runs: 4 runs for two factors, 8 for three, 16 for four, small numbers that already contain far more information than the same runs spent one factor at a time. The analysis fits a polynomial model to the responses,

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + \dots$$

in which the coefficients b_1 and b_2 are the main effects of the two factors and b_{12} is their interaction, the term one factor at a time work can never estimate. Effects are judged against experimental error, from replicate runs or centre points (runs at the middle settings, which also test for curvature), using analysis of variance. A compact example: a tablet study with binder level (X_1) and compression force (X_2) at two levels each, four batches, measuring dissolution at 30 minutes, finds binder lowers dissolution, force lowers it slightly, and the interaction term shows the binder penalty grows at high force, so the optimum direction is low binder with moderate force, a conclusion no sequential tinkering would have stated so cleanly. When curvature matters, the two level design is extended with centre and axial points into response surface designs (section 3.5). When factors are numerous, full factorials grow too large and the fractional and screening designs of the next section take over.

3.4 Screening designs

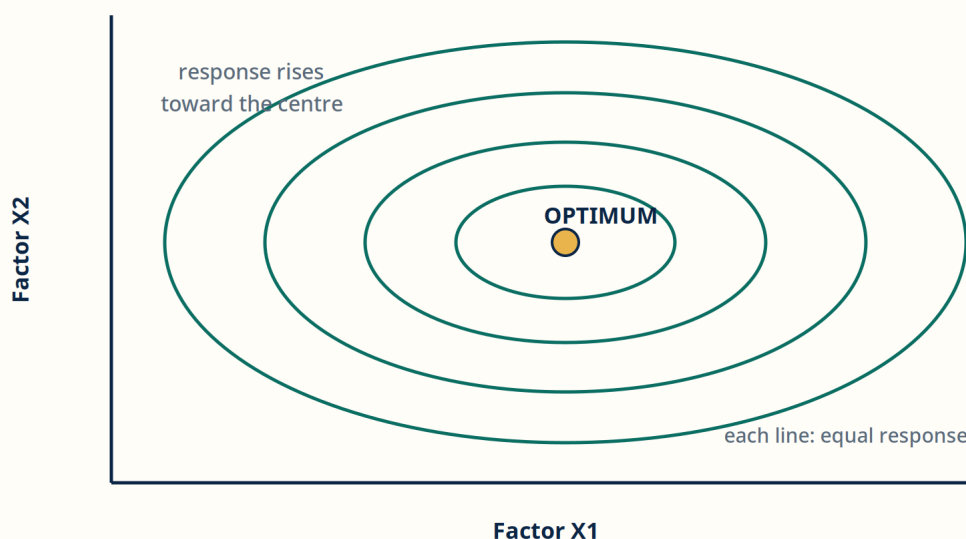
Screening is the stage before optimization proper: many candidate variables, little knowledge, and the need to find the vital few that actually move the responses, so that a factorial or response surface design can be afforded on them. Screening designs run far fewer experiments than a full factorial by accepting that some effects will be entangled with each other. The **fractional factorial design** runs a carefully chosen fraction (a half, a quarter) of the full combinations, keeping main effects clear while confounding interactions with each other, an acceptable bargain when interactions among many factors are mostly small. The **Plackett-Burman design** goes further, screening up to $N - 1$ factors in N runs (11 factors in 12 runs, a

classic layout), estimating main effects only, on the sparsity principle that in most systems a few factors dominate. Analysis ranks the effects, by size on a normal probability plot or against a significance yardstick, and the survivors pass to the optimization designs. Screening is also the risk assessment engine of QbD (section 1.10): it converts the long list of "could matter" variables into a short, evidence based list of critical ones, and its output decides where the development budget goes.

