

## **CHEMICAL INCOMPATIBILITY-**

It may be as a result of chemical interaction between the ingredients of the prescription and a toxic or inactive product may be formed.

Chemical incompatibilities often occur due to oxidation reduction, acid base hydrolysis or combination reactions. These reactions may be noticed by precipitation, effervescences decomposition, colour change or by explosion.



It is of two types

**Tolerated** – The chemical interaction can be minimized by changing the order of mixing or mixing the solution in dilute forms but no alteration is made in the formulation.

**Adjusted** – The chemical interaction can be prevented by addition or substitution of one of the reacting ingredients of the prescription with another of equal therapeutic value.

e.g. caffeine citrate can be substituted with caffeine in sodium salicylate and caffeine citrate mixture.

## **CHEMICAL INCOMPATIBILITIES : TYPES**

### **Precipitate yielding interactions**

- The precipitates so formed may be diffusible or indiffusible. The method A or B is followed in dispensing the prescription yielding diffusible and indiffusible precipitates respectively.

**Method A – Diffusible precipitate**

**Method B – Indiffusible precipitate**

- The preparation should contain a thickening agent if the precipitate is non-diffusible.

#### **Method A:**

- This method is suitable for diffusible precipitates and the following steps are carried out.
- Divide the vehicle into two portions.
- Dissolve the reactants in separate portions and mix the two portions slowly by adding one into other with rapid stirring.

### Method B -

- This method is followed for indiffusible precipitate forming solids.
- Divide the vehicle into two equal portions.
- Dissolve one of the reacting substance in one portion.
- Weigh a suitable quantity of compound tragacanth powder (2 gm /100 ml of finished product) & transfer in a mortar & use part of second portion of vehicle to produce smooth mucilage.
- Then add other reacting substances. Mix the two portions by slowly adding one portion to other with rapid stirring.

## Examples of chemical incompatibilities and methods of their correction

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- **Alkaloid incompatibility:-**
  - 1. Alkaloidal salts with alkaloid substances
  - 2. Alkaloidal salts with soluble iodides
  - 3. Alkaloidal salts with tannins
  - 4. Alkaloid salts with salicylates
  - 5. Alkaloid with soluble iodides and bromides.
  
- **Soluble salicylates incompatibility:-**
  - 1. Soluble salicylates with ferric salts
  - 2. Soluble salicylates with alkali bicarbonates
  - 3. Soluble salicylates and benzoates with acids.
  
- **Soluble iodides incompatibility:-**
  - 1. Oxidation of iodides with potassium chlorate
  - 2. Oxidation of iodides with quinine sulphate.

## Chemical incompatibility.

### Examples

\* Examples of chemical incompatibility.  
of methods of their correction.

- ① Alkaloidal incompatibility.
- ② Soluble Salicylates -II-
- ③ Soluble iodides -II-  
—
- ④ chemical incompatibilities causing Evaluation  
of  $\text{CO}_2$  gas
- ⑤ Miscellaneous chemical incompatibility.

①

Alkaloidal incompatibility.

① Alkaloidal salts  $\bar{c}$  alkaline substances  $\rightarrow$

- Alkaloids are weak bases  $\rightarrow$

Almost insoluble in  $H_2O$   
 $\downarrow$

But Alkaloidal salts are soluble in  $H_2O$

- IF these salts are dispensed  $\bar{c}$

Alkaline preparations eg.

Strong solution of ammonium acetate,

Aromatic spirit of ammonia, ammonium

bicarbonate, Solution of ammonia, sodium bicarbonate

salts + Alkaline prep  $\downarrow$

Alkaloid may be ppt., Not always ppt

$\downarrow$

Bcoz all alkaloids are slightly soluble in  $[H_2O]$

egbiberi eldul. is other libidina  
Rx

Strychnine HCl  
Aromatic spirit of Ammonia

$\text{H}_2\text{O} \longrightarrow \longrightarrow \text{upto 100 ml}$

- Strychnine HCl  $\rightarrow$  Alkaloidal salt
- Aromatic spirit  $\rightarrow$  Alkaline substance

↓

when they react  $\rightarrow$  Strychnine get ppt

(Bcoz ~~get~~ ~~diff~~ ~~diff~~ qty. of Strychnine HCl  
prescribed in prescription is more  
than its solubility in  $\text{H}_2\text{O}$  (1 in 7000))

Aromatic spirit of Ammonia contain  
negligible amt. of alcohol

↓

which can not dissolve Strychnine.

