

CHAPTER- 2 INCOMPATIBILITIES

Syllabus:

Definitions, study of types of incompatibilities – Physical, Chemical and Therapeutic

Inorganic incompatibilities involving metals and their salts, non-metals, acids and alkalis

Organic incompatibilities involving metals and their salts, purine bases, alkaloids, pyrazolone derivatives, amino acids, quaternary ammonium compounds, carbohydrates, glycosides, sulfonamides, local anaesthetics, dyes, surface active agents and vitamins.

Study of examples of prescriptions containing incompatibilities and their correction and dispensing methods.

Definition of incompatibility

When two or more ingredients of a prescription are mixed together, the undesired change that may take place in the physical, chemical or therapeutic properties of the medicament is termed as *incompatibility*.

Classification

Incompatibilities are of three types:

1. Physical incompatibility
2. Chemical incompatibility
3. Therapeutic incompatibility

PHYSICO-CHEMICAL INCOMPATIBILITIES

Physical incompatibilities: Where the incompatibility is caused by immiscibility, solubility or liquefaction or solubilization.

Chemical incompatibilities: Where incompatibility is due to a chemical reaction or complexation.

PHYSICAL INCOMPATIBILITY

It may cause unsightly, non-uniform products from which removal of an accurate dose is very difficult.

Immiscibility

1. **Problem:** Oils are immiscible with water.

Remedy: Emulsification or solubilization.

e.g. *Preparation of castor oil emulsion.*

Castor oil is not soluble in water. Hence, a third agent (gum acacia) is added to prepare a stable emulsion. This third agent is called emulsifier.

e.g. *Preparation of cresol soap solution*

Soap in high concentration in water forms micelles. The overall preparation is transparent.

e.g. *Oil-soluble vitamins A, D are solubilized by polysorbates (non-ionic surfactants)*

2. **Problem:** Concentrated hydroalcoholic solutions of volatile oils, such as spirits (e.g. lemon spirits) and concentrated aromatic water (e.g. concentrated cinnamon water), when used as adjunct (i.e. additive), e.g. as flavoring agents in aqueous preparations.

Consequence: Large globules of oils separate out.

Remedy:

- (i) The hydroalcoholic solution should be gradually diluted with the vehicle before mixing with the remaining ingredients.
- (ii) The hydroalcoholic solution should be poured slowly into the vehicle with constant stirring.
- (iii) Addition of high concentrations of electrolytes (e.g. salts) in which the vehicle is a saturated aqueous solution of a volatile oil.

Consequence: Oil separates and collects as an unsightly (looking bad) surface layer.

e.g. *Potassium Citrate Mixture B.P.C.*

Potassium citrate ← (electrolyte)

Citric acid

Lemon spirit

Syrup

Chloroform water D.S.

Water

** Quillaia Tincture 1%

When the lemon spirit, used for flavoring, is added the lemon oil is thrown out of the solution, partly by the change of solvent and partly by the salting out effect of the high concentration of soluble salt (potassium citrate).

To prevent separation of this oil as surface layer quillaia tincture is included as an emulsifier.

Insolubility

1. **Problem:** *Liquid preparations containing diffusible solids.*

Consequence: Indiffusible solids will produce suspensions those will settle quickly, from which uniform doses cannot be poured out.

Remedy: A thickening agent is necessary to increase the viscosity and reduce the rate of settling of particles.

Indiffusible solids

e.g. chalk, aromatic chalk powder, succinyl sulfathiazole and sulphadimidine (in mixture)

e.g. calamine and zinc-oxide (in lotion)

Thickening agents e.g. gum acacia, gum tragacanth, methylcellulose etc.

2. **Problem:** *Wetting problem with insoluble powders.*

Some insoluble powders like sulphur and certain corticosteroids and antibiotics are difficult to wet with water.

Consequence: When water is added to this powders a slowly dispersing foam is formed on shaking. This foam is stabilized by fine solid particles.

Remedy: Wetting agents like saponins or polysorbates are incorporated.

Preparation	Wetting agents used
Sulphur containing lotion	Saponin
Corticosteroid injections	Polysorbate
Antibiotic injections	Polysorbate

3. **Problem:** *Claying of suspensions.*

When large amount of wetting agents are used, a deflocculated suspension will be produced where all he particles will settle individually and will produce tightly packed sediment. This is called 'claying'.

Consequence: This tightly packed suspension is difficult to redisperse upon shaking.

Remedy: Reducing the amount of wetting agent will solve the problem. It will form smaller agglomerates of particles that will settle quickly but will be easily redispersed upon shaking.

4. **Problem:** When a resinous tincture is added to water the water insoluble resin agglomerates forming indiffusible clots.

Remedy: The undiluted tincture is added slowly to a diluted dispersion of a protective colloid with vigorous stirring.

e.g. Preparation containing either Compound Benzoin tincture
Benzoin Tincture
Lobelia Ethereal Tincture
Myrrh Tincture
Tolu Tincture

When these tinctures are diluted with aqueous vehicle the resins precipitate and adheres to the side of the container and forms non-dispersable clots in the liquid. To prevent this the tincture is mixed in a slow stream into the centre of Tragacanth Suspension and stirring rapidly.]

The hydrocolloids (acacia, tragacanth, and starch) are adsorbed over the surface of the resin particles and confer hydrophilic properties and prevent aggregation into clots.

4. **Problem:** Dispersions of hydrophilic colloids such as acacia or tragacanth mucilage are precipitated by high concentrations of alcohols or salts.

Remedy: Alcohols or salts are well diluted in the vehicle and then the electrolyte or alcohol solution is added slowly into mucilage (hydrophilic colloid) with constant stirring to avoid local high concentration that might neutralize the effect of the protective colloid.

e.g. *Lobelia and Stramonium Mixture, Compound B.P.C.*

Lobelia Ethereal Tincture	_____	Resin solutions
Stramonium Tincture	_____	
Tragacanth Mucilage	_____	Hydrophilic colloid
Potassium iodide	_____	Electrolyte
Chloroform Water D.S.	_____	Vehicle
Water	_____	

Method – I

1. Half of the vehicle + Tragacanth power

- Triturated in a mortar and pestle.
- Tragacanth mucilage is formed.
- 2. Tincture is poured slowly into the centre of the mucilage with constant stirring.
- 3. Dissolve the electrolyte into half of the remaining vehicle.
 - Added slowly and stirred to prevent local concentration.
- 4. The remaining vehicle is added to make up the volume.

