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4.1 INTRODUCTION TO SUPPOSITORIES

Suppositories are solid dosage form of medicament which is made for insertion into the body cavities. They may be Conical or ovoid medicated solids intended for insertion into several cavities of the body other than mouth are known as Suppositories. This term was derived from the Latin word suppositus, meaning "to place under." They may be inserted in the rectum, vagina, and to a lesser extent, the urethra for local or systemic effects. Rectal and urethral suppositories usually employ vehicles that melt or soften at body temperature, whereas vaginal suppositories, sometimes called *pessaries*, are also made as compressed tablets that disintegrate in the body fluids exert localized or systemic effects.

4.2 TYPES OF SUPPOSITORIES

1. **Rectal suppositories:** These are meant for insertion into the rectum for producing systemic effect. The rectal suppositories meant for adults usually weigh 2 gm and are torpedo shape, whereas the suppositories made for children are much smaller in size as compared to the adult suppositories. Children's suppositories weigh about 1 gm.

   The rectal suppositories which are used for systemic effects may contain analgesics, antispasmodic, transquillizers and sedative effects. Other than other these are used for antiseptic action, local anaesthetic action, for lubricating, soothing purposes.

   The rectal suppositories are used for evacuating bowel by irritating mucous membrane of rectum or by lubricating the membrane.

2. **Vaginal suppositories:** The vaginal suppositories are also known as Pessaries. They are meant for insertion into the vaginal cavities. They weigh about 3-5 gm and are molded in globular or oviform shape or compressed on a tablet press into conical shapes. The vaginal suppositories are larger than the rectal suppositories. They are used for their local action in vagina.
3. **Urethral suppositories:** These are also called as bougies and are of pencil shape. The urethral suppositories are meant for insertion into the urethra. The urethral suppositories intended for males weigh 4 gm each and are 100-150 mm long and those for females are 2 gm each and 60-75 mm in length.
4. **Nasal suppositories:** The nasal suppositories are also called as nasal bougies or buginaria. The nasal suppositories are meant for introduction in to nasal cavity. They are usually prepared with glycerogelatin base. They have similar shape as that of the urethral bougies. They weigh about 1 gm and have length of 9-10 cm.
5. **Ear cones:** Ear cones are used for insertion into the ear. They are also known as Aurinaria. They are used rarely. For preparation of ear cones generally theobroma oil is used as base. They are prepared in urethral bougies mould and cut according to size.

Advantages

1. Suppositories can exert local effect on rectal mucosa.
2. It is used to promote evacuation of bowel.
3. It avoid any gastrointestinal irritation.
4. Suppositories can be used in unconscious patients (e.g. during fitting).
5. Suppositories can be used for systemic absorption of drugs and avoid first-pass metabolism.
6. Babies or old people who cannot swallow oral medication.
7. It is useful for post operative people who cannot be administered oral medication.
8. A very suitable dosage form for people suffering from severe nausea or vomiting.

Disadvantages of Suppositories

1. Suppositories have a problem of patient acceptability.
2. In some cases, the total amount of the drug must be given will be either too irritating or in greater amount than reasonably can be placed into suppository.
3. Incomplete absorption may be obtained because suppository usually promotes evacuation of the bowel.
4. Suppositories are not suitable for patients suffering from diarrhoea.

4.3 IDEAL PROPERTIES OF SUPPOSITORIES BASES

1. It should melt at body temperature or dissolves in body fluids.
2. It should be good in appearance.

3. It should be non-toxic and non-irritant.
4. It should be compatible with any medicament.
5. Suppositories should releases medicament readily.
6. It should be easily moulded and removed from the mould. It shrinks sufficiently on cooling to release itself from the mold without the need for mold lubricants.
7. It should be stable to heating above the melting point.
8. It should be easy to handle and should retain its shape while handling.
9. It should be stable on storage such that it does not change colour, odour, or drug release pattern.
10. Acid value is below 0.2, saponification value ranges from 200 to 245, and iodine value is less than 7.
11. The "water number" is high, i.e., a high percentage of water can be incorporated in it.

4.4 TYPES OF BASES

1. Fatty Bases.
2. Water Soluble or Miscible Bases.
3. Emulsifying Bases.

4.4.1 Fatty Bases

1. Theobroma oil
2. Emulsified theobroma oil
3. Hydrogenated bases

They are designed to melt at body temperature.

