UNIT-4

Optimization techniques in pharmaceutical product development

Points to be covered in this topic

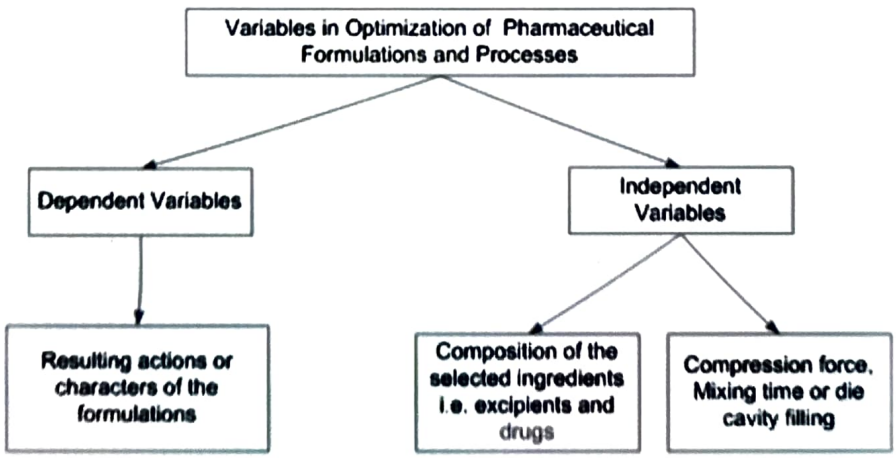
- Introduction to Optimization
- Optimization techniques with specific examples
- Optimization by factorial designs

❑ Introduction to Optimization

- To optimize means to **make as much perfect as possible**. In fact in the practice of pharmaceutical product development, optimization is the **process of obtaining optimum formulation**.
- According to Merriam Webster Dictionary optimization means; "an act, process, or methodology of making something (as a design, system, or decision) as fully perfect, functional, or effective as possible; specifically: the mathematical procedures". Optimization techniques are the research analytical tools for problems which researchers use to **develop quality pharmaceutical products**.
- In pharmaceutical product development problems are related to **composition of the formulation and process design**; and usually involve **mathematical techniques**.
- Optimization refers to obtaining response actions of researcher's interest by changing the independent variables in a logical sequence.
- In Mathematics, optimization is the process of obtaining of **maxima or minima.**

➢ Types of Variables in Optimization

In optimization, techniques employed for **various processes or formulations or products involves certain variables which a researcher manipulate as per technical requirements to produce a predicted output.**



(a) Dependent variable:

- The variable measured as the outcome of **interest is called dependent variable.**
- This variable is also known as response, which determines relationship of **independent variable to an observed phenomenon.**
- For example, in an experiment bioavailability of different dosage forms is compared.
- The dependent variable in this case would be area under curve (AUC) of concentration vs. time curve, and the independent variable would be dosage form.

(b) Independent variable:

- Independent variable is also called an experimental or predictor variable.
- It is manipulated in an experiment to observe the effect on a dependent variable, sometimes called an outcome variable.
- The independent variable is the cause for dependent variable.
- Examples of independent variables can be **concentration of component in formulation, solution strength, applied pressure, stirring time, selected temperature, etc.**

➢ Types of Problems in Optimization

There are two types of problems that are addressed in the optimization namely; unconstrained problems and constrained problems.

(a) Unconstrained optimization problems:

- Unconstrained optimization considers the problem of minimizing an objective function that depends on real variables with no restrictions on their values.
- These problems arise directly in some applications but they also arise indirectly from reformulation of constrained optimization problems.
- The **making of the hardest tablet is the unconstrained optimization problem.**

(b) Constrained optimization problems:

- Constrained optimization is the process of optimizing an **objective function with respect to some variables** in the **presence of constraints on those variables.**
- Constraints can be either hard constraints, which set conditions for the variables that are required to be satisfied, or soft constraints, which have some variable values to the extent that the conditions on the variables are not satisfied.
- For example, in **making the hardest tablet possible, it must disintegrate in less than 15 min.** Thus, **making a tablet that will disintegrate within 15 min. is a constrained problem.**

➢ Statistical Design of Optimization

There are two types of statistical design techniques used in optimization:

(1) Experimentation continues as optimization proceeds.