↓

∴ it get ppt. (Diffusible ppt.)

↓

∴ Follow mtd. A

ii

## Alkaloidal salts & Soluble iodides

eg -

In Cough mixtures  $\rightarrow$  KI (Expectorant)

+ (Calongi) Tincture ipecacuanha (Emetine)

qty. of emetine (usually low) + KI

lose hydroiodide  $\rightarrow$  BH iodide  $\xrightarrow{-X}$  can not react

PPT. as hydroiodide ] X

eg - Rx Strychnine  $\rightarrow$  very insoluble

Soluble iodide  $\rightarrow$  hydroiodide

PPT. diffusible

Follow mtd A.

### III Alkaloidal salts & tannins

Alkaloidal salts + drug containing tannins

Alkaloids form tannates

Tannates ↓ separated as diffusible pp

Follow mtd. A

Tannates of most alkaloids → insoluble in  $H_2O$

∴ Strong tea / Tannic acid solution

in alkaloidal poisoning

④ Alkaloidal salts & Salicylates

Quinine + Salicylates → Indiffusible ppt.  
comp. Quinine Salicylates

[a-bm]

↓  
Follow mtd [B]

Rx

Quinine HCl

1g

Sodium Salicylates

↓ 4g

H<sub>2</sub>O

100ml

- Quinine HCl + sodium salicylate

mtd [B]

← indiffusible ppt ← Quinine Salicylate

⑤ Alkaloidal salts & soluble iodides & bromides

- Alkaloids (strychnine, morphine, cocaine) + soluble I, Br

~~insoluble~~ <sup>↓</sup> Insoluble hydroiodides,  
HBr, HCl

I<sub>n</sub>td A

← PPT (insoluble)

Q2

Soluble Salicylates incompatibility.

i) Soluble Salicylates  $\rightleftharpoons$  ferric Salts

Ferric Salts + sodium salicylates



liberate indiffusible ppt (Ferric salicylate)



Mtd. B.

R

Ferric chloride

Sodium salicylate

$\text{H}_2\text{O}$

Ferric chloride + sodium salicylate  $\rightarrow$  Ferric salicylate

indiffusible ppt.

∴ Mtd. B

## ⑩ Soluble Salicylates $\rightleftharpoons$ alkali bicarbonates

Na salicylate  $\longrightarrow$  administered orally  $\downarrow$

it react  $\rightleftharpoons$   $\text{HCl}$  (in stomach)

Form salicylic acid (ppt)

$\therefore$  may irritate<sup>†</sup> gastric mucosa (causing pain in stomach)

$\therefore$  When Na salicylate (prescribed)

$\downarrow$   
it is usually given  $\rightleftharpoons$  double qty of  
Na bicarbonate as that of Na salicylate

$\downarrow$   
To neutralise the gastric juice &  
thus formation of ppt. of salicylic acid

\* When Na salicylate + alkaline substance  
(solution) (Na bicarbonate)

$\downarrow$   
Mixture absorb  $\downarrow$   $\text{O}_2$  from atmosphere

$\downarrow$   
4 Reddish brown (clr)

$\downarrow$   
Not affect therapeutic<sup>x</sup> efficiency but may  
lead confusion in patient

$\therefore$  clr. agent added to darken clr. or  
patient warned about clr. change

$\downarrow$   
clr. change retarded by adding Antioxidant  $\rightleftharpoons$   
prescriber permission.

⑩

### Soluble Salicylates $\rightarrow$ benzodates / acids

- Acids + Acid syrups (lemon syrup.)

decompose  $\downarrow$  Na salicylate, Na benzodate

ppt.  $\downarrow$  Salicylic acid / Benzoic acid

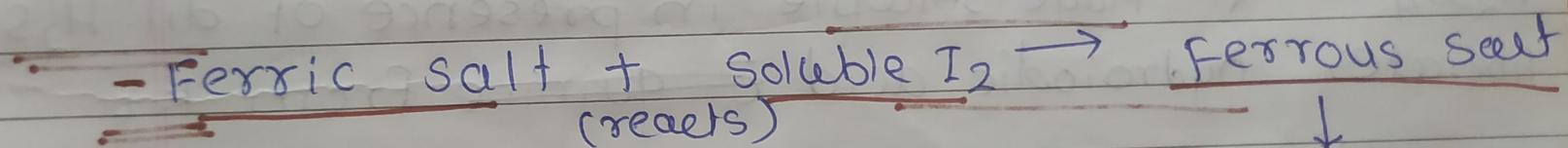
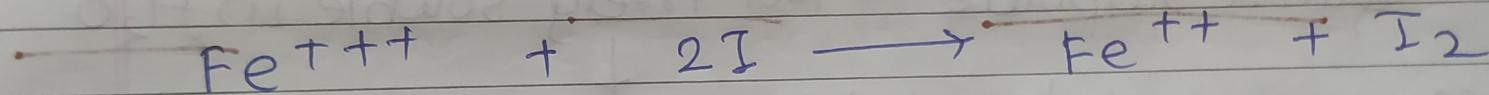
Mtd. B