1. Theobroma Oil (Cocoa butter)

It is a mixture of glyceryl esters of different unsaturated fatty acids.

Cocoa Butter is a triglyceride, yellowish white, solid, brittle fat, smells and taste like chocolate. Its melting point is between 30-35°C, its iodine value is "between" 34-38 and its acid value is not higher than 4, because cocoa butter can melt and rancid. So it must be stored in cool dry place protected from light.

Overheating changes its physical characteristics and it has a tendency to adhere to the mold when solidified. It may exist in four crystalline states.

α Form: This form is obtained by suddenly cooling the melted mass to 0°C. Its melting point is 24°C.

β Form: This form is obtained when cocoa butter is melted at 35 to 36°C and slowly cooled. It melts at 18 to 23°C.

β' Form: It reverts back to 3 forms and melts at 34 to 35°C.

γ Form: It is obtained by pouring a cool (20°C) cocoa butter into a container before it is solidified and cooled at deep freeze temperature. It melts at 18°C.

All the four forms are unstable and are converted to stable form over a period of several days. Thus, extreme care should be exercised while melting and cooling cocoa butter. As in general, the minimal use of heat during the melting process is recommended.

To overcome drawbacks of cocoa butter, emulsified theobroma oil, hydrogenated palm kernel and soyabean oils have been suggested.

Advantages

(a) A melting range of 30 - 36°C (solid at room temperature but melts in the body).
(b) Readily melted on warming, rapid setting on cooling.
(c) Miscible with many ingredients.
(d) Non-irritating.

Disadvantages

(a) Polymorphism: When melted and cooled it solidifies in different crystalline forms, depending on the temperature of melting, rate of cooling and the size of the mass.
(b) If melted at not more than 36°C and slowly cooled it forms stable beta crystals with normal melting point.
(c) If over-heated then cooled it produce unstable gamma crystals which melt at about 15°C or alpha crystals melting at 20°C.
(d) Cocoa butter must be slowly melted over a warm water bath to avoid the formation of the unstable crystalline form.
(e) Adherence to the mould.
(f) Softening point too low for hot climates.
(g) Melting point reduced by soluble ingredients.
(h) Rancidity on storage.
(i) Poor water-absorbing ability: Improved by the addition of emulsifying agents.
(j) Leakage from the body.

2. Emulsified Theobroma Oil

When large quantities of aqueous solutions are required to be incorporated then emulsified theobroma oil as a base can be used. There are many agents which are used to form emulsified theobroma oil, for example: 2-3% cetyl alcohol, 4% glyceryl monostearate, 10% lanette wax, 4% bees wax, and spermaceti up to 12% can be utilised for emulsified theobroma oil suppositories.

3. Hydrogenated Oils

They are used as a substitute to theobroma oil, many hydrogenated oils are used as a substitute, for example, coconut oil, palm kernel oil, hydrogenated edible oil, a mixture of oleic acid and stearic acid. They are known as synthetic fat bases.

Advantages

The synthetic fat bases have advantages over theobroma oil are as follows:

- Their solidifying points are unaffected by overheating.
- Because of the lower content of unsaturated fatty acids they have good resistance to oxidation.
- The difference between melting and setting points is small. Hence, they set quickly, the risk of sedimentation of suspended ingredients is low.
- Lubrication of mould is not necessary because they contract significantly on cooling.
- They are marketed in a series of grades with different melting point ranges, which can be chosen to suit particular products and climatic condition.
- They produce colourless, odourless and elegant suppositories.
- They contain a proportion of w/o emulsifying agents, and therefore, their water-absorbing capacities are good.

Disadvantages

- Brittle if cooled rapidly, avoid refrigeration during preparation.
- The melted fats are less viscous and more fluid than theobroma oil because of that there is a greater risk of drug particles to sediment during preparation.

4.4.2 Water Soluble or Water Miscible Base

(i) Glycero Gelatin

It is a mixture of glycerin and water which is made into a stiff jelly by the addition of gelatin. The proportion of gelatin can be varied according to the intended use of the preparation.

Gelato-glycerin bases dissolve in the body fluids liberating contained medicaments Gelato-glycerin Mass BP which contains 14% gelatin, 70% glycerin and water. USP formula contains 20% gelatin together with 70% of glycerin.

