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# Preformulation and ProductionDevelopment

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**Abstract-** Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form. This could provide important information for formulation design or support the need for molecular modification. Every drug has intrinsic chemical and physical properties which has been consider before development of pharmaceutical formulation. This property provides the framework for drugs combination with pharmaceutical ingredients in the fabrication of dosage form. Objective of preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish Physico-chemical parameter of new drug substances. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in preformulation study. Polymorphism having crystal and amorphous forms shows different chemical physical and therapeutic description of the drug molecule. This article explains some properties and techniques for preformulation evaluation parameters & production of drug.

**Keyword-** Preformulation studies and production development- Introduction, Physical Properties, Chemical Properties, Production Development.

## Introduction-

Discovering and developing new medicines is a long, complex and expensive process and the failure rate is high during the process. To minimise attrition it is essential, therefore, to understand the physicochemical characteristics of compounds or biological entities that are candidates for development into final products. Data acquired from preformulation studies also forms an important basis for understanding the potential pharmacokinetics of a drug in humans and animals[1]. Preformulation evolved in the late 1950s and early 1960s as a

result of a shift in emphasis in industrial pharmaceutical product development. Improvement in analytical methods that spurred the first programs that might bear the name “preformulation”. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass-produced. The active drug is released by acidic medium, enzyme action, etc. Prodrug formation may increase the absorption rate due to its lipophilicity (passive) or its water solubility (active). Prodrug formation may increase the duration of action. Prodrug formation may improve the drug stability, solubility, crystallinity, taste, odor and reduced pain on injection. For example Erythromycin base has a bitter taste and is rapidly hydrolyzed in stomach to inactive products[2]. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico-mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials.

This may influence

- Formulation design
- Method of manufacture of API and drug product
- Pharmacokinetic/biopharmaceutical properties of the resulting product.
- Packaging of the product (stability).

2. Literature Review 2.1 Ways of production 1. Production by Disintegration: By separating the contents of Crude oil or a mixture by which the desired products are produced. For example the crude oil is disintegrated into various fuel oils. Similarly salt production is also an example for. 2. Production by Integration: In this type of Production various Components of the products are assembled together to get the desired product. In this process, Physical and Chemical Properties of the materials used may change. The examples are: Assembly of Two wheelers, four wheelers and so on. 3. Production by Service: Here the Properties of materials (Chemical and Mechanical) are improved without any physical change. Example:-Heat Treatment of metals.

