Program	B. Pharmacy
Semester	1st semester
Subject /Course	Pharmaceutics-1
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Module No.	IV
Module Title	suppositories and Pharmaceutical Incompatibilities
Course coordinator	Dr. Neelam Sharma

Learning Outcome of Module-4

LO	Particular
103.5	To know methods of preparations, Displacement value and its calculations, evaluation of suppositories.
103.5	To know the Pharmaceutical Incompatibilities

Module Content Table

No.	Topic
1.	Suppositories: Definition, types, advantages and disadvantages, types of bases, methods of preparations. Displacement value and its calculations, evaluation of suppositories.
2.	Pharmaceutical Incompatibilities: Definition, classification, physical, chemical and therapeutic incompatibilities with examples.

SUPPOSITORIES

Definition:

- Suppositories are specially shaped solid dosage form of medicament for insertion into body cavities other than mouth.
- They may be inserted into rectum, vagina or the urethra.
- These products are so formulated that after insertion, they will either melt or dissolve in the cavity fluids to release the medicament.

TYPES OF SUPPOSITORIES

1. Rectal suppositories: These are meant for introduction into the rectum for local and systemic effect.
2. Pessaries: These are meant for introduction into vagina for local
3. Urethral bougies: These are meant for introduction into urethra.
4. Weight: 2 – 4 gm Length: 2 – 5 inches.
5. Nasal bougies: These are meant for introduction into nasal cavities. Weight: 1gm Length: 9 – 10 cm

Advantages of rectal suppositories:

i. *Mechanical action:* The rectal suppositories are extensively used as a mechanical aid to bowel evacuation which produce its action by either irritating the mucous membrane of the rectum (e.g. glycerol and bisacodyl) or by lubricating action or by mechanical lubrication.

ii. *Local action:* The rectal suppositories may be used for soothing, antiseptic, local anaesthetic action or for astringent effect. Therefore, they may contain *soothing* e.g. zinc oxide

iii. *local anaesthetic*- e.g. cinchocaine, benzocaine *astringents* e.g. bismuth subgallate, hamamelis extract and tannic acid

iv. antiinflammatory e.g.hydrocortisone and its acetate.

v. *To provide systemic action*: Suppositories are convenient mode of administration of drugs which irritate the gastrointestinal tract, cause vomiting, are destroyed by the hepatic circulation, or are destroyed in the stomach by pH changes, enzymes etc.

vi. *Partial bypass:* The lower portion of the rectum affords a large absorption surface area from which the soluble substances can absorb and reach the systemic circulation.

vii. Systemic treatment by the rectal route is of particular value for:

a. treating patients who are unconscious, mentally disturbed or unable to tolerate oral medication because of vomiting or pathological conditions of the alimentary tract.
b. administering drugs, such as aminophylline, that cause gastric irritation, and
c. treating infants.

PROPERTIES OF IDEAL SUPPOSITORY BASE

1. It should melt at rectal temperature (36^0) or dissolve or disperse in body fluid. For eutectic mixtures and in tropical climate the melting range of the base should be higher.
2. Release medicaments easily.
3. Shape should remain intact while handling.
4. Non-toxic and non-irritant to sensitive and inflammed mucous membrane.
5. It should be stable on storage i.e. it does not change color, odor, or drug release pattern.
6. Compatible with broad variety of drug and adjuvants.
7. It should shrink so that it comes out easily from the mould without the use of any lubricants.
8. *For fatty bases the following additional specifications are required:*
9. "Acid value" is below 0.2
10. "Saponification value" ranges from 200 to 245
11. "Iodine value" is less than 7
12. The interval point and solidification point is small.

SUPPOSITORY BASES

Classification of suppository bases

1. *Fatty bases* – they melt at body temperature.
2. *Water-soluble or water miscible base* – they dissolve or disperse in rectal secretions.
3. *Emulsifying bases* – they emulsifies small amount of aqueous solution of drug.

FATTY BASES

Example: Theobroma oil (Cocoa butter), Synthetic fats.

Theobroma oil (Cocoa butter)

- It is a yellowish-white solid having chocolate flavor.
- It is a mixture of glyceryl esters of stearic, palmitic, oleic and other fatty acids.

Advantages:

a. A melting point range of 30 to 36 ^{0}C; hence it is solid at normal room temperatures but melts in the body.
b. Ready liquefaction on warming and rapid setting on cooling.
c. Miscibility with many ingredients.
d. Blandness i.e. does not produce irritation.

Disadvantages:

Polymorphism

-crystals (unstable, m.p. 20αCocoa butter has three polymorphs ^{0}- crystals (stable, m.p. 36βC), ^{0}-crystals (unstable, 15γC) and ^{0}C).

When melted and cooled it solidifies in different crystalline forms, depending on the temperature of melting, rate of cooling and size of the mass. If melted below 36^0-crystals with normal melting point, but if over-heated it may produce, on cooling, unstableβC and slowly cooled it forms stable

-crystals, which melt at about 15γ^0-crystals, melting at about 20αC, or ^{0}C. These unstable forms eventually return to the stable condition but this may take several days and meanwhile, the suppositories may not set at room temperature or, if set by cooling, may remelt in the warmth of the patient's home.

