

## INCOMPATIBILITIES IN PRESCRIPTION

It is the result of mixing of two or more antagonistic substances and an undesirable product is formed which may affect the safety, efficacy and appearance of the pharmaceutical preparation.

Incompatibility occurs due to drug-drug interaction, drug-additive interaction, dosage error etc.

### **Incompatibilities occurs during: -**

Compounding, Formulation, Manufacturing, Packaging, Dispensing, Storage, Administration of drugs.

### **Types of Incompatibilities: -**

1. Physical Incompatibilities (Physical Changes).
2. Chemical Incompatibilities (Chemical Changes).
3. Therapeutic Incompatibilities (Related to drug action).

### **1. PHYSICAL INCOMPATIBILITIES: -**

When two or more than two antagonistic substances are combined together, a physical change takes place and an unacceptable product is formed, such incompatibilities known as Physical Incompatibility.

Physical incompatibility occurs due to Immiscibility, Insolubility, Precipitate formation and Liquefaction of solid ingredients. These changes are visible and can be corrected by using suitable procedure like-

1. Change the order of mixing.
2. Emulsification.
3. Change in the form of ingredients.
4. By addition, substitution or omission of therapeutically inactive substance i.e. Adjuvants.

### **Examples of Physical Incompatibilities and their method of correction: -**

#### **1. Immiscibility: -**

Oils and water are immiscible with each other but can be made miscible by emulsification.

Rx

Castor oil                      15 ml

Water upto                      60 ml

Make an emulsion.

In this preparation castor oil is immiscible with water. To overcome this problem an Emulsifying agent is used to form a stable emulsion.

## 2. Insolubility: -

It means the inability of material to dissolve in particular solvent system. The majority of physical incompatibilities are due to insolubility of the inorganic as well as organic compounds in a particular solvent system.

The liquid preparation containing indiffusible solid such as chalk, acetyl salicylic acid, phenacetin, zinc oxide and calamine etc a suspending agent incorporated to increase the thickness of preparation which helps to maintain uniform distribution of the insoluble substance for sufficient long time upon shaking.

Rx

Phenacetin	3 g
Caffeine	1 g
Orange syrup	12 ml
Water	90 ml

Make a mixture.

In this preparation Phenacetin is an indiffusible substance. Adding of Compound tragacanth powder or tragacanth mucilage will make a stable mixture.

## 3. Precipitation: -

The drug precipitated when it is insoluble in solvent.

For ex, Resins are insoluble in water. When tincture containing resinous matter is added in water, resin agglomerates and forms indiffusible precipitates. This can be prevented by slowly adding the undiluted tincture with vigorous stirring to the diluted suspension or by adding some thickening agent.

Rx

Tincture Benzoin compound	5 ml
Glycerine	15 ml
Rose water sufficient to make	100 ml

In this preparation tincture benzoin contain resin which will forms precipitate to overcome problem add the tincture with rapid stirring which gives fine colloidal dispersion so there is no need to add any suspending agent.

## Liquefaction: -

When low melting point solids are mix together a liquid or soft mass is form known as Eutectic Mixture. This is because of substances having low melting point below room temperature. Substances like menthol, camphor, phenol, thymol, chloral hydrate etc. shows this type of behavior. So dispensing of such preparation use one the following methods: -

1. Triturate together to form liquid and then mix with Adsorbent like light kaolin or light magnesium carbonate to produce free flowing powder.
2. Another method i.e. individual drug powdered separately and mixed with an adsorbent and then combined together and filled in suitable container.

Rx

Menthol	5 g
Camphor	5 g
Ammonium chloride	30 mg
Light magnesium carbonate	60 mg

Make an Insufflation.

To dispense this preparation first menthol, camphor & ammonium chloride triturate together to form a liquid and then add adsorbent light magnesium carbonate to form free flowing powder.

## 2. Chemical Incompatibility-

When two or more antagonistic substances are mixed together, the chemical reactions take place and forms toxic or inactive product.

Chemical incompatibility due to oxidation-reduction, acid-base hydrolysis or combination reaction and these reactions can be noticed by precipitation, effervescence, decomposition, colour change or by explosion.

## Types of Chemical Incompatibility-

### 1. Tolerated: -

In this incompatibility, chemical reaction can be minimised by changing the order of mixing or mixing the solution in dilute forms but no alteration is made in the formulation.

Ex.,

Rx

Sodium bicarbonate            1 gm.

Borax                                1 gm.

Phenol	0.5 gm.
Glycerine	20 ml.
Water upto	90 ml.

