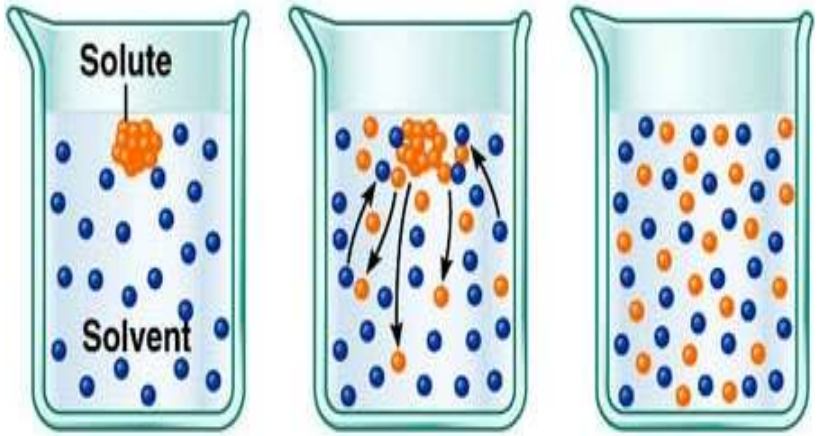
Solutions

Simple solution: is a liquid pharmaceutical preparation of one or more constituents of one phase system, or as a chemically and physically homogenous liquid consisting of at least 2 components:



Solute (small amount)

Solvent (large amount)

Classification of Solutions

- **According to the Type of solution:**
- Solution of liquid in liquid (ex: Glycerin in H2O)
- Solution of gas in liquid (ex: Ammonia in H2O)
- Solution of solid in liquid (ex: NaCl in H2O)
- **According to the method of preparation**
- Solution prepared by Simple solution
- Solution prepared by chemical reaction
- Solution prepared by simple solution with sterilization :
- Anticoagulant , irrigating and physiological solution
- Ophthalmic solution
- Ophthalmic solution prepared from sterile ophthalmic powder
- Solution prepared By Extraction
- **According to their Use**
- Gargles and Mouth Wash , used in mouth and throat
- Drops (eye, ear, nasal), instilled into body cavity
- Elixir, syrup & pediatric drops, as oral solutions
- Spray
- Solution for Injection

Colloid , ointment, liniments , lotions and paint, applied to body surface

-

Standard Solution: is a solution of Known concentration (Normality of Molarity) or its Concentration is exactly Measured

Disadvantages of solution

- They are less stable than solid dosage form (since deleterious changes takes place more readily in solution
- Unpleasant flavors can be difficult to mask
- They are bulky to carry around

Advantages of Solution

- Young children and some adults have difficulty in swallowing tablets and capsules
- They are more quickly effective than, for example, tablets which must disintegrate in the body before absorption can begin

Problems in preparation

- If we have fine powder and we add it on the surface of the solvent , it will float on the surface of the solvent so the powder must be placed in a mortar then add the solvent to the powder and dissolve it
- If the prescription Liberates CO2 gas then we must wait until CO2 liberation Ceases
- Triturate substances that has low solubility to decrease particle size and increase the solubility (ex: ferrous sulfate)
- Aspirin (insoluble) So add sodium citrate surfactant to make it soluble complex , if substance with large particle size (crystal) we must decrease Particle size by using mortar to increase the solubility
- If we have gum substances we must prepare it in a wide mouth bottle (because if narrow it will adhere around the stirrer)
- When we have 2 Solvents in the prescription , we must classify the the solute according to its solubility in the solvent , if the solute is soluble in water then dissolve it in water , if the solute is soluble in alcohol dissolve it in alcohol

The general procedure for preparation of simple Solution :

- Weigh the solid ingredients and dissolve them in ¾ of the liquid
- Subtract the volume of any liquid ingredient from ¾ volume of the Prescription , then dissolve the solids in the remaining part of the solvent
- Add the liquid ingredient (if present)
- Complete the volume by the addition of the required amount of the solvent
- Transfer the product to a Bottle and Label it.

Prescriptions

Rx1) Carminative mixture for infants

Sodium bicarbonate 0.06 g

Aromatic spirit of ammonia 0.06 ml

Compound tr. of cardamom 0.12 ml

Glycerine 0.3 ml

Peppermint water q.s. 4 ml

ft. mist.

mitte 20 ml

sig. fl. ʒit.i.d. p.c.

Calculations:

Factor = 20/4 = 5

0.06 × 5 = 0.3 g of NaHCO3

0.06 × 5 = 0.3 ml of aromatic spirit of ammonia

0.12 × 5 = 0.6 ml of compound tr. of cardamom

0.3 × 5 = 1.5 ml of glycerin

* Liquids = 0.3 + 0.6 + 1.5 = 2.4 ml
* (¾ × 20) = 15 ml

15 – 2.4 = 12.6 ml of **peppermint water** be used to dissolve NaHCO3 initially.

PS: strong tr. Of ginger cause damage to infant tissue because of its strong effect therefore it cannot be used for infant

Procedure:

Weigh 0.3 g of NaHCO3. , Measure 12.6 ml of peppermint water and place it in a beaker. , Dissolve the NaHCO3 in the beaker with stirring , Measure 0.3 ml of aromatic spirit of ammonia, 0.6 ml of compound tr. Of Cardamom and 1.5 ml of glycerin. Add them to the beaker and mix , Transfer to graduated cylinder and complete the volume to 20 ml with peppermint water , Transfer to suitable container and label it.

Rx2) Carminitive pediatric mixture with chloral hydrate

Chloral hydrate 0.03g
Aromatic spirit of ammonia 0.12ml
Cpd. Tr. Of cardamom 0.18ml
Glycerin 0.3ml
Peppermint water Q.S. 5ml
ft. mist.
sig. fl. ʒi t.i.d. p.c.

Rx3) Carminative mixture for adults

Sodium bicarbonate gr. VIII

Aromatic spirit of ammonia ℿ XV

Compound tr. of cardamom ℿ IX

Strong tr. of ginger ℿ i

Peppermint water q.s. fl. ʒi

ft. mist.

sig. fl. ʒsst.i.d. p.c.

Calculations: (Home Work)

Uses:

- Sodium Bicarbonate : antacid , carminative and react with acid in stomach to liberate CO2
- Spirit of ammonia : carminative , Antacid , reflex stimulant
- Tr. Of cardamom : flavoring , coloring , and carminative
- Strong tr. Of ginger : antispasmodic prevent griping
- Peppermint water : vehicle and flavor
- Glycerin : sweetening agent

Iodine Solutions

Rx4) Aqueous Iodine Oral Solution BP (Lugol's solution)

Iodine 50 g
KI 100 g
P.W. q.s. 1 L
ft. mist.
mitte 25 ml
sig. 0.3 ml diluted with milk or water t. i. d.

Procedure:

- Dissolve KI in ¾ water to make solution of KI
- Dissolve I_2 in previous solution
- Shake well until iodine dissolve
- Complete the volume with purified water

Rx5) Weak Iodine Solution

Iodine 25 g

KI 15 g

P.W.25 ml

Ethanol (90%) q.s. 1000 ml

sig. externally b. i. d.

Procedure:

- Dissolve KI in 25ml D.W.
- Dissolve I_2 in the previous solution
- Complete the volume with Alcohol

Rx6) Strong Iodine Solution

Iodine 100 g

KI 60 g

P.W.100 ml

Ethanol (90%) q.s. 1000 ml

sig. externally b. i. d.

Rx7) Ferrous sulfate Mixture

Ferrous sulfate gr X

Tr. Of Nuxvomica ℿ X

Tr. Of Hydrastis ℿ X

Syrup ʒi

Chloroform water Q.Sʒi

Ft. mist.

mittʒ vi

Sig: ʒssqidp.c

General Notes :

- To increase the solubility of a solute in a solvent

Mentioned In the Lecture

- To dispense a prescription we should use (Red Label) for external use and (White Label) for Internal use , and the label should contain :

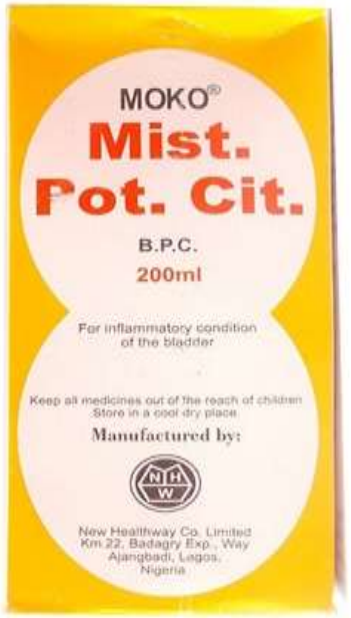
Mentioned In the Lecture

Solutions (part II)

Mist Diuretics: Prescriptions

Rx1: Mist Diuretic (Acidic)

Potassium citrate 2 g
Citric acid monohydrate 0.4g
Lemon syrup 1 ml
Conc. Chloroform water 0.2 ml
P.W. q.s. 20ml
ft. mist.
sig. 10 – 20 ml diluted with water t.i.d. p.c.
Mitte 20 ml



Rx2: Mist Diuretic (Alkaline)

Potassium citrate 20 g
Sodium bicarbonate 20 g
Conc. infusion of buchu 20 ml
Syrup of orange 40 ml
Chloroform water q.s. 300 ml
ft. mist.
Mitte 20 ml
sig. 10 – 20 ml diluted with water t.i.d. p.c.

