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Review Article

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Preclinical Drug Development Process: Formulation and Development Aspects

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ABSTRACT

Drug discovery and development process aims to make available new pharmacological entities to prevent, treat, mitigate or cure disease in a safe and effective manner. It involves rigorous testing and optimization of selected compounds to identify the drug that is most effective. Drug development starts with a target identification and validation, followed by drug candidate (hits) discovery, and lead drug (compound with favourable pharmaceutical, safety, efficacy and pharmacokinetic profile) selection and optimization then preclinical research, clinical research, FDA drug review, FDA post-market drug safety monitoring. In the stage of preclinical study, pharmaceutical preformulation and development and toxicity studies are the major concerns. The chapter focuses on preclinical formulations stressing upon different preclinical formulation strategies and deciphers the understanding of formulation approaches that could be employed. During preformulation studies the parameters evaluated are: solubility in different media and solvents, dissolution of the active pharmaceutical ingredient (API), accelerated stability studies under various conditions, solid state properties (polymorphs, particle size, particle shape, etc.), formulation development of new chemical entity (NCE),optimization of existing formulations, process development for selected dosage form, novel formulations for improved delivery of existing dosage forms, controlled release and sustained release formulations, micro and nano formulations, partition coefficient, pKa determination. It also emphasizes on Pharmacokinetic studies. The chapter also provides detailed information related to a vast pool of excipients available which is of immense help in designing preclinical formulations. A light is thrown on key aspects of preclinical formulation development by cited examples.

Keywords: Preformulation, Micromeritics, NDDS

INTRODUCTION

Drug development process is very tedious and time-consuming process. It required very long time, human resource as well as large finance for development. The process of drug development includes the identification of drug entity, synthesis, characterisation, screening and assay for pharmacological activity. When molecules produce satisfactory result in all the process of investigation, it will approve for drug development process subsequent to clinical trials. Drug development is very expensive process due to requirement of high budget of R&D and clinical trials. The average cost is required for the drug development process is 900million dollar to 2billion dollar and the process takes upto 12-16 years for the development of single molecules[1,2,3].When a new pharmaceutical compound is discovered, the FDA requires that an analytical method or test procedure for determination of the active component of the compound to be developed and validated before it can be applied to animal or human subjects[4].In clinics, drug can be rejected due to two reasons, either they do not work or they are not safe. Although, the most important steps in drug development process are target identification and validation[5,6].The chapter mainly focus on preclinical formulation strategy and formulations approach that could be employed. While Preformulation study the parameters such as solubility in different media and solvent, dissolution of API, accelerated stability study, solid state properties such as polymorphs, particle size, particle shape etc., optimisation, process development for selected dosage form, NDDS such as sustained release, controlled release formulation, micro and nano formulation, partition coefficient, pKa determination[7,8].

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STAGES OF DRUG DEVELOPMENT

- Drug Invention
- Product Characterization
- Formulation and development
- Pharmacokinetics and Drug Disposition
- Preclinical Toxicology Testing and IND Application
- Bio-analytical Testing
- Clinical Trials
- Regulatory review
- Marketing the product or drug
- Post-marketing monitoring (phase-IV) trials

We have given the stages of drug development process out of them we will discusses the stage i.e formulation and development.

Preformulation Study:

Preformulation evolved between the years 1950 to 1960 as a result of a shift in emphasis in industrial pharmaceutical product development. Preformulation is a group of studies that mainly focus on the physicochemical properties of a new drug entity that could affect the drug efficacy and the development of a formulation[9].This data is useful for selection of new chemical moiety for preclinical studies for their effectiveness, which is a major section under investigational new drug application[10]. Primary objective of Preformulation study is to develop the elegant (stable, effective, and safe) dosage form by implementing kinetic rate profile, compatibility with the other ingredients and produce physico-chemical parameter of new drug substance[11,12].The initial drug development phase involves a significant contribution from the pharmaceutical research group for pre-formulation profiling of the potential drug candidate. Assessment of aqueous solubility, permeability, hygroscopicity, and stability profile of the compound forms the backbone of these efforts[13,14].Among these physical properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in pre-formulation study. Polymorphism of drug having crystal and amorphous forms shows different chemical, physical and therapeutic behaviour. This article explains some properties and techniques for pre-formulation evaluation parameters of drug[15].