Make a spray solution.

Here, sodium bicarbonate, borax & glycerine reacts with each other and causes evolution of carbon dioxide gas (Effervescence), if the mixture transfer as such into the bottle then there are chances of bursting of bottle. To prevent such explosion, mix the ingredients in open vessel and allow the reaction to complete until the effervescence stops completely then add phenol and transfer the mixture into bottle.

## 2. Adjusted: -

In this incompatibility, the chemical interaction can be minimised by addition or substitution of one of the reacting ingredients of prescription with another of equal therapeutic value.

Ex.,

Rx

Caffeine citrate	1 gm.
Sodium Salicylate	3 gm.
Water upto	90 ml.

Make a mixture.

Caffeine citrate can be replaced with caffeine in sodium salicylate and caffeine citrate mixture.

The incompatibility may be **Intentional or Unintentional**.

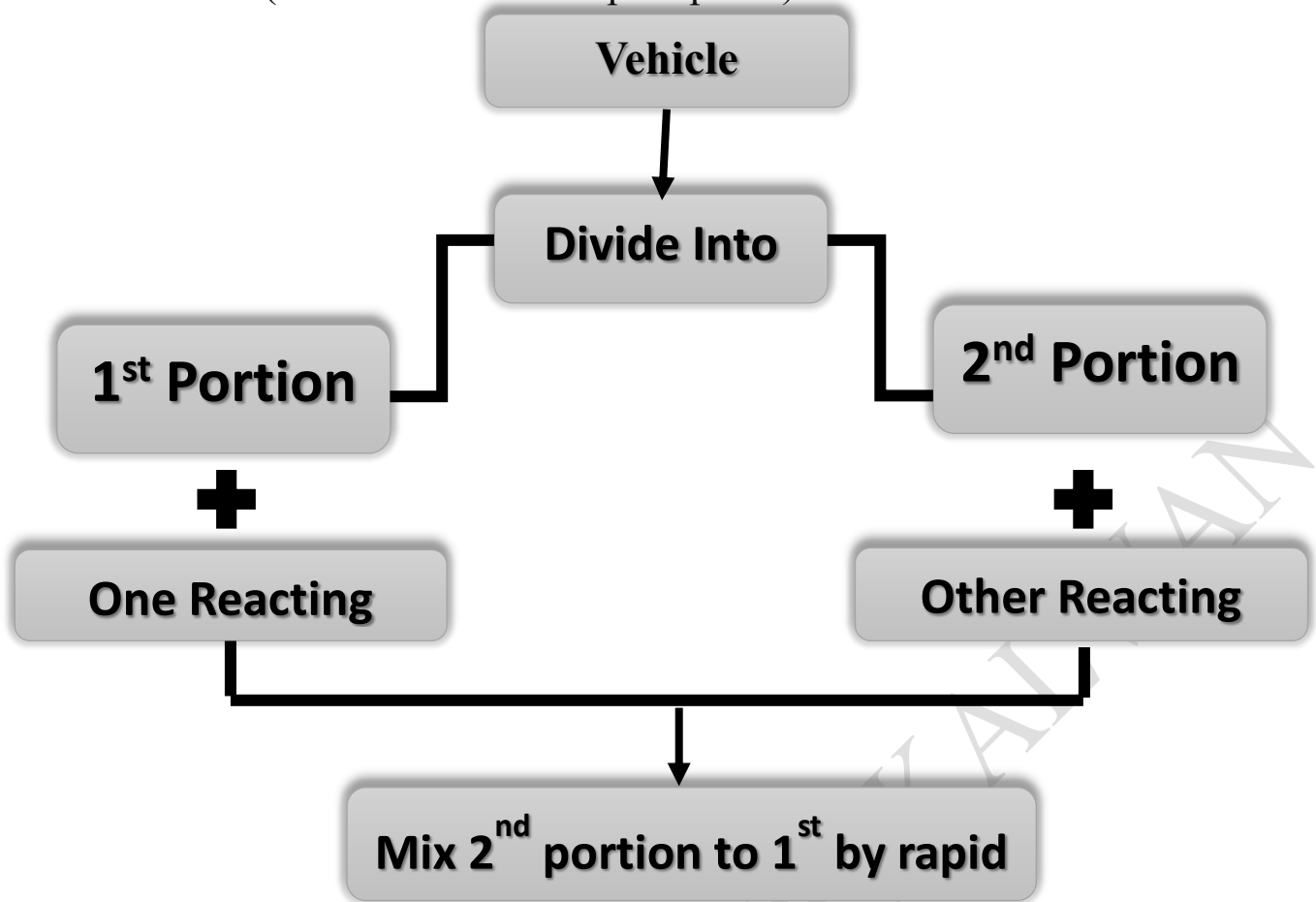
Intentional means when the prescriber knowingly prescribes the incompatible drugs whereas unintentional means when the prescriber prescribe the drugs without knowing that there is incompatibility between the prescribe drugs.