- Potassium citrate : used as a diuretic, Also act as potassium supplement, it increase the alkalinity of the urine and increase the excretion of salt
- Diuretics used in kidney problems such as renal stone and for their alkaline effect
- Alkaline diuretics is not used in Hypertensive Patients

Nasal Drops

Nasal solution are usually aqueous solutions which are designed to be administered to the nasal passage in drop or spray form,most of them are administered for their local sympathomimetic effect such as ephedrine sulfate or naphzolineHCl nasal solution to decrease nasal congestion .

Nasal drop usually contain substances like antiseptic like sea water and vasoconstrictor properties, it must be isotonic (0.9% Nacl) with nasal secretion & with approximately same PH.

Ephedrine Nasal Drops

Ephedrine HCl 500 mg
NaCl 500 mg
Chlorbutol 500 mg
D.W. q.s. 1000 ml
ft. mist.
mitte20 ml
sig. 2drops in each nostril as directed (internally)

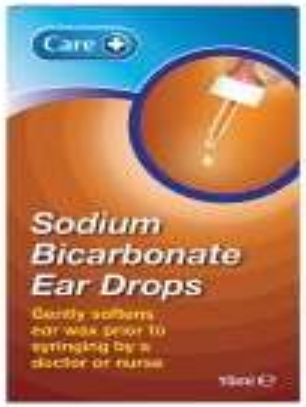
Ear Drop

Are suspensions, emulsions or solutions of one or more medicament in a vehicle suitable for instillation into the ear, it may contain antimicrobial & preservative
Glycerin may be added as a preservative, lubricant & to increase viscosity
Solvent used is water, glycerin, dil alcohol or propylene glycol
So the ear drop solution are mostly simple solutions of drugs in either water, glycerol, PG, alcohol or Alc/water Mixture .
They include antibiotics , antiseptic , cleansing sol. And wax softener

Sodium Bicarbonate Ear Drops BP

Sodium bicarbonate		5 g (wax softner)
Glycerine		30 ml(wax softner, lubricant&preservative)
P.W.	q.s.	100 ml
ft. mist.		
Mitte		20 ml

sig. as directed (externally)
Procedure:
Dissolve the $NaHCO_3$ in about 60 ml of P.W ,Add glycerin and sufficient P.W. to produce 100 ml and mix.



Gargles & Mouthwash Solutions

Gargles are aqueous solutions used to treat mouth and throat infections, they are dispensed in a concentrated form with direction of dilution with warm water so they are:

1)More Medicated 2) more Concentrated, than mouthwash

While mouthwashes are pleasantly flavored than gargles, ex: PotassiumChlorate and phenol gargles

Mouthwash are aqueous flavored and colored solutions used for their refreshing and antiseptic effect, it contain:flavors,colors ,sweetener, alcohol , glycerin , surfactant.

They are less concentrated and less medicated than gargles

Sodium Chloride Mouthwash

Sodium chloride 1.5 g

Sodium bicarbonate 1 g

Peppermint water q.s. 100 ml

ft. mist.

mitte20 ml

sig. dilute with equal volume of warm water before use. Rinse the mouth 3 – 4

Times daily as required

Throat Paint

Viscous liquid preparation used for mouth and throat infection (laryngitis & tonsillitis)

Mendel's throat paint

Iodine		12 g
KI		25 g
Ethanol (90%)		40 ml
D.W.		25 ml
Peppermint oil		4 ml
Glycerin	q.s.	1000 ml (increases viscosity, sweetening agent, & solvent)

ft. mist.

Mitt. 25 ml

sig. throat paint (externally)

Procedure:

- Dissolve iodine in concentrated aqueous solution of KI
- Mix peppermint oil with Alcohol
- Add iodine solution to the alcoholic mixture and mix well
- Complete the volume with glycerol to 1000 ml

Eye Drop

Are sterile aqueous or oily solution or suspension instillation into the eye, it should be sterile, isotonic, buffered and free from foreign particles to avoid irritation to the eye. It used as antiseptic, anesthetics, analgesic, and anti-inflammatory or AB.

External solutions

Solution 1 and Solution 2

(Solution no. 1) 20% w/v sodium thiosulphate

(Solution no. 2) 4-5% w/v tartaric acid

sig. external use

Direction for use

Apply solution 1 then after 2 minutes, apply solution 2

Sol2 will precipitate the sulfur from sol1 which is used in the treatment of skin disorders and it has an antifungal effect

Enemas

Are aqueous or oily solutions or suspensions intended for introduction into the rectum for their purgative, sedative, anti-inflammatory or nutritive effect, they are also used in X-Ray examination of the lower bowel , the volume of enema depend on the patient condition, for infant 100-200ml and for adult 400-500ml

Rx

Soft Soap 25g

P.W. 500ml

Sig. to be used as directed

Use: Evacuant Enema

Spirit & Elixir

Pharmaceutical Technology Lab.

Third Stage

Spirit

- Spirits are alcoholic or hydro-alcoholic solutions of volatile substances.

- Formerly, they were prepared by distillation but now generally made by simple dissolving a volatile substance in alcohol. The volatile substances in most cases are volatile oils.

- Spirits **may or may n**ot have therapeutic effect. Some are *used internally* and others are *used externally*.

- The **amount of volatile material** in spirits varies greatly and no fixed percentage can be given. In all cases, the volatile oil content of the official spirit is much greater than that of the corresponding aromatic water.

The difference between

spirits and aromatic water

e.g. peppermint spirit (aromatic spirit) and peppermint water:

- In aromatic water, only small quantity of oil give a saturated solution because water cannot dissolve large quantity of oil
- in **spirit** the alcohol is capable of dissolving greater quantity of oil (like dissolves like).

Alcohol Content of Spirit

The **alcohol content** of spirits also varies

- lowest percentage of alcohol can be found in Aromatic Ammonia Spirit USP which is **62 – 68%** v/v (a respiratory stimulant used to treat or prevent fainting)
- highest percentage is found in Camphor Spirit USP **(80 – 87%** v/v) which is used externally as a counterirritant.

**Alcohol USP contains 94.9 – 96% v/v ethanol

Preparation of spirits and its problems

- *Methods of preparation*: ***(Simple solution ,Maceration ,Chemical reaction and Distillation).***

- it must be kept in mind that the **oils dissolved in alcohol are precipitated causing turbidity when the solutions are mixed with water**. In order to avoid this turbidity, water should be avoided and *all equipment used should be dry and the filter paper should be moistened with alcohol (alcohol should not be less than 60%).*

- Spirits should be stored in a dry and light resistant container in a cool place to prevent evaporation of alcohol, volatilization of volatile oil, and any oxidative changes.

- Uses of official spirit

1. Carminative
2. Antacid
3. Mild reflex circulating stimulant (camphor spirit) as counter irritant
4. Flavoring agent

AROMATIC SPIRIT OF AMMONIA

Ammonium carbonate		34 g
Dilute solution of ammonia		90 ml
Oil of lemon		10 ml
Oil of lavender		1 ml
Oil of myristica		1 ml
Alcohol		700 ml
D.W.	q.s.	1000 ml
Mitte	50 ml	

1.Dissolve the solid material in dilute solution of ammonia with little amount of water.

2. The oils are dissolved in alcohol with little amount of water.

3. Filter each solution separately if needed, then add the aqueous solution to the alcoholic one. If the alcoholic phase is added to the aqueous one, sudden dilution takes place causing a precipitation of oils with turbidity.

Compound spirit of cardamom

Oil of cardamom	20 ml	(carminative)
Oil of orange	20 ml	
Oil of cinnamon	2 ml	(carminative)
Oil of clove	1 ml	
Anethol	1 ml	(mild expectorant)
Oil of caraway	0.1 ml	(antispasmodic)
Alcohol q.s.	200 ml	

Procedure:

- Mix all oils and anethol with sufficient alcohol to form a homogeneous solution then complete the volume to 200 ml with alcohol.

SPIRIT OF CAMPHOR

Camphor 1 ml

Alcohol q.s. 10 ml

** Used as ***counterirritant*** for temporary relief of minor aches and pains of muscles and joints associated with simple backache, arthritis, strains, bruises and sprains.