Physicochemical Parameters:

1. Organoleptic Properties:
   - Colour
   - Odour
   - Taste
2. Bulk Characterisation study:
   a) Crystallinity and Polymorphism
   b) Hygroscopicity
   c) Fine particle characterisation
   d) Bulk density
   e) Flow properties
   f) Compression properties
3. Solubility Analysis:
   a) Intrinsic solubility determination
   b) pKa determination
   c) Partition Coefficient
   d) Dissolution study
   e) Common ion effect
4. Stability Analysis:
   a) In toxicology formulation
   b) Solution stability
   c) Solid state stability

1. Organoleptic Properties:

a) Colour:

It should be appealing to the eye and determined by either instrumental methods or visible method. Record of early batches and establishing "specs" is very useful for later production. Coating of body in variable colour can be done if found undesirable called mottling.

b) Odour and Taste:

Odour may be pungent, sulphurous, fruity, aromatic and odourless. Taste may be acidic, bitter, bland, intense, sweet and tasteless.

2. Bulk characterization studies:

a) Crystallinity and polymorphism:

Polymorphism is a common phenomenon of crystalline solids. It describes the ability of materials to exist as two or more crystalline phases that have different arrangements of the molecules in the solid state but are otherwise identical in terms of chemical content. It should be noted that 'arrangement' here includes not just the packing and orientation of molecules that may differ, but also their conformations even if the packing is similar, if two crystals just differ in terms of the molecular conformations adopted then they are polymorphic. Polymorphism is the ability of a polymer to crystallize in different modifications, characterized by different crystal structures (polymorphs). Almost all crystalline polymers show polymorphic behaviour. The widespread results of polymorphism in polymers include a discussion of each specific case but the phenomenon can be rationalized establishing forth basic concepts. The main principles that govern the crystallization of polymers, that is the formation of ordered conformational sequences of monomeric units and their packing in a crystalline lattice Active pharmaceutical ingredients(APIs) are frequently delivered to the patient in the solid-state as part of such dosage forms as tablets, capsules, granules, powders, etc. No matter whether as pure drug substances or in formulated products, APIs can exist in many solid forms, such as polymorphs, pseudo-polymorphs (solvates and

hydrates), co-crystals, salts and amorphous solids. Each form may possess its own unique mechanical, thermal, physical and chemical properties that can remarkably affect the bioavailability, solubility, hygroscopicity, stability, melting point, compressibility and other performance characteristics of the drug. Hence, a thorough understanding of the relationship between the particular solid form of an API and its properties is crucial for selecting the most suitable form of the API for development into a drug moiety. Crystallization refers to the formation of solid particles from a vapour, the solidification from a liquid melt or the formation of dispersed solids from a solution. Crystallization, incorporating wider definition to include precipitation and solid-state transitions, is a major technological process for particle formation in pharmaceutical industry. It is estimated that over 70% of all solid materials are produced by crystallization. As a matter of fact crystallization plays a key role in defining the physicochemical properties of solid APIs and their final dosage forms[16-20].

b) Hygroscopicity:

Hygroscopy is a process of dragging and bonding with moisture from the atmospheric air present at surrounding environment at room temperature. Hygroscopicity is done by either absorption or adsorption of moisture from the atmospheric air. The nature of substance is physically changed due to absorption or adsorption of moisture from atmosphere. This may result in an increase in bulk volume, boiling point, viscosity, or other physical property of the substance. The physical and chemical stability of the solid dosage forms, excipients, and polymers for controlled release formulations mainly affected by Moisture adsorption. The drugs which undergo hydrolysis by absorbing or adsorbing the moisture form the environment. That is necessary to determine moisture adsorption kinetics which includes the rate of moisture uptake, and also the equilibrium moisture content (EMC). Moisture adsorption principles will provide handy data in case of solid dosage forms for selection of excipients, and also information on humidity control required to be done during manufacturing and storage. Influence in the flow, compression, and the hardness of solid dosage forms is depend upon the quantity of moisture adsorbed by pharmaceutical materials at a particular temperature and relative humidity. The percent relative humidity (% RH) determines the atmospheric water vapour pressure. The equilibrium moisture content (EMC) is defined as the quantity of moisture at which a solid material forms a water vapour pressure similar to the water vapour present in the surrounding environment's vapour pressure. Moisture absorbance rate are determined by the following factors:[21-25]

