ISSN : 2350-0743

www.ijramr.com

*International Journal of Recent Advances in Multidisciplinary Research*
*Vol. 04, Issue 12, pp.3111-3117, December, 2017*

# RESEARCH ARTICLE

## PREFORMULATION PARAMETERS OF FORMULATION AND DEVELOPMENT OF NEW DOSAGE FORM

***[1]Hareesh Reddy, M. and [2]Dr. Samalbasivarao, A.**

[1]Associate Professor, Shadan College of Pharmacy, Himayatsagar Road, Hyderabad
[2]Professor & Principal, Sri Indu Institute of pharmacy, Ibrahimpatnam, Hyderabad

**ARTICLE INFO**

***Article History:***
Received 22nd September, 2017
Received in revised form
14th October, 2017
Accepted 20th November, 2017
Published online 30th December, 2017

***Keywords:***

Preformulation, Bioavailability, Dissolution rate, Drug solubility, Pharmacokinetics'.

**ABSTRACT**

This review article focus on the various preformulation parameters which effect the development of new dosage form like drug solubility, dissolution rate, partition coefficient, polymorphic forms and stability. Every drug has intrinsic physical and chemical properties which have been consider before development of pharmaceutical formulation. This property provides the framework for drug's combination with pharmaceutical ingredients. Preformulation studies carried out by various researchers and scientists are reviewed. Preformulation studies conduct for newly synthesized compounds or extracted compound and it gives the information regarding the degradation process, any side effects relevant to the drug, bioavailability, pharmacokinetics and formulation of similar compound and toxicity. Preformulation studies strengthen the scientific foundation of the guide lines, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product quality in the manufacturing of dosage form. Objective of preformulation study is to develop the elegant, comfort, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish Physico- chemical factors of new drug substances.

## INTRODUCTION

Preformulation studies evolved in the late 1950s and early 1960s as a result of a shift in emphasis project in industrial pharmaceutical product development. It was 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 bioavailability of dosage forms which can be mass-produced.

Before starting the preformulation studies we should know the properties of the drug,

- Potency relative to the competitive products and the dosage form.
- Literature search providing stability and decay data.
- The proposed route of drug administration.
- Literature search regarding the formulation approaches, bioavailability and pharmacokinetics of chemically related drugs.

It also includes preliminary investigations and molecular optimization by the drug should be tested to determine by two steps

***Corresponding author:* Hareesh Reddy, M.**
Associate Professor, Shadan College of Pharmacy, Himayatsagar Road, Hyderabad

**Step-1:** The magnitude of each suspected problem area
**Step-2:** if a deficiency is detected, a molecular modification should be done. To overcome this deficiency molecular modification is done be salts, prodrugs, solvates, polymorphs or even new analogues. The dissolution rate of a salt form of a drug is generally quite different from that of the parent compound. Sodium(Na+) and potassium(K+) salts of weak organic acids and hydrochloride salts of weak organic bases dissolve much more readily than do the, respective free acids or bases. For Example Ephedrine base is very poorly water soluble molecules that characterized by low solubility and dissolution rates. So, it is modified in the form of the salt Ephedrine HCL that is freely ionized and offer higher water solubility and dissolution rate.

### Objectives

- It is first step in rational development of a dosage form of a drug substance before dosage form development.
- It is important to have an understanding of the physical description of a drug substance before dosage form development.
- To develop the elegant or uniform dosage forms (stable, effective & safe}Goals
- To establish the physico-chemical parameters of new drug substance.

- To establish the compatibility with the common excipient
- To establish the drug kinetic rate profile.
- To establish the physical properties.
- To choose the correct form of a drug substance.