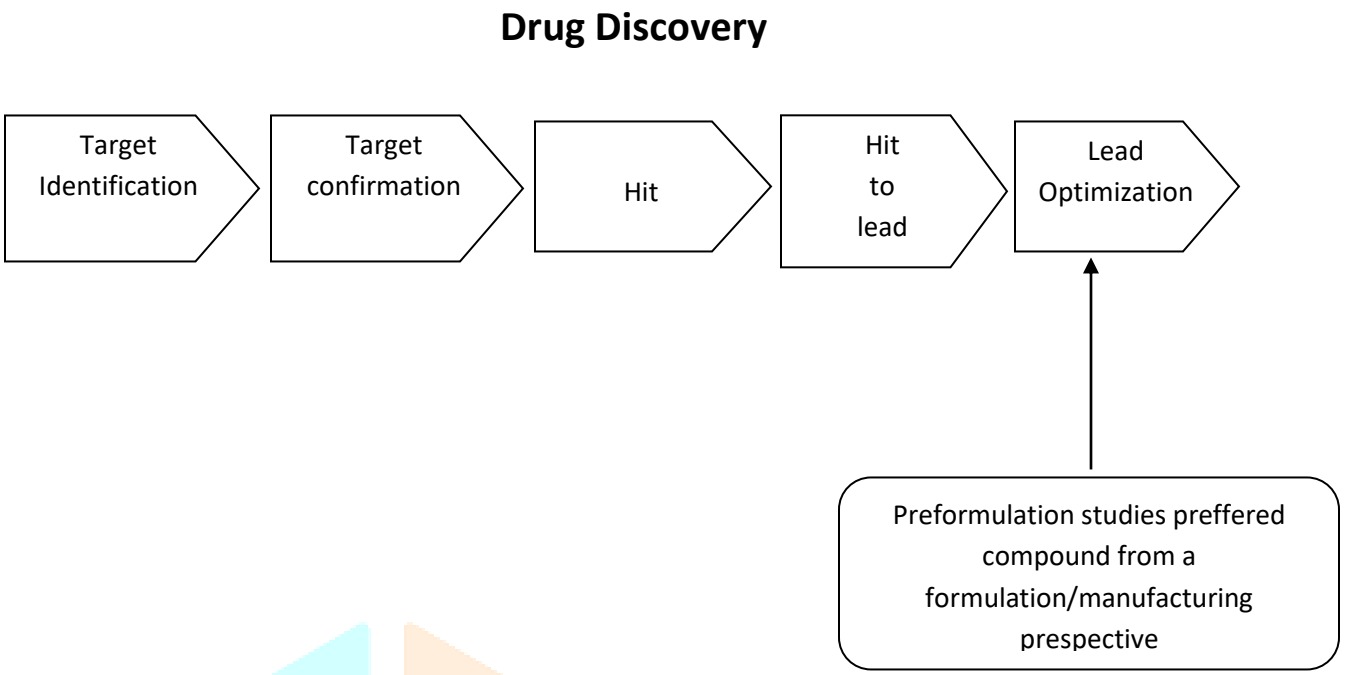


**Fig: Early stage of preformulation studies**

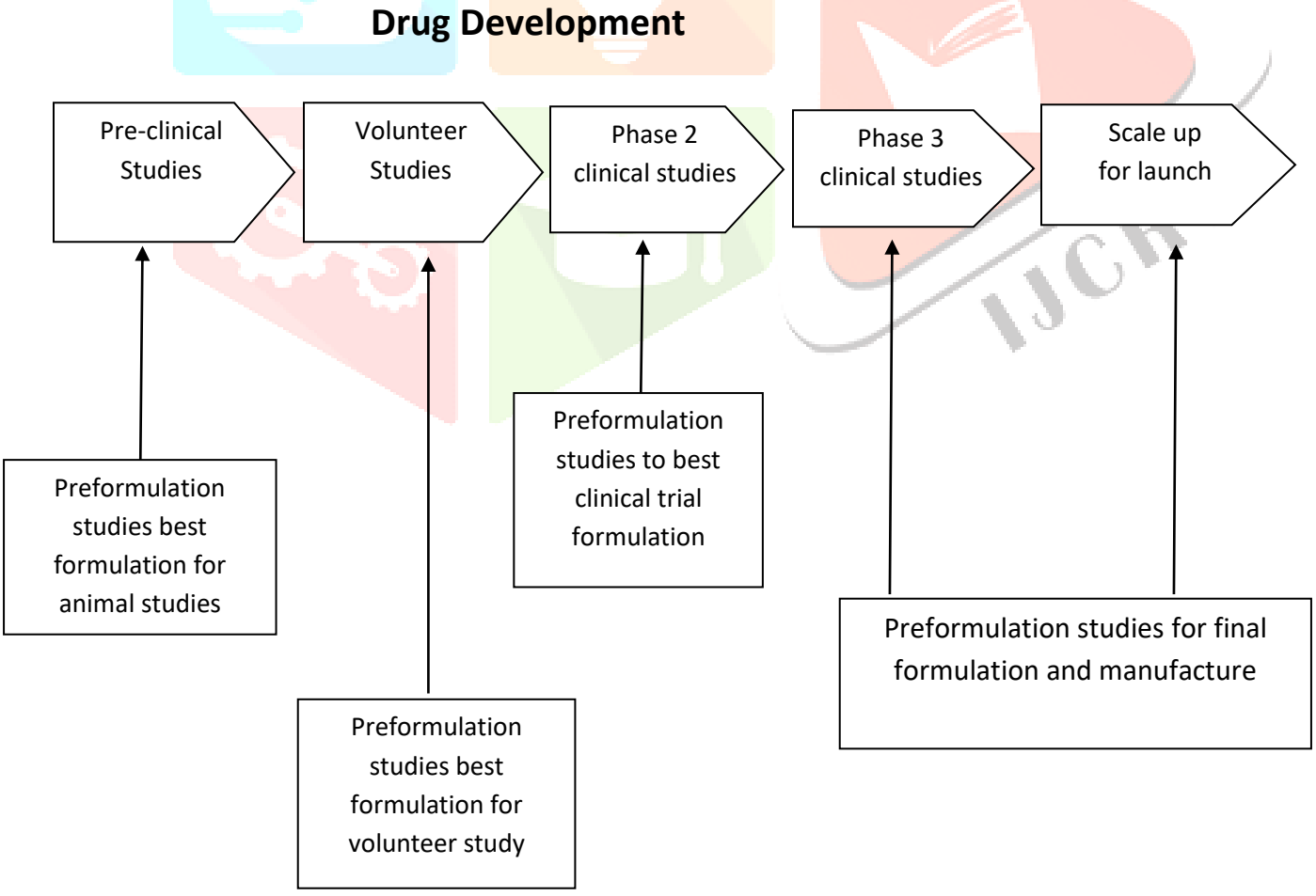


**Fig**: Preformulation studies at various stages of development.

**Physiochemichal parameters:**

**Table- 1**

| Test | Dosage form |
|---|---|
| A. Physical Parameters- | |
| 1) Organoleptic properties | General |
| 2) Purity of API and excipients | General |
| 3) Solubility | General |
| 4) Ionization/Dissociation constant (pKa) | General |
| 5) Partition Coefficient | General |
| 6) Dissolution Behaviour | Solid oral, suspension |
| 7) Powder Flow Property | Solid oral |
| 8) Stability | General |
| 9) Hygroscopicity | Solid oral |
| 11) Crystallinity & Polymerphism | General |
| B. Chemical Parameters | |
| 1) Hydrolysis | |
| 2) Oxidation | |
| 3) Reduction | |
| 4) Recemization | |
| 5) Polymerization | |
| 6) Isomerization | |

Conventional dosage such as tablet, Capsule, Oral liquid, Oral Suspension, Semisolid,
Parenteral, emulsion
Tablet and capsule

**1. Physical Parameters-**

**Organoleptic properties:**

A typical preformulation program should begin with the description of the drug substance. The color, odour and taste of the new drug must be recorded using descriptive terminology. The color, odor and taste of the new drug must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties in order to avoid also plays a role in the homogeneity of the final tablet. When large differences in size exist between the active components and excipients, mutual sieving (de- mixing) effects can occur making thorough mixing difficult or if attained difficult to maintain during the subsequent processing steps.