Examples: Evolutionary operations (EVOP) and simplex methods.

(2) Experimentation is completed before optimization takes place.

Examples: Classic mathematical methods and search methods.

In latter technique, it is necessary that the relation between any dependent variable and one or more independent variable is known.

The two possible approaches for statistical design of optimization includes:

(a) Theoretical approach:

- If theoretical equation is known, it needs no experimentation to be performed.

(b) Experimental (empirical) approach:

- With single independent variable, formulator performs experiments at several levels. The relationship with single independent variable can be obtained by simple regression analysis or by least squares method.

❑ OPTIMIZATION TECHNIQUES WITH SPECIFIC EXAMPLES

➢ Systematic Optimization Techniques

(a) Sequential optimization method:

- Sequential optimization method is also referred as the experimentation after optimization or Hill climbing method.
- In this method, initially small number of experiments are conducted, and then research is done by either increase or decrease of response. Thus, maximum or minimum (optimum solution) will be reached.
- **Examples: Evolutionary operations (EVOP) and simplex methods.**

(b) Simultaneous optimization method:

- In this optimization, the relation between any dependent variable and one or more independent variables is known.
- This technique involves the use of full range of experiments by an experimental design.
- Maximum or minimum response is then obtained through this fitted model.
- **Examples: Classic calculus and search methods.**

There are various types of experimental design methods available and the selection of specific method depends upon the resources available as well as desired outcome of the study. These design methods are categorized as follows:

(1) Completely Randomized Design (CRD)
(2) Randomized Block Design (RBD)
(3) Factorial Design (FD)
(a) Full factorial design
(b) Fractional factorial design
(4) Response Surface Method (RSM)
(a) Central composite design
(b) Box-Behnken design

(c) Classical optimization method:

- Classical optimization is useful in **finding the optimum solution or unconstrained maxima or minima of continuous and differentiable functions.**
- These being analytical methods, makes use of differential calculus in locating the optimum solution to the basic problem.
- It has limited applications for the problems that are not too complex and which do not involve more than two variables.
- This is because for **more than two variables graphical representation is difficult.**
- It is possible mathematically to make use of partial derivatives, matrices, determinants, etc.

Classical optimization techniques can be used to handle following problems:

1. Single variable functions.

2. Multivariable functions with no constraints.

3. Multivariable functions with both equality and inequality constraints.

➢ Numerical Optimization Techniques

Numerical methods of optimizations deal with selecting the best possible formulation using suitable factors.

Following are **four numerical methods** of optimization:

(a) Linear method: This method studies the case in which the objective function *f* **is linear and the set design variable space is specified using only linear equalities and inequalities.**

(b) Integer method: This method studies linear plan in which, some or **all variables are constrained to take on integer values.**

(c) Quadratic method: This method allows the objective function to have **quadratic terms, while the design variable space must be specified with linear equalities and in equalities.**

(d) Non-linear method: This method studies the general case in which the **objective function or the constraints or both contain non-linear**

❑ OPTIMIZATION BY FACTORIAL DESIGNS

➢ Fractional Factorial Design

Fractional Factorial Design (FD) is generally used for **screening of factor**. This design has **low resolution** due to **less number of runs**. Although these designs are economical in terms of number of experiments, the ability to **distinguish some of the factor effects is partly sacrificed by reduction in the number of experiments.**

(a) Plackett-Burman Designs:

- Plackett-Burman designs (PBD), also known **as Hadamard designs**, is a popular class of screening design specially used for **two-level FFDS for screening of factors.**
- These designs are very efficient when the main effects are of interest under the assumption that all interactions are **negligible when compared with important main effects.**
- For **example,** this design is used to screen high number of factors (11-47), out of which effects of 7 factors are important in the study. In such case, four dummy factors are introduced. The interpretations of results in this design are drawn with the help of Pareto chart and half-normal plot.