Liquefaction

When certain low melting point solids are powdered (triturated in a mortar & pestle) together, a liquid or soft mass is produced due to lowering of melting point of the mixture to below room temperature.

The medicaments those exhibits this behaviours are:

- (i) any pair among the following compounds:
 - camphor, menthol, phenol, thymol, chloral hydrate.
- (ii) Sodium salicylate and phenazone
- (iii) Aspirin and phenazone

Method-I

If menthol and thymol are required to be dispensed as powder, they are triturated in a mortar to form the liquid mixture. The the liquid is triturated with enough adsorbent powder e.g. light kaolin or light magnesium carbonate to give a free flowing product.

N.B. Kaolin and magnesium carbonate are efficient absorbent and the light category of the powder has a very large specific surface area.

Method-II

If the final bulk volume of powder is very small then menthol and thymol are triturated separately with small amount of adsorbent powder. Then the two powders are combined lightly and packing the resultant powder in capsules.

The absorbent powders coat the particles and prevent contact between the medicaments and absorb any liquid that may be produced while triturating.

CHEMICAL INCOMPTIBILITIES

Classification of chemical incompatibilities:

- (i) Inorganic incompatibilities
- (ii) Organic incompatibilities

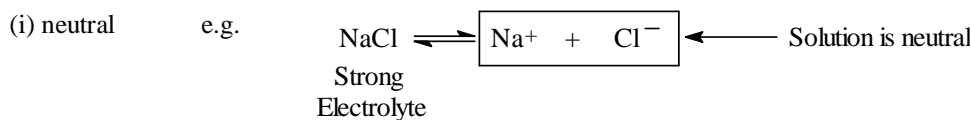
INORGANIC INCOMPATIBILITY

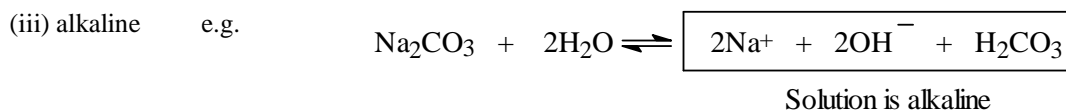
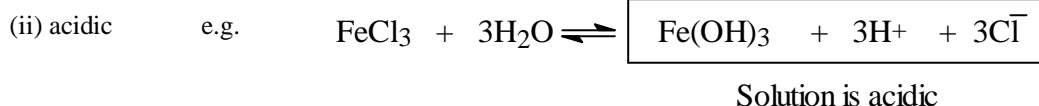
General Solubility Principles:

<i>SALTS OF</i>			
Sodium, Na ⁺ . Potassium, K ⁺ . Ammonium, NH ₄ ⁺ .	Common Anions	⇒	SOLUBLE IN WATER
Chloride, Cl ⁻ . Acetate, CH ₃ COO ⁻ . Chlorate, ClO ₃ ⁻ . Nitrate, NO ₃ ⁻ .	Cations of common metals	⇒	SOLUBLE IN WATER
Phosphate, PO ₄ ³⁻ . Carbonates, CO ₃ ²⁻ . Sulphide, S ²⁻ . Hydroxide, OH ⁻ .	Na ⁺ . K ⁺ . NH ₄ ⁺ .	⇒	SOLUBLE IN WATER
Phosphate, PO ₄ ³⁻ . Carbonates, CO ₃ ²⁻ . Sulphide, S ²⁻ . Hydroxide, OH ⁻ .	Cations except Na ⁺ , K ⁺ , NH ₄ ⁺ .	⇒	INSOLUBLE IN WATER

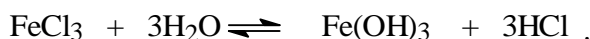
Hydrolysis

Salts may hydrolyze to form solutions which may be:





After hydrolysis the weak base or the weak acid may precipitate out if the amount of the solute is more than its solubility. Hydrolysis occurs to an appreciable extent when one of the products of hydrolysis is insoluble or volatile.



WHY hydrolysis occurs to an appreciable extent when one of the products of hydrolysis is insoluble or volatile?

Classification of inorganic incompatibilities:

(i) Metals and their salts:

<i>Group IA:</i>	Sodium (Na),	Potassium(K) and	Ammonium(NH ₄) salts.
<i>Group IB:</i>	Copper (Cu),	Silver(Ag),	Gold(Au).
<i>Group IIA:</i>	Magnesium (Mg),	Calcium (Ca),	Barium (Ba)
<i>Group IIB:</i>	Zinc (Zn),	Mercury (Hg)	
<i>Group IIIA:</i>	Aluminium(Al)		
<i>Group IVA:</i>	Tin (Sn),	Lead (Pb)	
<i>Group IVB:</i>	Titanium (Ti),	Zirconium (Zi)	
<i>Group VA:</i>	Arsenic (As),	Antimony (Sb),	Bismuth (Bi)
<i>Group VII B:</i>	Manganese (Mn)		
<i>Group VIII:</i>	Iron (Fe)		

(ii) Non-metals :

Carbon (C),	Sulphur (S),	Iodine (I)
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(iii) Incompatibilities of acids

Strong acids,	Weak acids,	Oxidizing acids and	Reducing acids
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Incompatibilities of Metals and their Salts

GROUP – I Alkali Metal Group [Na, K, NH₄]

Incompatibilities: All the common salts of sodium are soluble in water.
 Many sodium salts are soluble in glycerin.
 Sodium salts are nearly insoluble in **alcohol**.
 The anionic part of a sodium salt may be precipitated from solution by other metals

Sodium

Sodium bicarbonate (NaHCO₃) and Sodium perborate have lowest water solubility among the sodium salts.

Sodium salt	Solubility in water
Sodium bicarbonate	1 in 10
Sodium perborate	1 in 40

So these two sodium salts may precipitate if Na⁺, HCO₃⁻ or perborate ions remain in concentrations above their solubilities in a solution.

