Review on Preformulation - Study of Drug

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Abstract: Preformulation phase is a critical learning time about the physicochemical properties of drug candidate; these studies are mainly dealt with the effect of change in physicochemical properties on the drug formulation prior to its development. It has significant impact on manufacturing, storage and performance of drug product so one can avoid such problem through the proper preformulation studies of drug. It mainly includes intrinsic solubility studies, derived properties of the powder, importance of partition coefficient and much more. With these studies Formulator can able to select best drug candidate for development of new bioavailable dosage form. So these article give you a brief idea about such studies which are commonly carried out by formulator companies.

Keywords: Preformulation Parameters, Solubility, Bulk Properties & Stability Studies

1. Introduction

Formulation is a process of developing drug candidate into a drug product. Initially there are no of drugs candidate but all such candidate do not have that type of physicochemical properties which eventually leads to a stable drug formulation. so in order to study these physicochemical properties of drug a concept of Preformulation was evolved in the late 1950s & early in 1960, that utilizes biopharmaceutical principle in determination of physicochemical properties of drug substance. As these studies are performed on drug candidate before the development of its dosage form hence they are also known as First learning phase studies. Preformulation studies confirms that there are number of barriers present in the process of drug development.

Properties that are mandatory for new drug entity study are
- Intrinsic solubility
- Dissociation constant (pKa)

2. Objectives of Preformulation Study

- To generate information useful to formulator
- To increase drug stability
- To reduce excipient incompatibility
- To improve drug bioavailability

3. Preformulation parameters

3.1 Solubility studies

1) pKa determination
2) Common ion effect
3) Effect of Temperature
4) Solubilization
5) Partition coefficient
6) Dissolution

3.2 Bulk Characterization

1) Crystallinity
2) Polymorphism
3) Hygroscopicity

3.3 Stability analysis

1) Solution Stability
2) Solid state stability
3) Drug-excipient compatibility

Solubility Studies

Solubility is the concentration at which solution phase is in equilibrium with given solid phase at standard temperature & pressure. Solubility has significant impact on drug dissolution which relates the in vivo absorption of drug.

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Parts of solvent required for 1 part of solute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>Less than 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>From 1 to 10</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 1 to 30</td>
</tr>
<tr>
<td>Sparingly Soluble</td>
<td>From 30 to 100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>From 100 to 1,000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>From 1,000 to 10,000</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>10,000 and above</td>
</tr>
</tbody>
</table>

pKa Determination

pKa is pH at which 50% of drug renders in ionized state and 50% in unionized state. It is given by Henderson – hasselbalch equation

For Acidic drug

\[ \text{pH} = \text{p}K_a + \log \frac{[\text{ionized drug}]}{[\text{unionized drug}]} \]

For Basic drug

\[ \text{pH} = \text{p}K_a + \log \frac{[\text{unionized drug}]}{[\text{ionized drug}]} \]

\[ \% \text{ Ionization} = \frac{10^{(\text{pH} - \text{p}K_a)}}{1+10^{(\text{pH} - \text{p}K_a)}} \]
Methods of \( pK_a \) determination
- Potentiometric titration
- UV spectroscopy
- HPLC technique
- Capillary Zone Electrophoresis
- Foaming activity

Common ion effect
Solubility of ionic drug decreases as concentration of same ionic species present in solution increases. In gastric juice Chloride ion conc is in between 0.1M to 0.15M where hydrochloride salt of drug not readily soluble.

Effect of Temperature
When temperature of a solution containing drug is heated solubility increases when process is endothermic and heat of solution is positive e.g. NaCl in water etc, But Lithium chloride and other HCl salt the process shows exothermic i.e. heat of solution is negative & hence solubility decreases. Heat of solution is determined from solubility values for saturated solution at temperature range of 5, 25, 37, and 50°C. Non electrolyte and unionize weak acid & bases show heat of fusion around 4 to 8 kcal per mol.

