

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

- **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.
‡ methods of their correction.

- ① Alkaloidal incompatibility.
- ② Soluble salicylates -||-
- ③ Soluble iodides -||-
- ④ chemical incompatibilities causing Evaluation
of CO_2 gas
- ⑤ Miscellaneous chemical incompatibility.

① Alkaloidal incompatibility.

① Alkaloidal salts & alkaline substances →

- Alkaloids are weak bases →

Almost insoluble in H_2O



But Alkaloidal Salts are soluble in H_2O

- If these salts are dispensed &

Alkaline preparations eg.

Strong solution of ammonium acetate,
Aromatic spirit of ammonia, ammonium
bicarbonate, Solution of ammonia, Sodium bicarbonate

Salts + Alkaline prepⁿ ↓

Alkaloid may be ppt., Not always ppt



Bcoz all alkaloids are slightly soluble in H_2O

egbibai aldulac 5 etlac lobiolulla
Rx

Strychnine HCl
Aromatic Spirit of Ammonia
H₂O —————> upto 100 ml

- Strychnine HCl → Alkaloidal salt
- Aromatic spirit → Alkaline substance

↓

when they react → Strychnine get ppt

(Bcoz → ~~very~~ ~~much~~ qty. of Strychnine HCl
prescribed in prescription is more
than its solubility in H₂O (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.

② Alkaloidal Salts \bar{c} Soluble iodides

eg - In Cough mixtures \rightarrow KI (Expectorant)
+ (along \bar{c}) Tincture ipecacuanha (Emetine)

\downarrow
qty. of emetine (usually low) + KI
 \downarrow $\underbrace{\quad \times \quad}_{\text{can not react}}$

ppt. as hydroiodide \times

eg - Rx Strychnine \rightarrow very insoluble
 \bar{c} Soluble iodide \rightarrow hydroiodide

\downarrow
ppt diffusible

\downarrow
Follows into A.

(III) Alkaloidal salts \bar{c} tannins

Alkaloidal salts $+$ drug containing tannins

\downarrow
[A] Alkaloids form [tannates]

\downarrow
Tannates separated as diffusible ppt

\downarrow
 \therefore Follow mtd. [A]

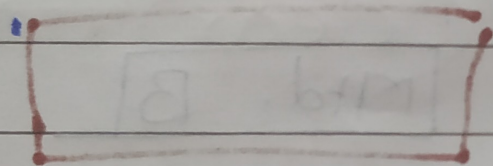
Tannates of most alkaloids \rightarrow insoluble in H_2O

\downarrow
 \therefore Strong tea / Tannic acid solution

\downarrow
(0) in alkaloidal poisoning

④ Alkaloidal salts & Salicylates

Quinine + Salicylates → Indiffusible ppt.
comp. (Quinine Salicylates)



Follow mtd B

R_x

Quinine HCl	1g
Sodium Salicylates	↓ 4g
H ₂ O	100ml

— Quinine HCl + sodium salicylate →

mtd B ← indiffusible ppt ← Quinine Salicylate

⑤ Alkaloidal salts \bar{c} soluble iodides & bromides
- Alkaloids (strychnine, morphine, cocaine) + soluble
I, Br

~~insoluble~~ Insoluble hydroiodides,
HBr, HCl

Mtd A

← ppt (insoluble)

② Soluble Salicylates incompatibility

① Soluble salicylates + ferric salts

Ferric salts + Sodium salicylates

↓
liberate indiffusible ppt (Ferric salicylate)

↓
Mtd. B.

* Ferric chloride

Sodium salicylate

H₂O

Ferric chloride + sodium salicylate → Ferric salicylate
↓
indiffusible ppt.

∴ Mtd. B.

② Soluble Salicylates \bar{c} alkali bicarbonates

Na salicylate \longrightarrow administered orally \downarrow

it react \bar{c} HCl (in stomach)

Form salicylic acid (ppt) \downarrow

\therefore may irritate gastric mucosa (causing pain in stomach)

\therefore When Na salicylate (prescribed)

\downarrow
it is usually given \bar{c} 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 O_2 from atmosphere

\downarrow
4 Reddish brown (clr)

\downarrow
Not affect therapeutic \times efficiency but may lead confusion in patient

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

\downarrow
clr. change retarded by adding Antioxidant \bar{c} prescriber permission.

③ Soluble Salicylates \bar{O} benzoates / acids

- Acids + Acid syrups (Lemon Syrup.)

↓
decompose Na salicylate, Na benzoate

↓
(ppt.) Salicylic acid / Benzoic acid

↓
Mtd. B

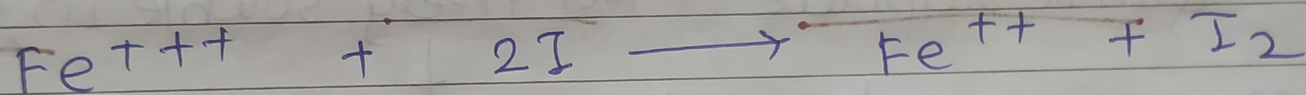
③ Soluble Iodides incompatibility

* Iodides undergo oxidation forming Iodine
↓
which is undesirable product

↓
∴ Follow following steps

↓
To avoid chemical incompatibility.