This lowering of the solidification point can also lead to sedimentation of suspended solids. Consequently, great care must be taken to avoid over- heating the base when making theobroma oil suppositories.

b. Adherence to mould

Because theobroma oil does not contract enough on cooling to loosen the suppositories in the mould, sticking may occur, particularly if the mould is worn. This is prevented by lubricating the mould before use.

c. Softening point too low for hot climates

To raise the softening point, whit beeswax may be added to theobroma oil suppositories intended for use in tropical and subtropical countries.

d. Melting point reduced by soluble ingredients

Substances, such as chloral hydrate, that dissolve in theobroma oil, may lower its melting point to such an extent that the suppositories are too soft for use. To restore the melting point, a controlled amount of white beeswax may be added.

e. Slow deterioration during storage

This is due to oxidation of the unsaturated glycerides.

f. Poor water absorbing capacity

This fault can be improved by the addition of emulsifying agents.

g. Leakage from the body

Sometimes melted base escapes from the rectum or vagina. This is most troublesome with pessaries because of their larger size, and therefore, these are rarely made with theobroma oil.

h. Relatively high cost

Synthetic fats

As a substitute of theobroma oil a number of hydrogenated oils, e.g. hydrogenated edible oil, arachis oil, coconut oil, palm kernel oil, stearic and a mixture of oleic and stearic acids are recommended. [N.B. Synthetic suppositories bases are by hydrogenation and subsequent heat treatment of vegetable oils such as palm oil and arachis oil. The oils are generally esters of unsaturated fatty acids. Hydrogenation saturates the unsaturated fatty acids and heat treatment splits some of the triglycerides into fatty acids and partial esters (mono- and di-glycerides).

Advantages of these synthetic fats over theobroma oil:

1. Their solidifying points are unaffected by overheating.
2. They have good resistance to oxidation because their unsaturated fatty acids have been reduced.
3. Their emulsifying and water absorbing capacities are good. [They usually contain a proportion of partial glycerides some of which, e.g. glyceryl monostearate, are w/o emulsifying agents and, therefore, their emulsifying and water absorbing capacity are good.
4. No mould lubricant is required because they contract significantly on cooling.
5. They produce colorless, odourless and elegant suppositories.

Disadvantages:

1. They should not be cooled in refrigerator because they become brittle if cooled quickly. Certain additives e.g. 0.05 % polysorbate80, help to correct this fault.
2. They are more fluid than theobroma oil when melted and at this stage sedimentation rate is greater. Thickeners such as magnesium stearate , bentonite and colloidal silicon dioxide, may be added to reduce this.

WATER SOLUBLE AND WATER MISCIBLE BASES

Glycero-Gelatin base

- This is a mixture of glycerol and water made into a stiff jelly by adding gelatin.

- It is used for the preparation of jellies, suppositories and pessaries. The stiffness of the mass depends upon the proportion of gelatin used which is adjusted according to its use.
- The base being hydrophilic in nature, slowly dissolves in the aqueous secretions and provide a slow continuous release of medicament. Glycerogelatin base is well suited for suppositories containing belladonna extract, boric acid, chloral hydrate, bromides, iodides, iodoform, opium, etc.
- Depending upon the compatibility of the drugs used a suitable type of gelatin is selected for the purpose. Two types of gelatins are used as suppository base
    i. *Type-A* or Pharmagel-A which is made by acid hydrolysis (has isoelectric point between 7 to 9 and on the acid side of the range behaves as a cationic agent, being most effective at pH 7 to 8.) is used for acidic drugs.
    ii. *Type-B* or Pharmagel-B which is prepared by alkaline hydrolysis (having an isoelectric point between 4.7 to 5 and on the alkaline side of the range behaves as an anionic agent, being most effective at pH 7 to 8) is used for alkaline drugs
    iii. *Disadvantages:*
    iv. Glycerogelain base suppositories are less commonly used than the fatty base suppositories because:
    v. Glycerol has laxative action.
    vi. They are more difficult to prepare and handle.
    vii. Their solution time depends on the content and quality of the gelatin and the age of the base.
    viii. They are hygroscope, hence must be carefully stored.
    ix. Gelatin is incompatible with drugs those precipitate with the protein e.g. tannic acid, ferric chloride, gallic acid, etc.

Soap-Glycerin Suppositories

- In this case gelatin and curd soap or sodium stearate which makes the glycerin sufficiently hard for suppositories and a large quantity of glycerin up to 95% of the mass can be incorporated.
- Further the soap helps in the evacuation of glycerin.
- The soap glycerin suppositories have the disadvantage that they are very hygroscopic, therefore they must be protected from atmosphere and wrapped in waxed paper or tin foil.

Polyethylene glycol bases / Macrogol bases (Carbowaxes)

Depending on their molecular weight they are available in different physical forms.