Table 2. – some prganoleptic properties to describe API

| Color | Odour | Taste |
|---|---|---|
| Off-white | Pungent | Acidic |
| Cream yellow | Sulfurous | Bitter |
| Tan | Fruit | Bland |
| Shiny | Aromatic | Intense |
| | Odourless | Sweet |
| | | Tasteless |

**Purity of API and expecients:**

Excipient purity is critical in all applications of drug formulation. Typically, the more sensitive or reactive an API, the more critical excipient purity becomes. When evaluating or choosing any excipient, however, purity should always be a priority. Excipient impurities can directly impact the stability of the drug active and its performance, which in turn will lead to poor bioavailability, and affect the end product's pharmacokinetics and pharmacodynamics. Side effects associated with excipient impurity are breakdown of the API and poor performance, and impurities in even the simplest formulation can lead to a failed end product. The work is then transferred to the commercial side for mass production, which is achieved on the commercial scale by putting in place good process controls and quality systems that ensure high purity material is produced on a consistent basis. Homogeneity index (HI) is defined as the ratio of the response (peak area) due to the main component, to the total response. According to ICH Q3A guidance, the allowable level of any given impurity or impurities that are permitted in API/drug product, without explicit non-clinical safety testing, is as presented in Table 3 (ICH, 2008).