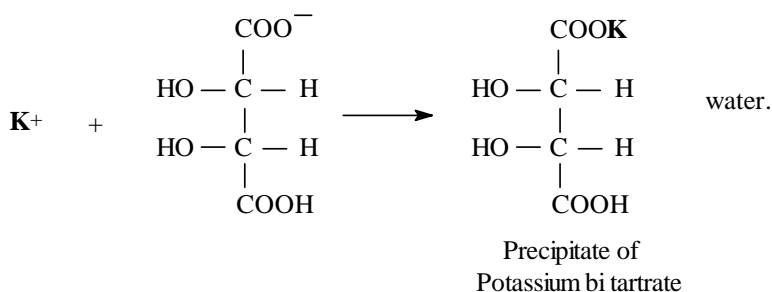
Example:

A prescription contains sodium salicylate and potassium bicarbonate.

Incompatibility: Sodium bicarbonate will be formed and precipitated. The solution will darken on standing due to the presence of salicylates in alkaline solution.

Potassium

Practically all potassium salts are soluble in water. Only potassium bitartrate (solubility 1 in 165 in water), form precipitates.



Example:

Potassium salts with acidic bitartrate solution

Incompatibility:

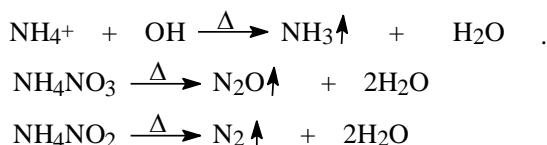
Potassium bitartrate will be formed which may precipitate.

Ammonium

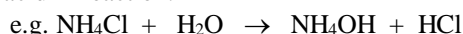
Ammonium salts are ammonium chloride (NH₄Cl), ammonium nitrate (NH₄NO₃), ammonium nitrite (NH₄NO₂).

Incompatibilities:

1. Ammonium salts will form a white precipitate with tartaric acid.
2. In presence of alkalis ammonium salts liberates ammonia.



3. Ammonium salts are strong acids are acid in reaction.



NH₄OH is a weak alkali while HCl is a strong acid hence in the solution number of H⁺ ion will exceed the number of OH⁻ ion i.e. the solution will have an acidic pH.

GROUP – IB Coinage Metal Group

Copper

Salts: Cupric acetate [Cu(CH₃COO)₂],
 Cupric nitrate [Cu(NO₃)₂]
 Cupric sulfate [CuSO₄],
 Cupric chloride [CuCl₂]

} are soluble in water.

Incompatibilities:

1. Soluble copper salts give precipitates with solutions of tannic acid, arsenates, arsenites, alkalis, carbonates and phosphates
2. Soluble copper salts + alkali hydroxide → precipitate of cupric hydroxide [Cu(OH)₂]
 This precipitation can be prevented by organic hydroxy compounds like glycerin, tartrates, citrates.
3. Cupric salts (in solution) + Iodides → Precipitation of cuprous iodide + Iodine
 e.g. $2\text{CuSO}_4 + 4\text{KI} \rightarrow \text{Cu}_2\text{I}_2\downarrow + \text{I}_2 + \text{K}_2\text{SO}_4$.
4. Cupric salts (in alkaline solution) + reducing agents (like glucose) → Cuprous oxide (Cu₂O)
 $\text{Cu}^{++} + \text{Glucose} + \text{OH}^- \rightarrow \text{Cu}_2\text{O}\downarrow$

Silver

Salts

Silver nitrate [AgNO ₃]	SOLUBLE IN WATER
Silver chlorate [AgClO ₃]	
Silver acetate [CH ₃ COOAg]	SLIGHTLY SOLUBLE IN WATER
Silver sulfate [Ag ₂ SO ₄]	
Silver chloride [AgCl]	
Silver bromide [AgBr]	
Silver iodide [AgI]	
Silver arsenate	PRACTICALLY INSOLUBLE IN WATER
Silver arsenite	
Silver borate	
Silver carbonate [AgCO ₃]	
Silver phosphate	

Incompatibilities:

1. Many silver salts are decomposed by light with the formation of metallic silver.
2. Silver nitrate [AgNO₃] + Organic compounds → Metallic silver (Ag)
 When applied on the skin silver nitrate is reduced by some organic compound of the skin to form metallic silver, which is black. This silver causes the black stain on the skin.
 $\text{Ag}^+ + \text{e}^- \rightarrow \text{Ag}$

3.

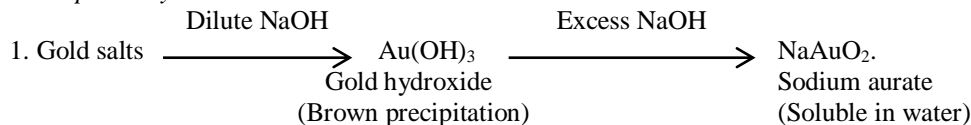
Silver salt solution	Tannic acid	Precipitate of silver tannate
	Sulphides (H ₂ S)	Precipitate of silver sulphide [Ag ₂ S]
	Alkaloids	Precipitate
	Proteins	Precipitate

Gold (Au)

Gold salts are unstable. They are reduced to metallic gold by even the weakest reducing agents such as organic matter or heat alone.

Gold salts: Gold tribromide
 Gold sodium thiomalate
 Gold sodium thiosulfate
 Used as antiarthritic agents.

Incompatibility:



2. Gold tribromide in aqueous solution \rightarrow Au + Br₂.

3. Gold sodium thiomalate
 Gold sodium thiosulfate } Both salts are soluble in water
 Both are practically insoluble in alcohol and other organic solvents.

4. Gold sodium thiosulfate darkens on exposure to air or light.

5. Gold-Au198 injection is a colloidal (red color) solution of radioactive gold. It is stabilized by the addition of gelatin and reducing agent.

