Drug Incompatibility

• **Definition of Drug Incompatibility:**
  Drug Incompatibility refers to interactions between two or more substances which lead to changes in chemical, physical, therapeutic properties of the pharmaceutical dosage form.

• **Types of Drug Incompatibility**
  1. Therapeutic incompatibility
  2. Physical incompatibility
  3. Chemical incompatibility

1. Therapeutic incompatibility

• **Definition of Therapeutic incompatibility**
  It is the modification of the therapeutic effect of one drug by the prior concomitant administration of another. (It is also called drug interactions)

• **Mechanisms of therapeutic incompatibility**
  They are divided into two groups:
  1. Pharmacokinetics:
     involve the effect of a drug on another from the point of view that includes absorption, distribution, metabolism and excretion.
  2. Pharmacodynamics
     are related to the pharmacological activity of the interacting drugs e.g. synergism, antagonism, altered cellular transport, effect on the receptor site.

• Pharmacokinetic interactions
  1. Altered GIT absorption
     a. Altered pH
     b. Altered bacterial flora
     c. Formation of drug chelates or complexes
     d. Drug induced mucosal damage and altered GIT motility
a. Altered pH:
The non-ionized form of a drug is more lipid soluble and more readily absorbed from GIT than the ionized form does. Therefore, these drugs must be separated by at least 2h in the time of administration of both.

b. Altered intestinal bacterial flora
EX., In 10% of patients receive digoxin…..40% or more of the administered dose is metabolized by the intestinal flora.

c. Complexation or chelation:
d. Drug-induced mucosal damage:

Antineoplastic agents  e.g., cyclophosphamide  vincristine  procarbazine  

Inhibit absorption of several drugs e.g., digoxin

e. Altered motility

e) Altered motility
Metoclopramide (antiemetic)

Increase the toxicity of cyclosporine  
Increase absorption of cyclosporine due to the increase of stomach emptying time

2. Displaced protein binding
It depends on the affinity of the drug to plasma protein. The most likely bound drugs is capable to displace others. The free drug is increased by displacement by another drug with higher affinity.

Phenytoin is a highly bound to plasma protein (90%), Tolbutamide (96%), and warfarin (99%)

Drugs that displace these agents are Aspirin  Sulfonamides  phenylbutazone

3. Altered metabolism
The effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but other organs can also do e.g., WBC, skin, lung, and GIT.
Drug Incompatibility

- CYP450 family is the major metabolizing enzyme in phase I (oxidation process).
- Therefore, the effect of drugs on the rate of metabolism of others can involve the following examples:

  - **EX1., Enzyme induction:**
    A drug may induce the enzyme that is responsible for the metabolism of another drug or even itself e.g.,
    *Carbamazepine* (antiepileptic drug) increases its own metabolism
    *Phenytoin* increases hepatic metabolism of theophylline leading to decrease its level
    Reduces its action and Vice versa
    *Note:* enzyme induction involves protein synthesis. Therefore, it needs time up to 3 weeks to reach a maximal effect

  - **EX2., Enzyme inhibition**
    It is the decrease of the rate of metabolism of a drug by another one. This will lead to the increase of the concentration of the target drug and leading to the increase of its toxicity.
    Inhibition of the enzyme may be due to the competition on its binding sites, so the onset of action is short may be within 24h.
    N.B; When an enzyme inducer (e.g. *carbamazepine*) is administered with an inhibitor (verapamil) → The effect of the inhibitor will be predominant

  - **EX., Erythromycin** inhibit metabolism of *astemazole and terfenadine*
    Increase the serum concentration of the antihistaminic agents leading to increasing the life threatening cardiotoxicity

  - **EX., Omeprazole** Inhibits oxidative metabolism of *diazepam*

  - **First-pass metabolism:**
    Oral administration increases the chance for liver and GIT metabolism of drugs leading to the loss of a part of the drug dose decreasing its action. This is more clear when such drug is an enzyme inducer or inhibitor.
    EX., *rifampin* lowers serum concentration of *verapamil* level by increase its first pass.
    Also, *rifampin* induces the hepatic metabolism of *verapamil*. 
4. **Altered renal excretion:**

   a. **Inhibition of renal tubular secretion:**
      
      - It occurs in the proximal tubules (a portion of renal tubules). The drug combines with a specific protein to pass through the proximal tubules.
      
      - When a drug has a competitive reactivity to the protein that is responsible for active transport of another drug. This will reduce such a drug excretion increasing its concentration and hence its toxicity.
      
      - **EX., Probenecid** ..... Decreases tubular secretion of *methotrexate*.