Table 3: Maximum allowable impurity limit for an API in a dosage form

| Threshold | MDD of API in drug Product | Threshold limit based on TDI |
|---|---|---|
| Reporting | ≤1g, >1g | 0.1%TDI, 0.05%TDI |
| Identification | <1mg, 1mg-10mg, 10mg-2g, >2g | 1.0%TDI or 5µg<br>0.5%TDI or 20 µg<br>0.2%TDI or 2mg<br>0.1%TDI |
| Qualification | <10mg<br>10mg-100mg<br>100mg-2g<br>>2g | 1.0%TDI or 50µg<br>0.5%TDI or 200µg<br>0.2%TDI or 3mg<br>0.1%TDI |

MDD: Maximum daily dose; TDI: Total daily intake

This is also true for excipients originating from natural source. So, impurity profiling of not only API but also excipients is important to avoid this unwanted consequence of drug degradation. Interestingly, this kind of problem is difficult to predict as it may not arise initially during product development, but at 2-5

Later stage of formulation development or even after commercial production; the product may undergo stability issue.

**Solubility-** The aqueous and lipid solubility characteristics of a drug substance are of fundamental importance in determining whether it is capable of reaching sites of absorption, its interaction with putative therapeutic targets and its ultimate metabolism and excretion.

An assessment of solubility characteristics is, therefore, usually a starting point for preformulation studies. Methods of Solubility analysis include: Solubility determination, pKa determination, Partition coefficient, Dissolution behavior, Common ion effect, Membrane permeability. Methods to improve drug solubility are chemical modification of the drug into salt or ester forms, through selection of a different solubilizing agent, use of co-solvents or other techniques such as micronization or solid dispersion and adjustment of the pH of the solvent in which the drug is to be dissolved. the drug has to be in solution in order to get absorbed through biological memberane, especially at the gastro-intestinal

tract. Without appropriate solubilisation strategy, APIs with solubility profile are very thorny to design into solid oral dosage forms due to their poor dissolution rate[6].