## Precipitate Yielding Interaction: -

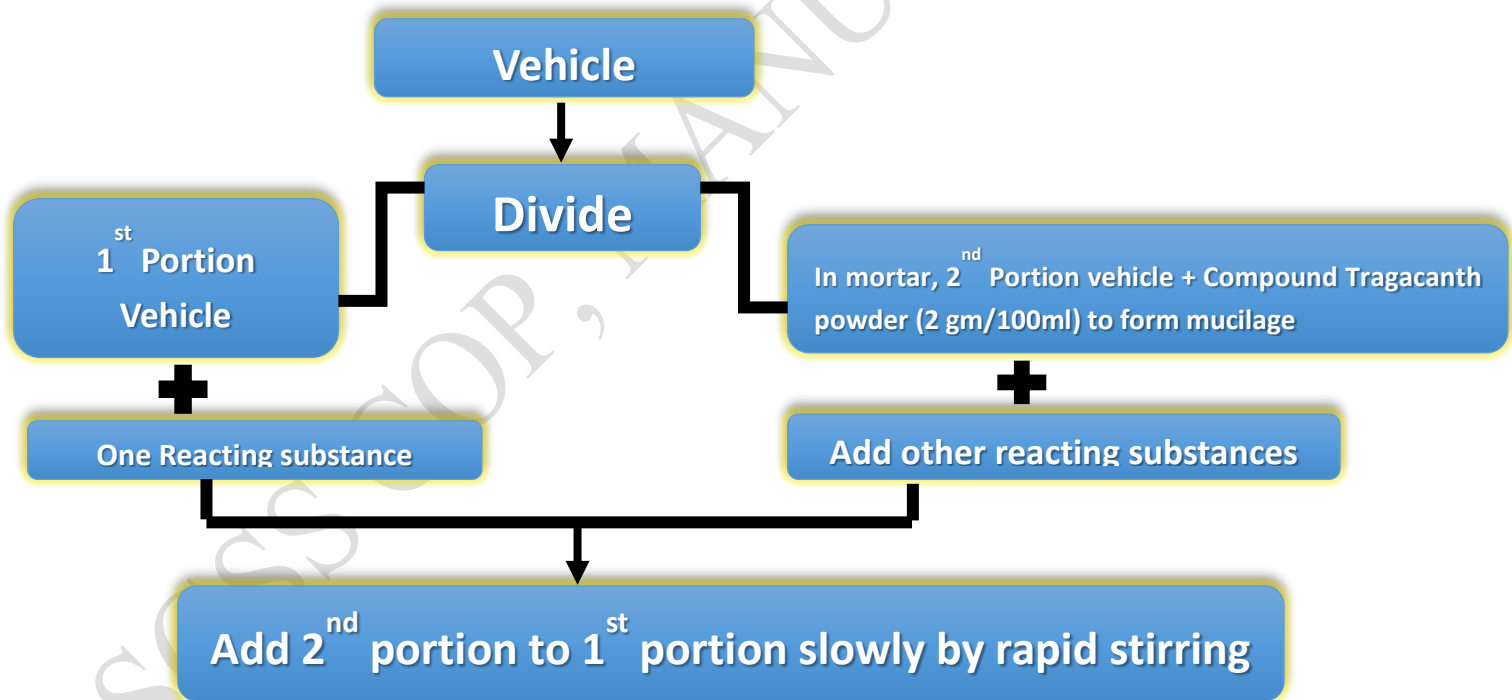
Reaction between strong solutions proceeds at a faster rate and form thick precipitates which is not diffuse readily. While dilute solutions upon mixing forms light diffusible precipitates.

The precipitate may be diffusible or indiffusible. To overcome this, follow Method A or Method B in dispensing the prescription that yields diffusible or indiffusible precipitates respectively.

**Method A: -** (Used for Diffusible precipitate)



**Method B: -** (Used for Indiffusible precipitate)



**Direction: -**

“SHAKE WELL BEFORE USE” should be given on the label whenever Method A & Method B is used dispense the prescription which contains diffusible or indiffusible precipitate.