SPIRIT OF ANISE

Oil of anise 100 ml

Alcohol q.s. 1000 ml

Mitt 20ml

ELIXIRS

- Are clear **Sweetened hydro-alcoholic** solutions intended for oral use and are usually flavored to enhance their ***palatability***. They are usually medicated but non-medicated elixirs are also available and used as vehicles

- In official elixirs, alcohol content varies from **4 – 40%** and generally there is enough alcohol just to keep the volatile oil or the medicinal substance in solution.

- Alcohol acts as : dissolving agent, preservative and taste masking agent for some unpleasant ingredients.

- Elixirs contain lower concentrations of sugar than syrups.

- The official elixirs are used most widely due to:

1. Their pleasant flavoring taste (due to presence of sugar and volatile flavoring agents).
2. Their relative stability (because of alcohol).
3. The ease of their preparation

Differences between spirits and elixirs

1. Elixirs contain sweetening agents
2. Elixirs are more viscous than spirits and may need preservatives while spirits are less viscous and preservatives are not usually needed.
3. Elixirs used internally only while spirits can be used internally or externally.
4. The primary solvent in elixirs are water and alcohol while in spirits the primary solvent is alcohol.
5. The percentage of alcohol is lower in elixirs than in spirits (4 – 40% versus 62 – 87%, respectively).

CLASSIFICATION OF ELIXIR

A-Non medicated elixir

Used as palatable vehicle, the purpose of this type is to make it possible for medicine to be dispensed in palatable form.

1-Aromatic elixir

2- Aqueous elixir of glycerhiza

3- Compound benzaldehyde elixir.

4- Isoalcoholic elixir

5- Red aromatic elixir

B-Medicated elixir

These elixir have therapeutic action and this group further classified according to their therapeutic activity

1. Antihistaminic elixir example allermine elixir(diphenhydranmine HCL) and allerfine elixir (chlorpheniramine elixir)
2. Expectorant example bisolvon and terpine elixir
3. Sedative and hypnotic example phenobarbital elixir,sodium phenobarbital and hypnoral elixir.
4. Digestive Elixir ex: pepsin elixir
5. B-plex , Ferro B , Toniphos Elixir
6. Miscellaneous medicated Elixir (Digoxin, dexon, acetaminophen, piperazin citrate, antipyrol)

Phenobarbital elixir

Phenobarbital		4 g
Tr. of sweet orange peel		30 ml (flavoring and sweetening agent)
Solution of amaranth		10 ml (coloring agent)
Alcohol		125 ml
Glycerin		450 ml (preservative, and viscosity)
Simple syrup		150 ml (sweetening agent)
D.W.	q.s.	1000 ml
Mitte	20 ml	
Sig. 3 i o.n.		

Phenobarbital elixir

Procedure:

1. Dissolve the phenobarbital in alcohol within a conical flask.

2. Add the following ingredients in sequence: tincture of sweet orange peel, glycerine, simple syrup and amaranth's solution.

3. Finally, add sufficient water to produce 1000 ml. (mix and filter if necessary).

Phenobarbital elixir

Notes:

Phenobarbital is acidic in nature with low water solubility. Therefore, elixir is prepared.

Used as : ***antiepileptic agent*** (e.g. in Revanin® suppositories). Can also act as enzyme inducer and muscle relaxant (muscle relaxant for pregnant women but now not used because of its adverse effects).

Pediatric paracetamol elixir

Paracetamol	120 mg
Alcohol	0.5 ml
Chloroform spirit	0.1 ml
Propylene glycol	0.5 ml (solubility, stability and viscosity)
Conc. of raspberry juice	0.125 ml (colour and flavour)
Amaranth solution	0.01 ml
Inverted syrup	1.375 ml (sweetening agent)
Glycerol	q.s. 5 ml

Pediatric paracetamol elixir

Procedure:

1. Dissolve the paracetamol in alcohol (paracetamol is not soluble that much in water).

2. Add chloroform spirit, propylene glycol, concentrate of raspberry juice, amaranth solution and syrup.

3. Complete the volume to 5 ml with glycerol and filter by cotton if required.

Note: Used as analgesic and antipyretic

Aromatic Elixir (non-medicated)
(Home Work)

Compound orange spirit		12 ml
Syrup		375 ml
Talc powder		30 gm
Alcohol water	} a.a Q.S	1000 ml

Mitt. 50 ml

Thank You

Suppositories and Inserts

Chapter 12

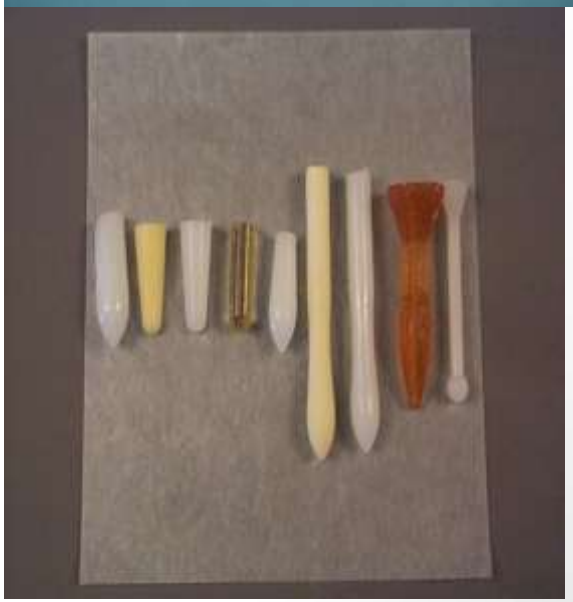
Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 9th Edition

SUPPOSITORIES

- Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert local or systemic effects.
- The derivation of the word suppository is from the Latin supponere, meaning “to place under,” as derived from sub (under) and ponere (to place).
- Thus, suppositories are meant both linguistically and therapeutically to be placed under the body, as into the rectum
- Suppositories are commonly used rectally and vaginally and occasionally urethrally
- They are used to deliver both systemically and locally acting medications

SUPPOSITORIES SHAPES

- Suppositories have various shapes and weights.
- The shape and size of a suppository must be such that it can be easily inserted into the intended orifice without causing undue distension, and once inserted, it must be retained for the appropriate period.
- Rectal suppositories are inserted with the fingers, but certain vaginal suppositories, particularly the inserts, or tablets prepared by compression, may be inserted high in the tract with the aid of an appliance.



Rectal suppositories

- Rectal suppositories are usually about 32 mm (1.5 in.) long, are cylindrical, and have one or both ends tapered. Some rectal suppositories are shaped like a bullet, a torpedo, or the little finger.
- Depending on the density of the base and the medicaments in the suppository, the weight may vary.
- Adult rectal suppositories weigh about 2 g when cocoa butter (theobroma oil) is employed as the base.
- Rectal suppositories for use by infants and children are about half the weight and size of the adult suppositories and assume a more pencil-like shape.

Vaginal suppositories

- Vaginal suppositories, also called pessaries, are usually globular, oviform, or cone-shaped and weigh about 5 g when cocoa butter is the base.
- However, depending on the base and the manufacturer's product, the weights of vaginal suppositories may vary widely.

Urethral suppositories

- Urethral suppositories, also called **bougies,** are slender, pencil-shaped suppositories intended for insertion into the male or female urethra.
- Male urethral suppositories may be 3 to 6 mm in diameter and approximately 140 mm long, although this may vary. When cocoa butter is employed as the base, these suppositories weigh about 4 g.
- Female urethral suppositories are about half the length and weight of the male urethral suppository, being about 70 mm long and weighing about 2 g when made of cocoa butter
- Urethral suppositories may be
- antibacterial or
- a local anesthetic preparative for a urethral examination.

Fate of the suppository

- Once inserted, the suppository base melts, softens, or dissolves, distributing its medicaments to the tissues of the region.
- These medicaments may be intended for retention within the cavity for local effects, or they may be intended to be absorbed for systemic effects.
- They may exhibit the effect immediately or sustain the release of the drug such as Long-acting or slow-release suppositories are also prepared.
- Morphine sulfate in slow-release suppositories is prepared by compounding pharmacists. The base includes a material such as alginic acid, which will prolong the release of the drug over several hours

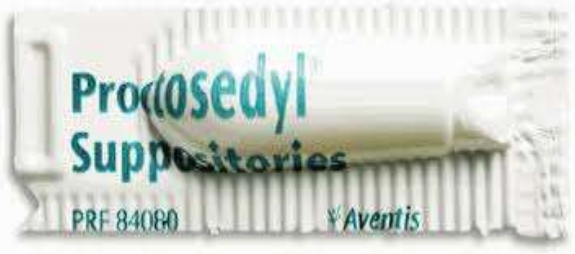
Local rectal suppositories

- Rectal suppositories intended for local action are most frequently used to relieve

1- constipation

A popular laxative, glycerin suppositories promote laxation by local irritation of the mucous membranes, probably by the dehydrating effect of the glycerin on those membranes.

2- the pain, irritation, itching, and inflammation associated with hemorrhoids or other ano-rectal conditions.



Anti-hemorrhoidal suppositories frequently contain a number of components, including local anesthetics, vasoconstrictors, astringents, analgesics, soothing emollients, and protective agents.

