PHARMACEUTICAL PREFORMULATION

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Preformulation

Definition:
• It 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 an important information for formulation design or support the need for molecular modification.
• 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.
• During the early development of a new drug substance, the synthetic chemist, alone or in cooperation with specialists in other disciplines (including preformulation), may record some data which can be appropriately considered as preformulation data.

What should we know before starting the preformulation studies?
1. The properties of the drug.
2. Potency relative to the competitive products and the dosage form.
3. A literature search providing stability and decay data.
4. The proposed route of drug administration.
5. A literature search regarding the formulation approaches, bioavailability, pharmacokinetics of chemically related drugs.

Preformulation

Preliminary investigations and molecular optimization:
• Step I: the drug should be tested to determine the magnitude of each suspected problem area.
• Step II: 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.

1. Salt formation:
The dissolution rate of a salt form of a drug is generally quite different from that of the parent compound. Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve much more readily than do the respective free acids or bases. The result is a more rapid saturation of the diffusion layer surrounding the dissolving particle and the consequent more rapid diffusion of the drug to the absorption sites.

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 ionized and offer higher water solubility and dissolution rate.

2. Prodrug formation: it is the formation of a synthetic derivatives of the drug (e.g. esters or amides) that liberate the active drug in-vivo.
• Prodrug may or may not have a pharmacological activity.
• The active drug is released by acidic medium, enz 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 by 1) blockade of a key metabolic pathway or 2) change drug organs distribution.
• Prodrug formation may improve the drug stability, solubility, crystallinity, taste, odor and reduced pain on injection.
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Example:
• Erythromycin base: has a bitter taste and is rapidly hydrolyzed in stomach to inactive products.
• Erythromycin estolate (prodrug of erythromycin):
  • is inactive and tasteless. It has 4 times absorption rate.
  • It is hydrolyzed by the acid in stomach to liberate the free base which is active.
  • It is only 24% hydrolyzed to inactive products.

Steps in preformulation pharmaceutical research
1. Stability
   a. Solid State
      (1) Temperature
      (2) Light
      (3) Humidity
   b. Solution
      (1) Salts
      (2) pH
   c. Light
2. Solid State Compatibility
   a. TLC Analysis
   b. DRS Analysis
3. Physico-chemical Properties
   a. Molecular Structure and Weight
   b. Color
   c. Odor
   d. Particle size, Shape, and Crystallinity
   e. Melting Point
   f. Thermal Analysis Profile
      (1) DTA
      (2) DSC
      (3) TGA
   g. Hygroscopicity Potential
   h. Absorbance Spectra
      (1) UV
      (2) IR
1. Solubility
   (1) Water and Other Solvents
   (2) pH-Solubility Profile
   (3) Salt Forms
   (4) Complexation
   (5) Compatability
   (6) Prodrug
   (7) Effect of pH on UV Spectra
   (8) Complexation
   (9) Volatility
   a. Polymorphism Potential
   b. Solvate Formation
4. Physico-mechanical Properties
   a. Bulk and Tapped Density
   b. Compressibility
   c. Photomicrograph
5. In Vitro Availability Properties
   a. Dissolution of Drug Crystal Per se
   b. Dissolution of Pure Drug Pellet
   c. Dissolution Analysis of Pure Drug
   d. Rat Everted Gut Technique
6. Other Studies
   a. Plasma Protein Binding
   b. Effect of Compatible Excipients on Dissolution
   c. Kinetic Studies of Solution
   d. Use of Radio-labeled Drug

In this course, we will cover:
1. Organoleptic properties
2. Assay development (UV, TLC and HPLC).
3. Bulk characterization:
   • Crystallinity and polymorphism.
   • Hygroscopicity.
   • Fine particle characterization.
   • Bulk density.
   • Powder flow properties.
   • Compression properties.
   • Physical description.
4. Solubility analysis:
   • Internal solubility.
   • PKa determination.
   • Partition coefficient.
   • Dissolution.
   • Common ion effect.
5. Stability analysis:
   • Solution stability.
   • Solid state stability.

Assay development
• The first step in preformulation is to develop an analytical method for the quantitation of the drug in different media.

UV spectroscopy:
Uses of TLC:
1. Qualitative determination of mixtures of components.

3. High performance liquid chromatography (HPLC):

Steps:
1. Prepare the mobile phase.
2. Prepare the stationary phase.
3. Prepare the solute.
4. Polar solutes will be retained and eluted faster as the polarity of the mobile phase decreases and vice versa.

HPLC modes according to type of stationary phase:
1. Normal phase HPLC. (the stationary phase is silica [hydrophilic] with a non-polar mobile phase.
2. Mobile phase is usually hexane with the addition of chloroform, isopropyl alcohol, or methanol (the order of increasing the polarity).
3. Separation occurs by a process of partitioning of the solute between the stationary and mobile phases (adsorption and desorption).
4. Polar solutes will be retained and eluted faster as the polarity of the mobile phase increases and vice versa.