- The pressure difference between the water vapour pressure of the material and the vapour pressure of water in the atmosphere.
- A reaction constant related to the solid characteristic.
- The water vapour of the exposed surface area of solid drug.
- The speed of movement of moisture air.
- Temperature

Table 1: Saturated salt solution for sustained constant relative humidity condition in desiccator

Saturated salt solution	% Relative humidity at Temperature 25°C
Lithium Chloride	11
Potassium Acetate	23
Magnesium Chloride	33
Potassium Carbonate	43
Magnesium Nitrate	52
Sodium Nitrate	64
Sodium Chloride	75
Potassium Bromide	83
Potassium Nitrate	93

c) Fine Particle Characterization:

Measurement of particle size distribution by laser diffraction is done by determining the angular variation in intensity of light or beam scattered as a laser beam passes through a dispersed particulate sample. Laser diffraction is a widely used particle size measurement technique, for materials ranging from hundreds of Nano-meters up to several millimetres in size. The key reasons for its success are:[26-29]

- Wide dynamic ranges from submicron to the millimetre size range.
- Rapid measurements results generated in less than a minute.
- Repeatability large numbers of particles are sampled in each measurement.
- Instant feedback monitor and control the particle dispersion.
- High sample throughput hundreds of measurements per day.
- Calibration not necessary easily verified using standard reference materials.
- Well established technique covered by ISO13320 (2009).

d) Bulk Density

The bulk density of the powder is the ratio of mass of without tapped powder sample and its volume including the contribution of inter particulate void volume. Accurately weighed quantity (g) of the pellets (w) were carefully taken into the graduated cylinder and the bulk volume (Vo) was measured. The graduated cylinder was closed with lid set into the density determination apparatus.

It is ratio between a given mass of powder and its volume Db=W/Vo

Where, W= Weight of sample (g)

Vo= Bulk volume of sample (ml)

e) Tapped Density

The tapped density is an increased bulk density attained after mechanically tapping a container containing sample. Tapped density is obtained by mechanically applying tapping a graduated measuring cylinder containing a powder sample. After determining the initial powder volume or weight, the measuring cylinder or weight change are determined. The number of tapes like 500, 750, 1200 taps of sample powder were carried out and the corresponding volume was noted as V500, V750, V1200 to the nearest graduated unit. The volume was measured and operation was taken continued till the two consecutive reading were equal, the tapped density was calculated using following formula: [30]

Tapped Density= Weight of mass/Tapped volume

Dt= M/V

Where, Dt= Tapped density

M= Weight of sample

V= Tapped volume of sample.

f) Hausner Ratio

In recent year the compressibility index and the closely related Hausner's ratio have become simple, fast and popular method of predicting beads flow characteristics. Both the compressibility index and the Hausner's ratio were determine by using bulk density and tapped density of beads [31-33].

Hausner's Ratio = tapped density/bulk density

Table 2: Hausner's Ratio

Hausner's Ratio	Type of Flow
1.0-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very Poor

g) Carr's Index

It is the measurement of the compressibility index of powder. Carr's index is a one point determination and does not always reflect the ease or speed with which the powder consolidate. It is expressed in percentage given by- [31-33]

Carr's Index = Tapped density – Bulk density / Tapped density

Table 3: Carr's Index

Carr's Index	Types of Flow
<10	Excellent
11-15	Good
16-20	Fare
21-25	Passable
26-31	Poor

h) True Density

The density of the particle that makeup a powder or particulate solid in contrast to bulk density, which is measure the average density of a large volume of the powder in specific medium. It is given by-

True Density δ = M1 / M2 + M2 - M3

Where,

M1 = Weight of empty bottle

M2 = Filled beads weight of bottle

M3 = Solvent + Beads sample

i) Angle of repose

The angle of repose is defined as the study the flow property of powder. A funnel with 10mm inner diameter of stem was fixed at a height of 2.5cm over the platform. About 5g of sample was solely passed along the wall of funnel till the tip of the pile formed touches the stem of the funnel.