Local vaginal suppositories

- Vaginal suppositories or inserts intended for local effects are employed mainly as

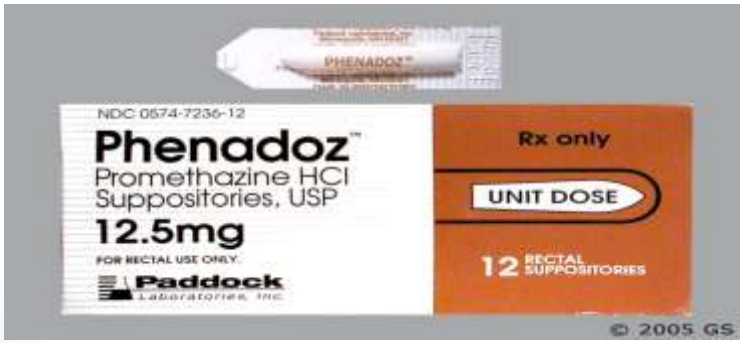
1. contraceptives, the drugs used are nonoxynol-9
2. antiseptics in feminine hygiene, trichomonacides to combat vaginitis caused by Trichomonas vaginalis
3. specific agents to combat an invading pathogen. Most commonly, antifungals to treat Candida (Monilia) albicans, and anti-infectives/antibiotics directed at other microorganisms

Systemic effect of rectal suppositories

- For systemic effects, the mucous membranes of the rectum and vagina permit the absorption of many soluble drugs.
- Although the rectum is used frequently as the site for the systemic absorption of drugs, the vagina is not as frequently used for this purpose.
- Among the advantages over oral therapy of the rectal route for systemic effects are these:
- (a) Drugs destroyed or inactivated by the pH or enzymatic activity of the stomach or intestines need not be exposed to these destructive environment
- (b) Drugs irritating to the stomach may be given without causing such irritation.
- (c) Drugs destroyed by portal circulation may bypass the liver after rectal absorption (drugs enter the portal circulation after oral administration and absorption).
- (d) The route is convenient for administration of drugs to patients who are unable or unwilling to swallow medication.
- (e) It is an effective route in the treatment of patients with vomiting.

Examples of drugs administered rectally for systemic effect

- (a) prochlorperazine and chlorpromazine for the relief of nausea and vomiting and as a tranquilizer;
- (b) oxymorphone HCl for opioid analgesia;
- (c) ergotamine tartrate for the relief of migraine syndrome;
- (d) indomethacin, a nonsteroidal anti-inflammatory analgesic and antipyretic; and
- (e) ondansetron for the relief of nausea and vomiting



SOME FACTORS OF DRUG ABSORPTION FROM RECTAL SUPPOSITORIES

- The dose of a drug administered rectally may be greater than or less than the dose of the same drug given orally, depending on such factors as
- the physicochemical nature of the drug and
- its ability to traverse the physiologic barriers to absorption,
- and the nature of the suppository vehicle and its capacity to release the drug and make it available for absorption.

Rectal absorption

- The factors that affect rectal absorption of a drug may be divided into two main groups:
- (a) physiologic factors and
- (b) physicochemical factors of the drug and the base

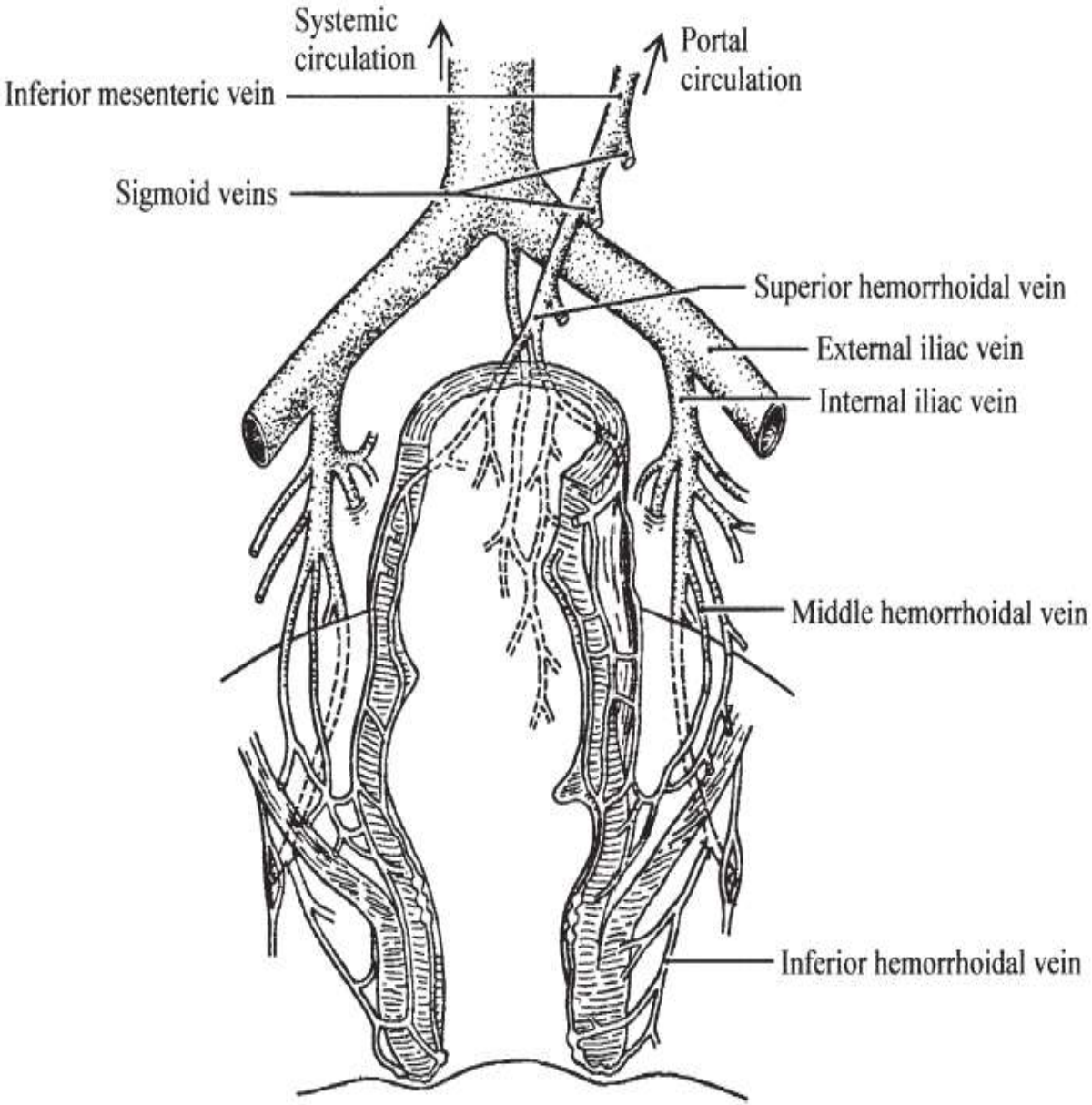


Figure 10. Anatomy of colonal and hemorrhoidal veins.

PHYSIOLOGIC FACTORS

- The human rectum is approximately 15 to 20 cm long.
- When empty of fecal material, the rectum contains only 2 to 3 mL of inert mucous fluid. (low volume of fluid available)
- In the resting state, the rectum is not motile; there are no villi or microvilli on the rectal mucosa .
- However, there is abundant vascularization of the submucosal region of the rectum wall with blood and lymphatic vessels.
- Among the physiologic factors that affect drug absorption from the rectum are the colonic contents,
- and the pH and lack of buffering capacity of the rectal fluids.

Colonic Content

- When systemic effects are desired, greater absorption may be expected from a rectum that is void than from one that is distended with fecal matter.
- A drug will obviously have greater opportunity to make contact with the absorbing surface of the rectum and colon in an empty rectum.
- Therefore, when deemed desirable, an evacuant enema may be administered and allowed to act before the administration of a suppository of a drug to be absorbed.
- Other conditions, such as diarrhea, colonic obstruction due to tumorous growths, and tissue dehydration can all influence the rate and degree of drug absorption from the rectum

Circulation Route

- Drugs absorbed rectally, unlike those absorbed after oral administration, bypass the portal circulation during their first pass into the general circulation, thereby enabling drugs otherwise destroyed in the liver to exert systemic effects.
- The lower hemorrhoidal veins surrounding the colon receive the absorbed drug and initiate its circulation throughout the body, bypassing the liver.
- Lymphatic circulation also assists in the absorption of rectally administered drugs

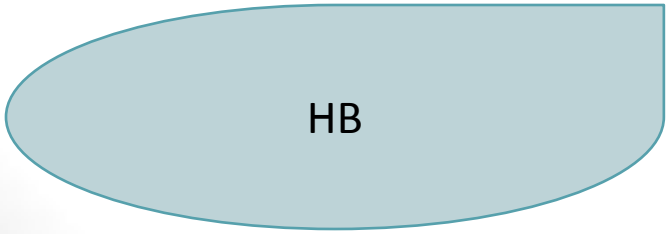
pH and Lack of Buffering Capacity of the Rectal Fluids

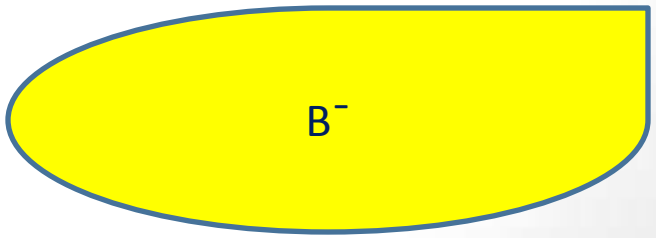
- Because rectal fluids are essentially neutral in pH (7) and have no effective buffer capacity, the form in which the drug is administered will not generally be chemically changed by the environment.
- The suppository base has a marked influence on the release of active constituents. While cocoa butter melts rapidly at body temperature, because of its immiscibility with fluids, it fails to release fat-soluble drugs readily.