GROUP-IIA (Alkaline earth group)

SALTS OF		
Mg ⁺⁺ Ca ⁺⁺ Ba ⁺⁺	Halides, Cl ⁻ , Br ⁻ , I ⁻ . Nitrates NO ₃ ⁻ .	Soluble in water. They are deliquescent. So they should be dispensed with suitable absorbents.
Mg ⁺⁺ Ca ⁺⁺ Ba ⁺⁺	Carbonate, Bicarbonate, Sulfates, Phosphates, Hydroxides, Borates, Oxalates, Arsenates	Insoluble in water

Magnesium (Mg)

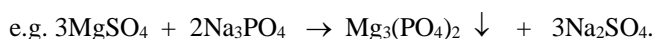
Salts: Magnesium trisilicate (Mg₂Si₃O₈),
 Magnesium sulfate (MgSO₄),
 Magnesium oxide (MgO)

Incompatibilities:

1. *Magnesium sulfate*

MgSO₄ is highly soluble in water.

Solution of	Solution of	Precipitation of
MgSO ₄ .	Phosphates	Magnesium phosphate, Mg ₃ (PO ₄) ₃ .
	Carbonates	Magnesium carbonate, MgCO ₃ .
	Hydroxides	Magnesium hydroxide, Mg(OH) ₂ .
	Silicates	Magnesium silicate



2. *Magnesium oxide (MgO)*

(a) MgO absorbs moisture and CO₂. It forms a cement-like mass with small amount of water.

Incompatibility: MgO in capsules sometimes causes the content to fuse into a hard insoluble mass.

(b) MgO is basic in nature. In solution it gives a pH ~ 10. Its alkalinity may cause destruction of certain drugs e.g. aspirin and prednisolone.

(c) Liquid preparation containing sodium bicarbonate and magnesium oxide produces caking that cannot be broken by shaking the bottle.

\rightarrow MgO is first hydrated and forms Mg(OH)₂.

\rightarrow Mg(OH)₂ slowly reacts with NaHCO₃.

\rightarrow Forms basic magnesium carbonate [Mg₂(OH)₂CO₃] which is a cement-like crystalline mass.

Light MgO is more reactive than **heavy MgO** because light MgO has smaller particle size.

Calcium

Calcium compounds are sparingly soluble or insoluble in water.
are soluble in acids (except CaSO₄)

Incompatibilities

Ca	Hydroxide Citrate Arsenate Carbonate Oxalate Tartrate Phosphate	⇒	Precipitate in aqueous solution but remain soluble in acid.
Ca	Sulfate	⇒	In high concentration these salts precipitate. In very low concentration these salts are soluble.

Incompatibilities

- Calcium hydroxide [Ca(OH)₂] is soluble in water
is soluble in syrup forming soluble sugar compounds sucrose.
is soluble in glycerin.
is insoluble in alcohol.
- Soluble calcium salts reacts with free fatty acids to form precipitates of Ca salt of fatty acids.
Ca⁺⁺ + RCOOH → (RCOO)₂Ca. ↓

Calcium chloride (CaCl₂)

CaCl₂ is deliquescent (i.e. it absorbs moisture and gets dissolved in it.)

Calcium bromide (CaBr₂)

- CaBr₂ + Sodium citrate → Ca-citrate ↓
- CaBr₂ + Sodium salicylate → Ca-salicylate ↓
- CaBr₂ + Sodium carbonate → Ca-carbonate ↓

Remedy: Replace CaBr₂ with NaBr.

Barium (Ba)

Barium sulfate (BaSO₄)

It is very less soluble in water and forms suspension.

BaSO₄ is used in diagnostic purpose.

N.B. Soluble barium salts are extremely toxic.

Soluble barium salts	Soluble salts of	Precipitate of
BaCl ₂ .	Sulfates	BaSO ₄ .
	Carbonates	BaCO ₃ .
BaI ₂ .	Tartrates	Barium tartrate
	Oxalates	Barium oxalate
	Phosphates	Barium phosphate
	Tannic acid	Barium tannate

GROUP-IIB (Zn, Hg)

Zinc (Zn)

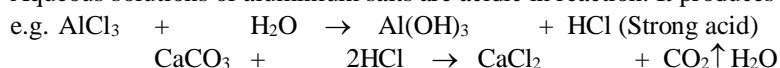
Soluble zinc salts	Insoluble zinc salts
Zinc chloride, ZnCl ₂ .	Zinc hydroxide, Zn(OH) ₂ .
Zinc nitrate, Zn(NO ₃) ₂ .	Zinc carbonate, ZnCO ₃ .
Zinc sulfate, ZnSO ₄ .	Zinc phosphate, Zn(PO ₄) ₃ .
Zinc acetate, Zn(CH ₃ COO) ₂ .	Zinc sulphide, ZnS.

Incompatibilities

1. Zinc salt + Sulfurated potash → ZnS ↓ (Zinc sulfide)
This incompatibility can be an advantage also in the preparation of lotion of zinc sulfide.
2. Solution of zinc salts undergo partial hydrolysis
ZnCl₂ + H₂O → Zn(OH)Cl ↓ + HCl

Incompatibility

1. Aqueous solutions of aluminium salts are acidic in reaction. It produces effervescence with any carbonate salts.



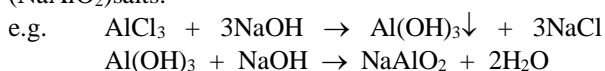
2.

Soluble aluminium salts	Soluble organic salts	Precipitates insoluble salts or complexes
$AlCl_3, Al_2(SO_4)_3$.	Penicillin Sulfonamide	Aluminium penicillin Aluminium sulfonamide Aluminium-penicillin-sulfonamide

3.

Auminium ions (Al^{3+})	NaOH, KOH Na ₂ CO ₃ , Borax ($Na_2B_4O_7, H_2O$)	Precipitation of Aluminium hydroxide Aluminium carbonate Aluminium borate
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These precipitations may be dissolved in an excess of sodium hydroxide through the formation of sodium aluminate ($NaAlO_2$) salts.



Aluminium hydroxide gel

Aluminium hydroxide gel is a suspension of aluminium hydroxide in water. The gel is destroyed by heat, freezing, electrolytes, acids, fixed alkalies and dehydration.

Aluminium silicates

- Bentonite is a mixture of $[H_2O.(Al_2O_3.Fe_2O_3.3MgO).4SiO_2.nH_2O]$ and $[K_2O.Al_2O_3.6SiO_2]$
- Kaolin $[Al_2O_3.2SiO_2.2H_2O]$ adsorbs drugs and inactivates them. e.g. strychnine and atropine.

