Pharmaceutical Technology
3rd Stage
College of Pharmacy

Lecture: 8
Drug Incompatibility

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Incompatibilities

- **Incompatibilities** have generally been discussed as being therapeutic, physical, or chemical. Therapeutic incompatibilities are often referred to as drug interactions.
- Physical incompatibilities are those in which the physical properties of the ingredients produce a mixture or preparation that is unacceptable in appearance or in accuracy of dosage;
- chemical incompatibilities are those in which the ingredients interact or decompose to give new compounds; these may or may not produce visible changes.
- Incompatibility is an undesirable reaction that occurs between the
  - **Drug and the solution, solvent**
  - **Drug and the container**
  - **Another drug**
  - **Drug -excipient interaction**
- Drug–drug or drug–excipient interactions can take place before the administration of a drug.
- With the decline in traditional forms of extemporaneous dispensing, this aspect of pharmaceutical incompatibility may seem to have decreased somewhat in importance, but other forms of extemporaneous preparation occur today.
- One example is the addition of drugs to intravenous fluids, a practice that should be carried out with pharmaceutical oversight to avoid incompatibilities and instabilities, particularly with new drugs and formulations and during clinical trials.
- The two types of incompatibilities are:
  - ❑ **Physical incompatibilities**
  - ❑ **Chemical incompatibilities**

Physical incompatibility

- Physical incompatibilities usually involve properties such as solubility, melting point, polymorphic forms, freezing point, dielectric constant, etc.
- Physical incompatibilities usually cause **nonuniform, unsightly, or unpalatable mixtures**, which pose the potential danger of nonuniform dosage.

Examples of physical incompatibility

1. **Incomplete solution can occur when two or more substances are combined and may not give a homogeneous product because of immiscibility or insolubility. Sometimes a change in pH or vehicle may correct it.**
    - **Addition** of high concentrations of **alcohol** to syrups or to colloidal dispersions may cause **precipitation**, such as mixing of elixirs with syrups or addition of topical clindamycin solution to isotretinoin gel result in a solvent change that affects product stability.
    - Drugs like **phenytoin, digoxin, and diazepam** are formulated in non- aqueous but water miscible solvents (alcohol-water mixture) or micellar system, addition of the formulation to water may result in precipitate depending on the final concentration of the drug and the solvent.
    - **Diazepam** injection may contain propylene glycol /alcohol/sodium benzoate / benzoic acid/benzyl alcohol. Upon dilution of the injection, both the drug and the co-solvent is diluted, precipitation will depend on the solubility of the drug in the diluted system, which mostly depends on the initial concentration of the drug in the cosolvent mixture.
    - When a drug dissolved in a **cosolvent** system is diluted with water, both the drug and cosolvent are diluted. The solubility of a drug in a cosolvent system generally increases with the percentage of cosolvent present. On dilution, the soluble drug concentration falls with a fall in the percentage of cosolvent. When the drug concentration is high, the system may become supersaturated on dilution, causing precipitation.

2. **Immiscibility occurs when a vehicle is added to a solution of something like an oil, but the oil is not soluble in the second vehicle, such as mixing concentrated hydroalcoholic solution of volatile oils (spirits) with aqueous preparations.**

- A simple example would be the addition of water to peppermint spirit, where the peppermint oil may come out of solution.

3. **Liquefaction of solid ingredients may occur with drug substances that form eutectics or crystalline hydrates that liberate their water of crystallization.**

- Some Solids of low melting p o i n t , when mixed together, the melting point be lower the solids liquefy at room temperature, like Camphor, menthol, phenol, thymol, and choral hydrate. Aspirin and phenazone For certain conditions like powders and capsules, it is advised to triturate with an adsorbent powder, such as light kaolin or light magnesium carbonate, separately before combining them.
- Some dosage forms take advantage of this phenomenon, such as **Menthol and thymol inhalation**, **Camphor and menthol ointment**, and **lidocaine and prilocaine cream**.
- The melting point of lidocaine is 68°C, and that of prilocaine is 38°C. When the dry solids are mixed together, they form eutectic mixtures and turn into a liquid.
- **A eutectic mixture** consists of two often similar materials whose melting point is below that of either individual component and is generally close to room temperature.
- In this case, the mixture of lidocaine and prilocaine forms a eutectic with a melting point reduction to 16 °C. The resulting "oil" is then used as the dispersed phase of an oil-in-water emulsion, forming a cream.