Effect of drug ionization and suppository base on release

- Un-ionized drug
- Although un-ionized drugs more readily partition out of water-miscible bases such as glycerinated gelatin and polyethylene glycol, the bases themselves tend to dissolve slowly and thus retard release of the drug

- Ionized drug
- For systemic drug action using a cocoa butter base, it is preferable to incorporate the ionized (salt) form rather than the un-ionized (base) form of a drug to maximize bioavailability.





PHYSICOCHEMICAL FACTORS OF THE DRUG AND SUPPOSITORY BASE

- Physicochemical factors of **the drug** include such properties as:

1. the relative solubility of the drug in lipid and in water and
2. the particle size of a dispersed drug, and surface properties
3. Amount of drug
4. pKa of the drug

- Physicochemical factors **of the base** include :

1. its ability to melt, soften, or dissolve at body temperature,
2. its ability to release the drug substance, and
3. its hydrophilic or hydrophobic character(composition of the base)
4. Rheological properties

Lipid-Water Solubility

- The lipid-water partition coefficient of a drug is an important consideration in the selection of the suppository base and in anticipating drug release from that base.
- A lipophilic drug that is distributed in a fatty suppository base in low concentration has less tendency to escape to the surrounding aqueous fluids than a hydrophilic substance in a fatty base.
- Water soluble bases—for example, polyethylene glycols—that dissolve in the anorectal fluids release for absorption water-soluble and oil-soluble drugs.
- Naturally, the more drug a base contains, the more drug will be available for absorption. However, if the concentration of a drug in the intestinal lumen is above a particular amount, which varies with the drug, the rate of absorption is not changed by a further increase in the concentration of the drug

Drug solubility and suppository formulation

Solubility in		
Fat	Water	Choice of base
Low	High	Fatty base
High	Low	Aqueous base
Low	Low	Intermediate

Particle Size

- For un-dissolved drugs in a suppository, the size of the drug particle will influence its rate of dissolution and its availability for absorption.
- The smaller the particle, the greater the surface area, the more readily the dissolution of the particle and the greater the chance for rapid absorption.

Nature of the Base

- The base must be capable of melting, softening, or dissolving to release its drug for absorption. If the base interacts with the drug to inhibit its release, drug absorption will be impaired or even prevented. Also, if the base irritates the mucous membranes of the rectum, it may initiate a colonic response and prompt a bowel movement, eliminating the prospect of complete drug release and absorption.
- Because of the possibility of chemical and/or physical interactions between the medicinal agent and the suppository base, which may affect the stability and/or bioavailability of the drug, the absence of any drug interaction between the two agents should be ascertained before or during formulation.

Properties of the ideal suppository base

1. **Non-toxic**, **non- irritating** to sensitive and inflamed tissues.
2. **Inert** and **compatible** with medicaments.
3. **Not deteriorated** or **contaminating** the drug during storage.
4. **Easily manufactured** by compression or molding.
5. **Dissolve** or **disintegrate** in mucous secretions or **melt** quickly at body temperature to allow the release of medicament.
6. **Remain molten** for a sufficient period of time to allow pouring into molds.
7. **Solidify rapidly** to minimize sedimentation of dispersed solids.
8. **Contract on cooling** to allow easy withdrawal of the suppository from the mold.
9. Has **wetting** and **emulsifying** properties.
10. **Stable on storage**, keeps its shape during storage or handle does **not change color, odor** and **drug release** pattern.

SUPPOSITORY BASES

- Requisites for a suppository base is that it *should remain solid at room temperature but soften, melt, or dissolve readily at body temperature so that the drug is fully available soon after insertion.* Certain bases are more efficient in drug release than others.

1. **Fatty bases or oleaginous bases** Cocoa butter (theobroma oil) melts quickly at body temperature, but is immiscible with body fluids As for fat-soluble drugs tend to remain in the oil and have little tendency to enter the aqueous physiologic fluids. For water-soluble drugs in cocoa butter, the reverse is usually true and good release results. Also, when irritation or inflammation is to be relieved, as in the treatment of ano-rectal disorders, cocoa butter appears to be the superior base because of its emollient or soothing, spreading action
2. **Water soluble or water miscible bases** glycerinated gelatin or polyethylene glycol, Fat-soluble drugs seem to be released more readily from these bases, but, both of which dissolve slowly in body fluids.
3. **Miscellaneous bases**, generally combinations of lipophilic and hydrophilic substances.

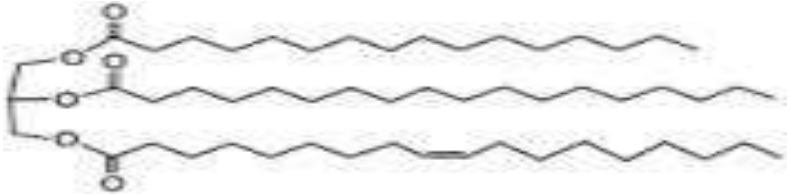
Fatty or Oleaginous Bases

1. Cocoa butter
2. hydrogenated fatty acids of vegetable oils, such as palm kernel oil and cottonseed oil.
3. fat-based compounds ,esters of glycerin with the higher-molecular-weight fatty acids, such as palmitic and stearic acids, such as glyceryl monostearate and glyceryl monopalmitate.

- The bases in many commercial products employ varied combinations of these types of materials to achieve the desired hardness under conditions of shipment and storage and the desired quality of submitting to the temperature of the body to release their medicaments.

Cocoa Butter, NF

- Fat obtained from the roasted seed of Theobroma cacao.
- At room temperature, it is a yellowish-white solid having a faint, agreeable chocolate-like odor.
- Chemically, the main constituent of cocoa butter is the triglyceride derived from palmitic acid, stearic acid, and oleic acid, primarily of oleopalmitostearin and oleodistearin



- Cocoa butter melts at 30°C to 36°C it is an ideal suppository base, melting just below body temperature and yet maintaining its solidity at usual room temperatures.
- However, because of its triglyceride content, cocoa butter exhibits marked polymorphism, or existence in several crystalline forms

Cocoa Butter polymorphism

- When cocoa butter is hastily or carelessly melted at a temperature greatly exceeding the minimum required temperature (about 35°C) and is then quickly chilled, the result is a metastable crystalline form (alpha crystals) with a melting point much lower than that of the original cocoa butter. In fact, the melting point may be so low that the cocoa butter will not solidify at room temperature. (melts at 22°C)
- However, because the crystalline form is a metastable condition, there is a slow transition to the more stable beta form of crystals having the greater stability and a higher melting point. This transition may require several days.
- Consequently, if suppositories that have been prepared by melting cocoa butter for the base do not harden soon after molding, they will be useless to the patient and a loss of time, materials, and prestige to the pharmacist.
- Cocoa butter must be slowly and evenly melted, preferably over a bath of warm water, to avoid formation of the unstable crystalline form and ensure retention in the liquid of the more stable beta crystals that will constitute nuclei upon which the congealing may occur during chilling of the liquid.

Melting point lowering

- Substances such as phenol and chloral hydrate have a tendency to lower the melting point of cocoa butter. If the melting point is low enough that it is not feasible to prepare a solid suppository using cocoa butter alone as the base, solidifying agents like cetyl esters wax (about 20%) or beeswax (about 4%) may be melted with the cocoa butter to compensate for the softening effect of the added substance.
- However, the addition of hardening agents must not be so excessive as to prevent the base from melting in the body, nor must the waxy material interfere with the therapeutic agent in any way so as to alter the efficacy of the product.