Reversed phase HPLC
1. The stationary phase is made lipophilic by coating the silica (derivatization). Examples: Octadecylsilane "ODS" (C18) and octylsilane (C8).
2. The mobile phase is hydrophilic such as methanol, acetonitrile, THF or mixtures to modify the polarity.
3. Polar solutes will be eluted quickly with a short retention time. Non polar solutes will be retained and eluted faster as the polarity of the mobile phase decreases and vice versa.

Preformulation
Assay development

3. High performance liquid chromatography (HPLC):

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Preformulation
Assay development

3. High performance liquid chromatography (HPLC):
**Classification of solid material:**

1. **Crystalline:** atoms in crystalline matter are arranged in regular and repeating patterns in three dimensions. E.g. metal and mineral.

2. **Amorphous:** atoms or molecules randomly placed without a regular atomic arrangement.

### Why do different crystals have different shapes and sizes?

1. **Crystallinity and polymorphism:**
   - **Change with internal structure usually alters crystal habit.**
   - Amorphous forms have higher solubility and dissolution rate than crystalline forms because they have higher thermodynamic energy. E.g. amorphous form of Novobiocin is well absorbed whereas crystalline form results in poor absorption.
   - Amorphous forms tend to revert to more stable forms upon storage, which means changing in physicochemical properties; therefore, this conversion makes them unstable during storage.
   - Amorphous forms have a characteristic temperature at which there is a major change in properties. This is called the glass transition temperature (Tg). Below Tg, the material will be brittle and is described as the glassy state; as the temperature is increased above Tg, the molecule becomes more mobile and the material is said to become rubbery. The transition temperature may be lowered by the addition of plasticizer. E.g. water.
   - Crystal habit and internal structure of a drug can affect physicochemical properties such as; bulk density, particle size, flowability and stability.

**Preformulation**

1. **Crystallinity and polymorphism:**
   - **Stoichiometric adduct (solvates):** a molecular complex that has incorporated solvent molecules into a specific site within the crystal.
   - When the incorporated solvent is water, it is called **hydrates.**
   - The compound not containing any water within its crystal structure is called **anhydrous.**
   - **Amorphous forms** are produced by rapid precipitation, lyophilization, rapid cooling of liquid melt.
   - It has higher energy, faster dissolution, lower melting point than the crystalline form of the drug.

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Preformulation

1. Crystallinity and polymorphism:
   ➢ Polymorphism
     It is the ability of the compound to crystallize as more than one distinct crystalline species with different internal lattice.
   ➢ Polymorphism: 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).

Type of polymorphs:
1) Enantiotropic: polymorphs can be interconverted below the melting point of either polymorph and the conversion is reversible at a defined temperature. e.g. sulfur.
2) Monotropic: the transition takes place in one direction (irreversible). e.g. glyceryl stearate and diamond graphite.
   • During preformulation, it is important to identify the polymorph that is stable at room temperature.

Preformulation

1. Crystallinity and polymorphism:
   Type of polymorphs:
   ✓ Chloromphenicol exist in A, B & C forms, of these B form is more stable and most preferable.
   ✓ Riboflavin has II & III forms, the III form shows 20 times more water solubility than form I.
   □ Stable polymorph: it has low free energy, low solubility and high melting point.
   □ Metastable polymorph: it is less stable with higher solubility and bioavailability and lower melting point.

Pharmaceutical applications of polymorphism

The transformation between polymorphic forms can lead to formulation problems.
For example:
• In suspension: phase transformation from unstable form to more stable polymorph can cause changes in crystal size and caking. e.g. Oxytetracycline (anthelmintic).
• In cream: crystal growth as a result of phase transformation can cause grittiness.
• In suspensions: changes in polymorphic forms could cause products with different melting characteristics (failure to melt after administration or premature melting during storage). e.g. theobroma oil “suppositories base”.

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Preformulation

1. Crystallinity and polymorphism:
   • Characterization of solids involves:
     1. Verifying the solid is the expected chemical compound.
     2. Characterization the internal structure.
     3. Describing the habit of the crystal.
     4. Determine how many polymorph may exist for the compound.
     5. Determine how stable are the metastable forms.
     6. Screening for the presence of an amorphous form.
     7. Can the metastable form be stabilized?
     8. What is the stability of each form?
     9. Will the more soluble form survive during the processing and storage?