### ③ Soluble Iodides incompatibility

\* Iodides undergo oxidation forming Iodine  
which is undesirable product  
Follow following steps

To avoid chemical incompatibility.

#### ① Oxidation of Iodides $\rightleftharpoons$ Ferric salts

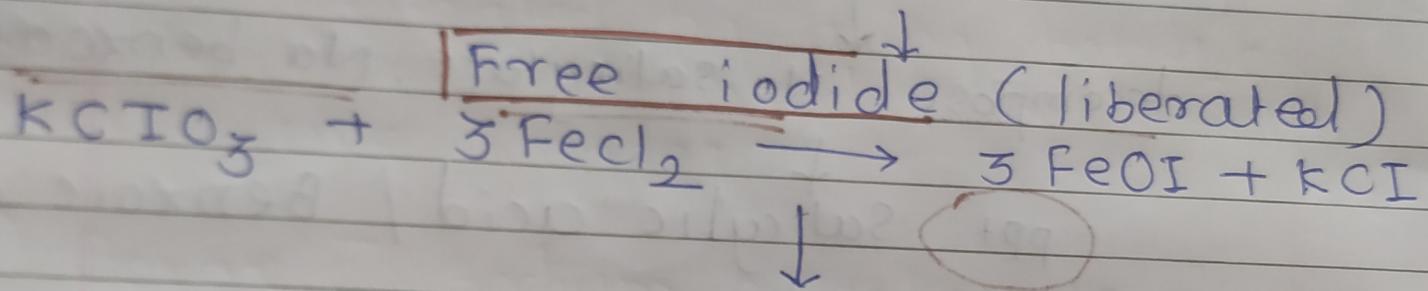


No satisfactory mtd to adjust Incomp.

Prescriber may substitute ferric salt  $\rightleftharpoons$  Iorn  
f ammonium citrate,  $\rightarrow$  Iorn  $\rightarrow$  organic  
compound  $\rightarrow$  X Ferric ions

⑪ Oxidation of iodides by potassium chlorate

Soluble Iodides react with potassium chlorate (+)



∴ Two reacting substances must  
dispensed separately

Rx

potassium chlorate

syrup of ferric iodide

water upto

180 ml

→ Fresh mixture (clear) → standing

∴ Reacting sub. sometime, Crystals of iodine deposited  
dispensed separately

III Oxidation of Iodides in quinine sulphate

Quinine sulphate  $\Rightarrow$  Not freely soluble in  $H_2O$

$H_2SO_4$   $\leftarrow$  Made soluble in presence of dil.  $H_2SO_4$   
liberates hydroiodic acid  $\leftarrow$  quinine from  $KI$

- Hydroiodic acid — partly oxidised by  $H_2SO_4 \rightarrow$   $Iodine (I_2)$
- $I_2 +$  Hydroiodic acid + quinine sulphate

Herapathite  $\downarrow$  / Iodosupphite of quinine

∴ Incompatibility can be removed by

- ① patient supplied  $\bar{e}$  mixture of 3 day only
- ② In case patient require mixture for more than 3 days  $\downarrow$

Both solutions prepared in half the volume of  $H_2O$  & supplied in separate bottle.

#### 4. Chemical incompatibilities causing evolution of carbon dioxide gas.

- When carbonates and bicarbonates are dispensed in the presence of an acid or acidic drug in a mixture, they react together with the evolution of carbon dioxide gas.
- If the reaction is not completed before transferring the mixture into a dispensing bottle and corked, there are chances of explosion with the bursting of the bottle.
- To prevent this the reaction must be completed before dispensing the mixture.
- To speed up the reaction mix the ingredients in an open vessel & allow the reaction to complete until effervescence ceases.