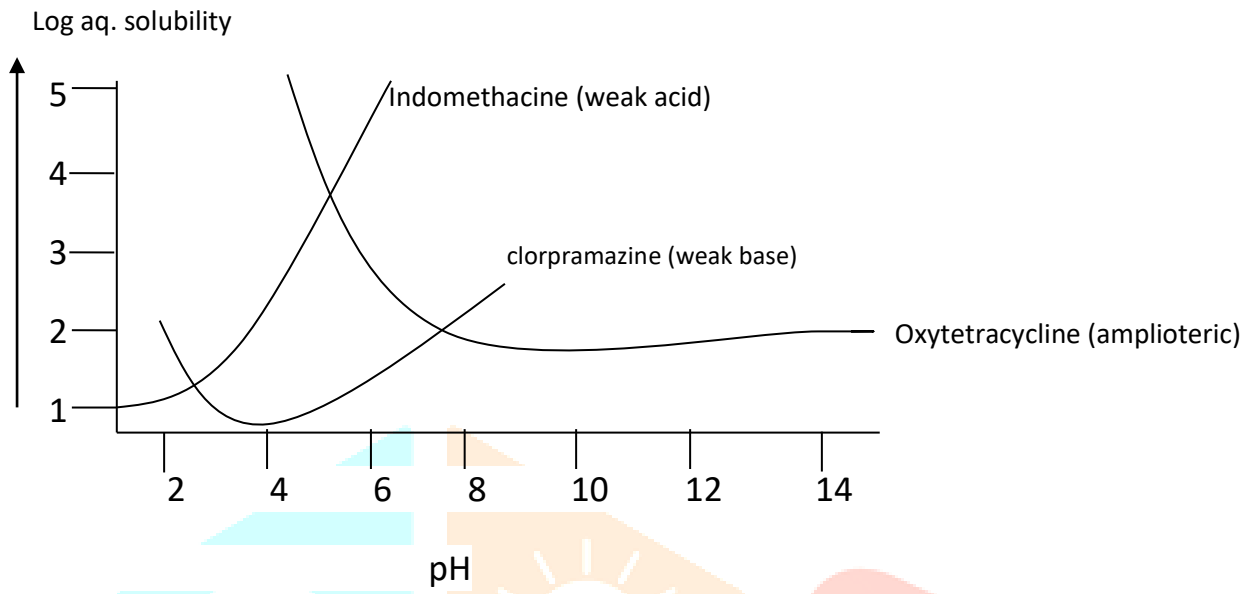


**Fig**: solubility of drugs as a function of pH, plotted as logarithum solution.

- Most od the available of drugs weakly acidic and weakly basic in nature and their solubility increases in basic and acidic pH respectively depending on their ionization state.
- However, neutral drugs remain unaffected.
- Solubility > 1 % => no dissolution-related adsorption problem.
- Highly insoluble drug administered in small doses may exhibit good absorption.

| Class | Permeability | Solubility |
|---|---|---|
| Class I | High Permeability | High Solubility |
| Class II | High Permeability | Low Solubility |
| Class III | Low Permeability | High solubility |
| Class IV | Low Permeability | Low Solubility |

## Ionization Constant (PKA)

The un- ionized species are more lipid-soluble and hence more readily absorbed. The gastrointestinal absorption of weakly acidic or basic drugs is thus related to the fraction of the drug in solution that is unionized.The conditions that suppress ionization favor absorption. The factors that are important in the absorption of weakly acidic and basic compounds are the pH at the sit e of absorption, the ionization constant, and the lipid solubility of the un- ionized species. These factors together constitute the widely accepted pH partition theory[7]. The relative concentrations of un-ionized and ionized forms of a weakly acidic or basic drug in a solution at a given pH can be readily calculated using the Henderson-Hasselbalch equations:

- **pH = pKa + log [unionized form] / [ionized form] ---- for weak bases.**

- **pH = pKa + log [ionized form] / [unionized form] ---- for weak acids.**

## Partition Coefficient –

A measurement of a drug's lipophilicity and an indication of its ability to cross cell membrane is the oil/water partition coefficient in systems such as octanol/water and chloroform/water. The partition coefficient is defined as the ratio of unionized drug distributed between the organic and aqueous phase at equilibrium.

**Po/w = Coi l/ Cwater**

For drug delivery, the lipophilic/hydrophilic balance has been shown tobe contributing factor for the rate and extent of drug absorption[8].

## Dissolution behavior -

In many instances, dissolution rate in the fluids at the absorption site, is the rate limiting steps in the absorption process. This is true for the drug administered orally in the solid dosage forms such as tablet, capsule, and suspension as well as drug administered I.M. in form of pellets or suspension.Dissolution is of 2 types. a) Intrinsic dissolution b) Particulate dissolution a)Intrinsic Dissolution The dissolution rate of a solid in its own solution is adequately describedby the Noyes-Nernst equation:

$$\frac{dC}{dt} = \frac{AD(Cs - C)}{hv}$$

A = surface area of the dissolving solid
D = diffusion coefficient
C = solute concentration in the bulk medium
h = diffusion layer thickness
V = volume of the dissolution medium
Cs = solute concentration in the diffusion layer

## Crystallity and Polymorphism-

Atoms in crystalline matter are arranged in regular and repeating patterns in three dimensions. e.g. metal and mineral and atoms or molecules randomly placed without a regular atomic arrangement in amorphous solids. Polymorphism is the ability of the compound to crystallize as more than one distinct crystalline species with different internal lattice and different crystal forms (at different free energy states) of the same compounds. They have different physicochemical properties (melting point, density, vapor pressure, X-ray, color, crystal shape, hardness, solubility, dissolution rate and bioavailability). During preformulation, it is important to identify the polymorph that is stable at room temperature. For examples: Chloromphenicol exist in A, B& C forms, of these B form is more stable and most preferable. Riboflavin has I, II& III forms, and the III form shows 20 times more water solubility than form I. Enantiotropic polymorphs can be inter converted below the melting point of either polymorph and the conversion is reversible at a define temperature. E.g. sulfur. Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism. The different crystal forms are called polymorphs.When polymorphism occurs, the molecules arrange themselves in two or more different ways in the crystal; either they may be packed differently in the crystal lattice or there may be differences in the orientation or conformation of the molecules at the lattice sites.