Examples of Macrogol bases:

	I	II	III	IV
Macrogol 400	-	-	20	-
Macrogol	-	-	-	75
1000	-	33	33	-
Macrogol	33	-	-	25
1540	47	47	47	-
Macrogol	20	20	-	-
4000				
Macrogol				
6000				
Water				

By choosing a suitable combination a suppository base with the desired characteristics can be prepared.

Advantages:

1. The mixtures generally have a melting point above 42^0C, hence, does not require cool storage and they are satisfactory for use in hot climate.
2. Because of the high melting point they do not melt in the body cavity, rather they gradually dissolve and disperse, releasing the drug slowly.
3. They do not stick to the wall of the mould since they contract significantly on cooling.

EMULSIFYING BASES

These are synthetic bases and a number of proprietary bases of very good quality are available, few of which are described below:

Witepsol

They consist of triglycerides of saturated vegetable acids (chain length C12 to C18) with varying proportions of partial esters.

Massa Esterium

This is another range of bases, consisting of a mixture of di-, tri- and mono- glycerides of saturated fatty acids with chain lengths of C11 to C17.

Massuppol

It consists of glyceryl esters mainly of lauric acid, to which a small amount of glyceryl monostearate has been added to improve its water absorbing capacity.

Advantages of these bases over cocoa butter:

1. Over heating does not alter the physical characteristics.
2. They do not stick to the mould. They do not require previous lubrication of the mould
3. They solidify rapidly.
4. They are less liable to get rancid.
5. They can absorb fairly large amount of aqueous liquids.

Factors affecting-absorption from rectal suppositories

A. Physiologic factors

The lower hemorrhoidal veins surrounding the colon and rectum directly goes to heart and the upper hemorrhoidal vein connects to liver via portal vein. So more than 50 to 70% of the drug administered rectally were found to directly passing to systemic circulation (i.e. bypassing the liver).

pH of rectal secretion

The principal method of drug absorption from the rectum is by passive diffusion. So a drug that remains mostly in unionized state will be absorbed more readily. Generally weakly basic and weakly acidic drugs remains in unionized state in the pH of rectum (6.8) and hence, absorbed readily than the stronger base or acids.

B. Physicochemical characteristics of the drug

The sequence of events that takes place before absorption n the anorectal area is as follows:

rectal mucosa→ Drug in colon fluids →Drug in vehicle

- *Partition coefficient*: Drugs with a high fat to water (Ko/w) partition coefficient are liberated very slowly from the fatty bases. So water soluble salt forms of drugs are more readily absorbed from anorectal area.*Rectal fluid volume*: Rectal fluid volumes also vary in different time and in different individuals. This influences the release rate and absorption of drug from suppository bases.

- *Physical state of medicament*: When a drug remains in suspension state in a suppository the drug particles should be very fine, so that the effective surface area is very high and thus dissolution rate is very high.

  Solution from a suppository will be faster when it melts quickly into a fluid of low viscosity that spreads into thin film over a large area in the rectum.

Generally, for *local action* fatty base is suitable and for *systemic action* water-soluble base is better for providing the quick release desirable for systemically active drugs.

- *Presence of surfactants* absorption is accelerated.→ new pores for absorption will be opened → help in washing the rectal mucosa, →: Surfactants can both increase or decrease the absorption rate of a drug from anorectal region. Surfactants can reduce the surface tension of the colon fluid

C. Physicochemical characteristics of the base and adjuvants.

- absorption rate is faster than higher m.p. fatty base + sod.phenobarbitone.→Lower m.p. fatty base + sodium phenobarbitone
- High molecular weight PEG bases produces faster absorption than low molecular weight PEG base.
- Fatty bases may be hardened several months after molding, these increase in melting range decrease the drug release.
- Adjuvants in the base changes the rheologic characteristics of the base or may affect the dissolution of the drug. e.g. addition of colloidal silicon oxide to fatty base dramatically changes the rheologic characteristics of the base.e.g. Salicylates were found to improve the rectal absorption of water- soluble antibiotics in lipophilic bases.
- Emulsifying agents such as wool fat, wool alcohols, macrogols, stearates and polysorbates, may be included in the suppository bases to facilitate the incorporation of aqueous solutions. They may cause unpredictable release and absorption of a medicament.
- Large amount of emulsifying agents may cause excessive foaming.
- Strong surface active agent may produce increased absorption of drug and may produce toxic effects.

MANUFACTURING OF SUPPOSITORIES

Moulds

The suppository and pessary moulds are made of metals and have four, six or twelve cavities. By removing a screw, they can be opened longitudinally for lubrication, extraction of the suppositories and cleaning. [N.B. The interior of the mould should never be scrapped or rubbed with abrasive. For cleaning they are immersed in hot water containing detergent, wiped gently with soft cloth and rinsed thoroughly.]