Methods of characterization:
1. Microscopy.
2. Thermal analysis.
3. X-ray
Thermal analysis:

1. Crystallinity and polymorphism:
   - X-ray diffraction:
     - Mechanism: the orientation of crystal lattice
       pattern of peak intensities at distinct angles
       (θ)
     - When beam of non-homogenous X-ray is allowed
       X-ray beam is diffracted and it is recorded by
       a photographic plate
     - A crystalline material has its characteristic
       X-ray pattern
     - Amorphous substances have a hallow pattern
     - It is used to investigate the interaction exit:
       plus excipients in a given dosage form.

2. Melting point.
   - Examples of exothermic transition
     - crystallization and degradation.

3. Density (influence the flow properties of powders).
4. Crystal shape (influence the flow properties of powders).
5. Tablet hardness (influence the compression properties and grinding processes).

2. Hygroscopicity:
   - Many drug substances exhibit a tendency to adsorb moisture. The
     amount of moisture adsorbed by a fixed weight of anhydrous sample in
     equilibrium with the moisture in the air at a given temperature is referred
     to as equilibrium moisture content.
   - The equilibrium moisture content may influence the flow and
     compression characteristics of powders and the hardness of final tablets
     and granulation.
   - The knowledge of the rate and extent of moisture pickup of new drug
     substances permits the formulator to take appropriate corrective steps
     where problems are anticipated.
   - In general, hygroscopic compounds should be stored in a well-closed
     container, preferably with a desiccant.
   - If a granulation step is needed in tablet operation these compounds, non-
     aqueous granulating solvents should be recommended.
3. Fine particle characterization:

- Certain physical and chemical properties of drug substances are affected by the particle size distribution, including drug dissolution rate, bioavailability, content uniformity, taste, texture color, and stability.
- In addition, properties such as flow characteristics and sedimentation rates, among others, are also important factors related to particle size.
- It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and product efficacy.
- Of special interest is the effect of particle size on the drug's absorption. Particle size has been shown to significantly influence the oral absorption profiles of certain drugs as griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin.
- There are several methods available to evaluate particle size and distribution including sieving or screening, microscopy, sedimentation, and stream scanning.
- The difficulty with using sieve analysis early in the pre-formulation program is the requirement of a relatively large sample size. The main advantage of the sieve method is simplicity, both in technique and equipment requirements.

3. Stream scanning

- This technique utilizes a fluid suspension of particles which pass the sensing zone where individual particles are sized, counted, and tabulated.
- Sensing units may be based on light scattering or transmission as well as conductance.
- Two popular units in the pharmaceutical industry for this purpose are the Coulter Counter and Hiac Counter. Both units electronically size, count, and tabulate the individual particles that pass through the sensing zone data generated in a relatively short time with reasonable accuracy.
- Thousands of particles can be counted in seconds and used to determine the distribution curve.
- All stream scanning units convert the particles to effective diameter, and therefore have the shortcoming of not providing information relative to particle shape.
- Nevertheless, stream scanning methods are powerful tools and can be used for evaluation of such parameters as crystal growth in suspension formulation.

3. Sedimentation techniques

- It must be representative of the bulk of the material and be properly suspended and thoroughly dispersed in a suitable liquid phase. In order to do a quantitative determination of such parameters as crystal growth in suspension formulation.
- The difficulty with using sieve analysis early in the pre-formulation program is the requirement of a relatively large sample size. The main advantage of the sieve method is simplicity, both in technique and equipment requirements.
4. Bulk density:

**True density:** In addition to bulk density, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds.

**Experimental:** The true density is determined by suspending drug particles in solvents of various densities and in which the compound is insoluble. Wetting and pore penetration may be enhanced by the addition of a small quantity of surfactant to the solvent mixtures. After vigorous agitation, the samples are centrifuged briefly and then left to stand undisturbed until flotation or settling has reached equilibrium. The samples that remain suspended corresponds to the true density of the material.

**Significance:**
- It can affect powder flow properties.
- It affects the size of drug or product or the homogeneity of a low dose formulation in which there are large differences in drug and excipients densities.

5. Powder flow properties:

- The flow properties of powders are critical for an efficient tablet operation.
- A good flow of the powders or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets.
- Powders considered "poorly flowable" may have to be pre-compressed or pre-granulated.

During the pre-formulation evaluation of the drug substance, therefore, its flow property characteristic should be studied, especially when the anticipated dose of the drug is large.
5. Powder flow properties:
- Significances: Proper selection of the formulation ingredients
- Poor flowability is due to particles where spherical particles do not flow as freely as large particles. The material rebound (elastically recover) when the compression load released.
- Efficient mixing of the lubricant should prevent sticking (sample C).
- Usually these materials showed low crushing strength and high friability.