(b) Central Composite Design:

- A central composite design (CCDs), also known as **Box-Wilson design**, encompasses the advantages of **FD or fractional FD or the star design.**
- It is composed of **2* FD or fractional** FD.
- It is the most frequently employed design for **non-linear responses requiring second-order models.**

(c) Box-Behnken Designs:

- Box-Behnken design (BBD) is a special design that **requires only three levels for each factor, viz. -1, 0 and +1.**
- It employs **15 experiments run with three factors at three levels.**
- It is economical than CCD because it requires less number of trials.
- The **examples** of optimization using BBD are tenofovir formulation and fabrication of Nataglinide nanoparticles.

(d) Taguchi Design:

- Taguchi refers to experimental design as **off-line quality control** because it is a method of ensuring **good performance in the development of products or processes.**
- It allows estimation of main effects while **minimizing variance**.
- This design treats optimization problems as **static problems and dynamic problems**. In static problems a process to be optimized has several control factors which directly decide the target or desired value of the output.
- It is also used for screening of factors and it provides **8 experimental runs for 7 factors.**
- **Example** of implementing this design in the optimization is in the gliclazide formulation development.

(e) Mixture Design:

- Mixture designs are used when the characteristics of the finished product **usually depend not so much on the quantity of each substance present but on their proportions.** The sum total of the proportions of all the excipients is unity, and none of the fraction can be negative.

➢ Full Factorial Designs

- Factorial designs are very frequently used **response surface designs**.
- A factorial experiment is one in which all levels of a given factor are combined with all levels of every other factor in the experiment.
- These are generally based upon **first-degree mathematical models**. Full FD involves studying the effect of all the factors (k) at various levels (0), including the interactions among them, with the total number of experiments being Levels Factors or X.
- If the number of levels is **same for each factor in the optimization study**, the FDs are said to be **symmetric**, whereas, in cases of a different number of levels for different factors, **FDs are termed asymmetric**.

❑ APPLICATIONS OF OPTIMIZATION

- Optimization is a tool used specifically to examine various problems **encountered during research, development and production**.
- The objective of using optimization techniques is to **maintain the quality, economy and safety of public and industry.**
- The primary objective **may not be optimizing absolutely but to compromise effectively to reduce or eliminate problems to produce best formulation within the given set of limits.**
- Optimization techniques being a part of development process, the levels of variables for obtaining **optimum response are evaluated**.

Following are some important applications of optimization:

(1) Optimization techniques help to reduce the time of experimentation as well as reduce cost with better returns on investment.

(2) These are used to elucidate compatibility between drug and excipients required in the preformulation phase.

(3) Helpful to find the best way of using the existing resources in the drug formulation, process and product development.

(4) It is used to calculate maximum allowable mean parameters for drugs and auxiliary materials to achieve a sufficient content uniformity.

(5) It can be used to identify working point for scale-ups and production; trouble shooting by using CCD and in multiple constraints using computerized grid search.

(6) It is used to reduce formulation and processing errors and providing more safety.

(7) It has applications in optimizing biopharmaceutical parameters in the development of modified release formulations.

(8) Provides solution to large scale manufacturing problems so that it leads to practical mass production of the optimized product.

Formulation Development

- Product development involves the **formulation design** in which, drugs are combined with **excipients to form a product with desired quality attributes.**
- Drug product attributes are dependent on their composition and therefore, this process requires optimal selection of both; the type and quantity of materials involved.

Some examples of application of optimization in product formulation are described below:

(1) Optimization has been applied in formulation development, for example, optimization of capsule and tablet drug products, specifically aiming at the selection of excipients. A formulation can be optimized with little experimental data using combination of genetic algorithms and a simplex lattice method. In this process, a blend flow and dissolution properties of drug and excipient powders using small laboratory scale experiments can be studied to generate effective and feasible data for manufacturing of formulations.

(2) Simulated annealing can be used to optimize child liquid-based acetaminophen formulations using solid drug product with the objective to develop a customizable formulation of acetaminophen syrup based on the availability and taste of co- solvents. The implementation of simulated annealing in the formulation protocol results in the selection of an optimal formulation in less computational time.