***Capacity of moulds*:** The nominal capacities of the common moulds are 1g, 2g, 4g and 8g.

Calibration

The nominal capacity of a mould varies with the base selected. Each mould should be calibrated before use by preparing a set of suppositories or pessaries using the base alone, weighing the products and taking the mean weight as the true capacity. This procedure is repeated for each base.

Displacement value

The volume of a suppository from a particular mould is uniform but its weight will differ with the density of the base.

Definition

It is the quantity of the drug that displaces one part of the base. e.g. Zinc oxide, D = 5.

Calculation of displacement value

Formula for calculation of the amount of base required in each mould

Capacityof each mould (gm)=Amount of base required for eachsuppositor y (gm) -

Lubrication of mould

Dose of drug (gm) Displacement value of the drug If the cavities are imperfect, i.e. poorly polished or scratched, it may be difficult to remove the suppositories without damaging their surfaces. So lubrication of the moulds is necessary.

In case of greasy or oily base water soluble lubricants are required. e.g. For cocoa butter the following lubricant solution formula may be used:

Soft soap 10g
Glycerol 10ml
Alcohol(90%)
50ml

For water soluble /miscible bases oily lubricant may be used. e.g. For glycero-gelatin base liquid paraffin or arachis oil may be used as lubricant.

Four methods are used in preparing suppositories:

1. **Hand molding [Cold Hand Shaping]**
2. Drug is triturated in a mortar into fine powder.

3. Cocoa butter is grated into small particles.
4. Drug is mixed with small portion of cocoa butter in a mortar.
5. One drop fixed vegetable oil is added to give plasticity to the mass.
6. Remainder of the cocoa butter is added by geometric dilution (i.e. by adding the same amount of base as is already in the mortar), triturated wit pressure. Heat generated by trituration results in a plastic mass, which is cohesive and ready to roll.
7. The mass is scrapped from the mortar with a spatula and rolled into a ball.
8. An ointment tile is taken, dusted lightly with starch powder, ball is placed on it, rolled with a flat faced spatula to form a cylinder. The cylinder is cut into desired number of pieces with a sharp blade.
9. One end of a suppository is held firmly with a finger and the other end is tapered with the spatula to give the shape of suppository.

2. Compression molding

In this case an instrument known as *compression mould* is used.

1. Drug is powdered and mixed with grated cocoa butter.
2. The mixture is filled into a chilled cylinder. The mixture is pressed within the cylinder by a piston until a pressure is felt.
3. Then the suppositories are expelled from the cylinder.

3. Pour molding (Fusion method)

This is the main method of preparing suppositories.

1. Drug is powdered in a mortar.
2. Carefully grated cocoa butter is taken into a beaker and heated in a water bath. When 2/3rd - crystals will form and the suppositories will remain in melted state at room temperature.]γ, and αportion is melted the beaker is taken out of the heat source. The rest of the mass is melted by stirring with a glass rod. [If cocoa butter is heated to clear liquid then unstable
3. Drug is added into the beaker and stirred thoroughly to mix with the “creamy” base.
4. The “creamy” melted base is then poured into previously lubricated mould.
5. -crystal after 24 hours of refrigeration).βThe mould is allowed to congeal, then placed in the refrigerator for 30 minutes to harden (forms stable

6. Mould is taken out from the refrigerator and surface is trimmed off. The mould is opened and the suppositories are expelled out of the mould by gentle pressure with the finger.

4. Automatic molding machine

Two types of molding machines are available: (a) rotary molding machine and (b) straight-line molding machine

Manufacturing cycles in rotary molding machine:

1. Prepared mass is filled in a into a filling hopper where it is continuously mixed and maintained at constant temperature.
2. The suppository molds are lubricated by brushing or spraying lubricant solution.
3. The molten mass is filled in the molds to a slight excess.
4. The mass is *cooled* to solidify and the excess material is *scrapped off* and collected for re-use.
5. In the ejecting section the mold is opened and the suppositories are pushed out by steel rods.
6. The mold is closed, and then moved to the first step of the cycle. The output of a typical rotary machine ranges from 3500 to 6000 suppositories an hour.

Manufacturing cycles in straight-line molding machine:

Here the cycle is similar to rotary molding machine but the individual molds are carried on a track through a cooling tunnel, where scrape-off and ejection occur.

PACKAGING OF MOLDED SUPPOSITORIES

Objective: The suppositories should be over-wrapped, or they must be placed in a container in such a way that they do not touch each other.

Why packing is required?

Suppositories in contact with one another may fuse with one another or with the container at roomtemperature.

Packing materials: Suppositories are usually over-wrapped in aluminium foils, paper strip or plastic strips.

Packaging machines

1. *Machine-I*: The chilled-hardened suppositories are placed in a notched turntable and then fed to the packing station, where the foil is unwounded from a roll, cut to size, and finally rolled around each suppository.

2. *Machine*-II*:* The suppositories are enclosed in cellophane or heal-sealed aluminium foils. Plastic may be thermoformed into two packaging halves. Suppository is mechanically placed in one half and the second half of plastic is sealed by heat.