The major areas of preformulation research are following-
PHYSICAL CHARECTERISTICS

Bulk Characterization

- Crystallinity and polymorphism
- Hygroscopicity
- Particle size
- Bulk density
- Powder flow properties
- Compression properties

Solubility Analysis

- Ionization constant(pka)
- pH solubility profile
- Common Ion Effect(Ksp)
- Thermal Effects
- Solubilization
- Partition Coefficient
- Dissolution

Stability Analysis

- Stability in Formulations
- Solution Stability
- pH Rate Profile
- Solid State Stability
- Bulk Stability
- Compatibility

CHEMICAL CHARACTERISTICS

- Hydrolysis
- Oxidation
- Photolysis
- Racemization
- Polymerization
- Isomerization

**Bulk characterization**

Bulk properties for the solid forms such as particle size, hygroscopicity, crystallinity, bulk density and surface morphology are also likely to change during process development.

**Crystallinity and polymorphism**

Elements can exist in two or more different forms, known as allotropes of that element e.g. Carbon: diamond in cubic (tetrahedral lattice arrangement) graphite in sheets of a hexagonal lattice. Polymorphs show the same properties in the liquid or gaseous state but they behave differently in the solid state. Different polymorphs of a compound are in general different in structure and properties in the same manner as the crystals of two different compounds. Furthermore polymorphism is remarkably common particularly within certain structural groups. A crystalline particle is characterized by definite internal and external structures. Crystal habit describes the external shape of a crystal, whereas polymorphic state refers to the definite arrangement of molecules inside the crystal lattice. Crystallization is invariably employed as the final step for the purification of a solid.

Methods to identify polymorphism

A) Optical crystallography
B) Melting point determination
C) X- Ray Diffraction method
D) Microcalorimetry
E) FTIR technique.
F) NMR technique
G) Thermal methods
H) Hot ostage microscopy

**Hygroscopicity**

Many compounds and salts are sensitive to the presence of moisture or water vapour. When compounds interact with moisture, they retain the water by bulk or surface adsorption, capillary condensation, chemical reaction and, in extreme cases, a solution (deliquescence). Deliquescence is where a solid dissolves and saturates a thin film of water on its surface. It has been shown that when moisture is absorbed to the extent that deliquescence takes place at a certain critical relative humidity, (CRH) the liquid film surrounding the solid is saturated. This process is dictated by vapour diffusion and heat transport rates. Moisture is also an important parameter that can affect the stability of candidate drugs and their formulations. Sorption of water molecules onto a certain drug (or excipient) can often induce hydrolysis. In this situation, by sorbing onto the drug-excipient mixture (DEM), the water molecules may ionize either or both of them and induce a reaction.

**Table 1. Different classes of hygroscopic substances**

| S.NO | Classification | Description |
|---|---|---|
| 1 | Non-hygroscopic | Moisture content does not increase, relative humidity below 90% |
| 2 | Slightly hygroscopic | Moisture content does not increase, relative humidity below 80% |
| 3 | Moderately hygroscopic | Moisture Content does not increase more than 5% after storage for one week at relative humidity below 60% |
| 4 | Very hygroscopic | Moisture content increase may occur at relative humidity in between 40 to 50% |

**Particle size**

Various physical and chemical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also in some instances on their biopharmaceutical factors. For example, the bioavailability of griseofulvin and phenacetin is directly related to the particle size distributions of these drugs. It is now generally recognized that poorly soluble drugs showing a dissolution rate- limiting step in the absorption process.

**Table 2. Common Techniques for Measuring Fine Particles of Various Sizes**

| S.NO | TECHNIQUE | PARTICLE SIZE (mm) |
|---|---|---|
| 1 | Sedimentation | >1 |
| 2 | Permeability | >1 |
| 3 | Sieve | >5 |
| 4 | Elutriation | 1-50 |
| 5 | Centrifugal | <50 |
| 6 | Microscopic | 1-100 |

**Table 3. Carr's compressibility index**

| S.NO | % of compressibility | Relative flow ability |
|---|---|---|
| 1 | 5-15 | Excellent |
| 2 | 12-16 | Good |
| 3 | 18- 21 | Fair |
| 4 | 23-28 | Slightly poor |
| 5 | 28-35 | Poor |
| 6 | 35-38 | Very poor |
| 7 | More than 40 | Extremely poor |

