SS INSTITUTE OF PHARMACY

INDUSTRIAL PHARMACY-1

UNIT-1

PREFORMULATION STUDIES

Content.....

- Introduction.
- Goals and objective of preformulation studies
- Preformulation considerations
- Application of Preformulation Considerations in the development of dosage forms.
- Impact of Preformulation considerations on Stability of dosage form.
- Conclusion

Introduction....

"*Preformulation studies are the investigations of physical and chemical properties of drug substance alone and in combination with other excipients to develop a Safe ,Effective and Stable dosage form*"

- These are the first step in the rational development of dosage forms of a drug substance.
- It is the phase of research and development of drug

Goals and objective of preformulation studies….

- To establish the physicochemical parameters of drug molecules for its stability for any desired dosage form.
- To determine the kinetic rate profile of a drug substance for drug stability
- To establish compatibility of any drug with formulation excipients for possible interactions
- Preparation of safe ,effective ,and stable dosage form with better therapeutic values

Preformulation considerations….

Preformulation studies can be divided into-

1. **Physical considerations**

- Organoleptic
- Microscopic
- Particle size and shape
- Partition coefficient
- Pka
- Solubility
- Dissolution
- Polymorphism
- Physical form(crystalline/amorphous)
- Flow properties

Preformulation considerations….

2- Chemical considerations

- Hydrolysis
- Oxidation
- Reduction
- Racemization
- Polymerisation
- Isomerisation
- Photostability

Physical Considerations…

1. *Physical form:-*

Drug may exist in **crystal** or **amorphous** form.

- ***Crystal form:-***

  It is characterized by repeated arrangements of atoms in three –dimensional (3-D) array.

- ***Amorphous form:-***

  it has atoms or molecules randomly placed and does not have any defined structure or molecular arrangement.

Physical Considerations…

2- Polymorphism:-

It is the ability of a solid material to exist in more than one form of crystal structure.

Polymorphs may divided in to two types-

- ***Enantiotropic*** **:-** Reversibly changes into another form at varying in temperature & pressure .

Example- carbamazepine ,acetozolamide .

- ***Monotropic*** **:-** Unstable at all temperature & pressure .

Example – flufenamic acid .

Physical Considerations…

3- Particle size:-

Particle diameter is also important consideration in the preformulation studies.

4- Particle shape:-

Particles may exist in various shape. Like- spherical, oval, rod-shaped etc.

Particle shape also important consideration in preformulation studies .

Physical Considerations…

5- Flow properties:-

Flow properties of material can be measured by following determinations.

- ***Angle of repose:-***

The angle of repose or the critical angle of repose, of a granular material is the steepest angle relative to the horizontal plane which a material can be piled without slumping or the surface material sliding.

[Angle of repose (ϑ)= $\tan^{-1}(2H/D)$]

- ***Carr's index(compressibility):-***

Carr's index can be calculated by formula

$$[\ C = \frac{\text{tapped density} - \text{bulk density}\ X100}{\text{tapped density}}\ ]$$

Physical Considerations…

6- Solubility profile:-

In solubility profile following parameters are considered .

- ***Partition co-efficient*:-**

"It is the ratio of drug amount dissolved in oil phase to the drug amount dissolved in aqueous phase"

Partition co-efficient (P) = $\frac{Xo}{Xw}$

- ***PKa* :-** it is also called dissociation constant .

This parameter gives information about drug ionization at any physiological PH condition . It can be calculated by-

[Henderson-Hasselbalch equation pH = pKa + log([A-]/[HA])]

- ***PH*:-** it is the measurement unit of acidity or alkalinity of any chemical compound .

Chemical Considerations…

1- Hydrolysis:-

It is the chemically breakdown reaction of any compound in the presence of water.

2- Oxidation – Reduction (Redox) reaction:-

An oxidation-reduction (redox) reaction is a type of - chemical reaction that involves-

- Oxidation is the **gain** of oxygen.
- Reduction is the **loss** of oxygen.
- Oxidation is the **loss** of hydrogen.
- Reduction is the **gain** of hydrogen.
- Oxidation is **loss** of electrons
- Reduction is **gain** of electrons

Chemical Considerations…

3- Racemization:-

It is the formation of racemic mixture from any optically active compound.

- Racemic mixture is the equimolar mixture of enantiomers and it is optically inactive.

4- polymerization:-

It is a continuous reaction between molecules , more than one monomer reacts together to form a polymer.

Application of Preformulation Considerations in the development of dosage forms……

All the considerations of preformulation studies are applicable to produce an optimized and stable dosage form of any known or new drug substance.

1. Drug–excipient compatibility study:-

Excipients are the non-pharmacological substances which are required to convert a drug into a desired dosage form.

- Excipient should be compatible with drug and should be inert, otherwise it may produce any other chemical entity by reacting with the drug.
- There are two methods for the assessment of drug-excipient compatibility.

(a)D.S.C method (digital scanning calorimeter)

(b) F.T.I.R method (fourier transform infrared spectrometer)

Application of Preformulation Considerations in the development of dosage forms……

2- Physical form:-

This is an important preformulation consideration related with the drug form, is either **crystalline** or **amorphous.**

Physical form of drug may affect –

- **Melting point**
- **Solubility**
- **Density**
- **Vapor pressure**
- **Compressibility**

For the optimization of above factors we need to study about the physical form of drug.

- ***Amorphous drugs are generally have higher solubility and less stability as compared to crystalline drug.***

Application of Preformulation Considerations in the development of dosage forms……

3- Polymorphism:-

Due to different shape of material, arrangement of atoms also differ that leads to vary in crystal energy.