## **Examples of chemical incompatibilities and methods of their correction: -**

### **1. Alkaloidal Incompatibility: -**

- i. Alkaloidal salts with alkaline substances.
- ii. Alkaloidal salts with soluble iodides.
- iii. Alkaloidal salts with tannins.
- iv. Alkaloidal salts with salicylates.
- v. Alkaloidal salts with soluble iodides and bromides.

### **2. Soluble Salicylate Incompatibility: -**

- i. Soluble salicylates with ferric salt.
- ii. Soluble salicylates with alkali bicarbonates.
- iii. Soluble salicylates and benzoates with acids.

### **3. Soluble Iodides Incompatibility: -**

- i. Oxidation of iodides with ferric salts.
- ii. Oxidation of iodides with potassium chlorate.
- iii. Oxidation of iodides with quinine sulphate.

### **4. Chemical Incompatibilities causing Evolution of Carbon Dioxide gas: -**

- i. Sodium bicarbonate with soluble calcium or magnesium salts.
- ii. Bismuth subnitrate and sodium bicarbonate.
- iii. Borax with sodium bicarbonate and glycerin.

### **5. Miscellaneous Chemical Incompatibilities: -**

- i. Soluble barbiturates with ammonium bromide.
- ii. Potassium chlorate with oxidizable substances.
- iii. Incompatibility of emulsifying agents.
- iv. Colour stability of dyes.
- v. Incompatibilities of liquorice liquid extract.

## 1. Alkaloidal Incompatibility: -

### i. Alkaloidal salts with alkaline substances: -

Alkaloids are weak bases and almost insoluble in water but alkaloidal salts are soluble in water. If these salts are dispensed with alkaline preparations s/a strong solution of ammonium acetate, aromatic spirit of ammonia, sodium bicarbonate etc, then free alkaloid may be precipitated. However, they are not always precipitated because all alkaloids are slightly soluble in water.

**Ex.**

Rx

Strychnine Hydrochloride solution	6 ml
Aromatic spirit of ammonia	4 ml
Water upto	120 ml
Make a mixture.	

When strychnine hcl reacts with aromatic spirit of ammonia, the strychnine gets precipitated. Because the given quantity of strychnine hcl is more than its solubility in water. The aromatic spirit of ammonia contains small amount of alcohol which can not dissolve strychnine hence precipitation is formed which acts as diffusible precipitate.

Hence follow Method A for precipitate yielding interaction.

### ii. Alkaloidal salts with soluble iodides: -

In cough mixture, potassium iodide is prescribed as expectorant with tincture ipacacuanha (containing emetine). The quantity of emetine present is so low that it can not react with potassium iodide to get precipitated as hydroiodide.

Similarly, when strychnine is prescribed along with soluble iodides it forms a insoluble hydroiodide as diffusible precipitates. Hence follow Method A to correct the incompatibility.

### iii. Alkaloidal salts with tannins: -

When alkaloidal salts combined with a drugs containing tannins then it forms tannates which separated as diffusible precipitates. So follow Method A for precipitate yielding interaction.

iv. **Alkaloidal salts with salicylates: -**

When quinine compounds are combined with salicylates. They form quinine salicylate as indiffusible precipitates. So follow Method B for precipitate yielding interaction.

**Ex.**

**Rx**

Quinine Hydrochloride	0.12 g
Sodium salicylate	4 g
Water upto	100 ml

Make a mixture.

Quinine hydrochloride on reaction with sodium salicylate form quinine salicylate as indiffusible precipitate. Therefore, follow Method B for precipitate yielding interaction.

**Ex.,**

**Rx**

Caffeine citrate	1 gm.
Sodium Salicylate	3 gm.
Water upto	90 ml.

Make a mixture.

Caffeine citrate is a mixture of equal weight of caffeine and citric acid. Citric acid on reacts with sodium salicylate liberates salicylic acid as a ppt.

So to overcome this problem, replace caffeine citrate with caffeine (substitute) which forms soluble complex with sodium salicylate and gives clear mixture.

v. **Alkaloidal salts with soluble iodides and bromides: -**

Alkaloids like strychnine, morphine, codeine etc. when combines with iodides and bromides then it forms insoluble hydroiodide and hydrobromide as diffusible precipitates respectively. Hence follow Method A for correcting the incompatibility.



**Ex.**

**Rx**

Potassium iodide	1.5 g
Tincture of stramonium	8.5 ml
Chloroform Water to make	100 ml

Tincture stramonium contains solanaceous alkaloid when combined with potassium iodide then it forms hydroiodide as diffusible precipitate. So, follow Method A in dispensing this prescription.