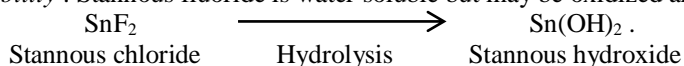
GROUP-IV A [Sn, Pb]

Tin(Sn)

Soluble salts	Precipitated by
Fluoride	Hydroxides
chloride	Sulfides
	Carbonates
	Tannins
	Phenols
	Many organic acids
	Plant extracts

Stannous fluoride is used in dentistry.

Incompatibility : Stannous fluoride is water soluble but may be oxidized and hydrolyzed.



Remedy

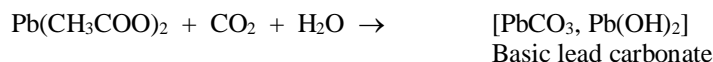
Therefore only freshly prepared solutions are used in dentistry.

Stannous chloride powder is also protected from moisture.

Lead (Pb)

Soluble salts	Slightly soluble	Insoluble
Acetate	Chloride	Arsenate
Subacetate	bromide	Arsenite
Chlorate		Borate
Nitrate		Carbonate
		Iodide
		Oxide
		Phosphate
		Sulfate
		Tannate

Incompatibility: On exposure to air, solutions of lead salts absorb CO₂ and become cloudy due to the precipitation of basic lead carbonate.



GROUP IV B (Ti, Zr)

Titanium

Titanium dioxide is used in sun-screen cream. It is neutral in action and is stable.

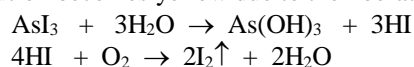
Zirconium

Zirconium carbonate and oxides are insoluble in water. They are used in ointments for external purpose and usually present no incompatibility.

GROUP-VA (As, Sb, Bi)

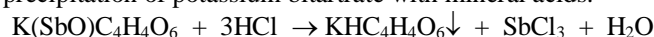
Arsenic (As)

- Arsenates and arsenites of alkali metals are soluble in water.
- Arsenites are slowly oxidized to arsenates by oxidizing agents and are slowly oxidized by atmospheric oxygen in neutral solutions.
- Arsenic triiodide is hydrolyzed in solution to arsenous acid [As(OH)₃] and hydroiodic acid (HI). On standing the solution becomes yellow due to the liberation of iodine.



Antimonu (Sb)

Antimony salts hydrolyze in aqueous solution. Acid must be added to avoid the precipitation of basic salts. *Tartar emetic* (Antimony potassium tartrate, K(SbO)C₄H₄O₆) forms precipitates with the salt solution of any metal. It forms a precipitation of potassium bitartrate with mineral acids.



Bismuth (Bi)

- Aqueous solutions of bismuth salts + Alkali hydroxide → Bi(OH)₃ ↓.
- Bismuth subnitrate undergoes hydrolysis to yield an acidic suspension.
 $2\text{BiONO}_3 + \text{H}_2\text{O} \rightarrow (\text{BiO})_2(\text{OH})\text{NO}_3\downarrow + \text{HNO}_3$.
 Thus this aqueous suspension will present the incompatibilities of acids
 e.g. effervescence from carbonate salts
 precipitation of salicylic acid from a solution of salicylate.
Remedy: Bismuth subnitrate is substituted with bismuth subcarbonate to avoid this problem.

GROUP-VIII (Fe)

Iron (Fe)

The common source of incompatibilities with iron salts are due to

- Iron salts hydrolyze in aqueous solution to produce acidic solution.
- Various oxidation-reduction situations.

Incompatibilities:

- Ferric chloride hydrolyze into ferric hydroxide plus the free acid.
 $\text{FeCl}_3 + 3\text{H}_2\text{O} \rightarrow \text{Fe}(\text{OH})_3\downarrow + 3\text{HCl}$
- Ferrous (Fe⁺⁺) salts are oxidized when exposed to air, being oxidized to ferric state (Fe⁺⁺⁺), usually with the precipitation of basic ferric salt.
 $4\text{FeSO}_4 + 2\text{H}_2\text{O} + \text{O}_2 \rightarrow 4\text{Fe}(\text{OH})\text{SO}_4\downarrow$
- Fe²⁺ salts + carbonates → precipitate of the corresponding ferrous salts
 arsenites
 arsenates
 oxalates
 phosphates
- Ferric salts are reduced to the ferrous state by iodides.
 $2\text{Fe}^{3+} + 2\text{I}^- \rightarrow 2\text{Fe}^{2+} + \text{I}_2$.

INCOMPATIBILITIES OF NON-METALS

Carbon (C)

Activated charcoal

1. It is easily oxidized so it is not triturated with oxidizing agents.
2. It has adsorptive action hence, it should not be dispensed with potent drugs like alkaloids because the potent drugs will be adsorbed and become inactive.

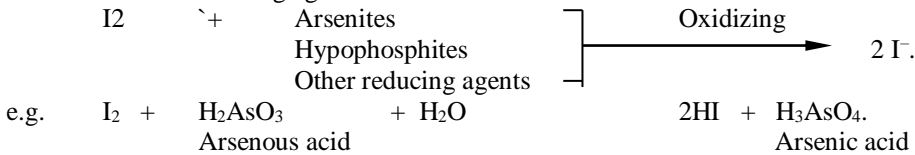
Sulfur (S)

In pharmacy three forms of powdered-sulfur are available: precipitated, sublimed and washed.

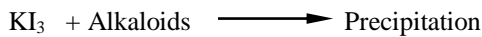
- These powders are soluble only in carbon-disulfide (CS₂) but insoluble in other solvents.

Iodine (I₂)

- Iodine is an oxidizing agent in alkaline solution



- $\text{I}_2 + \begin{array}{l} \text{Volatile oils} \\ \text{e.g. Turpentine oil} \end{array} \xrightarrow{\quad\quad\quad} \text{Substitution and oxidation}$
Explosion may result from such combinations.



- Solubility: 1 gm in 3000ml water
in 80 ml glycerin
in 13ml alcohol
in 4 ml carbon-di-sulfide.