4. Precipitation can occur when a vehicle is added to a substance that is soluble in one solvent and is not soluble in the second vehicle or solvent.

- An example would be the addition of water to the compound benzoin tincture.
- Addition of high concentration of a strong electrolyte to saturated solutions of volatile oils or to tinctures or to saturated solution of a weak electrolyte can precipitate the active constituent due to salting out or the common ion effect.
- Similarly, a drug can precipitate in vivo upon administration, resulting in loss of activity

Examples:

- **Pain on injection** may be the result of **precipitation** of a drug at the site of injection brought about by either solvent dilution or by alteration in pH.
- **Precipitation** of drugs from formulations used intravenously can lead to **thromboembolism**.
- Some drugs designed to be administered by the intravenous route cannot safely be mixed with all available intravenous fluids.
  - If the solubility of a drug in a particular infusion fluid is low, crystallization may occur (sometimes very slowly) when the drug and fluid are mixed.
  - Microcrystals may be formed that are not immediately visible. When infused, these have potentially serious effects. If the rate of infusion is sufficiently slow, the precipitated drug may redissolve and so this problem is avoided. However, this is not general for all drugs

Chemical incompatibility

- Chemical instability may give rise to the formation of inactive or toxic products.
- Chemical incompatibilities generally can occur immediately upon mixing, whereas others may occur over time.
- Some of these incompatibilities are also instabilities.
- **Instability describes degradation**, including hydrolysis, oxidation, and covalent chemical reactions that may be slowed but not stopped.
- It should be noted that some incompatibilities are intentional, as in the preparation of a product called White Lotion, and others are not intentional, as in the lowering of the pH of a dissolved sodium or potassium salt of the drug with the precipitation of the free form of the drug.
- These incompatibilities may be instantaneous (precipitate, color change, effervescence) or delayed (drug stability, precipitate) and occur at such a slow rate that no visible change occurs for a time.
- These incompatibilities should not be dispensed without correction.
- Examples of chemical incompatibilities include:
    1. Oxidation
    2. Reduction
    3. Racemization
    4. Evolution of a gas
    5. Color change due to chemical change
    6. Hydrolytic changes

Chemical incompatibility

- Some sources/forms of chemical incompatibility are:
  1. pH change
  2. Chemical interaction cationic –anionic interaction
  3. Complex formation

Effect of pH

In vitro pH effects

- Salts of weak acids or weak bases will ppt. when the pH changes but this depends on the
  I. Solubility of the un-dissociated weak acid or the weak base (pHp : pH limit of solubility)
  II. The pH of the solution
  III. The pKa of the acid or the base
  IV. Buffering capacity

Coadministration of drugs with fluids other than water

- The solubility of an ionisable drug is strongly influenced by the pH of the solution because of the effect of pH on the ionisation of the drug.
- **Un dissociated** drugs cannot interact with water molecules to the same extent as ionised drugs, which are readily hydrated and therefore more soluble.
- A change of **pH** can therefore sometimes lead to precipitation of ionised drugs.

An example is Barbiturates

Barbiturates

- Solutions of barbiturates salts are very alkaline and have limit pH solubility and are incompatible with acids, acidic salts such as (ammonium bromide), and acidic syrups (lemon syrup) it will precipitate when given simultaneously.