## **2. Soluble Salicylate Incompatibility: -**

### **A. Soluble Salicylate with Ferric salt: -**

When ferric salt reacts with sodium salicylate then it forms ferric salicylate as an indiffusible precipitate. Hence follow Method B.

**Ex.**

**Rx**

Ferric Chloride solution	2 ml
Sodium salicylate	3 gm
Water upto	90 ml
Make a mixture.	

**Direction: - SHAKE WELL BEFORE USE.**

Here, ferric chloride reacts with sodium salicylate and forms ferric salicylate as indiffusible precipitate. Hence follow Method B but this precipitate remains soluble upon addition of Sodium Bicarbonate to form clear mixture. So there is advantage of adding sodium bicarbonate in the prescription to form clear mixture.

**Rx**

Ferric Chloride solution	2 ml
Sodium salicylate	3 gm
Sodium Bicarbonate	8 gm
Water upto	90 ml
Make a mixture.	

Sodium Salicylate + Sodium Bicarbonate in 70 ml water



Add

Ferric Chloride solution



Effervescence produced

After ceasing of effervescence



Filter through cotton wool and Make up final volume.

#### B. Soluble Salicylate with Alkali Bicarbonate: -

When sodium salicylate taken orally then it reacts with Hcl present in stomach and forms salicylic acid precipitates which causes gastric irritation or pain in stomach. Hence to avoid such complications prescribed sodium bicarbonate in double quantity as that of sodium salicylate to neutralizes gastric acid and thus prevention of formation of sodium salicylate precipitates.

When sodium salicylate disperses in soluble form along with sodium bicarbonate (Alkaline substance) then this mixture absorbs oxygen from atmosphere and turns red colour mixture into reddish brown. This change will not affect the therapeutic efficacy of the mixture but may leads confusion to the patient. To avoid this, add colouring agent like liquorice liquid extract to darken the colour of mixture or patient may be warn about colour change or add suitable anti-oxidant like sodium metabisulphite (0.1 % w/v) with permission of prescriber.

**Ex.**

Rx

Sodium Salicylate                      8 gm

Sodium Bicarbonate                      8 gm

Sodium Metabisulphite                      0.08 gm

Chloroform Water upto                      120 ml

Make a mixture.

Sodium salicylate + Sodium bicarbonate in 90 ml water



Dissolve & Add

Sodium metabisulphite in above mixture



Filter the mixture



Through filtrate

Pass chloroform water to produce final volume

### C. Soluble Salicylates and Benzoates with Acids: -

Most of the acids and acidic syrup decomposes sodium salicylate and sodium benzoates which results in formation of salicylic acid and benzoic acid as indiffusible precipitate.

Ex.

Rx

Sodium Salicylate                      3 gm

Lemon syrup                      15 ml

Water upto                      60 ml

Make a mixture.

In this prescription, interaction between sodium salicylate & lemon syrup (citric acid) results in formation of salicylic acid as a indiffusible precipitate.

This incompatibility overcome by two way: -

1. Follow Method B or

2. Replace lemon syrup with simple syrup, lemon syrup is used as flavouring agent, so replacing does not affects the therapeutic efficacy of mixture.

### 3. Soluble Iodide Incompatibility: -

Iodides undergoes oxidation and forms iodine as an undesirable product.

A. Oxidation of iodides with ferric salts.

B. Oxidation of iodides with potassium chlorate.

C. Oxidation of iodides with quinine sulphate.

### C. Oxidation of Iodides with Quinine sulphate (Most Imp): -

Quinine sulphate is not freely soluble in water but made soluble in presence of dilute sulphuric acid. Interaction of sulphuric acid and potassium iodide forms hydroiodic acid and this acid partly oxidized by sulphuric acid gives iodine.

The iodine, hydroiodic acid and quinine sulphate then combined to form a compound called “Herapathite” or “Iodosulphite of quinine”.

#### Overcome: -

1. Supply mixture for 3 days because after 3 days Herapath Reaction occurs deposits bronze or olive-green crystals.
2. In case patient requires the mixture More Than 3 days then prepare two solutions using two portions of vehicle & supplied in a separate bottle. Mix the solution at the time of administration.

Ex.