① Oxidation of Iodides & Ferric salts



Ferric salt + Soluble I₂ (reacts) → Ferrous salt
↓

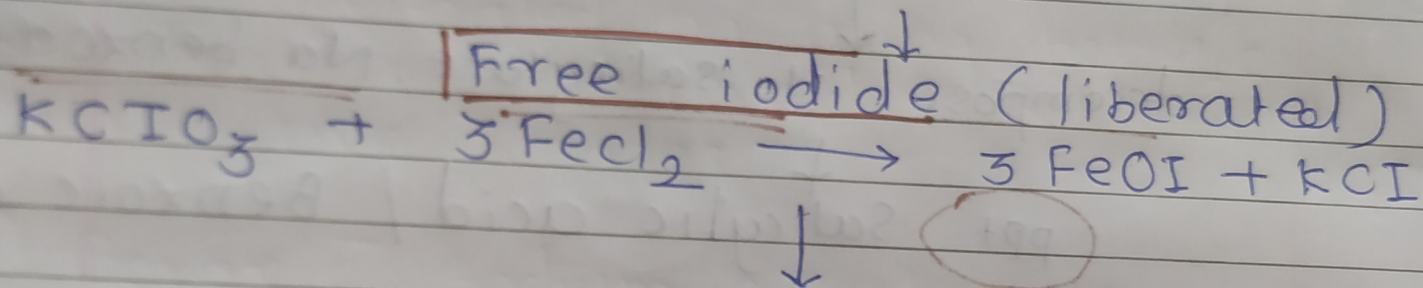
No Satisfactory mtd to adjust Incomp.

↓

∴ Prescriber may substitute ferric salt & Iorn
& ammonium citrate → Iorn → organic compound → X Ferric ions

② Oxidation of iodides \bar{c} potassium chlorate

Soluble Iodides react \bar{c} 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.

dispensed separately

← sometime, crystals of iodine
deposited

(iii) Oxidation of Iodides & quinine sulphate

Quinine sulphate → Not freely soluble in H_2O

H_2SO_4 ← Made soluble in presence of dil. H_2SO_4
liberates hydroiodic acid & quinine from KI

- Hydroiodic acid — partly oxidised by H_2SO_4 → Iodine (I_2)
- I_2 + Hydroiodic acid + quinine sulphate

Herapathite

↓ / Iodosulphite of quinine

∴ Incompatibility can be removed by

- ① patient supplied \bar{c} 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 is a chance 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 CO_2 gas

① Sodium bicarbonate + soluble calcium/Mg salts

Sodium bicarbonate + Soluble Ca, Mg Salts
↓ decomposition reaction

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

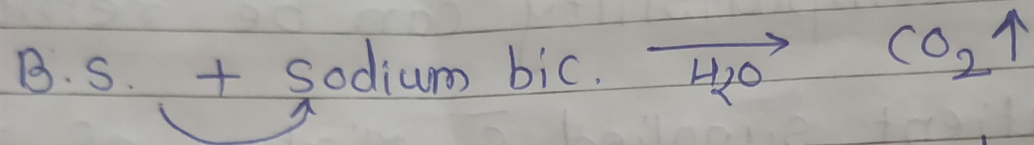
∴ Reaⁿ. proceeds slowly at ordinary temp.

To accelerate reaⁿ. Hot H_2O used,
mixture should be dispensed only when
effervescence ceases

Ppt. of carbonates formed diffusible in
nature → limited. A

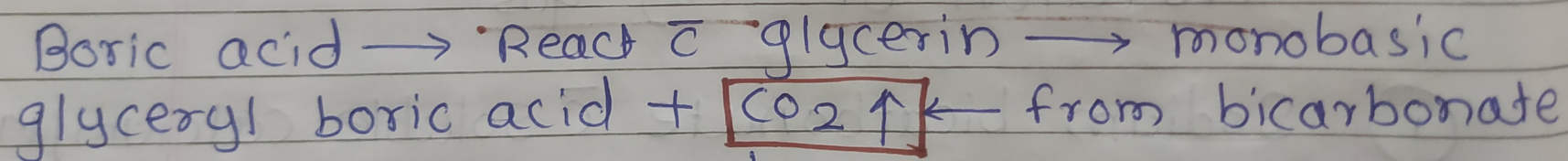
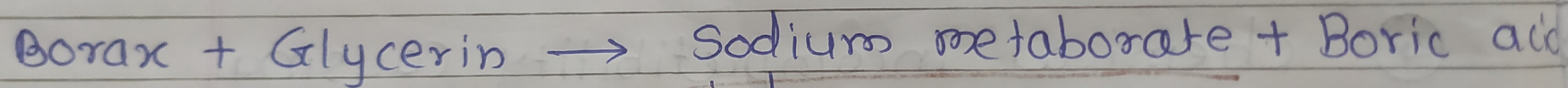
②)

⑪ Bismuth Subnitrate & sodium bicarbonate



∴ Rean. proceeds slowly at ordinary temp.
Rean. accelerated by using hot H₂O,
mix. should be transferred to bottle until
effervescence ceases.

⑫ Borax & sodium bicarbonate & glycerin



∴ To hasten rean. (ing. — mixed in open vessel)

① hot H₂O as vehicle), Transferred (After complete rean.)

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.