**Bulk density**

Apparently bulk density is determined by pouring presieved bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight. Tapped density is determined by placing a graduated cylinder containing known mass of drug or formulation on a mechanical tapper apparatus, which is operated for a fixed number of taps (approx 1000) until the powder bed volume reached a minimum. Using the weight of drug in the cylinder and this minimum volume, the tapped density may be computed. In addition to tapped density true density is also desirable. It can be computed by liquid displacement method and gas displacement method.

**Powder flow properties**

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the preformulation stage to be "poorly flowable," the problem can be solved by selecting appropriate excipients. In some cases, drug powders may have to be precompressed or granulated to improve their flow properties. Some of these methods are angle of repose, flow through an orifice, compressibility index, shear cell, etc. Changes in particle size and shape are generally very apparent; an increase in crystal size or a more uniform shape will lead to a smaller angle of repose and smaller Carr's index.

**Angle of Repose**

The maximum angle which is formed between the surface of pile of powder and horizontal surface is called the angle of repose. For most pharmaceutical powders, the angle-of- repose values range from 25 to 45°, with lower values indicating better flow characteristics.

$\tan \theta = h / r$

h = height of heap of pile, r = radius of base of pile

**Compressibility**

"Compressibility" of a powder can be defined as the ability to decrease in volume under pressure and "compactability as the ability of the powdered material to be compressed into a tablet of specified tensile strength.

It can be used to predict the flow properties based on density measurement.

Carr's index= Tapped density – pored density/Tapped density x 100

**Solubility analysis**

An important Physico-chemical property of a drug substance is solubility, especially aqueous solubility. A drug must possess some aqueous solubility for therapeutic efficacy in the physiological P H range of 1 to 8. For a drug to entering to systemic circulation, to exert therapeutic effect, it must be first in solution form. If solubility of drug substance is less than desirable, than consideration must be given to improve its solubility. Poor solubility (< 10mg/ml) may exist incomplete or erratic absorption over PH ranges from 1-7 at 37°C.

**Ionization Constant (PKA)**

Many drugs are either weakly acidic or basic compounds and, in solution, depending on the pH value, exist as ionized or un-ionized species. 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 un- ionized. 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. 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:

[Un- ionized form] pH = pka + log ---------- for bases [ionized form]

[Ionized form] pH = pka + log---------- for acids [un ionized form]

Weakly acidic compounds (pka< 4.3) were absorbed relatively rapidly; those with pka values ranging between 2.0 to 4.3 were absorbed more slowly; and strong acids (pka> 2.4) were hardly absorbed. For bases, those with pka values smaller than 8.5 were absorbed relatively rapidly; those with a pka a between 9 to 12 were absorbed more slowly; and completely ionized quaternary ammonium compounds were not absorbed. In pharmacokinetic area, the extent of ionization is imp. Affect of its extent and absorption, distribution, elimination. The extent of Pka, in many cases, highly dependent on PH of the medium containing the drug.

**Determination of Pka:**

- Potentiometric Titration
- Spectrophotometry Determination
- Dissolution rate method
- Liquid-Liquid Partition method

**Partition Coefficient**

The lipophilicity of an organic compound is usually described in terms of a partition coefficient; which can be defined as the ratio of the concentration of the unionized compound(log p), at equilibrium, between organic and aqueous phases:

Po/w = (C oil/water) equilibrium

Or

(un ionized compound) organic phase logP = (un ionized compound)aqueous phase

This ratio is known as the partition coefficient (or) distribution coefficient and is essentially independent of concentration of dilute solutions of a given solute species.

- logP = 0 means that the compound is equally soluble in water and in the partitioning solvent.
- log P = –2 means that the compound is 100 times more soluble in water
- log P = 5, then the compound is 100,000 times more soluble in the partitioning solvent. it is quite hydrophilic.