Disadvantages of theobroma oil:

1. **Polymorphism**: when melt &solidify it form **different crystal form** depending on the **temperature** if its melt at low temp, not exceed 36 ºC it will form β-polymorph form which is stable form, if melted suddenly &quickly at high temperature then freezing or cooling it will form unstable γ form that melt at 15 ºC, it may form α form that melt at 20 ºC.
2. **Adherence to the mold**, this can be solved by using lubricant agent that is immiscible with the base.
3. **Low m.p**, this can be solved by added medication, adding **white bees wax.**
4. **Low water absorbance (poor water-absorbing capacity)**, this can be solved by adding **surface active agent**.
5. **Stability** problem (slow deterioration during storage, chemical instability).
6. Not suitable for **warm countries**, m.p can be raised by adding white bees wax or a synthetic fatty base such as **Witepsol**.
7. Relatively high cost.

Other fatty bases

- Other bases in this category include commercial products such as
- Fattibase (triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostearate and polyoxyl stearate),
- the Wecobee bases (triglycerides derived from coconut oil) and Witepsol bases (triglycerides of saturated fatty acids C12-C18 with varied portions of the corresponding partial glycerides).

Water-Soluble and Water-Miscible Bases

- The main members of this group are glycerinated gelatin and polyethylene glycols.
- Glycerinated gelatin suppositories may be prepared by dissolving granular gelatin (20%) in glycerin (70%) and adding water or a solution or suspension of the medication (10%).
- A glycerinated gelatin base is most frequently used in preparation of vaginal suppositories, with which prolonged local action of the medicinal agent is usually desired. The glycerinated gelatin base is slower to soften and mix with the physiologic fluids than is cocoa butter and therefore provides a slower release.

Glycerinated gelatin suppositories disadvantages

1. Because glycerinated gelatin-based suppositories have a tendency to **absorb moisture** as a result of the hygroscopic nature of glycerin, they must be protected from atmospheric moisture if they are to maintain their shape and consistency, **difficult to prepare and handle**.
2. These suppositories may have a dehydrating effect and irritate the tissues upon insertion, exerting **a laxative effect**. The water in the formula for the suppositories minimizes this action; however, if necessary, the suppositories may be moistened with water prior to insertion to reduce the initial tendency of the base to draw water from the mucous membranes and irritate the tissues
3. Gelatin is incompatible with protein precipitants such as tannic acid.

Urethral Glycerinated gelatin suppositories

- Urethral suppositories may be prepared from a glycerinated gelatin base of a formula somewhat different from the one indicated earlier.
- For urethral suppositories, the gelatin constitutes about 60% of the weight of the formula, the glycerin about 20%, and the medicated aqueous portion about 20%.
- Urethral suppositories of glycerinated gelatin are much more easily inserted than those with a cocoa butter base owing to the brittleness of cocoa butter and its rapid softening at body temperature

Polyethylene glycols

- Polyethylene glycols are polymers of ethylene oxide and water prepared to various chain lengths, molecular weights, and physical states, the most commonly used being polyethylene glycol 300, 400, 600, 1,000, 1,500, 1,540, 3,350, 4,000, 6,000, and 8,000. Various combinations of these polyethylene glycols may be combined by fusion, using two or more of the various types to achieve a suppository base of the desired consistency and characteristics

PEG	Melting range	PEG	Melting range
300	-15°C -18°C	3350	54°C -58°C
400	4°C -8°C	4600	57°C -61°C
600	20°C -25°C	6000	56°C -63°C
1000	37°C -40°C	8000	60°C -63°C
1450	43°C -46°C		

Polyethylene glycol suppositories

- Polyethylene glycol suppositories do not melt at body temperature but rather dissolve slowly in the body's fluids. Therefore, the base need not be formulated to melt at body temperature.
- Thus, it is possible, in fact routine, to prepare suppositories from polyethylene glycol mixtures having melting points considerably higher than body temperature.
- This property permits a slower release of the medication from the base once the suppository has been inserted,
- and permits convenient storage of these suppositories without need for refrigeration and without danger of their softening excessively in warm weather.
- Further, their solid nature permits slow insertion without fear that they will melt in the fingertips (as cocoa butter suppositories sometimes do).
- Because they do not melt at body temperature but mix with mucous secretions upon dissolution, polyethylene glycol-based suppositories do not leak from the orifice, as do many cocoa butter-based suppositories.
- Polyethylene glycol suppositories that do not contain at least 20% water should be dipped in water just before use to avoid irritation of the mucous membranes after insertion. This procedure prevents moisture being drawn from the tissues after insertion and the stinging sensation

Miscellaneous Bases

- In the miscellaneous group of bases are mixtures of oleaginous and water-soluble or water-miscible materials. These materials may be chemical or physical mixtures.
- Some are preformed emulsions, generally of the water-in-oil type, or they may be capable of dispersing in aqueous fluids, these emulsions prompt emulsification when the suppository makes contact with the aqueous body fluids.
- 1- Polyoxyl 40 stearate, a surface-active agent that is employed in a number of commercial suppository bases. Polyoxyl 40 stearate is a mixture of the monostearate and distearate esters of mixed polyoxyethylene diols and the free glycols, the average polymer length being equivalent to about 40 oxyethylene units. The substance is a white to light tan waxy solid that is water soluble. Its melting point is generally 39°C to 45°C.
- 2-Other surface-active agents useful in the preparation of suppository bases also fall into this broad grouping. Mixtures of many fatty bases (including cocoa butter) with emulsifying agents capable of forming water-in-oil emulsions have been prepared. These bases hold water or aqueous solutions and are said to be hydrophilic.

PREPARATION OF SUPPOSITORIES

- Suppositories are prepared by three methods:
- (a) molding from a melt,
- (b) compression, and
- (c) hand rolling and shaping.
- The method most frequently employed both on a small scale and on an industrial scale is molding.

PREPARATION BY MOLDING

- The steps in molding include
- (a) melting the base,
- (b) incorporating any required medicaments,
- (c) pouring the melt into molds,
- (d) allowing the melt to cool and congeal into suppositories,
- (e) removing the formed suppositories from the mold.
- Cocoa butter, glycerinated gelatin, polyethylene glycol, and most other bases are suitable for preparation by molding.

Suppository Molds

- Molds in common use today are made from stainless steel, aluminum, brass, or plastic.
- The molds, which separate into sections, generally longitudinally, are opened for cleaning before and after preparation of a batch of suppositories, closed when the melt is poured, and opened again to remove the cold, molded suppositories.
- Care must be exercised in cleaning the molds, as any scratches on the molding surfaces will take away from the desired smoothness of the suppositories. Plastic molds are especially prone to scratching.

Lubrication of the Mold

- Depending on the formulation, suppository molds may require lubrication before the melt is poured to facilitate clean and easy removal of the molded suppositories.
- Lubrication is seldom necessary when the base is cocoa butter or polyethylene glycol, as these materials contract sufficiently on cooling to separate from the inner surfaces and allow easy removal.
- Lubrication is usually necessary with glycerinated gelatin. A thin coating of mineral oil applied with the finger to the molding surfaces usually suffices.
- However, no material that might irritate the mucous membranes should be employed as a mold lubricant.

Preparing and Pouring the Melt

- 1-Using the least possible heat, the weighed suppository base material is melted, generally over a water bath, because not a great deal of heat is required. A porcelain casserole, that is, a dish with a pouring lip and a handle, is perhaps the best utensil, because it later permits convenient pouring of the melt into the cavities of the mold.
- 2-Usually, medicinal substances are incorporated into a portion of the melted base by mixing on a glass or porcelain tile with a spatula.
- 3- After incorporation, this material is stirred into the remaining base, which has been allowed to cool almost to its congealing point. Any volatile materials or heat-labile substances should be incorporated at this point with thorough stirring

Molding from the melt

- 3-The melt is poured carefully and continuously into each cavity of the mold, which has been previously equilibrated to room temperature.
- If any un-dissolved or suspended materials in the mixture are denser than the base, so that they have a tendency to settle, constant stirring, even during pouring, is required, else the last filled cavity will contain a disproportionate share of the un-dissolved materials.
- The solid materials remain suspended if the pouring is performed just above the congealing point and not when the base is too fluid. If the melt is not near the congealing point when poured, the solids may settle within each cavity of the mold to reside at the tips of the suppositories, with the result that the suppositories may be broken when removed from the mold.
- Alternatively, a small quantity of silica gel (about 25 mg per suppository) can be incorporated into the formula to aid in keeping the active drug suspended.

Molding from the melt

- 4-To ensure a completely filled mold upon congealing, the melt is poured excessively over each opening, actually rising above the level of the mold. The excessive material may form a continuous ribbon along the top of the mold above the cavities. This use of extra suppository material prevents formation of recessed dips in the ends of the suppositories and justifies preparation of extra melt. When solidified, the excess material is evenly scraped off of the top of the mold with a spatula warmed by dipping into a beaker of warm water; this will make a smooth surface on the back of the suppository during trimming.
- The mold is usually placed in the refrigerator to hasten hardening.