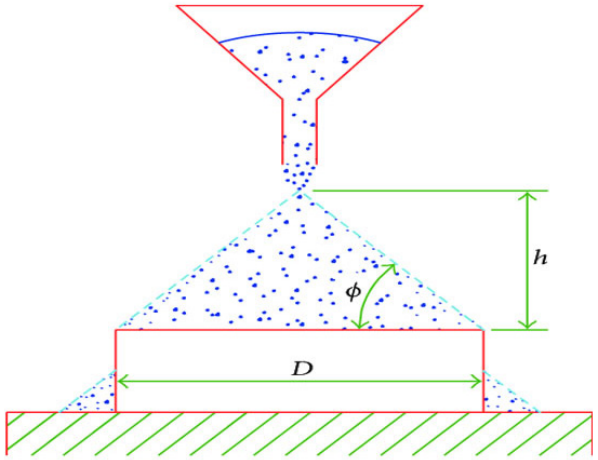

Figure 1: Diagrametic representation of Angle of repose.

A rough circle was drawn around the pile base and the radius of powder cone was measured. Angle of repose was calculated from three average using following formula: [31-33]

$$\Theta = \text{Tan-1 } (h/r)$$

Where,

h = height of cone

r = radius

Table 4: Angle of repose

Flow Property	Angle of Repose (Degree)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-50

3. Solubility Analysis:

Solubility may be defined as the amount of a substance that dissolves in a specified volume of solvents at a specified temperature. More specifically, compound solubility can be defined as unbuffered, buffered, and intrinsic solubility. Unbuffered solubility, usually in water, means solubility of a saturated solution of the compound at the neutral pH of the solution[34].Solubility and dissolution rate of drugs are of highly important in pre-formulation studies of pharmaceutical dosage forms. The solubility improvement allows the drugs to be potential bio waiver candidates and may be a good way to develop more dose-efficient formulations.

Table 5: Descriptive Solubility Index

Descriptive Term	Relative amount of solvent to dissolve 1 part of solute
Very Soluble	Less than 1
Freely Soluble	01-10
Soluble	10-30
Sparingly Soluble	30-100
Slightly Soluble	100-1000
Very Slightly Soluble	1000-10000
Insoluble or Practically Insoluble	More than 10000

The ability of the solubility of a compound in a specific solvent is measured as the saturation concentration, where adding a more solute does not increase the concentration of the solution and starts to precipitate the excess amount of solute. The solubility of a material/compound is an entirely different property from the rate of solution, which is how fast it dissolves. The smaller a particle is, the rapidly it dissolves although there are many factors to affect to this generalization.

Biopharmaceutical Classification System (BCS) is a scientific tool proposed by Amidon and colleagues (1995) and it is based on aqueous solubility and intestinal permeability characteristics of drug substances. Thereby, the drugs can be classified into four classes:

Class I: High solubility and high permeability.

Class II: Low solubility and high permeability.

Class III: High solubility and low permeability.

Class IV: Low solubility and low permeability[35].

a) Intrinsic Solubility Determination:

The intrinsic solubility is the equilibrium solubility of the free acid or base form of an ionisable compound at a pH where it is fully unionised[36]. Equilibrium solubility (the concentration of compound in a saturated solution when excess solid is present, and solution and solid are at equilibrium) can be measured by the classical shake-flask method, and while this method is accurate when performed to a high standard, it is slow. Kinetic solubility (the solubility at the time when an induced precipitate first appears in a solution) can also be measured, and while the measurements are much faster than shake-flask, the kinetic solubility obtained are often much higher than measured equilibrium solubility[37].To calculate the pH-dependent solubility (S_{tot}) from the HH equation, the intrinsic solubility (S_0), the pKa-value of the drug, and the pH of interest are used and a sigmoidal relationship between solubility and pH is obtained:

$$pKa = pH + \log * S_{tot}\text{-}S_o/S_o$$

Most drugs are ionisable in aqueous solution because they contain at least one acidic or basic functional group. These molecules can exist in neutral (uncharged) or ionized (charged) form depending on the pH of the solution. They are more soluble in charged form and their aqueous solubility is pH-dependent. When the molecule exists only in the monomer state, its pH-dependent equilibrium solubility is described by the Henderson-Hasselbalch equation[38-39].

b) pKa:

The pKa value is one method used to indicate the strength of an acid. pKa is the negative log of the acid dissociation constant or pKa value. A lower pKa value indicates a stronger acid. That is, the lower value indicates the acid more fully dissociates in water.The relationship between pH and pKa is described by the Henderson-Hasselbalch equation.

$$pH=pK_a+\log_{10}[(A^-)/(HA)]$$

Where,

pH= Acidity of buffer solution

pK_a= Negative logarithm of Ka

Ka= Acid dissociation constant

[HA]= Concentration of an acid

$[A^-]$= Concentration of conjugate base

- The pKa is the pH value at which a chemical species will accept or donate a proton.
- The lower the pKa, the stronger the acid and the greater the ability to donate a proton in aqueous solution.
- The Henderson-Hasselbalch equation relates pKa and pH. However, it is only an approximation and should not be used for concentrated solutions or for extremely low pH acids or high pH bases.

c) Partition Coefficient:

In the physical sciences, a partition coefficient (P) or distribution coefficient (D) is the ratio of concentrations of a compound in a mixture of two immiscible solvents at equilibrium.In the chemical and pharmaceutical sciences, both phases usually are solvents.

Figure 2: An equilibrium of dissolved substance distributed between a hydrophobic phase and a hydrophilic phase is established in special glassware such as this separatory funnel that allows shaking and sampling.

Most commonly, one of the solvents is water, while the second is hydrophobic, such as 1-octanol. Hence the partition coefficient measures how hydrophilic ("water-loving") or hydrophobic ("water-fearing") a chemical substance is. If one of the solvents is a gas and the other a liquid, a gas/liquid partition coefficient can be determined. For example, the blood/gas partition coefficient of a general anaesthetic measures how easily the anaesthetic passes from gas to blood[40].

d) Dissolution Study:

A dissolution test, as a release test, is required for virtually all pharmaceutical products that are not a true solution. Dissolution testing monitors the rate at which a solid or semisolid pharmaceutical dosage forms releases the active ingredient into a liquid medium at liquid/solid interface, under standardized conditions of temperature, agitation, flow rate, volume, and media composition. Dissolution, or in vitro release, of the drug substance from the product into a typically aqueous-based medium, is linked to the release of the drug into the body, making it available for absorption, and then efficacy or clinical outcome. In the current US Pharmacopoeial edition, USP 42, nearly all monographs for solid dosage form include a dissolution test. Dissolution is defined as a Category III test by the USP, i.e., an "*Analytical method for the determination of performance characteristics…*"

Dissolution testing is primarily used in industry as a quality control tool to monitor the consistency of formulation and manufacturing processes of the dosage form. Dissolution is considered by most regulatory agencies as a highly critical quality characteristic for most solid dosage forms.

Figure 3: Dissolution Appratus (USP-II) Paddle Type.

The analyst developing the dissolution test needs to know, for example, whether the dosage form is a tablet, capsule, semisolid (ointment or cream), or transdermal, and whether it is designed for immediate release or controlled release of the drug product. Of key importance is the potency of the dosage form or the amount of drug to be delivered and the rate at which the drug is to be delivered. This is related directly to the mathematical expression of dissolution rate, which is defined by the Noyes-Whitney equation:[41-42]

$$dW/dt = k_1 S (C_{sat} - C_{sol})$$

Where,

dW/dt= The dissolution rate

k_1= The dissolution rate constant.

C_{sat}= The concentration of a saturated solution.

C_{sol}= The concentration of the solution at any given time.

S= The surface area of the solid.

e) Common Ion Effect:

Common-ion effect is a shift in chemical equilibrium, which affects solubility of solutes in a reacting system. The phenomenon is an application of Le-Chatelier's principle for equilibrium reactions that has become a regular occurrence in chemistry analysis and industrial researches. It is an important phenomenon that can be used in practice, to understand some reaction conditions that could favour an increased product formation. In Chemistry, its principle is thought to rely on its

ability to exploit the availability of an ion present in each of the reacting compounds in a reacting system to suppress the solubility of one of the ionic substances upon contact with another ionic compound. Due to the precipitating effect of the presence of common-ions in equilibrium solutions, the common-ion effect is considered one of the factors that affect the solubility of a compound. The principle of common-ion effect applies in many chemical processes including those involved in buffering solutions, purification of salts, salting out of soap, precipitation of salts, manufacture of baking soda, water treatment and are frequently applied in many manufacturing industries including the pharmaceutical industries.