Solubilization
It involves the methods used to increased the solubility of drug
1) Use of cosolvents like Ethanol, Propylene glycol, glycerine etc
2) Use of Surfactant – enhances both solubility and permeability of drug
3) Supercritical fluid Recrystallization such as CO₂
4) Use of Amorphous, Anhydrates, Solvate, Metastable polymorph
5) Use of precipitation inhibitors like HPMc, PVP, PVA, PEG, etc
6) Use of salt form

Partition coefficient, \( \log P \), is ratio of unionized drug distributed between organic and aqueous phases at equilibrium. The defines hydrophilic lipophilic character of drug commonly determined by Shake flask method. It is important indicator of permeability.

\[
\log P = \left( \frac{C_{\text{oil}}}{C_{\text{water}}} \right)
\]

\( \log P \) equal to 0 means compound is equally soluble in water and partitioning solvent.\( \log P = -2 \) comp is 100 times soluble in water, i.e. it is hydrophilic log \( P \) =5, means compound is 100,000 times more soluble in partitioning solvent. Octanol-water partition coefficient is widely used as octanol contain polar head and non polar tail which resembles biological membrane component & solubility parameter of octanol is \( \delta = 10.24 \) lies midway in range of most of drugs \( (\delta = 8 - 12) \)

**Hypodiscriminating** – These solvent are more polar than octanol such as butanol and pentanol for transport across buccal membrane

**Hyperdiscriminating** – These solvent reflect transport across blood brain barrier & are less polar than octanol e.g Chloroform, cyclohexane

Lipinski Rule of Five- State that drug candidate undergoing passive diffusion will have poor absorption or permeability if drug exceed 2 or more of following
1) Log \( p \) value greater than 5
2) The molecular weight greater than 500
3) No of Hydrogen bond donor Exceed 5 (NH+OH)
4) More than 10 Hydrogen bond acceptor (N+O)

Dissolution
It helps to identify potential bioavailability problem
It is given by Noveys & Whitney Equation

\[
\frac{dC}{dt} = \frac{DA}{W} (C_s - C)
\]

Where,
D is diffusion coefficient
\( h \) is thickness of diffusion layer
A is surface area of drug
V is volume of media
\( C_s \) is saturated solution concentration
C is concentration of drug in solution
When, \( C_s >> C \), then above equation become

\[
\frac{W}{A} = kt
\]

Where, k is intrinsic dissolution rate constant expressed in mg/cm²/min

<table>
<thead>
<tr>
<th>USP Apparatus</th>
<th>Description</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Basket apparatus</td>
<td>Conventional, Chewable tablet ,CR</td>
</tr>
<tr>
<td>Type 2</td>
<td>Paddle apparatus</td>
<td>Orally disintegrating tablet , chewable tablet, CR, suspension</td>
</tr>
<tr>
<td>Type 3</td>
<td>Reciprocating cylinder</td>
<td>CR bed type pellet formulation</td>
</tr>
<tr>
<td>Type 4</td>
<td>Flow through cell</td>
<td>Poorly soluble API, Powder, granules, Implant</td>
</tr>
<tr>
<td>Type 5</td>
<td>Paddle over disc</td>
<td>Transdermal</td>
</tr>
<tr>
<td>Type 6</td>
<td>Rotating cylinder</td>
<td>Transdermal</td>
</tr>
<tr>
<td>Type 7</td>
<td>Reciprocating holder</td>
<td>Transdermal &amp; Non disintegrating CR</td>
</tr>
</tbody>
</table>

Unit of permeability is cm/sec and dissolution is mg/min

**Bulk Characterization**

**Crystallinity**
Physicochemical property of drug depend on crystal habit internal structure i.e. crystal lattice

Crystal habit means outer appearance of crystal and it is changes with change in crystal lattice & crystal lattice means molecular arrangement within the solid
Solubility order- Amorphous > Unstable > Metastable > Stable

Anhydrous compound is more water soluble than hydrous

**Amorphous** – No definite & regular geometry, do not have definite M.P. and heat of fusion, compress to some extent, irregular cleavage, pseudo solid or super cooled liquid, Isotropc refractive index, example - Lubricant, metallic glasses, polymer, gel, rubber etc.

**Crystalline** - They have definite shape and geometry, definite M.P. & heat of fusion, Non compressible, have clear cleavage, also called true solid, show Anisotropic type of R.I. Example - Diamond, quartz, snow flaker, table salt, mica

**Polymorphism**

It is ability of compound to exist in more than one crystalline form in nature they have different chemical stability and solubilities hence have direct effect on drug bioavailability and dosage form development.