6. Compression properties:

<table>
<thead>
<tr>
<th>Method of characterization</th>
<th>Sample code</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blend in tumbler mixer for:</td>
<td>5 min</td>
<td>5 min</td>
<td>30 min</td>
<td></td>
</tr>
<tr>
<td>Compress 1.5mm compacts in a hydrophilic press at compression force of:</td>
<td>75 Mpa</td>
<td>75 Mpa</td>
<td>75 Mpa</td>
<td></td>
</tr>
<tr>
<td>Dwell time of:</td>
<td>2 sec</td>
<td>30 sec</td>
<td>2 sec</td>
<td></td>
</tr>
<tr>
<td>Store tablets in a sealed container at Tr to allow equilibration for:</td>
<td>24 hours</td>
<td>24 hours</td>
<td>24 hours</td>
<td></td>
</tr>
<tr>
<td>Crushing strength of tablets:</td>
<td>A N</td>
<td>B N</td>
<td>C N</td>
<td></td>
</tr>
</tbody>
</table>

7. Physical Description:
- Problems of liquid drugs
  1. Liquid drugs pose an interesting problem in the design of dosage forms or drug delivery systems. Many of the liquids are volatile substances and as such must be physically sealed from the atmosphere to prevent their loss.
  2. Another problem associated with liquid drugs is that those intended for oral administration cannot generally be formulated into tablet form; the most popular form of oral medication, without undertaking chemical modification of the drug.
- Among the few liquid medicinal agents in use today are the following:
  1. Amyl nitrite, vasodilator by inhalation.
  2. Castor oil, Mineral oil cathartic and Glycerin, cathartic in suppository form.
  3. Clofibrate, antihyperlipidemic.
  4. Dimercaptop, antidote for arsenic, gold, and mercury poisoning.
  5. Dimethylsulfoxide, analgesic in interstitial cystitis.
  7. Nitroglycerin (as tablets), anti-angina
  8. Paraldehyde, sedative-hypnotic
  9. Paramethadione, anticonvulsant
  11. Propylhexedrine, vasoconstrictor by nasal inhalation.
  12. Undecylenic acid, fungistatic agent.

Problems of liquid drugs
- Amyl nitrite, for example, is a clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is maintained for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material. When amyl nitrite is administered, the glass is broken between the fingertips and the liquid wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilatation.
- Propylhexedrine provides another example of a volatile liquid drug that must be contained in a closed system to maintain its presence. This drug is used as a nasal inhalant for its vasoconstrictor action. A cylindrical roll, of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in a suitable, generally plastic, sealed nasal inhaler. The inhaler’s cap must be securely tightened each time it is used. Even then, the inhaler maintains its effectiveness for only a limited period of time due to the volatilization of the drug.
7. Physical Description: Evaluation tests of solid drug substances

1- Purity
- Materials with unnecessary impurities should be rejected.
- Testing purity is another control parameter for comparison with subsequent batches.
- Impurity can affect:
  - Stability: metal contamination in ppm
  - Appearance: off-colour recrystallized white
  - Toxic: aromatic amines carcinogenic

- Techniques used for characterizing purity are:
  - Thin Layer Chromatography (TLC)
  - High-Pressure Liquid Chromatography (HPLC)
  - Gas Chromatography (GC)
  - Melting Point Depression

- Impurity index (II) defined as the ratio of all responses (peak areas) due to components other than the main one to the total area response.
- Homogeneity index (HI) defined as the ratio of the response (peak area) due to the main component to the total response.

2. For certain liquid drugs, especially those employed orally in large doses or applied topically, their liquid nature may be of some advantage in therapy. For example, 15-mL doses of mineral oil may be administered conveniently as such.

2. Also, the liquid nature of undecylenic acid certainly does not hinder but rather enhances its use topically in the treatment of fungus infections of the skin.

3. Advantages of liquid drugs

   a. The latent heat of fusion is the quantity of heat absorbed when 1 g of a solid melts; the molar heat of fusion (\(\Delta H_f\)) is the quantity of heat absorbed when 1 mole of a solid melts. High-melting-point substances have high heats of fusion and low-melting-point substances have low heats of fusion.

   b. These characteristics are related to the types of bonding in the specific substance.

   c. Two things are noteworthy in contributing to the extent of melting-point lowering:

      i. Evident from this relationship is the inverse proportion between the lowering of the melting point (\(\Delta T\)) and the heat of fusion. When a second ingredient is added to a compound with a low molar heat of fusion a large lowering of the melting point is observed; substances with a high molar heat of fusion will show little change in melting point with the addition of a second component.

      ii. The extent of lowering of the melting point is also related to the melting point itself. Compounds with low melting points are affected to a greater extent than compounds with high melting points upon the addition of a second component (i.e., low-melting-point, compounds will result in a greater lowering of the melting point than those with high melting points.