Concentration of sodium phenobarbitone /10mL	pHp
30	7.5
60	7.9
100	8.3
200	8.6

pH and dispersed system

- Change in pH alters the gelling properties of the polymer and affects colloidal stability (physical incompatibility)
- At low pH (lower than the pKa) dispersions of anionic polymer such as Carbomer or sodium CMC lose viscosity very rapidly
- **Below pH 3** alginic acid will precipitate from dispersions of sodium alginate,
- **Strong acids** will precipitate CMC from mucilage of sodium CMC
- The gelling property of bentonite is greatly **reduced in acid media**, but **improved** by adding **alkaline** substances.
- When a dispersed (cream) is diluted with another of different pH **precipitation** and/or **degradation** of the active ingredient may occur (physical and chemical incompatibility).

Mixing drugs in I.V. fluids

- Although infusion times are generally not greater than 2 h, chemical changes following a change in pH may occur rapidly.
- pH changes often follow from the addition of a drug substance or solution to an infusion fluid. An increase or decrease in pH may then produce physical or chemical changes in the system.
- The pH of commercial available **NaCl** I.V. fluid is ~5.4 and of 5% **dextrose** water is~ 4.5
- For example, as little as 500 mg of ampicillin sodium may raise the pH of 500 cm^3 of some fluids to over 8, and carbenicillin or benzylpenicillin may raise the pH of 5% dextrose or dextrose saline to 5.6 or even higher. Both drugs are, however, stable in these conditions.
- The solubility of monobasic calcium phosphate Ca(H2PO4)2 in total parenteral nutrition (TPN) solutions is independent of the pH of the solution, since it is freely soluble in water. While dibasic calcium phosphate, CaHPO4, is pH dependent, being more soluble in acidic media.
- **TPN** solutions are, of course, clinically **acceptable** only when precipitation can be guaranteed not to occur.
- Calcium phosphate I.V solution is of low pH to ensure solubility.
- Sodium phosphate injection USP must be diluted and thoroughly mixed in a larger volume of fluid before use. Discard the I.V. admixture with precipitation immediately, Discard any I.V. admixture after 24 hours of mixing.

Cation- anion interactions

- The interaction between a large organic anion and an organic cation may result in the formation of a relatively insoluble precipitate.
  - **Gentamicin sulphate** and **heparin sulphate** groups interfere with the anticoagulant activity of heparin
  - **Cloxacillin sodium** and **ephedrine HCl**
  - The **soluble dyes** are usually sodium salts of large anions (amaranth, tartrazine) and should not be dispensed with **cationic dyes** (methylene blue, crystal violet) or with **cationic drugs** (antihistamine salts, chlorpromazine)
  - **Cationic dyes** may be ppt. by soaps and clays
  - **Ceftriaxone** is incompatible with any I.V. fluid containing **Calcium salts**, (Ringer, Ringer Lactate)

Chelation

- The term **chelation** is derived from the Greek chele meaning lobster's claw referring to the interaction between a metal atom or ion and another species known as a ligand
- **Chelation** changes the physical and chemical characteristics of both the metal ion and the ligand.
- These complexes are too large to penetrate the cell membrane, activity of the drug may be reduced
  - Act as a reservoir of drug to prolong drug release
  - Reduced irritancy and **improve stability** (Povidone iodine)
- **Tetracyclines**
  - Polyvalent cations such as Fe and Mg , Calcium , Al, and anions such as phosphate interfere with the absorption of tetracycline's
  - **Tetracycline** is responsible for *teeth discoloration or bone deformation in growing babies*
- **Chelation** of **ciprofloxacin** and other quinolones by aluminium hydroxide and calcium carbonate reduces bioavailability
- **Desferrioxamine** (as the mesylate) is used as a drug to sequester iron in iron poisoning or chronic iron overload
- **penicillamine** is similarly used to aid the elimination of **copper** in Wilson disease.