(3) Effervescent floating tablets (EFT) composition can be optimized in order to target a set of product attributes such as; specific buoyancy, hardness and floating time. Using a hybrid simplex lattice and multivariate regression approach it is possible to predict and optimize the EFT properties and develop principle approach to the type of tablet matrix erosion.

(4) The optimization can be used to study effects and optimal formulations of melt granulation floating tablet products with minimum experimentation.

➢ Drug Delivery Systems

- Optimization techniques such as; **direct search methods are commonly used in the development and optimization of many drug delivery systems.**
- Majority of the work for optimization of these systems focuses on **sustained release oral formulations.**

Some examples of application of optimization in drug delivery systems are described below

(1) A mathematical model can be successfully devised and optimized for the design and manufacturing of SR pellets using particle swarm theory as optimization algorithm.

(2) An ER oral drug product can also be designed using other modelling techniques.

(3) A random search method can be used to determine the optimal drug distribution in transdermal delivery devices. The optimal drug distribution can be selected as one with a maximum delivery in order to maximize its reservoir exhaustion.

➢ Manufacturing Processes

- Optimization in manufacturing processes is mainly focused on **finding the best process settings using various optimization methodologies.**
- Direct search methods have been used in **finding most beneficial process settings ranging from the selection of process conditions to the arrangement of manufacturing plants.**
- Multiple products are usually manufactured in one pharmaceutical plant with limited resources and time. Effective plant operation is based on the selection and scheduling of protocols for the manufacturing of such products.
- Most common method for **plant scheduling** uses **neural computing technique in combination with optimization techniques such as; simulated annealing (SA).**

Some examples of application of manufacturing process optimization are described below

(1) The critical process parameters used in tablet products for colon therapies can be optimized using simplex lattice methods. The optimal operational conditions of the coater could be established to provide a framework for the design of other coating processes. Coating spray rate and batch time can be studied and optimized to reduce final product variability and process.

(2) Optimization of process parameters affecting chromatographic separation selectivity can be accomplished using GA methods. An exponential unit model could be established, including key process parameters such as temperature and pH. The process parameters can be minimized to improve chromatographic responses between all analytes, simultaneously.

(3) PSO methods can be used to find multiple constant parameter values used in modelling high shear batch granulation processes.

(4) Iterative optimization technology (IOT) could be used to implement online and offline pharmaceutical processes involving unit operations such as blending using bin-blenders and compression using rotary press feed frame.

(5) SA can be used to schedule multiple unit operations (instances) in the no-wait restriction environment of a multipurpose pharmaceutical batch in the plant manufacturing bulk drugs. This method is more efficient at scheduling the instances than other simpler dispatching tools used in the industry.

❑ STUDY OF QBD

Quality by design is an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines.

- Over the last few decades use of **design of experiment (DOE) to pharmaceutical development has significantly increased.**
- The beginning developments were mainly focused on **chartbuster drugs and formulation development research was mainly focused on using one factor at a time (OFAT).**
- This is because the **outcomes are highly dependent on the starting point which is often limited by variables.**
- This approach was **unable to separate the noise of a process from actual improvement unless a significant number of process runs are repeated using the same conditions.**
- Now a days, among the various mathematical modeling approaches used, DOE is the most extensively used model for the implementation of quality.
- Quality by Design (QbD) concept was first developed by **Dr. Joseph M. Juran.** According to him, **"Quality should be designed into a product, and that most quality crises and problems relate to the way in which a product was designed in the first place".**