7. Melting Point Depression

- Where: \(\Delta T\) is the molar heat of fusion; \(T\) is the absolute equilibrium temperature, \(R\) is the melting point of pure \(A\), and \(R\) is the gas constant.
Preformulation

Solubility analysis
It focuses on drug-solvent interactions that could occur during the delivery of a drug candidate. For example, orally administered drug should be examined for solubility in simulated gastric media.

Quest
Why do we need to perform solubility analysis of a new drug?
- To provide a basis for later formulation work.
- It can affect drug performance. Drugs with an aqueous solubility less than 1% (10 mg/ml) will suffer from bioabsorption problems.

Solubility analysis includes:
- Solubility determination.
- pH determination.
- Partition coefficient.
- Dissolution behavior.
- Common ion effect.
- Membrane permeability.

Preformulation

1. Solubility
- One important goal of the pre-formulation effort is to devise a method for making solutions of the drug. A drug must possess some aqueous solubility for therapeutic efficacy. In order for a drug to enter the systemic circulation to exert a therapeutic effect, it must first be in solution. Relatively insoluble compounds often exhibit incomplete absorption.
- When a solute dissolves, the substance’s intermolecular forces of attraction must be overcome by forces of attraction between solute and solvent molecules. This involves breaking the solute-solute forces and the solvent-solvent forces to achieve the solute-solvent attraction.

Factors affecting the solubility of a drug
1. Effect of temperature
   Temperature is an important factor in determining the solubility of a drug and in preparing its solution. Most commonly, the solution process is endothermic, and thus increasing the solution temperature increases the drug solubility. For such solutes as lithium chloride and other hydrochloride salts that are ionized when dissolved, the process is exothermic such that higher temperature suppresses the solubility.

Preformulation

1. Solubility
Methods to improve drug solubility:
The methods used will depend on the chemical nature of the drug and the type of drug product under consideration.
1. The chemical modification of the drug into salt or ester forms is a technique frequently used to obtain more soluble compounds.
2. Through selection of a different solubilizing agent.
3. A pharmacist can, in certain instances, dissolve greater quantities of a solute than would otherwise be possible. For example, iodine granules are soluble in water only to the extent of 1 g in about 3000 ml of water. Using only these two agents the maximum concentration possible would be approximately 0.03% of iodine in aqueous solution. However, through the use of an aqueous solution of potassium or sodium iodide as the solvent, much larger amounts of iodine may be dissolved as the result of the formation of a water-soluble complex with the iodide salt. This reaction is taken advantage of, for example, in Iodine Topical Solution, USP, prepared to contain about 2% of iodine and 2.4% of sodium iodide.

Preformulation

1. Solubility
Factors affecting the solubility of a drug
1. Effect of temperature
2. Chemical and physical properties of both the solute and the solvent.
3. Pressure.
4. The acidity or basicity of the solution.
5. The state of subdivision of the solute and
6. The physical agitation applied to the solution during the dissolving process.

The solubility of a pure chemical substance at a given temperature and pressure is constant; however, its rate of solution, that is, the speed at which it dissolves, depends upon the particle size of the substance and the extent of agitation. The more fine the powder, the greater the surface area that comes in contact with the solvent, and the more rapid the dissolving process. Also, the greater the agitation, the more unsaturated solvent passes over the drug and the faster the formation of the solution.
### Intrinsic Methods

1. **Solubility**

   **Methods to improve drug solubility:**
   
   The methods used will depend on the chemical nature of the drug and the type of drug product under consideration.
   
   - It must be recognized, however, that if the pH of the aqueous solutions of these salts is changed by the addition of alkali, the free base may separate from solution unless it has adequate solubility in water.
   - Organic medicinals that are weak acids include the, barbiturate drugs (as phenobarbital and pentobarbital) and the sulfonamides (as sulfadiazine and sulfacetamide). These and other weak acids form water-soluble salts in basic solution and may separate from solution by a lowering of the pH.
   - Although there are no exact rules for predicting the solubility of a chemical agent in a particular liquid, experienced pharmaceutical chemists can estimate the general solubility of a chemical compound based on its molecular structure and functional groups. Perhaps the most written guideline for the prediction of solubility is that “like dissolves like,” meaning that a solvent having a chemical structure most similar to that of the intended solute will be most likely to dissolve it. Thus, organic compounds are more soluble in organic solvents than in water.

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### 2. pKa determination:

- **Interrelationship of the dissociation constant, lipid solubility, and pH at the absorption site and absorption characteristics of various drugs are the basis of the pH-partition theory.**
- **Dissociation constant or pKa is usually determined by potentiometric titration.**
- The majority of drugs today are weak organic acids or bases. Knowledge of their individual ionization or dissociation characteristics is important, because their absorption is governed to a large extent by their degrees of ionization as they are presented to the membrane barriers.
- Cell membranes are more permeable to the unionized forms of drugs than to their ionized forms, mainly because of the greater lipid solubility of the unionized forms and to the highly charged nature of the cell membrane which results in the binding or repelling of the ionized drug and thereby decreases cell penetration.
- Also, ions become hydrated through association with water molecules, resulting in larger particles than the undissociated molecule and again decreased penetrating capability.