Rx

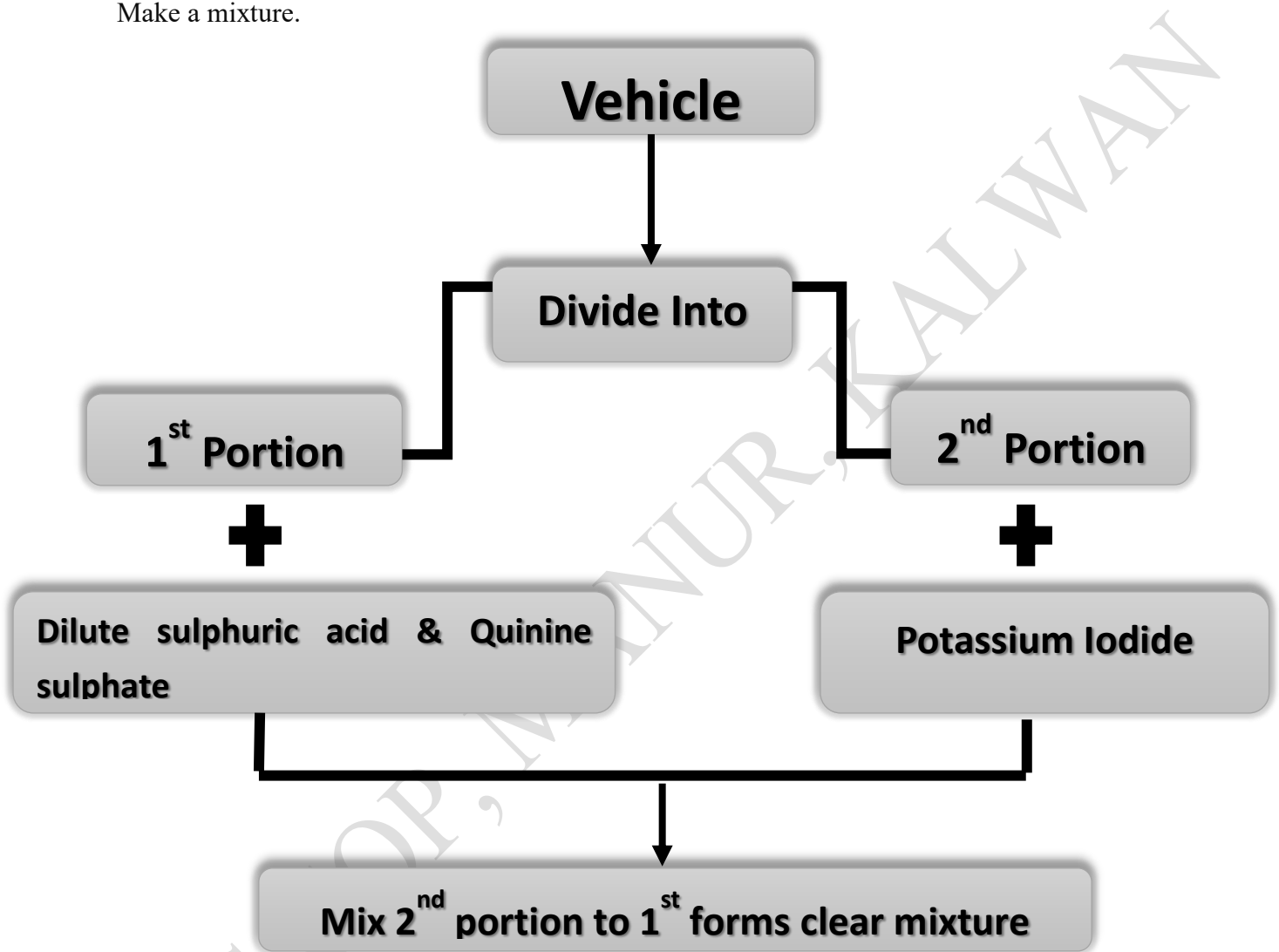
Quinine sulphate                      1.5 gm

Dilute Sulphuric acid                4 ml

Potassium Iodide                      8 gm

Water to make                          200 ml

Make a mixture.



This mixture after 3 days may deposit bronze or olive-green crystals, this reaction is known as Herapath reaction for quinine.

#### **Chemical Incompatibilities causing Evolution of Carbon Dioxide gas: -**

In mixture, when carbonates and bicarbonates combine with acid or acidic drugs then the reaction between these results into causes of evolution of carbon dioxide gas. If this mixture transfer as such into the bottle then there are chances of bursting the container.

To prevent such explosion, mix the ingredients in open vessel and allow the reaction to complete until the effervescence ceases. The reaction is slow at ordinary room temperature but can be speed up by adding hot water.