Drugs having values of P much greater than 1 are classified as lipophilic, whereas those with partition coefficients much less than 1 are indicative of a hydrophilic drug. Although it appears that the partition coefficient may be the best predictor of absorption rate, the effect of dissolution rate, pka, and solubility on absorption must not be neglected. Various organic solvents such as chloroform, ether, amyl acetate, isopropylmyristate, carbon tetrachloride, and n - Octanol can be used in the determination of the partition coefficient, with the latter gaining increasing acceptance. Methods of finding Partition coefficient:

1) Shake-flask method
2) Chromatographic method.
3) Counter current and filter probe method.
4) Tomlinson's filter probe method.
5) Microelectrometrictitratation method

Automated instrument is now available.

**Applications of Partition coefficient**

- Measure of Lipophilic character of molecules.
- Recovery of antibiotics from fermentation broth.
- Extraction of drug from biological fluid for therapeutic monitoring.
- Absorption of drug from dosage forms. (Ointments, Suppositories, Transdermal patches).
- Study of distribution of flavouring oil between oil & water in emulsion.

**Solubilization**

For drug candidates, with either poor water solubility or insufficient solubility for projected solution dosage form, preformulation study should include limited experiments to identify possible mechanism for Solubilization.

Methods for Increasing Solubility:

- Change in pH
- Co-Solvency
- Dielectric Constant
- Solubilization by Complexation
- Hydrotropy
- Chemical Modification of drug

**Thermal Effect**

We determine the effect of temperature on the solubility of drug candidate. This can be determined by measuring heat of solution i.e.

HS lnS = - ΔHS (1) + C R T

Where, S = molar solubility at temp. T (° K) R = gas constant. Heat of solution represents the heat released or absorbed when mole of solute is dissolved in large quantity of solvent. It is determined from solubility value for saturated solution equilibrated at controlled temperature over the range of interested. Typically the temperature range should include 5 °C, 25°C, 37°C and 50°C. If heat of solution is positive (endothermic process) thus, increasing solution temperature, increased the drug solubility. For non-electrolyte and un-ionized form of weak acid and weak bases dissolved in water, heat of solution range from 4 to 8 Kcal/mol.

**Common Ion Effect**

A common interaction with solvent, which often overlooked, is the common ion effect. The additions of common ion often decrease or reduce the solubility of slightly soluble electrolyte. This salting out results from the removal of the water molecule as the solvent due to competing hydration of other ions. So, weakly basic drug which are given as HCL salts have decreased solubility in acidic (HCL) solution. Examples - Bromhexine, Chlortetracycline, cyproheptadine methacyclin, papaverine,Triamterene To identify a common ion interaction, the intrinsic dissolution rate of hydrochloride salt should be compared between, Water and water containing 1.2%W/V Nacl 0.05MHcl and 0.9%W/V Nacl in 0.05M After this, if solubility is not decreased than we can give drug in chloride salt, otherwise it should be eliminated.

**Dissolution**

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 two types.

- Intrinsic dissolution
- Particulate dissolution

**Intrinsic Dissolution**

The dissolution rate of a solid in its own solution is adequately described by the Noyes-Whitney equation:

AD (Cs – C) dC / dt =---------- hv

Where, dC / dt = dissolution rate

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 during the early phase of dissolution, Cs » C and is essentially equal to saturation solubility (S). Surface area A and volume V can be held constant. Under these conditions and at constant temperature and agitation, Equation reduces to dC / dt = KS Where K =AD/hv = constant. Dissolution rate as expressed in Equation is termed the intrinsic dissolution rate and is characteristic of each solid compound in a given solvent under fixed hydrodynamic conditions.

**Stability Analysis**

**Solid State Stability Studies**

Solid state reactions are much slower and more difficult to interpret than solution state reactions, due to a reduced number of molecular contacts between drug and excipient molecules and to the occurrence of multiple phase reactions.