INCOMPATIBILITIES OF ACIDS

Categories of acids:

1. Strong acid: They are highly ionized in aqueous solution.

e.g. Perchloric acid (HClO₄), sulfuric acid (H₂SO₄), hydrochloric acid (HCl), Hydrobromic acid (HBr), Nitric acid (HNO₃), Phosphoric acid (H₃PO₄)

2. Weak acid: They are slightly ionized in aqueous solution.

e.g. Acetic acid (CH₃COOH), Carbonic acid (H₂CO₃), hydrogen sulfide (H₂S), hydrocyanic acid (HCN), boric acid (H₃BO₃).

3. Oxidizing acid:

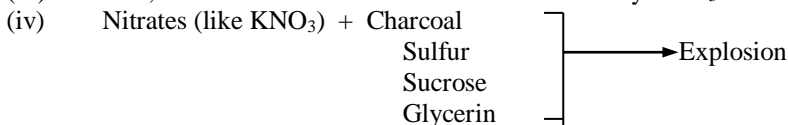
e.g. Nitric acid (HNO₃), Nitric acid + Hydrochloric acid mixture → HCl + HNO₃ + NOCl + Cl₂.
Permanganic acid (KMNO₄), Chromic acid (H₂CrO₄), Perboric acid (HBO₃) and Nitrous acid (HNO₂)

4. Reducing acid:

e.g. Hypophosphorous acid (H₃PO₂), sulfuric acid (H₂SO₃), hydroiodic acid (HI) thiosulfuric acid (H₂SO₃), thiocyanic acid (HSCN).

Nitric acid (HNO₃) Oxidising acid

- (i) HNO₃ reacts with some alkaloids to form colored compounds.
- (ii) It forms explosive nitroglycerin when rotated with sulfuric acid and glycerin.
- (iii) Fe⁺⁺, arsenous and mercurous salts are oxidized by HNO₃ into their oxidized state.



Hypochlorous acid (HOCl) (Reducing acid)

HOCl is unstable..

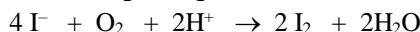
Hypochlorites (e.g. Sodium hypochlorite, NaOCl) are decomposed by acids, even H_2CO_3 with the liberation of unstable HOCl. Solutions of hypochlorites must be prepared at room temperature, because heat converts them into chlorates and chlorides.

Hydrogen peroxide (H_2O_2)

Hydrogen peroxide decomposes slowly with the evolution of oxygen. Heat increases the rate of reaction.

Hydroiodic acid (HI) (Reducing acid)

HI and I^- in acidic solution turn brown on standing, free iodine being released.

**Examples of acid preparation**

Fluid extract: Ergot, ipecac, nux vomica, aconite.

Elixir: Compound pepsin, compound glycerophosphates, lactated pepsin.

Solutions: Ammonium acetate, ferric chloride, iron and ammonium acetate, ferrous sulfate, Hydrogenperoxide, magnesium citrate.

Syrups: Citric acid, hydroiodic acid, cherry, ferrous iodide, orange, raspberry, squill, ipecac.

Glycerites: boroglycerin, pepsin

Tinctures: aconite, ferric chloride, camphorated opium, nux vomica, cinchona.

Miscellaneous: Squill vinegar

Preparations having an alkaline reactions

They have general incompatibilities of alkalis:

- e.g. (i) neutralization of acids,
 (ii) precipitation of alkaloids
 (iii) precipitation
 (iv) liberation of NH_3 from ammonium salts.

Alkaline preparation

Fluid extract: Senega

Ointments: Rose water

Solutions: lead subacetate, sodium hypochlorite, $\text{Ca}(\text{OH})_2$, soda and mint.

Spirits: aromatic ammonia

Syrups: senega, ginger, rhubarb

Water: Ammonia

GENERAL ORGANIC INCOMPATIBILITIES**1. Hydrocarbons:**

They include both saturated and unsaturated compounds of C and H.

- Over exposure to volatile hydrocarbons may cause damage to the heart, liver or kidneys.
- A hydrocarbon may produce Vitamin A, D, E and K deficiency on prolonged use or exposure.

(a) Saturated hydrocarbon

Saturated hydrocarbons used in pharmacy include:

Petroleum ether ($\text{C}_5 - \text{C}_7$)

Deodorized kerosene ($\text{C}_9 - \text{C}_{15}$)

Light mineral oil ($\text{C}_{15} - \text{C}_{20}$)

Mineral oil ($\text{C}_{18} - \text{C}_{24}$)

Petrolatum ($\text{C}_{18} - \text{C}_{30}$), White petrolatum ($\text{C}_{18} - \text{C}_{30}$)

Paraffin ($\text{C}_{24} - \text{C}_{30}$).

Some times unsaturated hydrocarbons may remain as impurities, which may degrade to produce rancidity. So dl- α -tocopherol (another name is Vit. E) is used as antioxidant.

(b) Unsaturated hydrocarbons

Contains double bonds (called *alkenes*), or triple bond(s) (called *alkynes*).

Reactions of unsaturated hydrocarbons:

- (i) addition type reactions : unsaturated bonds may add Br₂, HBr, H₂, H₂SO₄)
- (ii) may be oxidized at unsaturation point
- (iii) may be reduced at the unsaturation point.

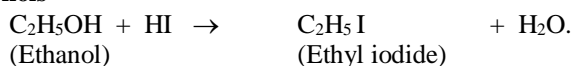
(c) Aromatic hydrocarbon

Benzene, naphthalene, anthracene – these are not found in prescription.

(d) Hydrogenated hydrocarbons

e.g. Chloroform (CHCl₃), ethyl bromide (C₂H₅Br) etc.

They are immiscible with water, soluble in alcohol and organic solvents.

(e) Alcohols

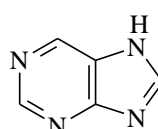
- Ethanol and methanol are incompatible with acacia, albumins and oxidizing agents such as chlorine, bromine, permanganate and chromic acid.