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### Preformulation

1. **Solubility**

   **Methods to improve drug solubility:**
   
   The methods used will depend on the chemical nature of the drug and the type of drug product under consideration.
   
   - Organic compounds may, however, be somewhat water-soluble if they contain polar groups capable of forming hydrogen bonds with water. In fact, the greater the number of polar groups present, the greater will likely be the organic compound’s solubility in water. Polar groups include OH, CHO, COH, CHOCH, CH2OH, COOH, NO2, CO, NH2 and SO3H.
   - The introduction of halogen atoms into a molecule tends to decrease water-solubility because of an increase in the molecular weight of the compound without a proportional increase in polarity. An increase in the molecular weight of an organic compound without a change in polarity generally results in decreased solubility in water.

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### Preformulation

2. **pKa determination:**

- **The extent of drug ionization has an important effect on the formulation and pharmacokinetic parameters of the drug.** The extent of dissociation/ionization is, in many cases, highly dependent on the pH of the medium containing the drug. In formulation, often the vehicle is adjusted to a certain pH in order to obtain a certain level of ionization of the drug for solubility, and stability purposes. In the pharmacokinetic area, the extent of ionization of a drug is an important factor of its extent of absorption, distribution, and elimination. For the practicing pharmacist, it is important in predicting precipitation in admixtures and in the calculating of the solubility of drugs at certain pH values.
- The degree of a drug’s ionization depends both on the pH of the solution in which it is presented to the biologic membrane and on the pKa, or dissociation constant, of the drug (whether an acid or base).
- The concept of pKa is derived from the Henderson-Hasselbalch equation:

\[
\text{pH} = \text{pK}_a + \log(\text{ionized drug} / \text{unionized drug})
\]

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### Preformulation

1. **Solubility**

   **Solubility determination**
   
   - First, all factors that affect the solubility and dissolution should be defined.
   - Steps:
     1. An excess amount of the drug is dispersed in the medium and agitated at constant temperature.
     2. Samples of the slurry are withdrawn as a function of time.
     3. Samples are clarified by filtration or centrifugation.
     4. The clear samples than assayed for its drug content to establish a plateau concentration. Analysis can be done using UV, HPLC, GC, etc.

### Preformulation

Intrinsic solubility determination

1. **Solubility analysis for a new drug candidate is performed in different media such as 0.9% NaCl, 0.1M HCl, 0.1M HCl, 0.1M NaOH and buffer pH 7-4.**
2. An increased solubility in acidic media indicating basic drug.
3. An increased solubility in alkaline media indicating acidic drug.
4. An increased solubility in both media indicating an amphipathic (Zwitter ion) drug.
5. No change in solubility in both media suggesting non-ionizable, neutral molecule.
6. Intrinsic solubility for acids is measured in alkaline medium and vice versa.
7. Intrinsic solubility is performed at 5°C (to ensure good stability) and 37°C (to support biopharmaceutical evaluation).
8. Phase solubility diagrams is made to test effect of impurities on drug solubility.
3. Partition coefficient:

- The oil/water partition coefficient is a measure of a molecule’s lipophilic character; that is, its preference for the hydrophobic or lipophilic phase. The partition coefficient should be considered in developing a drug substance into a dosage form.

- If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach equilibrium at a constant temperature. The distribution of the solute (un-aggregated & un-dissociated) between the two immiscible layers can be described as follows:

- It is the ratio of the unionized drug distributed between the organic (upper) phase and aqueous (lower) phases at equilibrium.

\[ P_{o/w} = \frac{C_{\text{oil}}}{C_{\text{water}}} \]

- For an ionizable drug, the following equation is applicable:

\[ P_{o/w} = \frac{(\text{conc. of drug in oil})}{(\text{conc. of drug in water})} \]

where \( a \) equals the degree of ionization.

- The determination of the degree of ionization or \( pKa \) value of the drug substance is an important physical-chemical characteristic relative to evaluation of possible effects on absorption from various sites of administration.

3. Partition coefficient:

- The most commonly used solvent for partitioning is n-octanol because its polarity lies in the midway in the range for the majority of drugs.

- The type of solvent used depends on the solute characteristics and the ability to measure drug concentration in both solvents.