Adsorption

- **Adsorbents** generally are nonspecific (such as charcoal, cholestyramine, bentonite, kaolin, pectin,) so will adsorb nutrients, drugs and enzymes when given orally.
- If the drug remains adsorbed until the preparation reaches the general area of the absorption site, the concentration of the drug presented to the absorbing surfaces will be much reduced.
  - A delayed absorption of **lincomycin** was observed when administered with kaolin and pectinic acid (Kaopectate)
  - **Talc**, a commonly used tablet lubricant, has been reported to adsorb cyanocobalamin and consequently to interfere with intestinal absorption of this vitamin.

Adsorption of the container

- **The plastic tubes** and connections used in intravenous containers and giving sets can adsorb or absorb a number of drugs leading to significant losses in some cases.
- Those drugs which show a significant loss when exposed to plastic, in particular poly(vinyl chloride) (PVC), include *insulin, glyceryl trinitrate, diazepam, chlormethiazole, vitamin A acetate, isosorbide dinitrate and a miscellaneous group of drugs such as warfarin phenothiazines, hydralazine hydrochloride and thiopental sodium.*
- **Preservatives** such as the methyl and propyl parabens present in formulations can be sorbed into rubber and plastic membranes and closures, thus leading to decreased levels of preservative and, in the extreme, loss of preservative activity.

Correction of incompatibility

- Incompatibilities are easier to **prevent than to correct**.
- If one can recognize a potential incompatibility and correct it, then it can save time, materials, and money.
- One must be cautious to not "imagine“ incompatibilities where they **may not exist**.
- If one cannot be certain, it may be beneficial to prepare a small quantity of a preparation for observation.
- It has been generally accepted that it is unnecessary to consult the prescriber if adding official emulsifying or suspending agents or adding inert ingredients, that is, diluents, stabilizers, solvents, buffers, stiffening agents, and preservatives.
- However, one should notify the prescriber if adding materials to change the dose and adding nonofficial suspending agents, emulsifying agents, chelating agents, or other materials that may interfere with the therapeutic effectiveness.
- Also, changes that may adversely affect the stability, omission of troublesome ingredients, dispensing ingredients separately, and changing the dosage form are situations where the physician should be notified.
- General methods and techniques used to correct incompatibilities are shown in the table below

TABLE 21.4. Methods and Techniques Used to Correct Incompatibilities
Modify the mixing order
Dispense with a "Shake Well" label
Dispense with a "Store in Refrigerator" label
Complete the reaction before packaging
Protect from air, light, heat, moisture
Addition of an ingredient Suspending agent Emulsifying agent Solubilizing agent Diluent Stiffening or softening agent
Removal of an ingredient Discard inactive sediment Separate into 2 prescriptions
Change the vehicle Increase the volume→ increase dose Decrease volume→ decrease dose Change vehicle→ same dose Change an ingredient Change the dosage form

Which of the following MOST strongly influences the precipitation of salts of weak acids or weak bases when pH changes?

A. The molecular weight of the active drug
B. The pKa of the solvent
C. Solubility of the un-dissociated weak acid/base and the pH limit of solubility
D. The viscosity of the formulation
E. Temperature changes during storage

Which statement BEST describes the effect of low pH on anionic polymer dispersions?

A. Viscosity increases rapidly due to polymer expansion
B. Viscosity decreases rapidly as polymers lose ionization
C. Polymers become more soluble and prevent precipitation
D. The system becomes buffered and stabilized
E. Alginic acid becomes more ionized and remains dispersed

Which condition most favors precipitation of calcium phosphate in TPN solutions?

A. Low pH, favoring monobasic phosphate
B. High glucose concentration
C. High pH, allowing dibasic phosphate to bind to calcium
D. Addition of amino acids
E. Excess sodium ion concentration

Concomitant administration of antacids MOST significantly reduces absorption of:

A. Chloroquine
B. Amphetamine
C. Levodopa
D. Tetracyclines and other acidic antibiotics
E. Theophylline