- Sample A - Prepare a small mixture of drug and excipient. Place above mix in vial. Place a rubber closure on vial and dip the stopper in molten carnauba wax to render it hermetically sealed
- Sample B - Sample preparation method is same as sample A, but 5% moisture is added in mixture.
- Sample C - Drug itself without any excipient is taken as a sample for solid state stability study.

***All the samples of drug-Excipient blends are kept for 1-3 weeks at specified storage conditions***

Then sample is physically observed for

- Caking
- Liquefaction
- Discoloration
- Odor
- Gel formation

It is then assayed by TLC or HPLC or DSC. Whenever feasible, the degradation products are identified by Mass spectroscopy, NMR or other relevant analytical technique

**Table 4. Types of stability and the condition maintained during the shelf life of the product**

| S.NO | Types of stability | Conditions maintained during the shelf life of the product |
|---|---|---|
| 1 | Chemical | Retains its chemical integrity and labeled potency |
| 2 | physical | Retains appearance, palatability, uniformity, dissolution and suspendability |
| 3 | Microbiological | Retains sterility effectiveness of antimicrobial agents |
| 4 | Therapeutic | Drug action remains uncharged |
| 5 | Toxicological | No significant increase in toxicity |

**Solution State Stability Studies**: It is easier to detect liquid state reactions as compared to solid state reactions. For detection of unknown liquid incompatibilities, the program set up is same as solid dosage forms. Now according to ―Stability guidelines‖ by FDA states that: Following conditions be evaluated in studies on solutions or suspensions of bulk drug substances:

- Acidic or alkaline pH.
- Presence of added substances- chelating agents, stabilizers etc.
- High Oxygen and Nitrogen atmospheres.
- Effect of stress testing conditions……

## MATERIALS AND METHODS

- Place the drug in the solution of additives.
- Both flint and amber vials are used.
- Autoclave conditions are employed in many cases. This will provide information about Susceptibility to oxidation. Susceptibility to light exposure. Susceptibility to heavy metals.
- In case of oral liquids, compatibility with ethanol, glycerin, sucrose, preservatives and buffers are usually carried out.

**Drug-Excipient Compatibility Studies:** In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipients, the preformulation scientist must generate the needed information. A typical tablet contains binders, disintegrants, lubricants, and fillers. Compatibility screening for a new drug must consider two or more excipients from each class. The ratio of drug to excipient used in these tests is very much subject to the discretion of the preformulation scientist.

**Importance of Drug Excipient Compatibility Study(DECS)**

- Stability of the dosage form can be maximized. Any physical or chemical interaction between drug and excipient can affect bioavailability and stability of drug.
- It helps to avoid the surprise problems. By performing DECS we can know the possible reaction before formulating final dosage form. It bridges the drug discovery and drug development. Drug discovery can emerge only new chemical entity. It becomes drug product after formulation and processing with excipients.
- By using DECS data we can select the suitable type of the excipient with the chemical entities emerging in drug discovery programs. DECS data is essential for IND (investigational new drug) submission. Now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

**Analytical techniques used to detect Drug- Excipient Compatibility:**

- Thermal methods of analysis
  - DSC- Differential Scanning Calorimetry
  - DTA- Differential Thermal Analysis

- Accelerated Stability Study
- FT-IR Spectroscopy
- DRS-Diffuse Reflectance Spectroscopy
- Chromatography
  - SIC-Self Interactive Chromatography
  - TLC-Thin Layer Chromatography
  - HPLC-High Pressure Liquid Chromatography
- Miscellaneous
- Radiolabelled Techniques
- Vapour Pressure Osmometry
- Fluorescence Spectroscopy

## CHEMICAL CHARACTERISTICS

**Hydrolysis:** It involves nucleophilicattack 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 second order kinetics as there are two reacting species, water and API. In aqueous solution, water is in excess so the reaction is first 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. Hydrolysis can be prevented by Adjusting the PH.