- According to the discriminating power of the partitioning solvent, they are classified as:
  1. Hyperdiscriminating: they are solvents less polar than octanol. It reflects more closely the transport across blood-brain barrier.
  2. Hypodiscriminating: they are solvents more polar than octanol. E.g., butanol. It gives values consistent with buccal absorption.

- Determination of partition coefficient:
  1. Shake flask method: the drug dissolved in one solvent is shaken with the other partitioning solvent for 30 min. The mixture allowed to stand for 5 min. The aqueous solution is centrifuged and then assayed for drug content \( (C_{\text{water}}) \).

3. Partition coefficient:

- More efficient extractions are obtained using successive small volumes of the extraction solvent (as compared to single larger volumes).

- This can be calculated as follows when the same volume of extracting solvent is used, but in divided portions. For example, the fraction \( L_n \) remaining after the \( n \)th extraction is given by:

\[ L_n = \frac{1}{(K_n + 1)^n} \]

\[ U = \frac{1}{(K_n + 1)^n} \]

EXAMPLE 1

- At 25°C and pH 6.8, the \( K \) for a second-generation cephalosporin is 0.7 between equal volumes of butanol and the fermentation broth. Calculate the \( U \), \( L_1 \), and \( L_2 \) (using the same volume divided into fourths).

The fraction of drug extracted into the upper layer \( U = 0.7(0.7 + 1) = 0.41 \)

The fraction of drug remaining in the lower layer \( L_1 = 4(0.7 + 1) = 0.59 \)

The total of the fractions in the \( U \) and \( L_1 \) \( 0.41 + 0.59 = 1 \)

- If the fermentation broth is extracted with four successive extractions accomplished by dividing the quantity of butanol used fourths, the quantity of drug remaining after the fourth extraction is

\[ L_4 = \frac{1}{(K_4 + 1)^4} = 0.525 \]

- From this, the quantity remaining after a single volume, single extraction is 0.59, but when the single volume is divided into fourths and four successive extractions are done, the quantity remaining is 0.525; therefore, more was extracted using divided portions of the extracting solvent. Inherent in this procedure is the selection of appropriate solvents, drug stability, use of salting-out additives, and environmental concerns.
4. Dissolution studies:

Factors:

The dissolution rate of a drug is determined by the rate at which the drug substance dissolves in a medium. It is influenced by factors such as the particle size, solubility, and dissolution constant. Dissolution rate data can be used to assess the bioavailability of a drug.

Dissolution principle:

As a drug particle undergoes dissolution, the drug molecules on the surface are the first to enter into solution creating a saturated layer of drug-solution which envelops the surface of the solid drug particle. This layer of solution is referred to as the diffusion layer. The drug molecules pass throughout the dissolving fluid and make contact with the biologic membranes and absorption ensues.

As the molecules of drug continue to leave the diffusion layer, the layer is replenished with dissolved drug from the surface of the drug particle and the process of absorption continues.

Factors affecting dissolution rate:

The dissolution rate of a drug is constant during dissolution is described by the Noyes-Whitney equation,

\[
\frac{dc}{dt} = \frac{D A (C_s - C)}{h V}
\]

where:
- \( D \): diffusion coefficient
- \( A \): surface area of the drug in contact with the dissolution medium
- \( C_s \): saturated solubility of the drug in the dissolution medium at exp. Temp.
- \( C \): concentration of the drug at time \( t \)
- \( h \): thickness of the diffusion layer at solid-liquid interface
- \( V \): volume of media

4. Dissolution studies:

Measurement of dissolution rate:

The dissolution rates of chemical compounds are generally determined by two methods: the constant surface method, which provides the intrinsic dissolution rate of the agent, and the constant concentration method, in which a suspension of the agent is added to a fixed amount of solvent without exact control of surface area.

Compress the powdered drug into solid compact. Dissolution study should be made using apparatus (basket) or apparatus II (paddle) USP dissolution apparatus. The amount of the drug released should be monitored with time. The dissolution rate is obtained by dividing the slope of the plot by the exposed surface area.

This method eliminates surface area and surface electrical charges as dissolution variables.

The dissolution rate obtained by this method is termed the intrinsic dissolution rate and is characteristic of each solid compound and a given solvent under the fixed experimental conditions.

The value is generally expressed as milligrams dissolved per centimeter squared per minute (mg/cm²/min).

4. Dissolution studies:

Significances:

Taking into consideration the intrinsic solubility data, dissolution studies can identify potential bioavailability problems. For example, dissolution of solvates and polymorphs can have an impact on the bioavailability and drug delivery.

It is useful in predicting probable absorption problems due to dissolution rate. In particulate dissolution, a weighed, amount of powdered sample is added to the dissolution medium in a constant agitation system. This method is frequently used to study the influence of particle size, surface area, and excipients upon the active agent.

Occasionally, an inverse relationship of particle size to dissolution is noted due to the surface properties of the drug.