Purine bases:

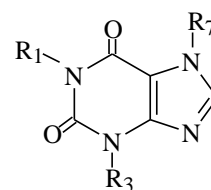
- e.g. Caffeine (1,3,7 trimethyl xanthine)
theobromine (3,7 dimethyl xanthine)
theophylline (1,3 dimethyl xanthine)

Properties:

They are very weak bases and cannot form salts with acid also.



Purine



Xanthine derivative

Alkaloids**Solubility**

Solvent	Free alkaloids	Alkaloidal salts
Water	No	Yes
Ether	Yes	No
Chloroform	Yes	No
Oils	Yes	No

Reactions

Reactants	Free alkaloids	Alkaloidal salts
Alkaline reactants Borax Sodium phosphate Potassium citrate		Precipitation of insoluble free alkaloids
Tannins	Precipitation of tannates	Precipitation
Organic acids Picric acid Iodine	Precipitation	Precipitation
Potassium iodide Potassium mercuric iodide Mercuric chloride Gold chloride	Precipitation	Precipitation

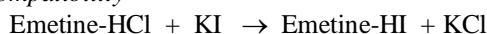
General remedies

1. In low concentration the alkaloid may not precipitate out of the solution, because the free alkaloid may also have slight solubility.
2. In many cases this problem may be solved by adding alcohol, because free alkaloidal bases are soluble in alcoholic solution.
3. If there is a possibility of precipitation then it is advisable to display the message “*Shake the bottle before use*” on the label.
4. In some cases it is feasible to add some acacia mucilage or other suspending agent to retard the settling of the precipitate.
5. Aqueous solutions of alkaloidal salts frequently show a precipitate due to mold growth. Chlorbutanol (0.5%) may be incorporated as preservative.

Examples of incompatibilities1. *Alkaloidal salts with soluble iodides*

Alkaloidal salts will react with soluble iodides and may precipitate insoluble iodide salts of alkaloids.

Alkaloidal salts	Soluble iodide
Emetine hydrochloride	Potassium iodide
Methadome hydrochloride	
Strychnine hydrochloride	
Papaverine hydrochloride	

Incompatibility

Solubility of Emetine-HI is less hence may precipitate.

Example: Potassium iodide is used as expectorant in some alkaloid containing cough mixtures.

Remedy: If the alkaloid concentration is very low then precipitation does not occur.

2. *Alkaloidal salts with tannins**Incompatibility:*

N.B. One advantage of this reaction is in case of alkaloidal poisoning strong tea (or tannic acid solution) is used to precipitate the alkaloids.

Remedy: Method-B (suspended with the help of tyragacanth mucilage) is used to suspend the precipitate.

Pyrazolon derivatives

e.g. Antipyrine, aminopyrine are non-narcotic analgesic

Incompatibilities

1. They produce color when mixed with oxidizing agents.
2. The solid compounds have a tendency to liquefy or form a soft mass when triturated with a number of hydrogen-bonding substances.

Aliphatic amino acids and derivatives

Amino acids are carboxylic acids which contain an amino (NH₂) group attached to any carbon atom in the radical attached to carboxyl.



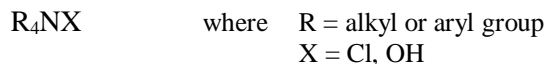
Solubility: Soluble in water, insoluble in alcohol.

They are amphoteric, forming either hydrochloride or sodium salts.

Examples of aliphatic amino acids : amino acetic acid, methionine.

Quarternary ammonium compounds

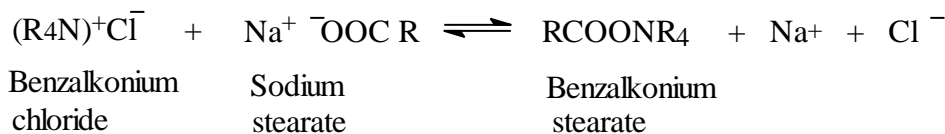
These compounds have the general formula of



e.g. Trimethylammonium chloride, (CH₃)₄N⁺Cl⁻.

Incompatibilities:

1. Quarternary ammonium bases are very soluble in water and readily absorb carbon dioxide from air.
2. These are highly ionized and reacts with the anions of weak acids (e.g fatty acids, acidic dyes, certain antibiotics, and barbiturates) to form insoluble complexes, e.g.



Thus the efficacy of quarternary ammonium germicides reduces in presence of alkali soaps or other anionic surfactants.

Remedy: The addition of inorganic or organic salts (e.g. NaCl) will solubilize such complexes.

Glycosides

Glycosides are compounds formed by condensation of sugars with other organic molecules containing hydroxyl (occasionally sulfhydryl group, –SH).

Incompatibilities:

1. In presence of water, glycosides are hydrolyzed by heat, enzymes or acids but are fairly stable towards alkaline hydrolysis. The hydrolyzed products may not show the desired therapeutic action.
2. Most glycosides are precipitated by tannic acid or lead subacetate.

A few natural drugs contains glycoside moieties:

e.g. aloe, cascara sagrada, digitalis, gentian, glycyrrhiza, jalap, stopanthus, and squill.

The useful glycoside molecules are:

Digitoxin, digoxin, lanatoside C, ouabain, rutin, and sennoside A and B.

Remedy: These are usually dispensed as solid dosage forms (such as tablets, capsules, powders) or as freshly reconstituted solutions because of their instability.

Local anaesthetics

Local anaesthetics may be divided into two categories depending on their solubility.

A. Slowly soluble local anaesthetics–

They are alkyl esters of aromatic acids. They are almost insoluble in water, hence they are unsuitable for injection but are used in the form of dusting powders, ointments, etc. on wounds of the skin or on mucous membrane.

e.g. local anaesthetics – benzocaine
 topical anaesthetic – lidocine
 dental anaesthetic – procaine
 narcotic anaesthetic – cocaine
 ophthalmic anaesthetic– benoxinate

B. Soluble local anaesthetic

These are polyfunctional amines or amino ester salts which may produce incompatibilities due to

- (i) their pH (ii) acids present (iii)hydrolysis of ester.