Bulk storage

The individually wrapped suppositories are packaged in slide, folding, or set-up boxes.

Suppositories containing hygroscopic or volatile material are packed in glass or plastic containers.

Many suppositories are not individually over-wrapped. They are placed in sectioned card-board boxes or plastic containers to hold 6 or 12 suppositories.

In-package molding

In this automatic method individual suppository is molded in their wrapping material. Either plastic or aluminium foil/propylene/lacquer laminate are used.

Advantage: If the suppository melts at higher storage temperature their shapes are retained which can be used just by chilling again.

In *plastic* wrapping the plastic is thermoformed into the shape of mould. The molten mass is injected through the top end and tops is cooled and sealed.

In *aluminium foil* method two aluminium foils are embossed and sealed to give the shape of a mold and then the mass is injected at the top and then the top is cooled and sealed.

SPECIFIC PROBLESM IN FORMULATING SUPPOSITORIES

1. Water in suppositories

Water is used as a solvent to incorporate a water-soluble substance in the suppository base. Incorporating water should be avoided for the following reasons.

a. Water accelerates the oxidation of fats.
b. If the water evaporates the dissolved substances crystallize out.
c. In presence of water reactions between various ingredients of suppositories may occur.
d. The water may be contaminated with bacteria or fungus.

3. Hygroscopicity

Glycerinated gelatin suppositories lose moisture in dry climates and absorbs moisture in high humidity.

Polyethylene glycol bases are also hygroscopic.

4. Incompatibilities

Poyethylene glycol bases are incompatible with silver salts, tannic acid, aminopyrine, quinine, ichthammol, aspirin, benzocaine, iodochlorohydroxyquin, and sulfonamides.

Many chemicals have a tendency to crystallize out of PEG e.g. sodium barbital, salicylic acid and camphor.

5. Viscosity

Viscosity of melted base is low in cocoa butter and high in PEG and glycerinated gelatin. Low viscosity base when melted the suspended particles may sediment very quickly producing nonuniform distribution of drugs.

Remedies:

a. The base should be melted at the minimum temperature required to maintain the fluidity of the base.

b. The base is constantly stirred in such a way that the particles cannot settle and no air is entrapped in the suppository..

c. A base with a narrow melting range closer to rectal temperature is used.

d. Inclusion of approximately 2% aluminium monostearate increase the viscosity of the fatty base and also helps in homogeneous suspension of particles.

e. Cetyl, stearyl, myristyl alcohol or stearic acid are added to improve the consistency of suppositories.

6. Brittleness

Cocoa butter base is not brittle but synthetic fat bases with high degree of hydrogenetation and high stearate containing bases are brittle.

Brittle suppositories produce trouble during manufacture, handling, packaging and during use.

Causes: Rapid chilling (shock cooling) of the melted bases in an extremely cold mold.

Remedies:

a. The temperature difference between the melted base and mold should be as small as possible.

b. Addition of small amount of Tween80, castor oil, glycerin or propylene glycol imparts plasticity to a fat and make it less brittle.

7. Volume contraction

When the bases are cooled in the mould volume of some bases may contract.

Volume contraction produces

a. good mold release facilitating the ejecting from mold.

b. contraction hole formation at the top: This imperfection can be solved by adding slight excess base over the suppositories and after cooled the excess is scrapped off.

8. Lubricants

Cocoa butter adheres to suppository molds because of very low volume of contraction. Aqueous lubricant may be used to remove the suppositories easily from the molds. They are applied by wiping, brushing or spraying. The mold surfaces may be coated with teflon to reduce the adhesion of base to mold wall.

9. Rancidity & oxidation

-tocopherols,β- and α-naphthoquinone, βDue to auto oxidation of unsaturated fatty acids present in the base, saturated and unsaturated aldehydes, ketones and acids may formed, which have very strong unpleasant odor – this phenomenon is called rancidification. To prevent this suitable antioxidants like hydroquinione, *gossypol* (present in cotton seed oil), *sesamol* (present in sesame oil) propyl gallate, gallic acid, tannins and tannic acids, ascorbic acid (Vit C.), butylated hydroxyanisole (BHA) and butylated hydroxyanisole (BHA).

INDRODUCTION

Incompatibility is definedas a change resulting and an undesirable product is formed, which may affect the safety, efficacy appearance and stability of the pharmaceutical product1.

Incompatibilities occur during2

- Compounding
- Formulation
- Manufacturing
- Packaging
- Dispensing
- Storage
- Administration of drugs

The incompatibilities may be detected by changes in the physical, chemical, and therapeutic qualities of the medicine.

TYPES OF INCOMPATIBILITIES:-

The incompatibilities occur when the components of a medicine interact in such a way that properties of that medicine are adversely affected3

Physical incompatibilities

2. Chemical incompatibilities

3. Therapeutic incompatibilities

PHYSICAL INCOMPATIBILITIES:-

When two or more than two substances are combined together, a physical change takes place and an unacceptable product is formed.

