



## Physicochemical drug interactions and incompatibilities

### Objectives:

This topic discusses the drug interactions from a physicochemical rather than a pharmacological or pharmacodynamic viewpoint.

Sometimes the interaction is beneficial and sometimes not. In reading this topic, you should appreciate that there are several causes of interactions and incompatibilities, which include:

pH effects – changes in pH which may lead to precipitation of the drug

Change of solvent characteristics on dilution, which may also cause precipitation

Cation\_ \_anion interactions in which complexes are formed

Salting-out and salting-in – the influence of salts in decreasing or increasing solubility, respectively

Chelation – in which a chelator molecule binds with a metal ion to form a complex

Ion-exchange interactions – in which ionised drugs interact with opposites charged resins

Adsorption to excipients and containers – causing loss of drug

Interactions with plastics – another source of loss of material



## Drug Incompatibility

Drug–drug or drug–excipient interactions can take place before administration of a drug.

**Incompatibility** occurs when one drug is mixed with other drugs or agents detected by the change in physical, chemical, or therapeutic qualities and produces an **unsuitable drug** for administration either because

-Modification of the effect of the active drug such as increase in toxicity, or inactivation (affect the safety, efficacy)

-Or because of some physical change such as decrease in solubility (affect appearance of a medicine) or the precipitation of the drug from solution, may lead loss of potency or instability.



## ◆ Types of Incompatibility

**Incompatibility is an undesirable reaction that occurs between the :**

Drug and the solution, solvent
Drug and the container
Another drug. (Drug –drug interactions)
Drug -excipient interaction

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 which 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 Result in decrease in solubility (precipitation), Loss of potency,
- Chemical Result in Chemical instability, complexation. They can occur even in the solid state under some circumstances.

## ◆ Physical Incompatibility

### **Solubility**

### **Precipitation of drugs in vitro**

**Example 1.** When mixing concentrated hydroalcoholic solution of volatile oils (spirits) or aromatic waters with aqueous preparations

- The spirit or aromatic water must be added gradually to prevent sudden change in solvent.

**Example 2** Addition of high concentration of a strong electrolyte

to saturated solutions of volatile oils
to tinctures or fluid extracts of slightly soluble active constituents
to colloidal dispersion
to saturated solution of a weak electrolyte

**Example 3** Addition of high concentration of alcohol to syrups or to colloidal dispersions may cause precipitation (examples: mixing of elixirs with syrups , addition of topical clindamycin solution to isotretinoin gel, etc. )



### Precipitation of drugs in vivo

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.

-If the rate of infusion is sufficiently slow, precipitated drug may redissolve and so this problem is avoided.

Drugs like phenytoin, digoxin and diazepam are formulated in non- aqueous but water miscible solvent (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, ppt. will depend on the solubility of the drug in the diluted system, which mostly depend on the initial concentration of the drug in co-solvent mixture.

When a drug dissolved in a cosolvent system is diluted with water, both 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.

### Eutectic Mixture

Some Solids of low melting 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                                |

### Some dosage forms are unaffected by this phenomenon such as:

- |                                |
|--------------------------------|
| -Menthol and thymol inhalation |
| -Camphor and menthol ointment  |

-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.

**Note**

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, crystallisation may occur (sometimes very slowly) when the drug and fluid are mixed.

Microcrystals may be formed which are not immediately visible. When infused, these have potentially serious effects.

**◇ Chemical incompatibility**

Chemical instability may give rise to the formation of inactive or toxic products.

**This type of chemical incompatibility is generally caused by:**

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 :

1-Solubility of the un-dissociated weak acid or the weak base ( $pH_p$ : pH limit of solubility)
2-The pH of the solution
3-The $pK_a$ of the acid or the base
4-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.

Undissociated 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.

**A. Solanaceous alkaloids.**

-Atropine solubility is 1 g in 400mL. Belladonna tincture contains 0.3mg alkaloids /1mL so the maximum volume of water required to dissolve 0.3mg of alkaloids is :

$$\frac{1000mg}{400ml} = \frac{0.3mg}{X} \quad X = 0.12ml$$

-Therefore, there is no risk of ppt. in alkaline conditions when given with soda drink

**B. 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**

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

**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<sup>3</sup> 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.