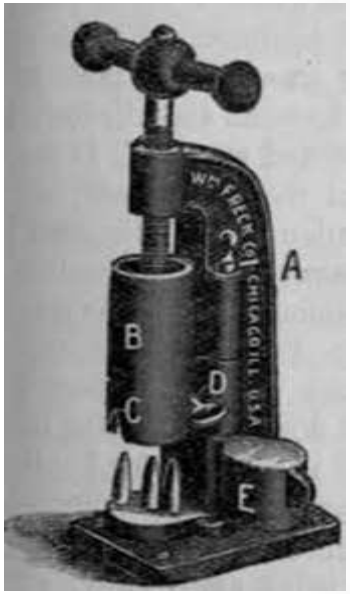
- 5-When the suppositories are hard, the mold is removed from the refrigerator and allowed to come to room temperature. Then the sections of the mold are separated, and the suppositories are dislodged, with pressure being exerted principally on their ends and only if needed on the tips. Generally, little or no pressure is required, and the suppositories simply fall out of the mold when it is opened.

PREPARATION BY COMPRESSION

- Suppositories may be prepared by forcing the mixed mass of the base and the medicaments into special molds using suppository-making machines. In preparation for compression into the molds, the base and the other formula ingredients are combined by thorough mixing, the friction of the process softening the base into a paste-like consistency.
- On a small scale, a mortar and pestle may be used. Heating the mortar in warm water (then drying it) greatly facilitates the softening of the base and the mixing.
- On a large scale, a similar process may be used, employing mechanical kneading mixers and a warm mixing vessel

Compression

- Compression is especially suited for making suppositories that contain heat-labile medicinal substances or a great deal of substances that are insoluble in the base.
- In contrast to the molding method, compression permits no likelihood of insoluble matter settling during manufacture.
- The disadvantage to compression is that the special suppository machine is required and there is some limitation as to the shapes of suppositories that can be made



Compression

- In preparing suppositories with the compression machine, the suppository mass is placed in a cylinder; the cylinder is closed; pressure is applied from one end, mechanically or by turning a wheel; and the mass is forced out of the other end into the mold 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 mass has been used. Various sizes and shapes of dies are available.
- It is possible to prepare suppositories of uniform circumference by extrusion through a perforated plate and by cutting the extruded mass to the desired length

PREPARATION BY HAND ROLLING AND SHAPING

- With ready availability of suppository molds of accommodating shapes and sizes, there is little requirement for today's pharmacist to shape suppositories by hand.
- Hand rolling and shaping is a historic part of the art of the pharmacist

Calibration of the Mold

- Each individual mold is capable of holding a specific volume of material in each of its openings. Because of the difference in the densities of the materials, if the base is cocoa butter,(density =1) the weight of the suppositories will differ from the weight of suppositories prepared in the same mold with a base of polyethylene glycols. (density =1.2)
- Similarly, any added medicinal agent alters the density of the base, and the weight of the resulting suppository differs from that of those prepared with base material alone.
- The pharmacist should calibrate each suppository mold for the usual base (generally cocoa butter and a polyethylene glycol base) so as to prepare medicated suppositories each having the proper quantity of medicaments.

Calibration of the mold

- The first step in calibration of a mold is to
- prepare molded suppositories from base material alone.
- After removal from the mold,
- the suppositories are weighed and the total weight and average weight of each suppository are recorded (for the particular base used).
- To determine the volume of the mold, the suppositories are carefully melted in a calibrated beaker, and the volume of the melt is determined for the total number as well as for the average of one suppository.

Determination of the Amount of Base Required

- Calculate the amounts of materials needed for the preparation of one or two more suppositories than the number prescribed to compensate for the inevitable loss of some material and to ensure having enough material (prepare an extra 1 or 2 supp.)
- Verify the required amount of drug is provided in each suppository. Because the volume of the mold is known (from **mold calibration** the determined volume of the melted suppositories formed from the base),
- the volume of the drug substances subtracted from the total volume of the mold will give the volume of base required.
- The total volume of these materials is subtracted from the volume of the mold,
- and the appropriate amount of base is added.

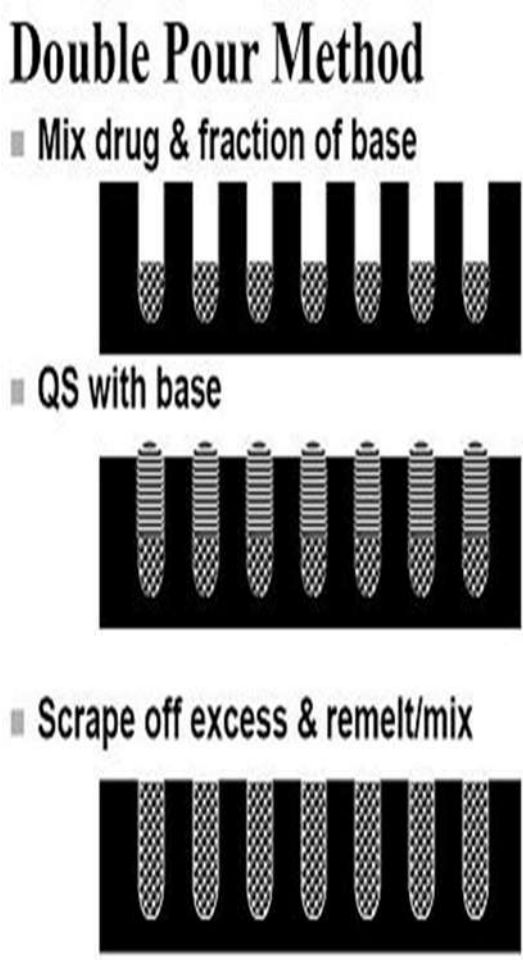
Because the bases are solid at room temperature, the volume of base may be converted to weight from the density of the material

Medicated suppositories

- If the added amounts of medicaments are slight, they may be considered to be negligible, and no deduction from the total volume of base may be deemed necessary. In preparation of suppositories, it is generally assumed that if the quantity of active drug is less than 100 mg,/ 2-g suppository weight then the volume occupied by the powder is insignificant and need not be considered
- Obviously, if a suppository mold of less than 2 g is used, the powder volume may need to be considered.
- However, if considerable quantities of other substances are to be used, the volumes of these materials are important and should be used to calculate the amount of base actually required to fill the mold.

Other calibration method

- Another method for determination of the amount of base is called the **double pour method** in the preparation of medicated suppositories requires the following steps:
- (a) weigh the active ingredient for the preparation of a single suppository;
- (b) dissolve it or mix it (depending on its solubility in the base) with a portion of melted base insufficient to fill one cavity of the mold, and add the mixture to a cavity;
- (c) add additional melted base to the cavity to fill it completely;
- (d) allow the suppository to congeal and harden; and
- (e) remove the suppository from the mold and weigh it.
- The weight of the active ingredients subtracted from the weight of the suppository yields the weight of the base. This amount of base multiplied by the number of suppositories to be prepared in the mold is the total amount of base required



Example

- For example, if 12 mL of cocoa butter is required to fill a suppository mold and if the medicaments in the formula have a collective volume of 2.8 mL, 9.2 mL of cocoa butter will be required. By multiplying 9.2 mL times the density of cocoa butter, 0.86 g/ mL, it may be calculated that 7.9 g of cocoa butter will be required. After adjusting for the preparation of an extra suppository or two, the calculated amount is weighed.

Displacement value DV

- Displacement value is defined as the
- The quantity of drug that displaces one part of the base
- Ex hydrocortisone has a displacement value of 1.5
- Means 1.5g hydrocortisone displaces 1g the suppository base
- If the density of the drug equals the density of the base. The drug will displace the same amount of base
- If the density of the drug is more than the density of the base the drug will displace low amount of base
- if the density of the drug is less than the density of the base the drug will displaces high amount of base
- DV for liquids equals 1

Calculations using displacement values

- Prepare six codeine phosphate suppositories (D.V=1.1)using mold of 1g size each supp. Containing 60mg /supp.
- prepare 10 supp. to compensate for any loss
- 60X10=600mg=0.6g codeine phosphate
- Supp. Base 1gX10=10g total wt. of pure base

- Drug base
- 1.1 displace 1g base replaced=(1gX0.6)/1.1=0.55
- 0.6 ?