Interaction between two or more substances which may lead to change in color, odor, taste, viscosity and morphology. It is also called as pharmaceutical incompatibility5.

Manifestations of physical incompatibility:-

The following list outlines the various ways incompatibility between or among drug agents may be manifested.

A. Insolubility:-insolubility of prescribed agents in vehicle

B. Immiscibility:-Immiscibility of two or more liquids

C. Precipitation:-It occurs due to solvent is insoluble when it is added to solution

d. Liquefaction:-Liquefaction of solids mixed in a dry state (called eutexia)

INSOLUBILITY

It means the inability of material to dissolve in a particular solvent system. The majority of incompatibilities is due to insolubility of the inorganic as well as organic compounds in particular solvents6.

The following factors affect the solubility of prescribed agent in vehicle and may render it less soluble.

- Change in PH
- Milling
- Surfactant
- Chemical reaction
- Complex formation
- Co-solvent

Any change in previous factors may lead to precipitation of drugs and change in their properties.

Substances like chalk, acetyl salicylic acid, succinylsulphothiazzole, zinc oxide, and calamine are the commonexamples of in diffusible solids.

Some tinctures containing resins or chlorophyll may provide precipitation when added to the aqueous system.

E.g.:-Mixture of prepared chalk

Rx

Chalk powder –2g

Tincture catechu – 2ml

Cinnamon water – 2ml

Causes: - Chalk powder is not soluble in water.It gets precipitated when added to aqueous medium.These precipitates are found in diffusible in nature which results in physical incompatibility.

Remedy: - Use of suspending agents is necessary to suspend the precipitated chalk particles. Generally 2% W/V of compound tragacanth powder is recommended as suspending agent.

The corrected prescription is

Mixture of prepared chalk

Rx

Chalk powder –2g

Tragacanth – 0.4g

Tincture catechu – 2ml

Cinnamon water up to 30ml

IMMISCIBILITY

When two suchingredients are combined resulting in a non- homogenous product, such ingredients are called immiscible to each other and the phenomenon is called immiscibility.This manifestation appears clearly in emulsions, creams, lotions, some types of ointments. Separation in two phases is noticed in this pharmaceutical dosage form.Storage must be in room temperature to prevent separation.

The following factors lead to immiscibility

Incomplete mixing

Addition of surfactant with

Unsuitable concentration

False time of addition

Unsuitable for the type of emulsion

Presence of micro – organisms

Some bacteria grow on constituents of mixture.

E.g.:- Gelatin Arabic gum

Others produce enzymes which oxidize the

surfactant.

Temperature

Oils and water are immiscible with each other which ϖ shows physical incompatibility

E.g.:- Castor oil emulsion

Rx

Castor oil – 15ml

Water – 60ml

Causes: -In this prescription castor oil is immiscible with water due to high interfacial tensions, which is a sign of incompatibility.

Remedy:-To overcome this type of incompatibility emulsification is necessary with the help of an emulsifying agent. The corrected prescription is

Castor oil emulsion

Rx

Castor oil – 15ml

Acacia – 2% W/V

Water– upto 60ml

LIQUIFACTION

When certain low melting point solids are mixed together, a liquid or soft mass know as eutectic mixture is produced.This occurs due to the lowering of the melting point of the mixture to below room temperature and liberation of hydrates.

If such conditions take place, compounding such powders becomes difficult since the ultimate mixture turns to liquid. The medicaments showing this type of behavior are camphor, menthol, phenol, thymol, chloral hydrate, aspirin, sodium salicylates, etc……

E.g.:-Insufflations

Rx

Menthol – 5g

Camphor – 5g

Water – 60ml

Causes: - This mixture is a physical incompatibility because both the ingredients in the prescription are liquefiable of mixed together.

Remedy:-These substances can be dispensed by any one of the following method.Triturate together to form liquid and mixed with an absorbent (light kaolin, magnesium carbonate) to produce the following powder. The individual medicaments is powdered separately and mixed with an adsorbent and then combined together tightly and filled in a suitable container12.

Hence the corrected prescription is

Rx

Menthol – 5g

Camphor – 5g

Light kaolin– 0.2g

PRECIPITATION

Solubilized substances may precipitate from it solution if a non-solvent for the substances is added to the solution.

E.g.:- Resins are insoluble in water

Alcoholic solution of resins + water =precipitated resins.

Aqueous dispersions of hydrophilic colloids (polysaccharide mucilage + high concentration of alcohol or salts) =precipitated colloids.

a) High concentration of electrolytes causes cracking of soap emulsion by salting out the emulsifying agents.

Vehicles (one or more organic liquids) use to dissolve medicaments of low solubility; water soluble adjuvant practically inorganic salts may be precipitated in such vehicles. Whentinctures containing resinous matter are added in water, resin agglomerates forms in diffusible precipitates. This can be prevented by slowly adding the undiluted tincture with vigorous shake.Suspension or by adding some suitable thickening agent.