For dispensing purposes, good quality powdered gelatin should be used. In order to control the consistency, glycerin can be partially or wholly substituted by propylene glycol and polyethylene glycols. The incompatibility of some medicaments can be avoided by the use of either Pharmagel A (cationic) or Pharmagel B (anionic). Glycerin suppositories being liable to mould growth, preservatives should be added.

Disadvantages

(a) Physiological effect: osmosis occurs during dissolving in the mucous secretions of the rectum, producing a laxative effect.
(b) It can cause rectal irritation due to small amount of liquid present.
(c) Unpredictable solution time.

(d) **Hygroscopic:** So, they should be packaged in tight containers and also have dehydrating effects on the rectal and vaginal mucosa leading to irritation.
(e) Microbial contamination likely.
(f) Long preparation time.
(g) Lubrication of the mould is essential.

(ii) Soap Glycerin

In this case, soap is employed instead of glycerin for hardening. Sodium stearate can incorporate up to 95% of glycerin. Sodium stearate (soap) is produced in-situ by interaction of sodium carbonate with stearic acid. Soap glycerin suppositories are however hygroscopic.

(iii) PEG Bases

Different mixtures of polyethylene glycols are marketed under the trade names of Postonals, Carbo waxes and Macrogols.

Most of the drugs commonly administered in suppository form are compatible with these bases. Polyethylene glycols are however incompatible with phenols and reduce the antiseptic effects of quaternary ammonium compounds.

4.4.3 Emulsifying Bases

Massa Esterinum, Witepsol and Massupol are the trade names under which the emulsifying bases are marketed.

1. **Massa Esterinum** is a mixture of the mono-, di- and tri-glycerides of the fatty acids having the formula $C_{11}H_{23}COOH$ to $C_{17}H_{35}COOH$.
2. **Witepsol** bases consist of hydrogenated triglycerides of lauric acid with added monoglycerides. These are available in nine grades.
3. **Massupol** consists of glyceryl esters namely of lauric acid and addition of very small quantity of glyceryl monostearate.

All these bases are free from the drawbacks of cocoa butter and do not require lubrication of mould.

Water-dispersible bases essentially consist of surfactants. They melt at body temperature. Some formulae of dispersible bases containing surfactants are outlined below.

Glyceryl monostearate 10, Glyceryl monostearate 15, Tween 60, 40.

4.5 METHODS OF PREPARATION

Suppositories can be prepared by one of three methods:

1. Hand Rolling

- It is the simplest and oldest method of suppository preparation and may be used when only a few suppositories are to be prepared in a cocoa butter base. It has the advantage of avoiding the necessity of heating the cocoa butter.

- By triturating grated cocoa butter and active ingredients in a mortar a plastic-like mass is prepared. The mass is formed into a ball in the palm of the hands, then rolled into a uniform cylinder with a large spatula or small flat board on a pill tile. The cylinder is then cut into the appropriate number of pieces which are rolled on one end to produce a conical shape.
- The suppository "pipe" or cylinder tends to crack or hollow in the center, especially when the mass is insufficiently kneaded and softened.

2. Compression Molding

Compression molding is a method of preparing suppositories from a mixed mass of grated suppository base and medicaments which is forced into a special compression mould using suppository making machines. The suppository base and the other ingredients are combined by thorough mixing. The base softens because of the friction in the process. A mortar and pestle can be used for small scale. On the other hand the large scale manufacturing involves mechanically operated kneading mixers and a warmed mixing vessel. In the compression machine, the suppository mass is placed into a cylinder which is then closed. After that from one end pressure is applied to release the mass from the other end into the suppository mould or die. When the die is filled with the mass, a movable end plate at the back of the die is removed and when additional pressure is applied to the mass in the cylinder, the formed suppositories are ejected. The end plate is returned, and the process is repeated until all of the suppository mass has been used. When active ingredients are added, it is necessary to omit a portion of the suppository base, based on the density factors of the active ingredients.

3. Fusion Moulding

Fusion Moulding process involves the following steps:

- Firstly melting the suppository base.
- Then the drug is either dispersed or dissolved in the melted base.
- The mixture is then removed from the heat and poured into a suppository mould.
- The melt is allowed to congeal.
- Now the suppositories are removed from the mould.