**i. Sodium bicarbonate with soluble calcium or magnesium salts: -**

Sodium bicarbonate + soluble calcium & magnesium salt

↓  
Decomposition reaction  
↓  
Forms

Insoluble carbonate as diffusible ppt and evolve CO<sub>2</sub> gas

↓  
Follow Method A



The mixture should be dispensed only when the effervescence are ceases.

**ii. Bismuth subnitrate and sodium bicarbonate: -**

Bismuth Subnitrate + Sodium bicarbonate + Water

↓  
Evolve CO<sub>2</sub> gas  
(Effervescence)



**iii. Borax with sodium bicarbonate and glycerin: -**

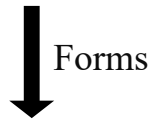
Borax + Glycerin mixed

↓  
Forms

Sodium metaborate and boric acid

↓

Further, boric acid reacts with sodium bicarbonate + glycerin



Glyceryl boric acid & liberates CO<sub>2</sub> gas.

Mix these ingredients in open vessel and hot water to speed up the reaction

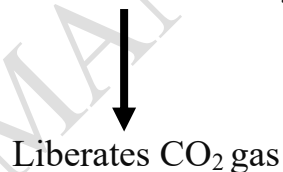
**Ex.**

Rx

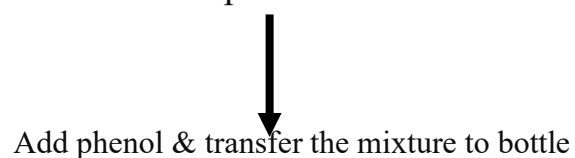
Sodium Bicarbonate	1 g
Borax	1 g
Phenol	0.5 g
Glycerin	20 ml
Water upto	90 ml

Make a spray solution.

Sodium bicarbonate + Borax + Glycerine + Water



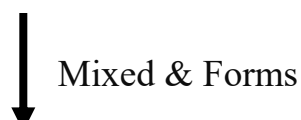
Allow the reaction to complete until the effervescence ceases



## 5. Miscellaneous Chemical Incompatibilities: -

### i. Soluble barbiturates with ammonium bromide: -

Sodium barbiturate + Ammonium bromide



Barbitone as indiffusible precipitate



Follow Method B for precipitate yielding interaction

**Ex.**

Rx

Phenobarbitone sodium 0.6 g

Ammonium Bromide 8 g

Water upto 100 ml

Make a Mixture.

Here, Barbitone forms as indiffusible precipitate.

Overcome either by following Method B for precipitate yielding interaction or by replacing ammonium bromide with equivalent amount of sodium or potassium bromide which has similar sedative action with ammonium bromide. This replacement gives clear mixture.

ii. **Potassium chlorate with oxidizable substances: -**

When potassium chloride (by heating or trituration) combined with oxidizable substances like charcoal, Sulphur or sugar organic compounds then there are chances of explosion.

**Overcome: -**

Separately powdered the ingredients using clean & dry mortar then mixed them gently on ointment tile without any friction.

**Ex.**

Rx

Potassium chloride 0.6 g

Tannic Acid 0.3 g

Sucrose 0.3 g

Make a Mixture.



iii. **Incompatibility of emulsifying agents (Reaction with salt): -**

Emulsifying agents like Alkali metal, ammonium and triethanolamine soaps are incompatible with salts. Using of such agent in emulsion produces polyvalent or divalent cations which causes phase inversion in emulsion i.e. from o/w to w/o or vice-versa.

Ex.

Rx

Phenol                      0.5 g

Menthol                    0.1 g

Tragacanth                0.5 g

Olive oil                    50 ml

Lime water upto        100 ml

Prepare an emulsion.

Here, olive oil containing free acid reacts with lime water produces divalent soap which results in w/o type of emulsion whereas Tragacanth produces o/w type of emulsion.

**Overcome:** - Prescription either referred back to prescriber or replace lime water with purified water or omit tragacanth.

iv. **Colour Stability of Dyes: -**

Colour stability of dyes depends upon pH of solution.

**For Ex.,** phenolphthalein dye is colourless in acidic solution but red in alkaline mixture due to their ionization.

Reducing agents cause fading of colour. Anionic dyes like amaranth, tartrazine are stable at acidic pH.

v. **Incompatibilities of liquorice liquid extract: -**

Liquorice liquid extract used as flavouring agent. Its flavouring property is due to glycyrrhizin which is a mixture of potassium and calcium salts of glycyrrhizinic acid. Acid decomposes glycyrrhizin into glycyrrhizinic acid which is insoluble precipitate. The precipitate is then clots and forms sticky black sediment which difficult to diffuse. Hence, in

case of acidic mixture, liquorice liquid extract will not suitable as flavouring agent. So, the prescription may refer back to prescriber for change the flavouring agents.