Types –

1) Enantiotropic – One polymorph reversibly changed into another by varying temperature & pressure e.g. Sulphur

2) Monotropic- One polymorph form is unstable at all temp & pressure e.g. Glyceryl stearate

Transition temperature – It is temperature at which two polymorph of the compound have the identical solubility and identical vapour pressure. Van’t Hoff plot of free energy is solubility Vs temperature. During storage one form of polymorph changes to another form which ultimately changes the behavior of the drug.

**Analytical methods for characterization of solid forms**

1) Microscopy

2) Hot stage microscopy – to identify pseudopolymorphism, it is fusion technique in which silicon oil is used

3) Thermal Analysis- Primarily two methods are used Differential Scanning colorimetry’s (DSC) & Differential Thermal Analysis (DTA)

4) X-Ray diffraction- Based on Bragg’s equation used for crystalline solids only

5) IR Spectroscopy- It is based on stretching frequencies of molecule which changes with arrangement of molecule

6) Dissolution & solubility analysis

**Hygroscopicity**

Substances having tendency to adsorb water/ moisture from atmosphere are said to be those materials which adsorb moisture to such extent that they dissolve completely are called Deliquescent. The European Pharmacopoeia Technical Guide has classified hygroscopicity into 4 classes:

1) Slightly Hygroscopic - Weight increased by $\geq 0.2 \%$ w/w & $< 2 \%$ w/w

2) Hygroscopic - Weight increased by $\geq 0.2 \%$ w/w & $< 15 \%$ w/w

3) Very hygroscopic- Weight increased by $\geq 15 \%$ w/w

Change in moisture content greatly influences the chemical stability, flowability, and compactability of powder drug. So methods like gravimetry, TGA, Karl Fischer titration or gas chromatography is used to measure moisture content of drug.

**Micromeritic Properties**

**Particle Characterization**

It involves the methods used to determine particle size of the powder. Different methods are used as per the nature of dosage form, quantity of same & discussed as below

**Method**

1) Optical microscopy- 0.2 to 100 micron, involves direct measurement of particle size & measures Ferret, martin & projected area diameter based on no distribution

2) Sedimentation- 1 to 200 micron, It works on principle of Stokes law i.e. rate of settling is directly proportional to particle size. Here stokes diameter is measured (Weight distribution). Stokes law can not be used if Reynolds no is greater than 0.2 or in case of suspension concentration greater than 2 % w/v. for this purpose 10 mL of Anderson pipette is used

3) Coulter counter- 0.5 to 1000 micron, particle volume is measured and converted into particle size works on the principle of Conductivity (Volume distribution). calibration done by Polystyrene sphere

4) Laser light scattering

**Density & Porosity**

It is the derived property of powder that can be derived from particle size distribution, particle shape, and surface area. Density is the ratio of mass of powder to its volume

**True density**- Density of material itself exclusive of voids and intramolecular pores measured by displacement of Helium

**Granular density**- It is density of material inclusive of intraparticle space measured by Mercury displacement or Pycnometer

**Bulk density**- It is calculated when solid is non porous i.e. true & granular density are identical so measured by Mercury displacement or Helium densitometer. It is ratio of bulk weight to bulk volume

Light powder has low bulk density and large bulk volume whereas Heavy powder has high bulk density and small bulk volume (Bulkiness)

Bulkiness is reciprocal of bulk density

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1092
Porosity ($\varepsilon$)-
It is the ratio of void volume to bulk volume & expressed in percent
Bulk volume = True volume + Void volume
So, Void volume = Bulk volume - true volume

Flow properties
It is most important property of powder which measure cohesiveness in terms of Carr's index Hausner's ratio and angle of repose.