Suppository Moulds

Small scale moulds are capable of producing 6 or 12 suppositories in a single operation. Industrial moulds produce thousands of suppositories per hour from a single moulding.

Fig. 4.1

Calibration of the Mould

The calibration of mould is necessary because the size of the suppositories remains same from a particular mould but there weight varies because the density of the different types of bases and the medicaments used are different. The first step is to prepare moulded suppositories from base material alone. The suppositories are combined and average weight is recorded. To determine the volume of the mould, the suppositories are melted in a calibrated beaker, and the volume of the melt is determined.

Lubricants used in Mould

Cocoa butter and glycero-gelatine bases are required lubrication of moulds. This is prevent sticking of bases to the wall of moulds cavity. It is also useful in easy removal of suppositories from the moulds. The lubricants forms a film between the wall of mould cavity and base of suppositories so, it prevent adhering of bases to the moulds. The nature of lubricants should be different from nature of bases.

Lubricant must be compatible with medicament or adjuncts. In industry silicone fluid is used as lubricant. Mould is lubricated using a pad of gauze or muslin or with a small fairly stiff brush. Cotton wool is not used because some fibres adhere to the mould. Excess of lubricant can be removed by inverting the mould on a clean white tile.

Following lubricants may be used for the preparation of theobroma oil suppositories.

Examples:

(a) For cocoa butter bases

Alcohol(90%)- 50 ml

Glycerol - 10 ml

Soft soap - 10 gm

(b) For glycerol-gelatin base

Liquid paraffin or Arachis oil is used as lubricant

Fig. 4.2

Packaging

Suppositories must be packed in such a manner that they do not touch each other.

Poorly wrapped and packaged suppositories can lead to staining, breaking or deformation by melting caused by adhesion. Suppositories usually are foiled in tin or aluminium, paper or plastic strips. Overwrapping is done with hand or machine.

Hand packing yields a non-uniform products so machine are utilised to overcome this problem and machines can wrap 8000 suppositories per hour.

Storage

Suppositories should be protected from heat, preferably by storing in the refrigerator.

Polyethylene glycol suppositories and suppositories enclosed in a solid shell are less prone to distortion to temperature slightly above body temp.

Labelling

Suppositories should be labelled as:

(a) "STORE IN A COOL PLACE"

(b) "FOR EXTERNAL USE ONLY"

(c) "NOT TO BE TAKEN ORALLY".

4.6 EVALUATION TESTS FOR SUPPOSITORIES

1. Test of Appearance

All the suppositories should be uniform in size and shape. They should have elegant appearance. Individual suppositories should be examined for cracks and pits due to entrapment of air in the molten mass.

2. Breakage Test (Test of physical strength)

The tensile strength of suppositories is measured in this test to assess their ability to withstand the rigors of normal handling.

The apparatus used is called as breaking test apparatus. It consists of a double-wall chamber. Through the walls of the chamber, water is pumped. The inner chamber consist of a disc which holds the suppositories. To this disc, a rod is attached. The other end of the rod consists of another disc on which weights are placed.

Procedure

On the first disc the test suppository is placed. On the second disc a 600 g weight is placed. At 1 minute interval, 200 g weights are added till the suppository crumbles. All the weights used are added which gives the tensile strength. Likewise, few more suppositories are tested and the average tensile strength is calculated. Tensile strength indicates the maximum force which the suppository can withstand during production, packing and handling. Large tensile strength indicates less tendency to fracture.

3. Test of Dissolution Rate

It is the amount of dosage form that gets dissolved in body fluid in unit time. It is a measure of the rate of drug release from the suppository.

Two types of apparatus are available for testing the dissolution rate. They are:

(a) Suppository dialysis cell: Lipophilic suppositories are tested using suppository dialysis cell, which is also called as modified flow-through cell.

(b) Stationary basket: Rotating paddle apparatus (USP dissolution test apparatus). Hydrophilic suppositories are tested using stationary basket - rotating paddle apparatus.

4. Test of Melting Range

Both macromelting range and micromelting range are determined as follows:

(a) Macromelting range

It is a measure of the thermal stability of the suppository. It is the time taken by the entire suppository to melt in a constant temperature water bath. The test is conducted using the tablet disintegration apparatus. The suppository is immersed in a constant water bath. Finally, the melting range is recorded.