Certain salts like calcium chloride and magnesium sulphate cause partial pptation of glycyrrhizin which remain diffusible, hence follow Method A.

### 3. Therapeutic Incompatibility: -

Also called Physiological Incompatibility.

It is a result of mixing of two or more incompatible drugs that produces an undesirable pharmacological reaction occurs within the patient.

Prescribing of such drugs to the patient with the intension to produce specific pharmacological effect but the nature and intensity of the action shown by drug is different from that intended by prescriber.

#### Reasons of Therapeutic Incompatibility: -

1. Error in dosage.
2. Wrong dose or dosage form.
3. Contra-indicated drugs.
4. Synergistic & Antagonistic drugs.
5. Drug Interactions.

#### 1. Error in dosage: -

One of the reasons for therapeutic incompatibility due to error in prescription writing, so the prescription should be neatly and correctly written by prescriber.

Pharmacist also check any overdose of medicament.

**Ex.**

Rx

Atropine sulphate                      0.006 g

Phenobarbitone                        0.015 g

Aspirin                                    0.300 g

Prepare 10 capsule.

**Error: -** Dose of atropine is more than its maximum recommended dose (0.2 to 2 mg).

So, the prescription should refer back to the prescriber to correct the dose.

## 2. Wrong dose or dosage form: -

There are certain drugs which have quite similar names, so care should be taken while dispensing of such drugs.

For ex., Tab. Dulcolax (Laxative tab), Tab. Duoclox (Antibacterial tab).

Prednisone and Prednisolone, Digoxin and Digitoxin.

Many drugs are available in different dosage forms like tab, caps, inj. Etc.

For ex., Tab. Clavam-625 (Amoxycillin and clavulanic acid).

Clavam Dry syrup.

Tab. Diclofenac

Inj. Diclofenac

So proper dosage form clearly mentioned by prescriber if not then prescription should refer back to prescriber for correction.

## 3. Contra-indicated drugs: -

Certain drugs should not be given in particular disease conditions.

For ex., i) Corticosteroids contraindicated in patients with peptic ulcer.

ii) Penicillin or Sulpha drugs contraindicated in patients who have allergic to it.

iii) Barbiturate or Morphine should not be given to Asthmatic patient.

Ex.

Rx

Sulphadiazine                      250 mg

Sulphamerazine                      250 mg

Ammonium Chloride                      500 mg

*Direction-* Take 2 capsule after every six hours.

Here, Ammonium chloride is urinary acidifier cause deposition of sulphonamide crystals in kidney hence, prescription should refer back to prescriber.

#### 4. Synergistic or Antagonistic Drugs: -

##### **Synergism: -**

Syn means Together

Ergon means Work

When two drugs administered in combination, they increase the response of one another or each other. This combination effect is greater than the response produced by the individual drugs, phenomenon called Synergism.

For ex., Sulphamethoxazole and Trimethoprim combination used as Antibacterial.

##### **Additive Effect: -**

Ex.

Rx

Amphetamine sulphate	20 mg
Ephedrine sulphate	100 mg
Syrup upto	100 ml
Make a Mixture.	

In this prescription, there is a combination of two sympathomimetic drugs with additive effect to treat Asthma. So, need to reduce dose of each drugs. Hence the prescription should refer back to the prescriber.

***\*Synergism is intentional to increase the activity of drug.***

##### **Antagonism: -**

When two or more drugs administered simultaneously, the effect one drug is opposed or reduced by another drug, such agents known as Antagonistic agents and the phenomenon is known as Antagonism.

Ex.

Rx

Acetyl Salicylic Acid                      0.6 g

Probencid                                      0.5 g

In this prescription, both the drugs are used to treat gout. However, this combination results in neutralization. So prescription is referred back to prescriber.

### 5. Drug Interaction: -

When two or more drugs taken simultaneously, effect of one drug is altered by another drug such interaction is called Drug Interaction.

Interaction not only seen between drug-drug but can also be seen between drug-food, drug-beverages or drug-supplement.

Ex.

Rx

Tetracycline                      250 mg

Send 10 capsules.

*Direction:* - Take 1 capsule after every six hours with milk.

If tetracycline administered with milk then it is inactivated by calcium ions present in the milk.

The interaction between tetracycline and calcium ions results in formation of insoluble complex known as Chelate. The formation of chelate decreases the absorption of tetracycline. So, this incompatibility is unintentional. Hence, prescription should refer back to the prescriber.