As most of the potent drugs are weakly acidic or weakly basic in nature. Formulate the drug solution close to its PH of optimum stability or by Addition of water miscible solvent in formulation or by Using Optimum buffer concentration to suppress ionization or by Addition of surfactant such as non-ionic, cationic and anionic surfactant stabilizes the drug against base catalysis or the solubility of pharmaceuticals undergoing ester hydrolysis can be reduced by forming less soluble salts or ester of drug. eg: phosphate ester of Clindamycin or Store with desiccants, using complexing agents.

**Oxidation:** It is a very common pathway for drug degradation in liquid and solid formulations. Oxidation occurs in two ways

**Auto- oxidation:** Reaction of any material with molecular oxygen producing free radicals by hemolytic bond fission of a covalent bond. These radicals are highly unsaturated and readily accept electron from other substance causing oxidation is called Auto- oxidation.

**Free radical chain process:** Free radical chain process involves Initiation, Propagation, Hydro peroxide decomposition and Termination. Factors affecting oxidation process are Oxygen concentration, light, and 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 content-oxidative 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. Oil soluble and Water soluble. Oil Soluble Antioxidants are Free radical acceptors and inhibit free radical chain process eg: hydroquinone, propylgallate, lecithin whereas Water soluble Antioxidants Oxidizes itself and prevents oxidation of drug Eg: sodium met bisulphate, sodium bisulfate, thioglycolic acid, thioglycerol.

**Reduction:** is a relatively more common pathway of drug metabolic process. Hepatic microsomescatalyze diverse reductive chemical reaction* and require NADPH for this purpose. Azo and nitro reduction is catalyzed by cytochrome P- 450.Chloral hydrate is reduced to it's active metabolite trichloroethanol by alcohol dehydrogenase. Reduction of prednisolone and cortisone results in the formation of their active metabolites hydrocortisone. Azo dyes used as coloring agents in pharmaceutical products or foods are reduced to form amines in the liver and by the intestinal flora.

**Photolysis:** Mechanism of photodecomposition: Electronic configuration of drug overlaps with the spectrum of sunlight or any artificial light where energy is absorbed by the electron resulting in excitation. As they are unstable, they release the acquired energy and return to the ground state by decomposing the drug. The phenomenon where molecules or excipients which absorb energy but donot participate themselves directly in the reaction but transfer the energy to others which cause cellular damage by inducing radical formation is known as photosensitization. Photosentizer Convert oxygen from its ground state to singlet excited state and Generate superoxide molecule which is an anion radical and acts as a powerful oxidizing agent.

**Photo Decomposition Pathway**

1. **N-dealkylation:** eg: Dipenhydramine, Chloroquine, Methotrexate
2. **Dehalogenation:** eg:-Chlorpropamide, Furosemide
3. Dehydrogenation of ca++ channel blockers
4. **Decarboxylation in anti-inflammatory drugs:** Naproxen, Flurbiprofen, Benzoxaprofen
5. **Oxidation:-** Chlorpromazine and other phenothiazines give n- oxides in the presence of sunlight.
6. **Isomerization and cyclization:-** Nor adrenaline, Dopamine
7. **Rearrangement:** Metronidazole and oxidiazine yellow color Photodecomposition canbe Prevented by-suitable packing, antioxidant, protection of drug from light, avoiding sunbath, photostabilizer, and coating.

**Polymerization**

It is a continuous reaction between molecules. More than one monomer reacts to form a polymer. Eg. Darkening of glucose solution is attributed to polymerization of breakdown product [5- (hydroxyl methyl) furfural].

**Racemization**

The interconversion from one isomer to another can lead to different P'cokinetic properties (ADME) as well as different P'cological& 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.