<table>
<thead>
<tr>
<th>Examples of drugs that Inhibit renal tubular secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs causing inhibition</strong></td>
</tr>
<tr>
<td>Probenecid</td>
</tr>
<tr>
<td>Sulphinpyrazone</td>
</tr>
<tr>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Sulphonamides</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Indomethacin</td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Quinidine</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Indomethacin</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
</tbody>
</table>

   b. **Alteration of urine flow and pH:**
      
      - Excretion and reabsorption (Passive tubular reabsorption) of drugs occur in the tubules by passive diffusion which is regulated by concentration and lipid solubility.

      *Note: Ionized drugs are reabsorbed lower than non-ionized ones*

      - Loop and thiazide diuretics indirectly increase proximal tubular reabsorption of \( \text{Li}^+ \) (which is handled in a similar way as \( \text{Na}^+ \)) and this can cause \( \text{Li}^+ \) toxicity in patients treated with lithium carbonate for mood disorders.

      - The effect of urinary pH on the excretion of weak acids and bases is put to use in the treatment of poisoning, but is not a cause of accidental interactions.
• **Pharmacodynamic interactions**

  It means alteration of the drug action without change in its serum concentration by pharmacokinetic factors.

  a. **Additive effect**-occurs when two or more drugs having the same effect are combined and the result is the sum of the individual effects relative to the doses used. This additive effect may be beneficial or harmful to the client.

  b. **Synergistic effect**-occurs when two or more drugs, with or without the same overt effect, are used together to yield a combined effect that has an outcome greater than the sum of the single-drugs active components alone.

  c. **Potentiation**-describes a particular type of synergistic effect—a drug interaction in which only one of two drugs exerts the action that is made greater by the presence of the second drug.

  d. **Antagonistic**-reactions have the opposite effect of synergism and result in a combined effect that is less than either active component alone. (eg. Protamine administered as an antidote to anticoagulant action of heparin)

  **EX., Propranolol + verapamit**

  **Synergism means** = 1 + 1 = 3

  **Additive means** = 1 + 1 = 2

  **Potentiation means** = 1 + 0 = 2

  **Antagonism means** = 1 + 1 = 0 or 0.5

  **Synergistic or additive effect**

  On the other hand

  **Effect at the receptor site**
  - Antiadrenergic
  - Anticholinergic

  **Examples:**
  - β-adrenoceptor antagonists diminish the effectiveness of β-receptor agonists, such as salbutamol or terbutaline.
- Many diuretics lower plasma potassium concentration, and thereby enhance some actions of digoxin and predispose to glycoside toxicity.

- Monoamine oxidase inhibitors increase the amount of norepinephrine stored in noradrenergic nerve terminals and thereby interact dangerously with drugs, such as ephedrine or tyramine that work by releasing stored norepinephrine. This can also occur with tyramine-rich foods—particularly fermented cheeses such as Camembert.

- Warfarin competes with vitamin K, preventing hepatic synthesis of various coagulation factors. If vitamin K production in the intestine is inhibited (e.g. by antibiotics), the anticoagulant action of warfarin is increased. Drugs that cause bleeding by distinct mechanisms (e.g. aspirin, which inhibits platelet thromboxane A2 biosynthesis and can damage the stomach) increase the risk of bleeding caused by warfarin.

- Sulphonamides prevent the synthesis of folic acid by bacteria and other microorganisms; trimethoprim inhibits its reduction to tetrahydrofolate. Given together the drugs have a synergistic action of value in treating Pneumocystis carinii.

- Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or indomethacin, inhibit biosynthesis of prostaglandins, including renal vasodilator/natriuretic prostaglandins (PGE2, PGI2). If administered to patients receiving treatment for hypertension, they cause a variable but sometimes marked increase in blood pressure, and if given to patients being treated with diuretics for chronic heart failure can cause salt and water retention and hence cardiac decompensation.

Note: The interaction with diuretics may involve a pharmacokinetic interaction in addition to the pharmacodynamic effect described here, because NSAIDs can compete with weak acids, including diuretics, for renal tubular secretion.

- H1-receptor antagonists, such as mepyramine, commonly cause drowsiness as an unwanted effect. This is more troublesome if such drugs are taken with alcohol, and may lead to accidents at work or on the road.
Physical Incompatibility

Physical incompatibilities are often called pharmaceutical incompatibilities. **Def:** Interaction between two or more substances which lead to change in color, odor, taste, viscosity and morphology.