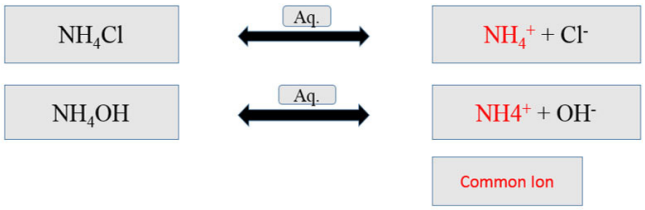

Figure 4: Common Ion effect.

Common-ion effect can be illustrated in the reactions between Ammonium hydroxide (NH4OH) and Ammonium chloride (NH4Cl) whereby the ammonium chloride suppresses the ionization of ammonium hydroxide leading to decrease in the hydroxide ion concentration and an increase in the hydrogen ion concentration with subsequent decrease in the pH value of solution[43].

4. Stability Analysis:

Stability studies are performed in life sciences, chemical, and food and beverage industries to determine the effects of environmental conditions on product quality. Environmental conditions can impact product shelf life, and the viability of product formulation.

Table 6: Stability Study.

Study	Storage Condition	Time Period
Long Term	25°C±2°C/60%RH±5RH OR 300C±20C/65%RH±5%RH	12 Month
Intermediate	300C±20C/65%RH±5RH	6 Month
Accelerated	400C±20C/75%RH±5%RH	6 Month

Factor Influencing Drug stability:

- Temperature or thermal effect
- Moisture and relative humidity
- Light and radiation energy
- pH
- Presence of reacting solvents
- Order of reaction
- Microorganisms

a) In toxicology formulations:

These studies are advisable to evaluate samples of toxicology preparations for stability and potential homogeneity problems. Usually, a drug is administered to the animals in their feed, or by oral gavages of a solution or suspension of drug in an aqueous vehicle. Water, vitamins, minerals (metal ions), enzymes and moisture levels present in feed, which can severely reduce the shelf life of a drug and decrease stability. Solution and suspension toxicological preparation should be checked for ease of manufacture and stored in flame-sealed ampoules at various temperatures. In chemical stability the suspension should be subjected to an occasional shaking to check dispersability and drug solubility is analysed by pH decomposition[44].

b) Solution Stability:

The solution stability is stability of standard and extracted sample solution (ready to inject) from the sample or matrix and analysed as per official method, and it should be stored properly in room temperature and refrigerated condition depending upon the stability of the sample and standard solution. These studies include the effect of pH, Ionic strength, Co-solvent, Light, Temperature and Oxygen. Ready-to-use solutions are the most preferable and most common dosage forms for injectable and topical ophthalmic products. Drugs formulated as solution almost always have chemical and physical stability challenges as well as solubility limitations and the need to prevent inadvertent microbial contamination issues[45].

c) Solid State Stability:

Solid-state stability analysis is a very important for drug stability testing. It identifies the stable storage conditions for drug products and also identify any physical or chemical properties of the drug molecule that may affect the stability of a drug product.

Solid-state properties are critically important in pharmaceutical product development and manufacturing, because they can directly affect the quality of a drug product. Common to the different types of pharmaceutical solids is that solid-state transformations can lead to reduced or unpredictable therapeutic effects. Such changes can affect the active pharmaceutical ingredient directly (e.g. different physicochemical properties of different forms) or indirectly (e.g. by influencing the stability of the product). There is a need to understand, control and monitor solid-state behaviour during pharmaceutical processes and storage. Formulation and manufacturing processes affect the solid-state structure,

and they must be designed so that the product has the intended properties that also remain stable during storage. Reliable analytical methods for solid-state characterisation are crucial[46].

NOVEL DRUG DELIVERY SYSTEM

Controlled Drug Delivery System:

Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations[47-49].