(b) Micromelting range

The melting range of the fatty base is measured in capillary tubes.

5. Liquefaction time (softening)

Softening time is the time for which the suppository melts completely at a definite temperature. This test measures the softening time of suppositories which indicates the hardness of the base.

Liquefaction temperature/time test was done using fabricated instrument. A big pipette was taken having a narrow opening on one side and broad opening on another side. The pipette was dipped in hot water maintained at 35 ± 0.2°C so that narrow end faces towards hot water. The sample suppository was introduced from the top of the pipette through broad end and carefully pushed down its length until it reaches narrow end. A glass rod was then inserted so that it rests over the suppository. The temperature at which the glass rods just come down was noted, that represents the liquefaction temperature. The time at which glass rod reaches to narrow end after complete melting of suppositories represents the liquefaction time.

Test of uniformity of drug content

This test is to assess the uniformity of the mixed suppository mass. Different suppositories are assayed for the drug. All the suppositories should contain the same labelled quantity of the drug.

Test of drug uptake

Both *in-vitro* and *in-vivo* tests should be conducted to assess the amount of drug absorbed into the systemic circulation.

(a) *In-Vitro* test

The test conditions should be similar to those inside the human body. The dissolution apparatus is used which consists of simulated gastric and simulated intestinal fluids. Definite number of suppositories are placed in the apparatus. Aliquot portions of the dissolution medium are withdrawn at definite intervals of time and drug uptake is measured using a U.V. spectrophotometer.

(b) *In-Vivo* test

This test is carried in animals or human volunteers. The suppository is placed in the intended body cavity. At regular intervals of time, blood samples are collected and the amount of drug present is determined.

Stability Problems of Suppositories

Blooming: During storage cocoa butter suppositories sometimes show deposition of white powder on the surface. This result in suppositories of disagreeable appearance.

Hardening: During storage, the suppositories made of fatty bases become hard. Hardening is occurs due to crystallization of bases. This also effect the melting and rate of absorption of drugs.

4.7 DISPLACEMENT VALUE

A suppository mould is filled by volume, but the suppository is formulated by weight.

The volume of a suppository from a particular mould is uniform but its weight can vary when a drug is present due to difference in densities between the drug and base.

The quantity of the drug which displaces one part of the base is called as displacement value.

The displacement values of some of the medicament used in suppositories with reference to cocoa butter are given below:

Drug	Displacement value
1. Aminophyllin	1.5
2. Boric acid	1.5
3. Castor oil	1.0
4. Tannic acid	1.0

The displacement value of a given medicament may be determined as follows:

1. Prepare and weigh 6 suppositories containing theobroma oil for other base) = a gram.

2. Prepare and weigh 6 suppositories containing, say 40% medicament = b gram.
3. Calculate the amount of theobroma oil present in medicated suppositories.

$$\frac{60}{100} \times b = c \text{ gram}$$

4. Calculate the amount of medicament present in the medicated suppositories.

$$\frac{40}{100} \times b = d \text{ gram}$$

5. Calculate the amount of theobroma oil displaced by d gram of medicament = (a – c) gram.
6. Displacement value of medicament = $\frac{d}{a - c}$.

Example: Calculate the displacement value of ZnO in theobroma oil suppositories containing 40% of ZnO and is prepared in a 1 g mould. The weight of eight suppositories is 11.74 g.

Solution: Weight of eight suppositories containing theobroma oil = 1 × 8 = 8 g

Weight of 8 suppositories containing 40% of ZnO = 11.74 g

Amount of theobroma oil present is 8 suppositories = 60/100 × 11.74 = 7.044 g

Amount of medicament present in 8 suppositories = $\frac{40}{100} \times 11.77 = 4.696\%$

Amount of theobroma oil displaced by 4.696 g of medicament (a – c) = 8 – 7.044 = 0.956.

Displacement value = $\frac{4.696}{0.956} = 4.912$

4.8 PHARMACEUTICAL INCOMPATIBILITIES

Incompatibilities is the result of prescribing or mixing two or more substances which are antagonist in nature and an undesirable product is formed which may affect the safety, purpose or appearance of the preparation. It is usually unintentional.

It may occur *in-vitro* between drugs and other components during preparation, storage or administration.