Carr's compressibility index = \[
\frac{\text{Tape density} - \text{Bulk density}}{\text{Tape density}} \times 100
\]
Hausnerr's ratio = \[
\frac{\text{Tape density}}{\text{Bulk density}}
\]

Angle of Repose ($\theta$) – it measure resistance to particle movement i.e. maximum angle between obtained between surface of powder and horizontal plane \[
\tan \theta = \frac{2h}{D}
\]
Where, h is the height of pile of surface & D is diameter of circle

Measurement of angle of repose
1) Static angle of repose-Fixed funnel method and fixed cone method
2) Kinetic or Dynamic angle of repose – Rotating cylinder method and Tilting box method

Table 3: Powder flow properties

<table>
<thead>
<tr>
<th>Carr’s Index</th>
<th>Hausner’s ratio</th>
<th>Angle of repose</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 15</td>
<td>1.05 - 1.18</td>
<td>25 - 30</td>
<td>Excellent</td>
</tr>
<tr>
<td>12 - 16</td>
<td>1.14 - 1.20</td>
<td>31 - 35</td>
<td>Good</td>
</tr>
<tr>
<td>18 - 21</td>
<td>1.22 - 1.26</td>
<td>36 - 45</td>
<td>Fair-passable</td>
</tr>
<tr>
<td>23 - 35</td>
<td>1.30 - 1.54</td>
<td>46 - 55</td>
<td>Poor</td>
</tr>
<tr>
<td>33 - 38</td>
<td>1.50 - 1.61</td>
<td>56 - 65</td>
<td>Very poor</td>
</tr>
<tr>
<td>&gt;40</td>
<td>&gt;1.67</td>
<td>&gt;66</td>
<td>Very, very poor</td>
</tr>
</tbody>
</table>

Stability analysis
Stability of formulation dictate shelf life of marketed product, so to achieve this preformulation is performed. Drugs degraded during storage via hydrolysis, oxidation, or photochemical reaction.

Solution Stability
In solution state decomposition occurs through
Hydrolysis- Follows second order kinetic, order of hydrolysis is Lactum > Ester > Amide > Imide e.g. Anesthetic, antibiotic, vitamins and barbiturate

Oxidation- loss of electron or addition of oxygen or removal of hydrogen or increase in valency is called oxidation. No of drugs undergoes oxidation like epinephrine, vitamins etc

Photolysis- drugs like Tetracycline, Fluoroquinolones are sensitive to light & even such drugs shows sunlight tanning as side effect

Racemization- Follows first order kinetics, optically active substances converted into optically inactive without any change in its chemical composition. Biologically levo form is more active e.g Dextro adrenaline is 10 to 15 times less potent than Levo form

Being precise & Accurate nowdays HPLC Assays are commonly used for Stability studies.

Solid state stability
Main objective of this studies is investigation of stable storage condition for drug in solid state and identification of compatible excipient. These studies are affected by purity and crystallinity of drug.

Polymorphism changes during storage are usually detected by Infra Red analysis. Surface discoloration (mainly in tablet) is measured on tristimulus or diffuse reflectance equipment which is more sensitive than HPLC assay.

If humidity is not the problem in drug stability then Arrhenius plot predict the shelf life of the formulation.

Drug-Excipient compatibility
Formulation stability is not only depend on drug but also it is affected by excipient. Excipient play important role in dosage form but side by side it also increases compatibility problem so proper selection of excipient is very important in development of formulation. Incompatibility can be result in any of following changes
1) Changes in organoleptic properties
2) Changes in dissolution performance
3) Decrease in potency
4) Increase in degradation rate

Example- Lactose shows maillard reaction with amine containing drug due to presence of 5-hydroxymethyl-2-furfuraldehyde as impurity.

4. Conclusion
Preformation studies play an important role in anticipating formulation problem, bioavailability problem and drug degradation pathways. Preformation studies gives complete idea about in vivo drug performance, stability its degradation rate, shelf life of drugs and also provide a tool to overcome such problems. It helps to select the most appropriate stable drug candidate by performing HPLC Assay testing, determination of partition coefficient, and nature of drug in ionic state, these studies eventually gives us a direction to accomplish our goal. Every multinational companies carried out such studies before the development of drug formulation.

References


Author Profile

Anand S More completed the Diploma in Pharmacy from Nanded Pharmacy College, Nanded in 2018 and Currently Pursuing the B. Pharmacy from MVP Samaj’s College of Pharmacy, Nasik, Maharashtra, India.