Advantage of CDDS:

- Reduction in frequency of drug administration.
- Improved patient compliance.
- Reduction in drug level fluctuation in blood.
- Reduction in total drug usage when compared with conventional therapy.
- Reduction in drug accumulation with chronic therapy.
- Reduction in drug toxicity (local/systemic).
- Stabilization of medical condition (because of more uniform drug levels).
- Improvement in bioavailability of some drugs because of spatial control.
- Economical to the health care providers and the patient.

Potential Limitation:

- Delay in onset of drug action.
- Possibility of dose dumping in the case of a poor formulation strategy.
- Increased potential for first pass metabolism.
- Greater dependence on GI residence time of dosage form.
- Possibility of less accurate dose adjustment in some cases.
- Cost per unit dose is higher when compared with conventional doses.
- Not all drugs are suitable for formulating into ER dosage form.

Sustained Drug Delivery System:

Sustained Release Drug Delivery System (SRDDS) is designed to release a drug at a predetermined rate by maintaining a uniform drug level for a specific time period with minimum side effects. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to some interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. The major goal of designing sustained released formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decrease the dosing frequency, reduced side effects, decreasing the required dose employed and providing the shortest possible time by using smallest quantity of drug administered by the most suitable route.SR dosage forms are designed to transport the blood level of a drug rapidly to therapeutic concentrations by means of an initial dose portion and then maintain this level for a predetermined time with the continuation portion. SR of drugs in GI tract following oral administration is not affected by the absorption process. The main goal of sustained released dosage forms is the improvement of drug therapy compared by the relationship between advantages and disadvantages of the use of sustained released systems[50-53].

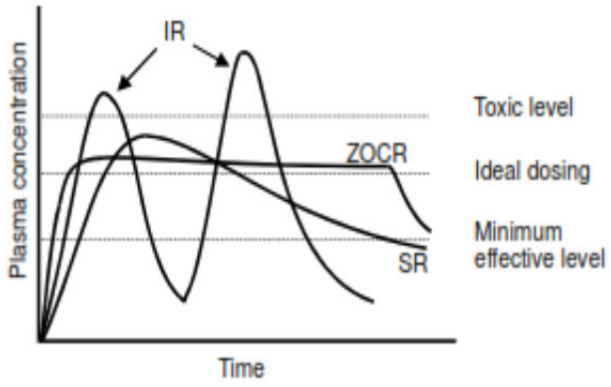

Figure 5: Graphical representation of plasma concentrations of a conventional Immediate Release (IR), a Sustained Release (SR) and an idealized zero-order controlled release (ZOCR) drug delivery systems.

Advantages:

- Improved patient compliance due to less frequent drug administration.
- Reduced fluctuation in steady-state drug levels.
- Maximum utilisation of the drug.
- Increased safety margin of potent drug.

- Reduced healthcare costs through improved therapy.
- Shorter treatment period.
- Less frequency of dosing.

Disadvantages:

- Reduced potential for accurate dose adjustment, administering a fraction of a tablet or capsule in order to obtain fine dose adjustment is more difficult with some sustained release products than others.
- If the drug has short half-life, it has to be administered frequently, so there are chances of missing the dose.
- If the drug is not taken at periodic interval, peak valley plasma concentration time profile obtained is not steady.
- The fluctuations of drug plasma level that occurs during conventional release may produce under medication or overmedication.
- Necessitate for additional patient education and counsel. E.g., "do not crush or chew the dosage unit" and "tablet residue may appear in stools".
- Cost of the formulation is high.
- Poor IVIVC (In vitro – in vivo correlation).

Challenges to Sustained Release Drug Delivery:

- Biocompatibility
- Cost of formulation, preparation and processing
- Fate of controlled release system if not biodegradable
- Fate of polymer additives, e.g., plasticizers, stabilizers, antioxidants, fillers etc.

CONCLUSION

After completion of preformulation evaluation of new drug candidates, it is recommended that a comprehensive report be prepared highlighting the pharmaceutical problems associated with molecules. It helps in developing phase I formulations and in preparing regulatory documents and aid in developing subsequent drug candidates. If, drug is found satisfactory then sufficient quantity is synthesized to perform initial toxicity studies, initial analytical work and initial preformulation. Once past initial toxicity, phase I (clinical toxicology) begins for actual formulations. After that phase II and III clinical testing begins, and during this phase an order of magnitude formula is finalized. After completion of all above, an NDA is submitted and after approval of NDA, production can start.

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