E.g.:- Lotion of compound tincture of benzoin

Rx

Tincture benzoin compound – 5g

Glycerin – 10ml

Rose water upto 100ml

Causes: - Tincture benzoin compound contain resins.This change in solvent system results in an unavoidable precipitate.

Remedy: - Addition of tincture with rapid stirring yields a fine colloidal dispersion. So there is no need of any suspending agents.

CHEMICAL INCOMPATIBILITIES

Reaction between two or more substances which lead to change in chemical properties of pharmaceutical dosage form. As aresult of this a toxic or inactive or product may be formed.

Occurrence:-

Chemical incompatibilities occur, due to the chemical properties of drugs and additive like,

PH change

Oxidation-reduction reactions

Acid-base hydrolysis

Double decomposition

Complex formation

These reactions may be noticed by

Precipitation

Effervescence

Decomposition

Color change

Explosion

TYPES OF CHEMICAL INCOMPATIBILITIES

Based on chemical interactions

Tolerated incompatibility: - In this type incompatibility, the chemical interactions can be changing the order of mixing the solutions indilute forms, without or by changing the order of mixing.

Adjusted incompatibilities: - In adjusted incompatibility change in the formulation is needed with a compound having equal therapeutic value. E.g.: substitution of caffeine citrate with caffeine in sodium salicylate and caffeine citrate mixture.

Based on natureof chemical reaction

Immediate incompatibilities: - If the chemical reaction takes place, immediately after combining the prescription ingredients, they are called immediate incompatibilities. Hence, they should be dispensed only after correction.

Delayed incompatibility: - When the chemical reaction proceeds at a very slow rate and no appreciable visible change occurs which may develop on keeping the product for along time are called delayed incompatibility.

Based on the prescriber

Intentional:- When the prescriber knowingly prescribes the incompatible drugs.

Unidirectional:- When the prescriber prescribes the drugs without knowing that there is incompatibility between the prescribed drugs19.

Generally reaction between strong solution proceed at a faster rate and the precipitates are formed are thick and do not diffuse readily.Reaction between the dilute solutions proceeds at a slow rate and the precipitates formed are light and diffuse readily in the solution.Hence the reacting substances should be diluted as much as possible before mixing.

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

Method A:

This method is suitable for diffusible precipitates following steps are carried out.

Divide the vehicle into two portions.

Dissolve the reactants in separate portions and mix the two portions by slowly by adding one into other with constant stirring.

Method B:

This method is suitable for in diffusible precipitates following steps are carried out.

Divide the vehicle into two portions.

Dissolve the one of the reacting substance in one portion.

Place second portion of vehicle in mortar and incorporate suitable amount of compound.Tragacanth powder (2g/100ml of preparation) with constant trituration until a smooth mucilage is produced.

Add and dissolve the other reacting substance to the mucilage.

Add the solution of first reactant to the mucilage slowly with constant stirring.

A secondary label —**SHAKE THE BOTTLE BEFORE USE**‖ should be fixed on the container whenever method A or method B is followed in dispensing the prescription.

Examples of chemical incompatibilities and 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 causing evolution of carbon dioxide gas:-

1.Sodium bicarbonate with soluble calcium or magnesium salts

2.Bismuthsubnitrate and sodium bicarbonate

3.Borax with sodium bicarbonate and glycerin.

Miscellaneous incompatibilities:-

1.Soluble barbiturates with ammonium bromide

2.Potassium chlorate with oxdisible substances

3. Incompatibility of emulsifying agent

4. Color stability of dyes

5. Incompatibilities of liquorices liquid extract

Eg-1: strychnine hydrochloride mixture

Rx

Strychnine hydrochloride solution -6ml

Aromatic spirit of ammonia -4ml

Water up to - 120ml

Causes:-

The quantity of strychnine hydrochloride is more than its solubility in water (1:30).

The aromatic spirit of ammonia contains negligible amount alcohol.

Remedy: - Strychnine hydrochloride gets precipitated yielding diffusible precipitate, hence follow method A.

E.g-2.:Quinine hydrochloride mixture

Rx

Quinine hydrochloride -0.12ml

Sodium salicylate -4g

Water -100ml

Causes: - When quinine hydrochloride combined with the sodium salicylates it forms quinine salicylates which is an in diffusible precipitate.

Remedy: - Hence follow method B for precipitate yielding interactions.

THERAPEUTIC INCOMPATIBILITY

It is the modification of the therapeutic effect of one drug by the prior concomitant administration of another. It may be as a result of prescribing certain drugs to a patient with the intention to produce a specific degree of pharmacological action, but have restore or intensity ofthe action produced is different room that intended by the prescriber25.

MECHANISM:

It is divided into two groups. They are

Pharmacokinetic: It involves the effect of a drug on another from the point of view that includes absorption, distribution, metabolism and excretion.

Pharmacodynamics: These are related to the pharmacological activity of the inter-acing drugs.

E.g., Synergism, antagonism, altered cellular transport, effect on the receptor site.