Incompatibility may be:

(a) Pharmaceutical/Physical Incompatibility.
(b) Therapeutic Incompatibility.
(c) Chemical Incompatibility.

4.8.1 Physical Incompatibility

In this type of incompatibility a visible physical change takes place. An unacceptable, non-uniform, unpalatable product is formed. It is a result of insolubility and immiscibility, precipitation, liquefaction, adsorption and complexation of solid materials.

The changes which occur due to physical incompatibilities can be corrected by one or more methods: Order of mixing, alteration of solvents, change in the form of ingredients, alteration of volume. Emulsification and addition of suspending agent, addition, substitution or omission of therapeutically inactive substances.

Examples of physical incompatibility.

1. Immiscibility

Immiscibility is the result of the mixture of two or more immiscible liquid or an immiscible solid with a liquid. Acceptable liquid product can be obtained by emulsification or solubilization.

R_x

Olive oil- 30 ml

Water up to 120 ml

Make an emulsion use a suitable emulsifying agent.

Methods of Rectifying Immiscibility

Immiscibility can be overcome by:

- Vigorous shaking / stirring.
- Emulsification or solubilization for example, Fats soluble Vitamins, Certain antibiotics like Chloramphenicol, Amphotericin B, Analgesics like Aspirin, Acetanilide and phenacetin many alkaloids and glycosides etc. are made soluble by the technique of solubilization.

2. Insolubility

Liquid preparation with indiffusible solids (e.g. Sulphamethoxasole, phenacetin, Zinc oxide, calamine etc.) a suspending agent is required to uniform distribution of the solids in the liquid phase for sufficiently long time so as to facilitate accurate measurement of dose.

R_x

Sulphamethoxazole - 4.0 g
Trimethoprim - 0.8 g
Sodium CMC - 0.5 g
Purified water - q.s to 100 ml
Prepare a solution.
Sulphamethoxazole and Trimethoprim are indiffusible in water. To make them diffusible a suspending agent is used.

Methods of Rectifying Insolubility

Cosolvency: for example, we may use alcohol, propylene glycol, syrups.

Complexation: for example, formation of tri-iodide complex, complexation of caffeine with Sodium Benzoate.

Hydro trophy: for example, Hyoscyamine with tween.

Solubilization: for example, Fats soluble vitamins, certain antibiotics.

3. Precipitation

A solubilised substance may precipitate from solution if a non-solvent (i.e. a solvent in which the drug is insoluble) is added to the solution. Alcoholic solution of Resins and water is equal to precipitated Resins Aqueous dispersion of Hydrophillic colloids and polysaccharide mucilage plus high concentration of Alcohol or salts is equal to precipitated colloids. But significant amount is tolerated if well diluted and added in small amount with vigorous stirring.

4. Liquefaction

Some low melting point solids sometimes liquefy when mixed together due to the formation of eutectic mixture or liberation of water. e.g: Menthol, Thymol, Camphor, Phenol, Naphthol and chloral hydrate when mixed together forms eutectic mixtures.

The eutectic forming ingredient may either be dispensed separately or these may be mixed separately with enough quantity of adsorbent powder like magnesium carbonate or Kaolin to form free flowing product.

Example

R_x

Menthol = 2.0 g

Camphor - 2.0 g

Ammonium carbonate - 20.0 g

Make a powder.

In this case, if the ingredients are mixed together, they shall liquefy due to formation of a eutectic mixture. Hence, to dispense them in the form of a powder, it is necessary to mix them separately with sufficient quantity of a suitable adsorbent like magnesium carbonate. Then they are mix together to obtain a powder.

Methods of Rectifying Liquefaction

By the use of absorbent like kaolin, light magnesium carbonate.

Techniques to Rectify:

Order of mixing.

Alteration of solvent.

Change in the form of ingredients.

Alteration of volume.

Emulsification.

Addition of suspending agents.

Addition/Substitution/omission of therapeutically inactive substance.

4.8.2 Chemical Incompatibilities

Chemical incompatibilities is said when a chemical interaction takes place among the ingredients of a prescription. Such interactions may take place immediately upon compounding then these are termed as immediate incompatibilities. It is due to oxidation-reduction, acid base hydrolysis or combination reactions. These reactions may be noticed by effervescence, decomposition, colour change. It may be as a result of chemical interactions between the ingredients of a prescription and a toxic or inactive product may be formed.