➢ Objectives of QbD

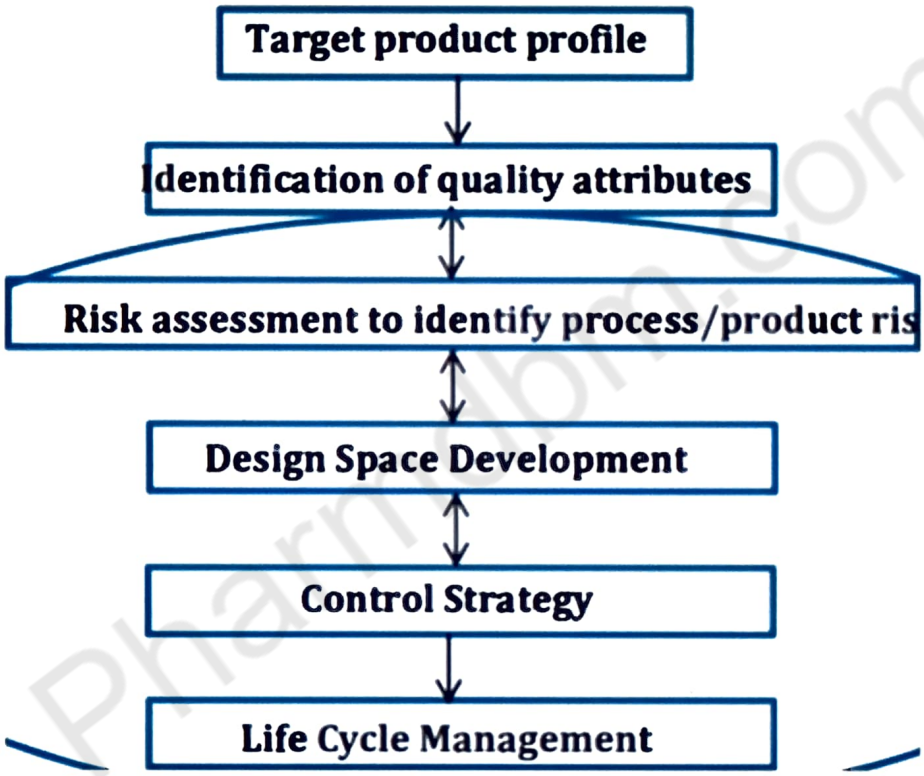
The goals of pharmaceutical QbD may include the following:

- ✓ To achieve meaningful product quality specifications based on clinical performance.
- ✓ To increase process capability and reduce product variability and defects; by enhancing product and process design, understanding, and control.
- ✓ To increase product development and manufacturing efficiencies.
- ✓ To enhance root cause analysis and post approval change management.

➢ Elements of QbD

Different elements of pharmaceutical development include,

- ❖ Defining an objective
- ❖ Determination of critical quality attributes (CQA)
- ❖ Risk assessment
- ❖ Development of experimental design
- ❖ Designing and implementing control strategy
- ❖ Continuous improvement



❖ Defining an objective (QTPP):

- ✓ Quality target profile (QTP) forms the basis of QbD, which is in relation to the predefined objective criteria mentioned in the definition of QbD.
- ✓ Considerations for the Quality Target Product Profile could include:
- **Intended use in clinical setting, route of administration, dosage form, delivery Systems.**
- **Dosage strength(s), Container closure system.**
- **Therapeutic moiety release or delivery and attributes affecting, Pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance).**

- **Drug product quality criteria like sterility, purity, stability and drug release as appropriate for dosage form the intended for marketing**
- **QbD requires a Target Product Profile; it may be called as Quality Target Product Profile (QTPP) which defines the expectations in final product. In case of analytical method development it is called as analytical target profile (ATP), it is also called as Target Product Profile (TPP).**
- **The TPP will help to identify critical quality attributes such as potency, purity, bioavailability or Pharmacokinetic profile, shelf-life,**

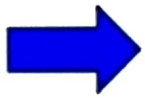
QTPP Element	Target	Justification
Dosage form	Transdermal patch	Pharmaceutical equivalence requirement: same dosage form as RLD.
Route of administration	Transdermal	Pharmaceutical equivalence requirement: same dosage form as RLD.
Strength	Same delivery rate (Residual Drug consideration)	Pharmaceutical equivalence requirement: same dosage form as RLD.
Pharmacokinetics	Meet Bioequivalence requirement	Bioequivalence requirement.
Stability	At least 24-month shelf-life stored at room temperature.	Equivalent or better than the shelf-life of RLD.

❖ Determination of critical quality attributes (CQA)

- ✓ According to ICH Q8 R2 "A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality".
- ✓ QAs are generally linked with the drug substance, excipients, intermediates (in process materials) and drug product.
- ✓ For example CQAS of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability whereas for Parenterals they are Sterility and clarity.