Therapeutic incompatibilities occurs due to following reasons

a. Error in dosage

b. Wrong dose or dosage form

c. Contra-indicated drugs

d. Synergistic and antagonistic drugs

e. Drug interactions

ERROR IN DOSAGE

Many therapeutic incompatibilities result from errors in writing or interpreting the prescription order. The most serious type of the dosage error in the dispensing is overdose of a medication26.

E.g., Atropine sulphate capsules

Rx

Atropine sulphate - 0.005g

Phenobarbitone - 0.015g

Aspirin - 0.300g

Causes:- In this prescription, the quantity of the atropine sulphate in each capsule is more than its recommended dose.

Remedy:- The prescription is referred back to the prescriber to correct the overdose of the atropine sulphate. The recommended dose of atropine for a single capsule is 0.25 to 2mg.

WRONFG DOSE OR DOSAGE FORM

There are certain drugs which have quite similar names and there is always a danger of dispensing the wrong drug27.

E.g., Prednisone and Prednisolone

Digoxin and Digitoxin

Sometimes many drugs are available in the different dosage forms and hence, if the dosage form is not clearly mentioned on the prescription, it becomes necessary to seek clarification from the prescriber.

The responsibility of the pharmacist becomes to check the prescription intensively and if he finds these types of errors he should immediately consult the prescriber for the clarification.

PRESCRIBING CONTRA-INDICATED DRUGS

There are certain drugs which may be contra-indicated in a particular disease or a particular patient who is allergic to it28.

Corticosteroids are contra-indicated in the patients having peptic ulcers.

The penicillin and sulphur drugs are contra-indicated in the patients who are allergic.

Vasoconstrictors are contra-indicated in hypertensive patients.

Barbiturates and morphine should not be given to the asthmatic patients.

E.g., Sulphadiazine capsules Causes:-Ammonium chloride is a urinary acidifier. It causes the deposition of the Sulphonamide crystals in the kidney.

Remedy: - Before prescribing such substances a doctor must be careful. If he does not, a Pharmacist shows his caliber to point out such type of the doctor's error. Such must Immediately be referred back to the concerned doctor and get corrected.

PRESCRIBING SYNERGISTIC OR ANTAGONISTIC DRUGS

When two drugs are prescribed together, they tend to increase the activity of each other which is known as SYNERGISM. When two drugs are prescribed together, they tend to decrease the activity of each other which is known as ANTAGONIS

E.g., A combination of aspirin and paracetamol increases the analgesic activity.

A combination of penicillin and streptomycin increases the antibacterial activity.

Amphetamines show its antagonists effect with the barbiturates.

E.g., Amphetamine sulphate syrup

Causes:-In this prescription, there is a combination of two sympathomimetic drugs There by causing additive effect.

Remedy:- The prescription is referred back to the prescriber for necessary corrections.

DRUG INTERACTIONS

The effect of one drug is altered by the prior or simultaneous administration of another drug. The drug interaction can usually be corrected by the proper adjustment of dosage if the suspected interaction is detected30. **E.g., Tetracycline capsule - 250mg capsules** Direction: Take one capsule every 6 hours with milk.

Causes:-Tetracycline is inactivated by calcium present in milk. So, it should not be taken with milk.

Remedy: In this prescription, the therapeutic incompatibility is unintentional. So, the prescription is referred back to the prescriber to change the direction.

IMPORTANT QUESTIONS

Very short questions (2marks)

1. Define incompatibilities. Classify them.
2. What are 'Tolerated' and 'Adjusted' incompatibilities? Discuss them with suitable example.
3. Discuss incompatibilities causing evolution of gas with suitable example.
4. What is the therapeutic incompatibility? What are various errors committed by the doctors giving rise therapeutic incompatibility.
5. Discuss untoward reaction between soluble salicylate and alkali bicarbonates. How do you prevent this incompatibility?
6. Discuss various aspect of alkaloid incompatibilities with suitable example

Short questions (5marks)

1. Define suppositories and displacement value.
2. Discuss different suppository bases.
3. Write in brief, the preparation , packaing and storage of suppositories
4. Short note on packing of suppositories.
5. Short notes on suppository bases.
6. Factors affecting drug absorption from rectal suppositories.
7. Write an notes on " chemical incompatibilities".
8. Write an notes on "physical incompatibilities"
9. Write an notes on " therapeutic incompatibilities

Long questions(10marks)

1. What are incompatibilities ? Discuss in detail about the various causes of physical incompatibilities and their remedies with suitable example.
2. Write short notes on the following with regard to therapeutic incompatibility: a) Prescribing improper dose of drugs. b) Prescribing wrong drugs and dosage form. c) Prescribing contraindicated drugs. d) Prescribing synergistic or antagonistic drugs. e) Prescribing drugs with wrong direction.
3. Write a detail note on – liquids containing: a) Liquid extract of liquorice in acid media. b) Sodium barbiturate with ammonium bromide.
4. Give the ideal properties of suppository bases.
5. Discuss the problems encountered in manufacturing of suppositories such as hygroscopicity, incompatibilities, viscosity etc.