Chemical instability may give rise to the formation of inactive or toxic products. This increase or decrease in pH may then produce physical or chemical changes in the system.

The titratable acidity or alkalinity of a system may be more important than pH itself in determining compatibility and stability.

The solubility of calcium and phosphate in total parenteral nutrition (TPN) solutions independent on the pH of the solution. TPN solutions are, of course, clinically acceptable only when precipitation can be guaranteed not to occur.

Dibasic Calcium Phosphate	Monobasic Calcium Phosphate
CaHPO <sub>4</sub> (pKa =7.2)	Ca(H <sub>2</sub> PO <sub>4</sub> ) <sub>2</sub>
Solubility 0.03%w/v at pH 7.4 (60%)	Solubility 1.8%w/v in acidic media < pH 5 (90%)

At low pH the monobasic form predominates, while at higher pH values (physiological pH) the dibasic form becomes available to bind with calcium and precipitates tend to form.

Calcium phosphate I.V solution is of low pH
Discard I.V. admixture with precipitation immediately,
Discard any I.V. admixture after 24hr of mixing

### ◆ In vivo pH effects

Gastric pH is 1-3 in normal subjects, this pH has a marked influence on the absorption and thus on the activity of drugs. Ingestion of antacids, food, and weak electrolytes will all change the pH of the stomach. Weakly acidic drugs, being unionised in the stomach, will be absorbed from the stomach by passive diffusion.

One might expect, therefore, that concomitant antacid therapy would delay or partially prevent absorption of certain acidic drugs. The main mechanism would be an increase in pH of the stomach, increasing ionisation of the drug and reducing absorption.





Drugs whose absorption may be affected by antacid administration	
Drug whose activity would be reduced	Drug whose activity would be potentiated
Tetracyclines	Chloroquine
Nalidixic acid	Theophylline
Nitrofurantoin	Mecamylamine
Benzylpenicillin	Amphetamine
Sulphonamides	Levodopa

-Levodopa is metabolised within the gastrointestinal tract and more rapidly degraded in the stomach than in the intestine, so the rate at which the drug is emptied from the stomach can affect its availability.

-The use of cimetidine, ranitidine, nizatidine, famotidine and other H<sub>2</sub> antagonists' drugs inhibit gastric acid secretion, so increase in absorption of acid-labile drugs is predictable.

-The aqueous solubility of tetracycline at pH 1-3 is a hundred-fold greater than at pH 5-6. Co administration with sodium bicarbonate will decrease the solubility of tetracycline.

-Increasing the pH of the stomach increasing ionization of acidic drugs (Tetracycline, Nalidixic acid, Nitrofurantoin, Benzyl penicillin, sulphonamides) thus reducing absorption

### ◆ 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.



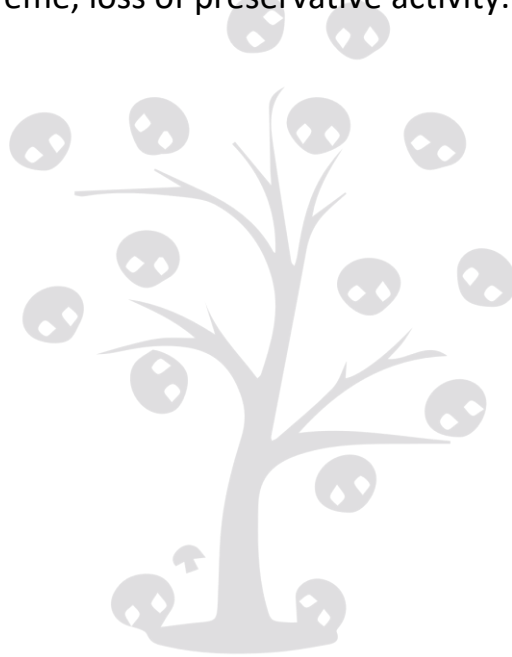


### Adsorption of the container

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.



## Pharmacy Drug