QTPP and CQAs

QTPP components
Dosage Form
Route of administration
Strength
Pharmacokinetics
Stability
Appearance
Identity
Assay
Impurities
Residual Solvents/Monomers
Adhesion Test(Peel Test, Peel from Liner Test , Probe Tack)
Cohesion Test(Shear)
Drug Release



CQAs
Assay (Efficacy)
Adhesion (Efficacy)
Impurities (safety)
Residual Monomer(Safety)
Stability (Efficacy)

❖ Risk assessment

✓ It is commonly understood that risk is defined as the combination of the **probability of occurrence of harm and the severity of that harm.**

Risk assessment helps to increase quality of method or process. Also it is determinant for effect of input variable on method or processes. From risk assessment one can recognize critical attributes that are going to affect final quality of product. A risk assessment is helpful for effective communication between FDA and industry, research/development and manufacturing and among multiple manufacturing sites within company. There may be risk and uncertainty in validation of bioanalytical method though the guidelines for validation are given by various regulatory bodies there may be a variation in interpretation of those guidelines and hence in experimental method designing which leads to unfit method development for intended purpose.

Principles of quality risk management are: **Scientific knowledge based evaluation of the risk to quality which eventually links to the protection of the patient.**

Adequate effort should be taken; formality and documentation of the quality risk management process should be done with the level of risk involved. Risk management is joint responsibility of **quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical department**

❖ Development of experimental design

✓ Experimental design is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Design space is proposed by the applicant and is subject to regulatory assessment and approval of ICH Q8 (R2).

❖ Designing and implementing control strategy

✓ Control strategy is required to ensure that material and process are within **the expected lower and upper limits. Parameter and material are routinely controlled during production in order to assure reproducibility. The control space should be within the design space.** Generally scale up is trial and error basis. During scale up processes parameters may differ but attributes which affect quality remain the same **hence control strategy is required.** QbD gives trace on reproducibility and robustness. Process capability index expresses reproducibility of process.

❖ Continuous Improvement throughout product life cycle

✓ Product quality can be improved throughout the product life cycle; companies have **opportunities to opt inventive approaches to improve quality.**

Process performance can be monitored to make sure consistency in quality. Additional experience and knowledge is gained during routine manufacture which contributes to method/process development. Periodic maintenance can be done within a company's own internal quality system; but design space should be unchanged. The QbD approach avails the continuous improvement throughout products' life cycle this is distinguishing point from the conventional method which is much frozen process.

➢ Advantages of QbD

(1) QbD help to enhance the assurance of safe and effective drug supply to the S consumer.
(2) It offers promise to significantly improve manufacturing and quality performance.
(3) It helps in better understanding of the process.
(4) Batch failures can be minimized using QbD.
(5) It is more efficient and effective control of change.
(6) It gives higher returns on investment as well as saves various costs.
(7) It provides opportunities for more flexible regulatory approaches.
(8) It is useful to generate robust processes and products.
(9) It helps to have better life cycle management (LCM) of the product.

➢ APPLICATION DEVELOPMENTON OF QbD IN PHARMACEUTICAL PRODUCT

- Quality refers to product free of contamination and delivers the therapeutic benefit promised in the label to the consumer.
- The quality of the pharmaceutical product can be evaluated by in vivo or in vitro performance tests.
- QbD assures in vitro product performance which provides assurance of in vivo product performance; and is therefore related to the product performance.

Some of these applications listed below:

(1) QbD is used to continually monitor and improve the quality of product.

(2) It is used for better understanding of the process to have less batch failures.

(3) It can help to provide more efficient and effective control of change.

(4) It helps to give return on investment/cost savings.

(5) QbD provides opportunities for more flexible regulatory approaches

(6) It helps to establish manufacturing changes within the approved DS without further regulatory review.

(7) Employing QbD helps to minimize post-approval submissions.

(8) QbD imparts better innovation process improvements without resubmission to the regulatory authorities being within the DS.

QbD has different and wide range of applications such as analytical method development, design and formulation development and in technology development.