Design	Runs for the question	What it estimates	Stage used
Plackett-Burman	N runs for up to N minus 1 factors	Main effects only	Screening many factors
Fractional factorial	A half or quarter of 2^k runs	Main effects, some interactions confounded	Screening with some interaction cover
Full factorial, 2^k	2^k runs	All main effects and interactions	Optimization of few factors
Central composite	2^k plus centre and axial points	Full quadratic model, curvature	Response surface optimization
Box-Behnken	Three level combinations, no corner runs	Full quadratic model	Response surface where corners are impractical

3.5 Optimization technology: response surfaces and the search for the optimum

Response Surface: Contour Plot and Optimum



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Figure: A contour plot of a fitted response surface. The formulator reads the terrain directly: where the contours crowd the response is sensitive, and the optimum sits where they close.

Optimization technology is the layer that turns fitted models into decisions. For quantitative factors and a continuous response, the fitted polynomial of section 3.3 is drawn as a **response surface**, or its two dimensional shadow, the **contour plot**, on which lines of equal response let the formulator see the ridge, valley or summit structure of the system directly. With several responses, the contour plots are overlaid and the acceptable windows intersected (the overlay plot), and the overlapping region is the formulation sweet spot, the same object as a QbD design space drawn for two variables. A formal alternative is the desirability approach: each response is converted to a desirability score between 0 (unacceptable) and 1 (at target),

the scores are combined into one overall desirability, and the software searches the factor space for the settings maximising it, handling maximise, minimise and in window targets together. The search itself, over the model rather than the bench, is where the computer earns its title in this subject: grid searches and numerical optimisers evaluate thousands of candidate settings in seconds. Standard statistical and DOE software packages (the widely used examples include Design-Expert and Minitab) automate design generation, model fitting, diagnostics and this search. Two disciplines protect the result: the model must pass its checks (residual patterns, lack of fit, agreement between fitted and predicted values) before it is believed, and the predicted optimum must be confirmed by real batches, whose results are compared with the prediction as the final validation of the whole exercise.

3.6 Computers in pharmaceutical formulation: emulsions

An emulsion, oil droplets dispersed in water or the reverse, is a formulation whose quality lives in its globule size distribution and its resistance to creaming, coalescence and phase inversion, and computer methods help at each design decision. The first decision, which emulsifier and how much, is guided by the hydrophilic lipophilic balance (HLB) system, in which the required HLB of the oil phase is matched against tabulated emulsifier values and blends are calculated arithmetically, a computation software handles exactly, including the blend proportions for a target HLB. Phase behaviour studies, which map where a given oil, water and emulsifier composition forms a stable emulsion, a separated system or a gel, produce diagrams that are plotted and stored computationally, building a formulation knowledge base for the oil in question. Processing variables (homogeniser speed, time, temperature, order of addition) are optimized by the designs of this unit, with globule size and stability indices as responses. Prediction enters through stability modelling: accelerated stability data are extrapolated by statistical models to estimate shelf life, and expert system and neural network approaches reported in the literature learn from banks of past formulations to suggest starting compositions for new oils and drugs.

3.7 Microemulsion drug carriers

Microemulsions are the refined relatives of emulsions: thermodynamically stable, transparent, isotropic mixtures of oil, water and surfactant (usually with a cosurfactant) that form spontaneously with droplets in the tens of nanometres range, and that solubilise poorly soluble drugs in their oil cores and interfacial films, which is why the syllabus names them as drug carriers. Their formulation is a mapping exercise perfectly suited to the computer. The formulator titrates mixtures across the composition triangle and records where the system is a clear microemulsion, where it is turbid or separated, and software plots the results as a **pseudoternary phase diagram**, three components at the corners (oil, water, and surfactant with cosurfactant combined as one corner), the diagram's clear region being the territory in which carrier formulations can be chosen. Within that region, drug loading, dilution behaviour (the carrier must survive dilution in gut fluids without precipitating its drug), globule size and release are then optimized by factorial methods. Self microemulsifying drug delivery systems (SMEDDS) are the practical dosage form of the idea: an anhydrous preconcentrate in a capsule that forms a microemulsion on contact with gastrointestinal fluid, a marketed strategy for lipophilic drugs with dissolution limited absorption, and a direct bridge between this unit's phase diagrams and Unit 2's absorption modeling.