Hence every shape of material possess different reactivity , that affects-

- **Chemical stability**
- **Solubility**
- **Bioavailability**
- **Melting point**

To stabilize the above factors ,we should have proper knowledge about the phenomenon of polymorphism

Application of Preformulation Considerations in the development of dosage forms……

4- Particle size :-

Particle size & size distribution affects-

- **Dissolution rate**
- **Absorption rate**
- **Content uniformity**
- **Taste**
- **Texture**
- **Color**
- **Stability**

Particle size should be optimum for every dosage form.

Application of Preformulation Considerations in the development of dosage forms……

5- Angle of repose:-

angle of repose tells about that flow properties of material. flow properties affect-

- **Production rate**
- **Uniformity of dose**
- **Efficacy of dosage form**

Angle of repose	Type of flow
<20	Excellent
20-30	Good
30-34	Passable
>40	Poor flow

Application of Preformulation Considerations in the development of dosage forms……

6- Carr's index(compressibility) :-

it is an indication about the compressibility of material, on the basis of Carr's index of powder we decide the compression methods during tablet formulation.

- **Direct compression** *(if powder material compressible)* **.**
- **Dry granulation**
- **Wet granulation**

Carr's index	Type of flow
5-15	Excellent
12-16	Good
18-21	Passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Application of Preformulation Considerations in the development of dosage forms……

7- Partition co-efficient:-

It is the measurement of **hydrophilicity** and l**ipophilicity** of any drug substance.

Hydrophilicity and lipophilicity of any drug affects its-

- **Absorption** through biological membrane
- **Solubility** in aqueous media

- If Partition co-efficient is more than one then drug is lipophilic in nature, highly lipophilic drug may cross blood brain barrier and blood-placental barrier.
- If partition co-efficient is less than one then drug is hydrophilic in nature and may easily dissolve in aqueous media.

Application of Preformulation Considerations in the development of dosage forms……

8- Pka:-

This parameter gives information about drug ionization at any physiological PH.

- By determining the **PH** and **Pka** of any drug we can easily predict the absorption rate of any drug at any PH.

9- Hydrolysis:-

H+ and **OH-** are the reactive species ,responsible for drug hydrolysis in solutions.

- Hydrolysis is mainly considered in solutions and deal with the **drug stability** during **shelf life** and its **degradation**.

Application of Preformulation Considerations in the development of dosage forms……

10- Racemization:-

Racemization may occurs due to heat or any chemical reaction , in which half of the optically active compound becomes its mirror image.

Racemization may affect-

- **Solubility**
- **Dissolution rate**
- **Absorption**
- **Bioavailability**
- **Drug-receptor interaction**
- **Pharmacological efficacy**

➢ Hence it has to be establish that racemization does not occur under the labeled conditions of storage until shelf life.

Impact of Preformulation considerations on Stability of dosage form….

Preformuation considerations affect the stability of dosage forms If they are not in optimized condition.

1-Physical form(Crystal or Amorphous):-

Crystalline form is more stable than amorphous form because crystal has arranged internal structure.

Eg:- Crystalline Penicillin-G is more stable than amorphous form.

Tablet stability may affect due to crystal packing arrangement of drug.

Impact of Preformulation considerations on Stability of dosage form…

2- Polymorphism:-

polymorphism is the phenomenon of changing in shape and size of solid material at different temperature and pressure ,so it may cause instability in the dosage form during storage.

- Polymorphs are also evaluated to be sure that they are not changing their shape and size during unit operations of formulation ,like- drying , milling etc.

Impact of Preformulation considerations on Stability of dosage form….

3- Particle size:-

Particle size reduction less than 10u causes incorporation of gas/air between particles ,this prevents water penetration between particles and reduce wetting properties of particles ,which may cause-

- **Sedimentation**
- **Creaming**
- **Cracking**

➢ Extreme size reduction increase higher surface area which may leads to-

- Polymorphic changes
- Rapid degradation when exposed to- Air, Heat, Light, Humidity ,and oxygen.

Larger particle size also cause instability in the formulations.

Impact of Preformulation considerations on Stability of dosage form….

4- Carr's Index:-

Powder material's compressibility should be optimum otherwise fragmentation may occur after formulation of tablet.

5- Hydrolysis :-

It mainly consider in preformuation study of solution.

- In the presence of water certain drug are degraded.
- Hydroxyl ions of water are strong nucleophiles
- In solution of the acidic PH(<7), H+ ions cause hydrolysis reactions.
- These degradation reactions are higher in alkaline solutions than in water.
- Hydrolysis is affected by the PH of solution , presence of buffer salts & co-solvents, complexing agents & surfactants .

Impact of Preformulation considerations on Stability of dosage form…..

6- Oxidation:-

Most common cause of drug decomposition in solutions

- It is promoted by the presence of oxygen and reaction can be initiated by the action of heat , light or trace metal ions that produce free radicals , these free radicals propagate the oxidation reaction that cause drug degradation.

7- Racemization:-

Conversion of enantiomer in its mirror image may leads to instability of drug ,because in this reaction drug's structure is changed that may propagate other reactions.

Impact of Preformulation considerations on Stability of dosage form…

8- Polymerization:-

It leads to increase in viscosity of the formulation that may cause difficulties in drug stability during storage.

Conclusion .....

Drug development is a very complex , Expensive and time consuming process and there is higher risk of failure.

- To minimize the risk of failure we have to optimize preformulation considerations.
- For optimization we should have proper knowledge about the drug's physicochemical properties

Hence preformulation study is the obligatory phase to avoid loss of time and money and to develop a Safe , Effective & Stable dosage form


THANKS