Chemical incompatibilities are of two types:

(a) Tolerated: This reaction can be minimized by applying some suitable order of mixing or mixing the solution in dilute form but no change in the active ingredients of the preparation.

(b) Adjusted: The reaction is prevented by addition or substitution of one of the reacting substances with another of equal therapeutic value but does not affect the medicinal value of the preparation.

E.g. of Chemical Incompatibilities: Alkaloidal Incompatibility.

1. Alkaloidal Salt with Alkaline Substances, Iodies, Salicylates

Most alkaloidal salts are soluble in water but alkaloidal bases practically insoluble in water and are freely soluble in organic solvents. When an alkaline substance like aromatic spirit of ammonia, solution of ammonia, ammonium bicarbonate, sodium bicarbonate, borax, etc., is added to an alkaloidal salt solution the free alkaloid may be precipitated. However they are not always precipitated, because all alkaloids are slightly soluble in water and other added substances.

(a) Example

R_x

Strychnine hydrochloride solution - 5 ml

Aromatic spirit of ammonia - 3 ml

Purified water to 100 ml make a mixture

Strychnine HCl used in the mixture is an alkaloidal salt, whereas aromatic spirit of ammonia is an alkaline substance. On reaction between the two, insoluble strychnine is precipitated. since the precipitate formed is diffusible, the incompatibility may be taken care by suitable formulation. In this case, strychnine HCl solution should be dissolved in half the required quantity of water while aromatic spirit of ammonia should dissolved in the remaining portion of water. The two portion should be mixed slowly.

(b) Gas formation

Gas may be evolved due to chemical reaction between the ingredients of a formulation.

Example: Carbonates or bicarbonates with an acid or acidic drug resulting in the evolution of carbon dioxide. Reaction of sodium bicarbonate, borax and glycerol.

R_x

Sodium bicarbonate - 1.5 g

Borax - 1.5 g

Phenol - 0.75 g

Glycerin - 25 ml

Water to - 100 ml

Prepare a spray

(c) Colour change

The colour of most of the dyes used in formulations is influenced by their ionization which in turn depends on the pH of the solution. Colour change due to change in pH can be prevented by properly buffering the vehicle or by preventing reaction that cause formation of free acid or base in the medium.

R_x

Sodium salicylate - 4 g

Sodium bicarbonate - 4 g

Peppermint water to - 60 ml

Make a mixture

Sodium salicylate gets oxidized in presence of sodium bicarbonate and the mixture darkens on storage. This alkaline catalyzed oxidation may however be prevented by the use of a suitable antioxidants like 0.1% sodium meta-bisulphite.

2. Ionic Reactions

The therapeutic or pharmaceutical properties of many organic compounds are usually associated with a large cation or anion. Interaction of such ions of opposing types may yield compounds which may totally lack the useful properties of the interacting molecules. For instances, Cream prepared using cationic emulgents may crack if mixed with a cream prepared using an anionic emulgents. Similarly an anionic solubilizers may lower the antimicrobial activity of a cationic medicament or preservative.

3. Explosive Combination

Oxidizing agents are chemically incompatible with reducing agent and a combination of the two in a formulation may lead to an explosive reaction. For example, if potassium chlorate is prescribed with an oxidisable substance like Sulphur, tannic acid, etc. and the two are triturated or heated together, there is a fair chance of an explosive reaction taking place. In such case, it is better to dispense the components separately or if it is necessary to mix them together, the mixing should be done very lightly.

Some chemical incompatibility:

(a) All oxidizing agents, such as potassium chlorate, chromic acid, potassium permanganate, silver oxide, are liable to explode when combined with organic matter, and such oxidizable inorganic matter as sulfur or carbon.

Strong nitric acid and its preparations produces effervescence with preparations containing tannin, or with oil of turpentine, sometimes with explosive violence.

(b) Hypophosphites are liable to explode when heated above 100°C, or when combined with oxidizing substances such as nitrates, chromates or permanganates.

(c) Iodine is liable to explode when treated with ammonia or with oil of turpentine.