3.8 Legal protection of innovative uses of computers in R&D

Computer based innovation is valuable, so the law of its protection is part of the subject. The available instruments differ by what they protect. **Patents** protect inventions: a novel process, formulation or use discovered with a computer is patentable like any other, and computer implemented inventions occupy a middle ground that varies by jurisdiction, pure software and mathematical methods as such being excluded in several systems (in India, section 3(k) of the Patents Act excludes computer programmes per se, while

inventions with a technical application beyond the programme itself are examined under the computer related inventions guidelines), so drafting focuses on the technical contribution, a better controlled process or a new formulation found, rather than on the code. **Copyright** protects the expression of software, its code and documentation, automatically on creation, but not the underlying method. **Trade secrets** protect confidential know how, which in this field includes trained model parameters, curated databases and the negative results of screening campaigns, for exactly as long as secrecy is maintained, and access controls and contracts are the practical protection. **Databases** attract their own rights in some jurisdictions, and the licensing terms of commercial software and data (what the licence permits, especially model training and redistribution of outputs) are a working legal constraint on every modelling team. The examination point is the matching: choose the instrument that fits the asset, patent the invention, copyright the code, keep the data secret, and read the licence before the model, not after the dispute.

3.9 The ethics of computing in pharmaceutical research

Computing power creates ethical exposures that this syllabus head names directly. **Data integrity** is the first: a computer can alter, select or regenerate data invisibly, so the ethical rule is that electronic records must be complete, attributable and preserved in original form (the regulatory machinery for this is Unit 4, section 4.11), and the temptation a spreadsheet offers, to delete the awkward point, is exactly the falsification that ends careers and licences. **Honest modelling** is the second: a simulation reported without its assumptions, or a model tuned until it agrees with the desired answer, misleads patients and regulators as surely as fabricated data; the ethics are the statistics of Unit 1 read as duties, report the confidence region, the sensitivity, the failed checks. **Credit and authorship** is the third: work done by shared software, databases and, now, generative artificial intelligence must be attributed accurately, and submitting machine generated text or analysis as one's own unaided work breaches the same honesty rule in examinations and publications alike. **Animal and human welfare** is the fourth, and it cuts the other way: good in silico work is an ethical good, because prediction that replaces an animal study or a doomed clinical trial follows the replacement principle of the 3Rs, while careless prediction that sends a bad molecule into animals or patients is an ethical failure, not merely a technical one. Finally, **bias and access**: models trained on unrepresentative data inherit its blind spots, a point that returns with artificial intelligence in Unit 5.

3.10 Computers in market analysis

The last head of this unit leaves the laboratory for the business the laboratory serves. Pharmaceutical market analysis is data work: companies buy and analyse prescribing and sales audit data (the large commercial audits of which IQVIA is the best known supplier), hospital and retail panel data, and epidemiological estimates of disease prevalence, and model them to answer development questions. Which indication and patient population justify a programme. How large is the treated population, and how will diagnosis and treatment rates change. What will a new product's uptake curve look like against entrenched competitors, modelled from analogue launches and the product's modelled profile. When will patent expiry expose the brand to generics, and what is the product worth across its lifecycle under price and competition scenarios. The techniques are those of Unit 1 in commercial dress: regression and time series forecasting, sensitivity analysis over price and uptake assumptions, and scenario simulation. The connection to the rest of the subject is direct: the target product profile that opens a QbD programme (section 1.10) is written from market and clinical analysis of exactly this kind.

The optimization workflow of Unit 3

Define responses and targets

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Choose variables and ranges

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Screening design: find the vital few factors

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Factorial or response surface design: fit the model

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Check the model: residuals, lack of fit

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Predict the optimum on the model, confirm at the bench

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