### Methods to identify polymorphism

- Optical crystallography
- Hot 0stage microscopy
- X- Ray Diffraction method
- NMR technique
- FTIR technique.
- Microcalorimetry
- Thermal methods
- Melting point determination

## B. Chemical parameters –

**a) Hydrolysis-** It involves nucleophilic attack of labile groups eg: lactam ester amide imide. When the attack is by the solvent other than water, then it is known as solvolysis. It generally follows 2nd order kinetics as there are two reacting species, water and API. In aqueous solution, water is in excess so the reaction is 1st order. Conditions that catalyze the breakdown are Presence of hydroxyl ion, hydride ion, divalent ion and heat, light, ionic hydrolysis, solution polarity and ionic strength, high drug concentration.

**b) Oxidation-** It is a very commonpathway for drug degradation in liquid and solid formulations. Oxidation occurs in two ways

1. Auto-oxidation
2. Free radical chain process.

Free radical chain process involves Initiation, Propagation Oxidation is an environmental phenomenon requiring oxygen (or an oxidizing agent), light, and trace metals capable of

catalyzing the reaction. If molecular oxygen is involved, the reaction is generally rapid and termed —autooxidation. Chemically, oxidation is classed as a loss of electrons, which requires an electron acceptor, or oxidizing agent, which could be, for example, iron undergoing a ferric (Fe3+) to ferrous (Fe2+) change., Hydro peroxide decomposition and Termination. Factors affecting oxidation process are Oxygen concentration, light, heavy metals particularly those having two or more valence state (copper, iron, nickel, cobalt), hydrogen and hydroxyl ion, temperature. Oxidation can be Prevented by Reducing oxygen contentoxidative degradation of drug takes place in an aqueous solution, so the oxygen content can be decreased by boiling water or by storing the formulation in in a dark and cool condition or by addition of an antioxidant/reducing agent /chain inhibitors of radical induced decomposition.

Antioxidants are of two types based on Solubility-

1. Oil soluble
2. Water soluble.

**Racemization**: The interconversion from one isomer to another can lead to different pharmacokinetic properties (ADME) as well as different pharmacological & toxicological effect. Eg. L-epinephrine is 15 to 20 times more active than D-form, while activity of racemic mixture is just one half of the L-form. It follows first order kinetics. It depends on temperature, solvent, catalyst & presence or absence of light.

**Production development-** While a more or less common understanding of the term product development exists [e.g. 1], Production development is a term less common. Sometimes, it is understood as the development of the production process, sometimes of the factory or production equipment. In the context of this paper, it covers the scope of product development applied on production systems and equipment, thereby including more common terms such as layout planning, production planning and design of production equipment. These steps following-

- Process perspective
- Methods perspective
- Tool/IT perspective
- Comparison

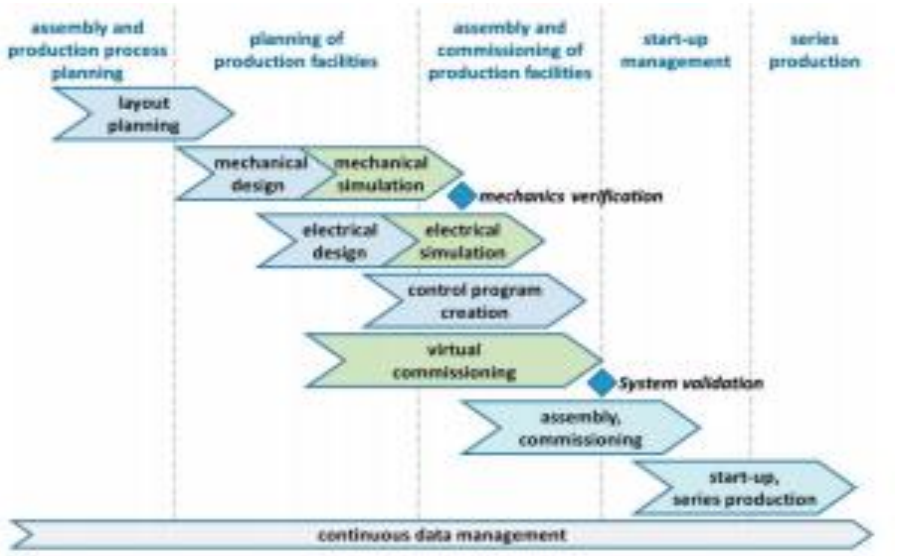


Fig. 3. Production development process (adapted from [6]).