- **Cementation of ingredients:** In some cases all or part of the ingredients of a prescription may set into a mass cement-like hardness.
- Separation of an immiscible liquid when certain organic chemicals are decomposed by certain reagents, such as the decomposition of chloral, by the action of an alkali into chloroform. (Some authors consider the formation of chloral alcoholate as a chemical incompatibility).
- Development of heat or cold.
- Other types of chemical changes, like polymerization, substitution and addition.
- Hydrolytic changes (hydrolysis).
- Invisible changes (This is most likely overlooked).
- Development of poisonous substances (may also be considered under therapeutic incompatibilities).

Types of Chemical Changes

1. **Oxidation:** Oxidation is defined as loss of electrons or gain of oxygen. Auto-oxidation: It is a reaction with oxygen of air which occur spontaneously without other factors. Pre-oxidants: are substances catalyze oxidation process i.e. metals, some impurities.
2. **Hydrolysis:** A chemical reaction in which water is used to break down a compound; this is achieved by breaking a covalent bond in the compound by inserting a water molecule across the bond.
3. **Polymerisation:** In polymerization, small repeating units called monomers are bonded to form a long chain polymer.
   e.g.: Formaldehyde Paraformaldehyde (Polymer: white precipitate). To avoid this formaldehyde must be stored in suitable temperature and addition of methanol 15%. Ampicillin in high temperature forms polymers which cause allergy.
4. **Isomerization:** It means conversion of drug to its isomer. Isomers have identical molecular formulae and a different arrangement of atoms.

4.8.3 Therapeutic Incompatibility

It may be the result of prescribing certain drugs to the patient with the intention to produce a specific degree of action but the nature or the intensity of the action produced is different from that intended by the prescriber.

Therapeutic Incompatibility occurs due to the following reasons: It may be due to the administration of:

(a) Overdose.
(b) Improper or wrong dosage form.
(c) Contraindicated drug.
(d) Synergistic and antagonistic drugs.
(e) Drug interactions.

(a) Over dose: Many therapeutical incompatibility results from errors in writing the prescription. The most serious type is over dose of a dosage form. This is the duty of pharmacist to check the dose which is written in the prescription before dispensing the medicine to patient.

R_x

Codeine phosphate - 0.5 gm

Make powders.

It is a unintentional incompatibility. The pharmacist wants to give 5 mg and yet prescribes 500 mg. This is the example of overdose medication. The prescription should be given back to prescriber for necessary correction.

(b) Wrong dosage form: There are some drugs which have almost similar names and there are possibilities of dispensing wrong drug. Many drugs are available in different dosage forms hence if the dosage form is not clearly mention on the prescription it becomes difficult for the prescriber to dispense the medicine. Examples prednisone and prednisolone, digoxin and digitoxin.

(c) Contraindicated Drugs: There are certain drugs which may be contraindicated in a particular disease. Penicillin and sulphonamides are not prescribed for those patients who are allergic to it also corticosteroids are never prescribed in peptic ulcer condition. The drugs which will excrete into milk are never prescribed in lactating mothers. e.g. Phenytoin, Phenobarbitone, chloramphenicol etc.

(d) Drug interaction: The effect of drug is changed by either prior administration or simultaneous administration of another drug.

R_x

Tetracycline Hydrochloride - 250 gm

Directions for Pharmacist

Make Capsules.

To Take 10 capsules every six hours with milk.

Tetracycline is inactivated by the milk due to the presence of calcium in it. Avoid administration of tetracycline with milk to prevent the formation of insoluble complex.

(e) Synergism: Many drugs shows synergistic effect, when two drugs are given together the effect of each drug is increased, this is known as synergistic effect. Synergism is usually intentional as the prescriber has given the combination of two drugs which increases the activity of the drugs.

Aspirin and Paracetamol increases analgesic activity Penicillin and streptomycin increases antibacterial activity.

R_x

Amphetamine sulphate - 20 mg

Ephedrine sulphate - 100 mg

Simple syrup up to - 100 ml

Make a mixture.

Both are sympathomimetic drugs cause additive effect. Hence of individual drugs dose should be reduced to avoid the therapeutic incompatibility.

(f) Antagonism: When two drugs are given together and one drug opposes the pharmacological activity of another drug it is known as antagonism.

R_x

Aspirin - 0.6 g

Probenecid - 0.5 g

Aspirin and probenecid both are anti-gout agents. When prescribed together their combination produces neutralization effect.