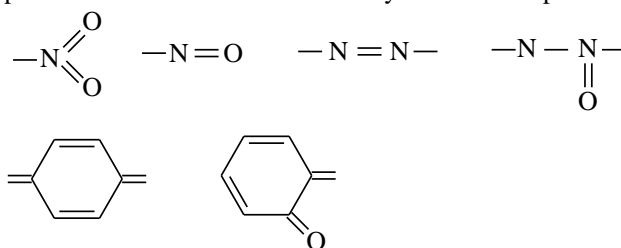
Examples: Lidocaine, procaine and tetracaine.

Dyes

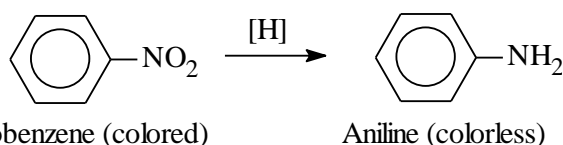
Most of the dyes used in pharmacy may be classified as

- (i) cationic, (ii) anionic (iii) nonionic.

- The first two categories produce most of the problems in compounding since they may interact with oppositely charged components to form insoluble complexes.
- Dyes other than colored compounds usually contain certain unsaturated color bearing groups known as chromophores: The presence of any of these groups on an aromatic nucleus is usually sufficient to produce a color. Reduction of the



radical to the saturated state results in the loss of color. e.g.



- Some drugs gives color after decomposition e.g. Neomycin, streptomycin, procaine. In some preparation loss of color or change of shade occurs e.g. amaranth. All these may be the effects of light, acid, alkali, reducing agents, oxidizing agents, catalysts etc.

Basic dyes (Cationic)

Structure: R⁺ X⁻, e.g. methylrosaniline chloride, methylene blue.

- (i) They usually contain amine or quaternary groups.
- (ii) They form salts with acids, the colored ion being positively charged. E.g. methylrosaniline chloride.
- (iii) Basic dyes are soluble in hot water and readily soluble in alcohol.

(iv) Basic dyes +

Soaps	}	Precipitate
Tannins		
Tartar emetic		

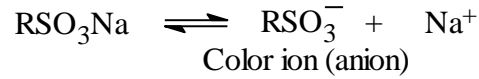
(v) Negatively charged surface + basic dyes → adsorption
(e.g. filter, glass ware)

(vi) They should be stored in dark as they rapidly decolorised in sunlight.

(vii) Basic dye + acid dye → precipitation

Acid dyes (Anionic dyes)

They usually contains $-SO_3H$ and $-COOH$ groups which forms salts with alkalies
e.g. $-SO_3Na$, $-COONa$, In aqueous solution RSO_3Na will produce



(i) they are soluble in water,

(ii) Acid dyes +

tannins	}	NO precipitation
Other dyes		

insoluble in alcohol.

(iii) Acid dyes + Basic dyes → precipitation.

THERAPEUTIC INCOMPATIBILITY

Usually this incompatibility arises when one or more drugs produce response or intensity different from that intended in the patients.

Classification

- Over doses
- Under doses
- Improper consumption by the patient
- Contra-indicated drugs

A) Over doses: This can be subgrouped as follows:

Excessive single dose

Sometimes a single dose may become overdose depending on the health of the patient e.g. a normal dose (taking body weight as 70 kg for an adult male) may be overdose for a lowly built person. However it should not be more than 2 to 3 normal dose.

Remedy: The pharmacist should consult the physician and clarify the dose.

e.g. 1 Rx

Atropine sulphate	6 mg	
Phenobarbital		360 mg

Make capsules.

Label: One capsule to be taken three times a day before meals.

Comments: In this prescription the doses of both atropine sulphate and phenobarbital are 12 times the normal doses. The physician intended for 12 capsules to be dispensed but he has mistaken or may be it is an incomplete prescription. Hence, before dispensing the pharmacist should consult the physician again.

Correct prescription

Rx

Atropine sulphate	6 mg	
Phenobarbital		360 mg

Make capsules. Supply 12 capsules.

Label: One capsule to be taken three times a day before meals.

e.g. 2 Rx

Strychnine sulphate	20 mg	
Iron and ammonium citrate		500 mg

Prepare capsules. Supply 12 capsules.

Label: One capsule to be taken three times a day after meals.

Comment: 10 times overdose of strychnine hydrochloride than that of normal. The pharmacist should consult the physician and obtain the permission to change the dose.

Corrected prescription

Strychnine sulphate	2 mg	
Iron and ammonium citrate		500 mg

Prepare capsules. Supply 12 capsules.

Label: One capsule to be taken three times a day after meals.

Excessive daily dose

In this case the daily dose of drug is exceeded .

e.g.1 Rx

Codeine phosphate	15 mg	
Ammonium chloride		500 mg

Prepare capsules and supply 24 capsules.

Label: Two capsules to be taken every hour for cough.

Comment: The U.S.P. recommends that the prescribed dose should be taken after every four hours and not every hour. Hence the physician should be consulted.

Additive and synergistic combinations:

There are certain drugs possessing similar pharmacological activity. If these drugs are combined together, they may produce additive or synergistic action. In such case advice of the physician is necessary.

e.g. Rx

Amphetamine sulphate	20 mg	
Ephedrine sulphate		50 mg
Syrup q.s.		100 ml

Let a mixture be made

Label: Take 25 ml every four hours.

Comment: Both of the drugs are sympathetic stimulants and they are prescribed in their full dose. The formulation will produce additive overdose effect. Hence, The dose of individual drug should be reduced.

(B) Under dose In this type of incompatibility, effect of one drug is lessen or antagonised by the presence of another drug. This can be exemplified by combination of following types of drugs:

Stimulants like nux-vomica, strychnine sulphate, caffeine etc. with **sedatives** like barbiturates, paraldehyde etc.

Sympathomimetic or **adrenergic** like ephedrine, nor-adrenaline with **sympatholytic** drugs like ergotamine.

Sympathetic stimulants like methamphetamine with **parasympathetic stimulants** like pilocarpine.

Purgatives like castor oil, liquid paraffin etc with **antidiarrheal** agents like bismuth carbonates.

Acidifiers like dilute hydrochloric acid and **alkalisers** like sodium bicarbonate, magnesium carbonate.

Comment: In all the cases the pharmacist should consult with the doctor who had prescribed it and one drug should be removed from the prescription.