Early formulation studies should include the effects of pharmaceutical ingredients on the dissolution characteristics of the drug substance.
Preformulation

5. Common ion effect:
   - The addition of a common ion reduces the solubility of the slightly soluble electrolyte.
   - This salting out (drug pitation) results from the removal of solvent molecules from the surface of the electrolyte by the hydration of the common ion.
   - Salting in: larger anions (hydrates) e.g. benzoates, salicylates can open the water molecules allowing an increase in solubility of poorly water soluble drugs.
   - Example: hydrochloride salts often exhibit lower solubility in gastric juice due to the abundance of the chloride ions.

Method of characterization:
- To explore a common ion interaction, the dissolution rate of a hydrochloride salt should be compared in different media:
  1. Water and 1.2% w/v NaCl.
  2. 0.05 M HCl and 0.9% w/v NaCl in 0.05 M HCl.

If a decrease in the dissolution rate was observed, other salts forms such as sulphates, tosylates, mesylates, … etc should be examined.

Significances:
- The choice of a suitable salt form for the proper dissolution and accordingly enhanced absorption.

Preformulation

6. Membrane permeability:
- Modern pre-formulation studies include an early assessment of passage of drug molecules across biological membranes.
- Data obtained from the basic physical-chemical studies, specifically, pKa, solubility, and dissolution rate provide an indication of absorption expectations.
- To enhance these data, a technique utilizing the “everted intestinal sac” may be used in evaluating absorption characteristics of drug substances. In this method, a piece of intestine is removed from an intact animal, everted filled with a solution of the drug substance, and the degree of passage of the drug through the membrane sac is determined. Through this method, both passive and active transport can be evaluated.
- In the latter stages of pre-formulation testing or early formulation studies, animals and man must be studied to assess the absorption efficiency, pharmacokinetic parameters and to establish possible in vitro/in vivo correlation for dissolution and bioavailability.

Solution stability (cont.)

Factors affecting degradation rates:
1. Temperature:
   Drug samples are stored at different temperatures and in each case the degradation constant is calculated.
   $$\log K = \log A - \frac{Ea}{2.303 RT}$$
   Arrhenius plot: a plot of Log K values at different temperatures against 1/T. From the plot, K at room temperature can be obtained by extrapolation and the shelf life accordingly. Moreover, the activation energy (Ea) can be obtained from the slope.

2. Effect of pH:
   Drug samples prepared under the same condition at different pHs are stored at the same temperature. Degradation rates are then calculated and plotted against the pH values. From this profile, the pHs of the minimum and maximum degradation can be determined.

3. Other factors:
   - Such as ionic strength, co-solvent, presence and absence of O2, presence of antioxidants, presence of chelating agent.

Preformulation

Stability analysis

Commercial pharmaceutical products should have a shelf life of about 5 years during which the drug content should not go below 90% and the product should look and perform as it did when first manufactured.

Drug degradation mechanisms:
- Hydrolysis (Major): It occur by water for compounds having the following bonds: lactam, lactone, ester, amide and imide. Conditions that catalyze this process are: OH-, H+ polyvalent ions, heat, light, polarity, … etc.
- Oxidation (Major): It occur by oxygen for compounds containing unsaturated bonds. Conditions that catalyze this process are: O2, oxidizing agents, polyvalent ions, heat, light, polarity, … etc.
- Photoisomerization (minor).
- Trace metal catalysis (minor).

Methods of characterization:
- Decay experiments are done at extreme pHs and temperatures.
- The degraded samples are used to confirm assay specificity as well as to provide estimates for maximum rates of degradations.

Solution stability (cont.)

Solutions stability:

Commercial pharmaceutical products should have a shelf life of about 5 years during which the drug content should not go below 90% and the product should look and perform as it did when first manufactured.

Drug degradation mechanisms:
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- Oxidation (Major): It occur by oxygen for compounds containing unsaturated bonds. Conditions that catalyze this process are: O2, oxidizing agents, polyvalent ions, heat, light, polarity, … etc.
- Photoisomerization (minor).
- Trace metal catalysis (minor).

Methods of characterization:
- Decay experiments are done at extreme pHs and temperatures.
- The degraded samples are used to confirm assay specificity as well as to provide estimates for maximum rates of degradations.

Characterization methods:
- Analytical data from TIC, fluorescence, UV, HPLC or GC may be required to precisely determine the kinetics of decay products and to establish a room temperature shelf life for drug candidate.
- Other methods:
  - Polymorphic changes: It can be detected by DSC.
  - Exipients compatibility:
    - To detect any interaction that may exist between the drug and the investigated excipients. This is helpful for the proper selection of the dosage form components.

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😊 THANK YOU
QUESTIONS ???