- **Manifestations of physical incompatibility:**
  The following list outlines the various ways incompatibility between or among drug agents may be manifested.
  1. Insolubility of prescribed agent in vehicle
  2. Immiscibility of two or more liquids
  3. Liquification of solids mixed in a dry state (called eutexia)

1. **Insolubility:**
   The following factors affect the solubility of prescribed agent in vehicle and may render it less soluble:
   1. Change in pH
   2. Milling
   3. Surfactant
   4. Chemical reaction
   5. Complex formation
   6. Co-solvent

   Any change in previous factors may lead to precipitation of drugs and change in their properties.

**Example 1:**

<table>
<thead>
<tr>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzalkonium chloride</td>
</tr>
<tr>
<td>Sodium lauryl sulfate</td>
</tr>
</tbody>
</table>

They are not mixed together because benzalkonium chloride is positive charged while sodium lauryl sulfate has negative charge.

By mixing together a precipitate is formed.
2. Immiscibility of two or more liquids

- This manifestation appears clearly in emulsion, creams, lotions, some types of ointments.
- Separation in two phases is noticed in these pharmaceutical dosage forms.
- The following factors lead to immiscibility:
  1. Incomplete mixing
  2. Addition of surfactant with:
     - Unsuitable concentration
     - False time of addition
     - Unsuitable for the type of emulsion
  3. Presence of microorganisms
     - Some bacteria grow on constituents of mixture i.e. gelatin Arabic gum
     - Others produce enzymes which oxidize the surfactant
  4. Temperature
     Storage must be in room temperature to prevent separation

3. Liquification of solids mixed in a dry state (eutexia)

- **Def.**: it means that when two solid substances are mixed together, conversion to a liquid state take place.
- It happens through the following methods:
  1. Formation of liquid mixture: when the solid substance is soluble in another solid substance which lead to decrease of its melting point and conversion to a liquid in certain ratios.
  2. Exit of crystalline water: By mixing hydrated crystals and dry crystals, crystalline water diffuse to dry crystals.

---

**Example 2:**

```
Rx
Ephedrine sulfate
Menthol
Liquid paraffin
```

This prescription is not prescribed because ephedrine sulfate is a salt which is soluble in water but insoluble in organic solvents, oil and paraffin.
Chemical Incompatibility

- **Def.**: Reaction between two or more substances which lead to change in chemical properties of pharmaceutical dosage form.

- **Types of chemical changes**:
  1. Oxidation
  2. Hydrolysis
  3. Polymerization
  4. Isomerization
  5. Decarboxylation
  6. Absorption of CO\(_2\)
  7. Combination
  8. Formation of insoluble complexes

1. **Oxidation**:
   
   Def.: Oxidation is defined as loss of electrons or gain of oxygen

   *Auto-oxidation*: It is a reaction with oxygen of air, which occur spontaneously without other factors.

   *Pre-oxidants*: are substances catalyze oxidation process i.e. metals, some impurities.

- **Factors lead to oxidation**:
  1. Presence of oxygen
  2. Light: it can cause photo-chemical reactions: chemical reaction occur in presence of light
  3. Temperature: elevated temperature accelerate oxidation reaction
  4. PH: each drug has its ideal pH for stability. Any change in pH affect drug stability and may accelerate oxidation reaction
  5. Pharmaceutical dosage form: oxidation reaction occur in solutions faster than in solid dosage forms
  6. Presence of pre-oxidants as metals and peroxides
  7. Type of solvent used: oxidation reaction occur faster in aqueous solution than others.
  8. Presence of unsaturated bonds: as double and triple bonds (oils) which undergo easier than saturated bonds (margarine) for oxidation.
**Protection of drugs from oxidation:**

1. Addition of Antioxidants: Vitamin E, vitamin C and inorganic sulfur compounds: thiosulfate and polysulfide
2. Addition of chemicals which form complexes with metals i.e. EDTA, Benzalkonium chloride
3. Protection from light:
   a. Using of dark container
   b. Storage in dark places
   c. Packaging with substances which absorbed light i.e. Oxybenzene
4. Choice of suitable pharmaceutical dosage forms which reduce the possibility of oxidation process (solid dosage forms are better than solutions)
5. Maintenance of pH by using buffer solution
6. Choice of suitable solvent (rather than water)
7. Storage in low temperature
8. Protection from air by:
   a. Using good closed containers
   b. Replacement of oxygen by nitrogen

**Chemical groups which undergo oxidation:**

1. Phenolic compounds: Phenylephrine
2. Catechol derivatives: Adrenaline and noradrenaline
3. Some antibiotics: Tetracyclines
4. Oils (fixed and volatile)
5. Vitamins (lipid and water soluble)

**How to identify oxidation in pharmaceutical dosage form?**

1. Change of color, odor, viscosity of dosage form
2. For fixed and volatile oils: change of color, taste, odor, and viscosity

**2. Hydrolysis:**

- **Def.:** A chemical reaction in which water is used to break down a compound; this is achieved by breaking a covalent bond in the compound by inserting a water molecule across the bond
• **Types of hydrolysis:**
  1. **Ionic hydrolysis:**
      - In which the compound is broken into ions by water.
      - The covalent bond between ions of compound is broken down.
      - It is reversible Ex: Codeine phosphate $\xrightarrow{\text{H}_2\text{O}}$ Codeine + Phosphate
      - This type take place spontaneously
      - Most affected are weak bases and salts.