④ chemical incompatibility causing evolution of  $\text{CO}_2$  gas

① Sodium bicarbonate + soluble calcium/Mg salts

sodium bicarbonate + soluble ca, Mg salts  
↓ decomposition reaction

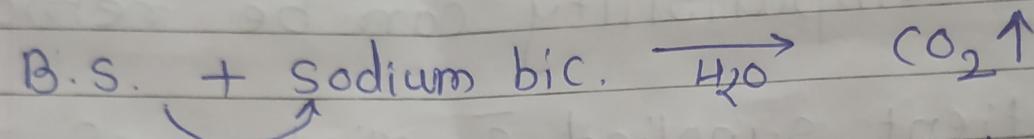
insoluble carbonate +  $\text{CO}_2 \uparrow$

1. Rea<sup>n</sup>. proceeds slowly at ordinary temp.  
↓

To accelerate rea<sup>n</sup>. Hot H<sub>2</sub>O used,  
mixture should be dispensed only when  
effervescence ceases

2) Ppt. of carbonates formed diffusible in  
nature  $\longrightarrow$  mtd. A

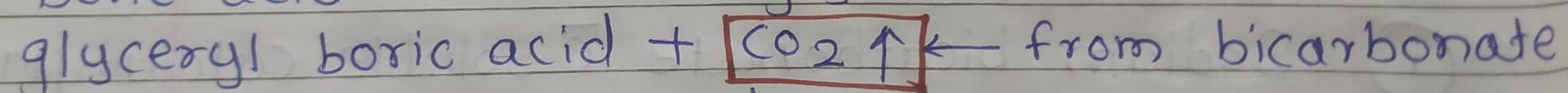
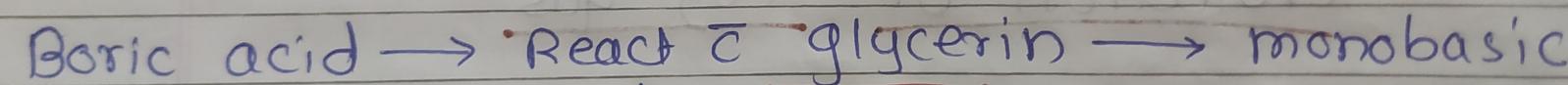
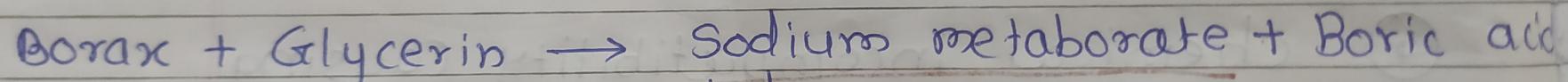
⑪ Bismuth Subnitrate + sodium bicarbonate



∴ Reac. proceeds slowly at ordinary temp.

, Reac. accelerated by using hot H<sub>2</sub>O,  
mix. should ~~x~~ transferred to bottle until  
effervescence ~~x~~ ceases.

⑫ Borax + sodium bicarbonate + glycerin



∴ To hasten reacn. (ing. — mixed in open vessel

⑬ hot H<sub>2</sub>O as vehicle), Transferred (After <sup>complex</sup> reacn)

## 5. Miscellaneous incompatibilities

**Soluble barbiturates with ammonium bromide** when soluble barbiturates is combined with ammonium bromide in the presence of water the barbitone is separated as indiffusible precipitates which are insoluble in water. Follow method B for precipitate yielding interactions for dispensing the prescription.



## Potassium chlorate with oxidisable substances

When potassium chlorate is prescribed along with charcoal, sulphur, sugar organic compounds or any other readily oxidisable substance there are chances of explosion.

## Incompatibility of emulsifying agents

Emulsions prepared with alkali metal, ammonium and triethanolamine soaps are incompatible with salts producing polyvalent cations . Due to double decomposition , a polyvalent soap is formed which inverts the emulsion.

## Colour stability of dyes

The colour of the most of the dyes used in pharmaceutical formulations are influenced by their ionisation which depends on pH of the solution.



## Incompatibilities of liquorice liquid extract

Liquorice liquid extract is

used as flavoring agent. The flavoring property is due to glycerrihizine which is a mixture of potassium and calcium salts of glcerrihizinic acid.

Acid decomposes glycyrrhizin into glcerrihizinic acid. Which is insoluble in water and get precipitated. The precipitate clots and forms a sticky black sediment which is difficult to diffuse.

The prescription may be referred back to the prescriber for the changes in flavoring agent.