**Table 5. Evaluation parameters used in preformulation of drug**

| S.NO | Parameters | Evolution parameters |
|---|---|---|
| 1 | Physico-chemical properties | Colour, Odor, particle size and shape, crystallinity, molecular structure and weight, melting point. |
| 2 | Physico-mechanical properties | Bulk and tapped density, compressibility. |
| 3 | Solid state stability | Temperature, light, humidity, solvent, PH |
| 4 | Solid state compatibility | TLC and DRS analysis |
| 5 | Thermal analysis profile | DTA,DSC,TGA |
| 6 | Absorbance spectra | UV,IR |
| 7 | In-vitro availability properties | Rat Everted Gut Technique Dissolution and analysis of drug crystal, pellets. |
| 8 | Other properties | Hygroscopicity, volatility, optical activity, solvate formation polymorphism, crystallinity. |
| 9 | Other studies | Plasma-protein binding, ionization constant effect, compatibility of excipients in dissolution kinetic studies of solution degradation, use of radio-labeled drug |

## Conclusion

Preformulation studies influences selection of the drug candidate itself, selection of formulation components, API & drug product manufacturing processes, determination of the most appropriate container closure system, development of analytical methods, assignment of API retest periods the synthetic route of the API, toxicological strategy. Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the formulation development and evaluation process, improve public safety standards, enhance product quality, facilitate the implementation of new technologies, and facilitate policy development and regulatory decision making. Preformulation studies give directions for development of formulation in choice of drug form, excipients, composition, physical structure, helps in adjustment of pharmacokinetic and biopharmaceutical properties. This review article gives details of above studies which prove that number of pharmaceutical preparation can be formulate without preformulation studies.

## REFERENECES


Banker, G.S. and Rhodes, C.T. 2008. Modern Pharmaceutics. Revised and expanded, Marcel Dekker, Inc. Newyork, Edition 4, vol.121, 167-185.

Borka, L. 1991. Review on crystal polymorphism of substances in the European Pharmacopoeia. *Pharm. Acta Helv.* 66, 6–22.

Borka, L.; Haleblian, J.K. 1990. Crystal polymorphism of pharmaceuticals. *Acta Pharm. Jugosl.* 40, 71–94.

Brahmankar, D.M. and Jaiswal, S.B. 1995. Absorption of drugs in:. Biopharmaceutics and Pharmacokinetics A treatise. Vallabh Prakashan, Edition 1, 5-75.

Chein YW: Novel drug delivery systems. North corolina, Edition 2, revised and expanded, vol. 50: 381-528.

Giron, D. 1995. Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates. Thermochim. Acta, 248, 1–59.

Gopinath, R., 2011. Naidu RAS: pharmaceutical preformulation studies- current review. *International Journal of pharmaceutical and biological archives*, 2(5): 1391- 1400.

Hilfiker, R.; Blatter, F.; von Raumer, M. Relevance of solid-state properties for pharmaceutical products polymorphism. In the Pharmaceutical Industry; Hilfiker, R., Ed.

Jain, N.K. and Sharma, S.N. 2004. A Text book of professional pharmacy. Vallabh prakashan, Pitampura Delhi, 317-333.

Kuhnert-Brandstätter, M. 1971. Thermomicro-scopy in the Analysis of Pharmaceuticals; Pergamum Press: Oxford, UK.

Kulkarni, G. T., Gowthamarajan, B. and Suresh, B. 2004. Stability testing of pharmaceutical products-An overview. *Indian Journal of Pharmaceutical Education*, 38(4): 194-198.

Lachman, L., Lieberman, H. A. and Joseph, L. K. 1990. The Theory and Practice of Industrial Pharmacy. Varghese publishing house, Bombay, Edition 3, 171-196.

Vincent, H.K. Li, Vincent, H.K. Lee, and Robinson, J.R. 1987. Influence of drug properties and drug administration on the design of sustained and controlled release system. Controlled drug delivery fundamental and applications. Marcel Dekker, New York, Edition 2, 3-61.

Winfield, A.J. and Richards, R.M.E. 2004. Pharmaceutical practice. Churchill livingstone, Sydney Toronto, Edition 3, 247-263.


*******