  2. **Molecular hydrolysis:**
      - In which the molecule it self is broken down.
      - It is slow process and irreversible.
      - It must be avoided.
      - Ex.: Acetylsalicylic acid $\xrightarrow{\text{H}_2\text{O}}$ Salicylic acid + Acetic acid
      - So there is no solutions as dosage forms for Aspirin

• **Chemical groups which undergo hydrolysis:**
  1. **Esters:**
     
        O
        \[ \xrightarrow{\text{H}_2\text{O}} \]
        R-C-OR

    Ex: Benzocaine, Procaine

  2. **Amides:**
     
        O
        \[ \xrightarrow{\text{H}_2\text{O}} \]
        R-C-NH-R

    Ex: Chloramphenicol, Sulfonamide, Procainamide

  3. **Nitriles:**
     
        (NO_3, N_2O, NO_2)

• **Factors induce hydrolysis:**
  1. Presence of water
  2. pH (Ex. Atropine: optimal pH=3.1-4.5)
  3. High temperature (Problem by autoclave i.e. procaine)
• *Protection from hydrolysis:*
  1. Protection from moisture by:
     - Packaging with substances impermeable for moisture
     - Addition of substances that absorb water (CaCO₃)
  2. Using of solvent rather than water
  3. Maintenance of pH by using buffer system
  4. Formation of complexes: which protect the drug from the effect of water
  5. Using of surfactants (micelle formation)
  6. Reducing of solubility of substance (i.e. Suspension instead of solution)

3. Polymerization:
• In polymerization, small repeating units called monomers are bonded to form a long chain polymer.

  ![Polymerization Diagram]

  - Ex:
    - Formaldehyde \[\xrightarrow{\text{Heat}}\] Paraformaldehyde (Polymer: white precipitate)
      To avoid this formaldehyde must be stored in suitable temperature and addition of methanol 15%.
    - Ampicillin in high temperature forms polymers which cause allergy.

• *Factors induce Polymerization:*
  1. Temperature
  2. Light
  3. Solvent
  4. pH
  5. Impurities
4. Isomerization:

- It means conversion of drug to its isomer
- Isomers have:
  - Identical molecular formulas.
  - A different arrangement of atoms.

- Types of isomerization:
  a. **Optical isomerization:**
     - *Conversion of optical active drug into less active*
     - *Ex:*
       a. L-Adrenaline is converted to d-adrenaline by change of pH or temperature
       b. L-adrenaline is more therapeutically active than d-adrenaline, *although they have the same physical properties but different arrangement of atoms.*
       c. *This is not general for other drugs: d-tubocurarine is more active than l-type*
     - Factors affect optical isomerization:
       1. Temperature
       2. pH
       3. Solvent
       4. Impurities
  
  b. **Geometric isomerization:**
     - One type of isomers
     - Expressed by cis or trans
     - Cis: means the groups A in the same direction: \( \overset{\text{A}}{\text{C}} \overset{\text{A}}{\text{C}} \)
     - Trans: means the group A in opposite direction: \( \overset{\text{C}}{\text{A}} \overset{\text{C}}{\text{A}} \)
     - Cis is more therapeutically active than trans (ex.: Vitamin A)

5. Decarboxylation:

- *Ex:*
  \[
  \text{NaHCO}_3 \xrightarrow{\text{Autoclaving}} \text{Na} + \text{CO}_2 \uparrow
  \]

*All drugs contain bicarbonate are not sterilized in high temperature*
- The factors that cause decarboxylation are the same as described previously.

6. \( CO_2 \) – absorption:
   - When some pharmaceutical dosage forms contain \( CO_2 \), precipitate is formed:
   - Ex:
     \[
     Ca(OH)_2 + CO_2 \rightarrow CaCO_3
     \]

7. Combination:
   - Take place when the pharmaceutical dosage form contain substances with different charges
   - Ex.: Surfactants with positive and negative charges

8. Formation of insoluble complexes:
   Ex.: Tetracycline + heavy metals