**Conclusion-** Preformulation scientists act as intermediaries between synthetic chemists and formulation scientist. With a holistic aim of of designing and developing a stable, cost-effective and therapeutically sound-friendly dosage form, they reduce burden of of formulation scientist and help the pharmaceutical industries to evade unanticipated consequences. The right selection of API, excipients, dosage form, manufacturing processes, packaging materials, analytical methods and storage condition among many other are important for the benefit of th products of life cycle and usage. This review article gives details of above studies with respect to any sustained release dosage forms can be developed without preformulation studies.

Results and. Micromeritics Properties-

Results of micromeritics studies as presented in Table 3 showed that Hauser's ratio was 1.2 and Carr's index was 17.5% which indicates that omeprazole magnesium has fair compressibility and flowability properties, respectively. Therefore it is important to improve flow and compressibility property [4]. The results of sieve analysis show that omeprazole magnesium has a *D*50 value of 100 $\mu$m which is within the range of 90 to 125 $\mu$m and it indicates that omeprazole magnesium powder is moderately fine [4]. The results of Hauser ratio and compressibility index obtained have shown that flowability of omeprazole magnesium was fair. This will help in selection and determination of the optimal excipients and amount of the excipients to be used. That is, it is recommended that about 0.07% of magnesium stearate should be used to improve the flowability of the powder during formulation. The flowability and compressibility of omeprazole magnesium powder indicate that the powder is suitable for both direct compression and wet granulation method depending on the other excipients used with their respective amounts that could be used instead. Physical observation during drug excipient compatibility studies and physical observation indicates no significant drug-excipient interaction was observed except for the mixture of omeprazole and aerosil 200 which show change.

***Stability in Toxicology Formulation:*** It is often advisable to evaluate samples of the toxicology preparations for stability and potential homogeneity problems. Water, vitamins, minerals, enzymes are present in feed, which can severely be reduce the shelf

life of drug. Solution and suspension toxicology preparations should be checked for ease of manufacture and then stored in flame-sealed ampoules at various temperatures. In addition to chemical stability, the suspension should be subjected to an occasional shaking to check dispersibility.

***Solid state stability****:* Chemical instability normally results from either of the following reaction hydrolysis, oxidation, photolysis and pyrolysis, Chemical structure of the drug is the determination of drug to either of these attacks. Esters and lactase and to lesser extent, amides are to prone to solvolysis, instauration or electron rich centre in the structure make the molecule vulnerable for free radical.

mediated or photo-catalyzed oxidation. Physical properties of drugs. Amorphous materials are less stable than their crystalline forms. Denser materials are more stable to ambient stress.

***Compatibility studies****:* The knowledge of drug excipients interaction is useful for the formulation to select appropriate excipients. The described preformulation screening of drug excipients interaction requires only 5mg of drug in a 50% mixture with the excipients to maximize the likelihood of obscuring an interaction. Mixtures should be examined under nitrogen to ultimate oxidation and paralytic effect at a standard heating rate on DSC, over a temperature range, which will encompass any thermal changes due to both the drug and appearance or disappearance one or more peaks in thermograms of drug excipient mixtures are considered of indication of interaction.

***Solution stability***: As compared with the dry form, the degradation is much rapid in solution form. It is important ascertain that the drug doesn't degrade when exposed to GI fluid. The pH based stability study, using different stimulator GI condition can be designed. A poor solution stability of drug may urge the formulator to choose a less soluble salt form, provided the bioavailability is not compromised.

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