- Amount of base needed is 10g-0.55= 9.45g

Displacement values D.V. of some common drugs incorporated into suppositories

Drug	D.V.	Drug	D.V.
Aminophylline	1.3	Morphine sulphate	1.6
Aspirin	1.1	Paracetamol	1.5
Bismuth subgallate	2.7	Phenobarbital	1.1
Castor oil	1	Phenobarbital Sod.	1.2
Chloral hydrate	1.4	Resorcinal	1.5
Codeine phosphate	1.1	Sulfur	1.6
Diphenhydramine HCl	1.3	Theophylline sodium acetate	1.7
Hydrocortisone	1.5	Zinc oxide	4.7
Metronidazole	1.7	Zinc sulphate	2.4
Morphine HCl	1.6		

Density (Dose Replacement) Calculations for Suppositories

- The density factors of various bases and drugs need to be known to determine the proper weights of the ingredients to be used. Density factors relative to cocoa butter have been determined. If the density factor of a base is not known, it is simply calculated as the ratio of the blank weight of the base and cocoa butter
- Three methods of calculating the quantity of base that the active medication will occupy and the quantities of ingredients required are illustrated here:
- (a) dosage replacement factor,
- (b) density factor, and
- (c) occupied volume methods

DETERMINATION OF THE DOSAGE REPLACEMENT FACTOR METHOD

$$f = \frac{[100\,(E - G)]}{[(G)(X)]} + 1$$

- where
- E is the weight of the pure base suppositories, and
- G is the weight of suppositories with X% of the active ingredient.
- Cocoa butter is arbitrarily assigned a value of 1 as the standard base

DOSAGE REPLACEMENT FACTORS FOR SELECTED DRUGS

Balsam of peru	0.83	Phenol	0.9
Bismuth subgallate	0.37	Procaine HCl	0.8
Bismuth subnitrate	0.33	Quinine HCl	0.83
Boric acid	0.67	Resorcin	0.71
Camphor	1.49	Silver protein, mild	0.61
Castor oil	1.00	Spermaceti	1.0
Chloral hydrate	0.67	White or yellow wax	1.0
Ichthammol	0.91	Zinc oxide	0.15-0.25
Phenobarbital	0.81		

Example 1

- Prepare a suppository containing 100 mg of phenobarbital (f = 0.81) using cocoa butter as the base. The weight of the pure cocoa butter suppository is 2.0 g. What will be the total weight of each suppository?
- Because 100 mg of phenobarbital is to be contained in an approximately 2.0-g suppository, it will be about 5% phenobarbital.
- $f = \frac{[100(E-G)]}{[(G)(X)]} + 1$
- $0.81 = \frac{[100(2-G)]}{[(G)(5)]} + 1$
- G= 2.015g weight of the medicated suppository

DETERMINATION OF DENSITY FACTOR METHOD

1. Determine the average blank weight, A, per mold using the suppository base of interest.
2. Weigh the quantity of suppository base necessary for 10 suppositories.
3. Weigh 1.0 g of medication. The weight of medication per suppository, B, is equal to 1 g/10 supp = 0.1 g/supp.
4. Melt the suppository base and incorporate the medication, mix, pour into molds, cool, trim, and remove from the molds.
5. Weigh the 10 suppositories and determine the average weight (C).
6. Determine the density factor as follows:

$$density\ factor = \frac{B}{A - C + B}$$

- A is the average weight of blank,
- B is the weight of medication per suppository, and
- C is the average weight of medicated suppository

DENSITY FACTORS FOR COCOA BUTTER SUPPOSITORIES

Alum	1.7	Digitalis Leaf	1.6	Quinine HCl	1.2
Aminophylline	1.1	Glycerin	1.6	Resorcinol	1.4
Aspirin	1.3	Ichthammol	1.1	Sodium bromide	2.3
Barbital	1.2	Iodoform	4.0	Spermaceti	1.0
Belladonna Extract	1.3	Menthol	0.7	Sulfathiazole	1.6
Benzoic Acid	1.5	Morphine HCl	1.6	Tannic acid	1.6
Bismuth Carbonate	4.5	Opium	1.4	White wax	1.0
Bismuth Salicylate	4.5	Paraffin	1.0	Witch hazel fluid extract	1.1
Bismuth Subgallate	2.7	Peruvian Balsam	1.1	Zinc oxide	4.0
Bismuth Subnitrate	6.0	Phenobarbital	1.2	Zinc sulfate	2.8
Boric Acid	1.5	Phenol	0.9		
Castor Oil	1.0	Potassium Bromide	2.2		
Chloral Hydrate	1.3	Potassium Iodide	4.5		
Cocaine HCl	1.3	Procaine	1.2		

Example 2

- **Prepare 12 acetaminophen 300 mg suppositories using cocoa butter. The average weight of the cocoa butter blank is 2 g and the average weight of the medicated suppository is 1.8 g.**
- Take the weight of the medication required for each suppository and divide by the density factor of the medication to find the replacement value of the suppository base
- $density\ factor\ D.F\ = \frac{B}{A-C+B} = \frac{0.3}{2-1.8+0.3} = 0.6$
- Replacement value =B/D.F=0.3/0.6=0.5
- Subtract this quantity from the blank suppository weight
- 2-0.5=1.5
- Multiply by the number of suppositories required to obtain the quantity of base and the drug required for the prescription
- 12X1.5= 18 g of cocoa butter required
- 12X0.3= 3.6g of the drug required

DETERMINATION OF OCCUPIED VOLUME METHOD

1. Determine the average weight per mold (blank) using the designated base.
2. Weigh out enough base for 12 suppositories.
3. Divide the density of the active drug by the density of the base to obtain a ratio.
4. Divide the total weight of active drug required for the total number of suppositories by the ratio obtained in step 3. This will give the amount of base displaced by the active drug.
5. Subtract the amount obtained in step 4 from the total weight of the prescription (number of suppositories multiplied by the weight of the blanks) to obtain the weight of base required.
6. Multiply the weight of active drug per suppository times the number of suppositories to be prepared to obtain the quantity of active drug required

Example 3

- **Prepare 10 suppositories, each containing 200 mg of a drug with a density of 3.0. The base has a density of 0.9, and a prepared blank weighs 2.0 g. Using the determination of occupied volume method, prepare the requested suppositories.**
- From step 1: The average weight per mold is 2.0 g.
- From step 2: The quantity required for 10 suppositories is 2 g× 10 = 20 g.
- From step 3: The density ratio is 3.0/0.9 = 3.3.
- From step 4: The amount of suppository base displaced by the active drug is 2.0 g/3.3 = 0.6 g.
- From step 5: The weight of the base required is 20 - 0.6 g = 19.4 g.
- From step 6: The quantity of active drug required is 0.2 × 10 g = 2.0 g.
- The required weight of the base is 19.4 g, and the weight of the active drug is 2 g

Practical examples

- **Example: Calculate the quantities required to make 10 theobroma oil supp. (2g mold) each containing 400 mg of zinc oxide (DV= 4.7).**

1. Calculate the total weight of zinc oxide required. 0.4X10=4g
2. Calculate what weight of base would be required to prepare10 un medicated supp. 2gX10=20g
3. Determine what weight of base would be displaced by the medicament. Replaced base =drug/DV = 4/4.7=0.85
4. Calculate, therefore, the weight of base required to prepare the medicated supps. 20-0.85= 19.15g wt of base required

- **Glycero-gelatin base** has a **density 1.2 times greater than theobroma oil**. Therefore, a 1 g supp. mold will produce a 1 g theobroma oil supp., but a 1.2 g glycero-gelatin supp. This factor must be taken into account in displacement value calculations.

Example

- **Calculate the quantities required to make six glycero gelatin supp. (4 g mold), each containing100 mg aminophylline (Displacement value = 1.3)**
- **Drug 6X100=0.6g**
- **glycerin gelatin Base 6X4gX1.2 =28.8g**
- **glycerin gelatin Base replaced = 0.6/1.3=0.46X1.2=0.55g**

- **Base required 28.8-0.55g=28.25g of the base required**

Example

- **prepare 10 supp. non-medicated (only theobroma oil) weight 12 gm. Then prepare 10 medicated supps weighted 14 g, the weight of drug incorporated =4.2 gm, calculate the replacement value?**
- 14 - 4.2= 9.8 g
- 12 - 9.8 = 2.2 g the amount of theobroma oil displace by the drug
- Base Drug
- 2.2 gm 4.2 gm
- 1 x = 1.909≈ 1.91 D.V

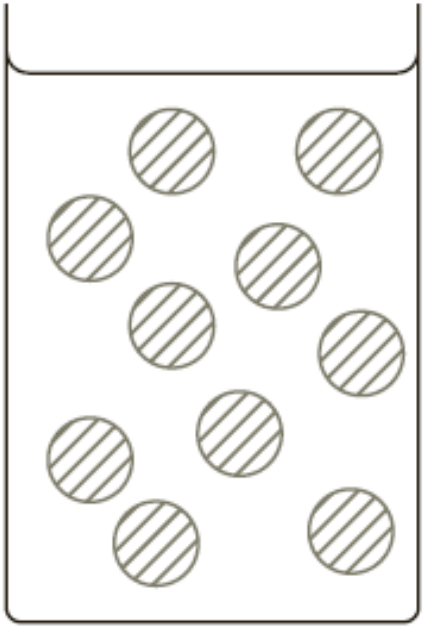
Example

- **what quantities are required to prepare 8 theobroma oil supps, in a 4 g mold, containing 1% w/w lignocaine hydrochloride?**
- **Base required 8 X 4= 32g**
- Calculate the total weight of the drug required (1% of the total weight). 1%of 32g=0.32g drug

EXAMPLES OF RECTAL SUPPOSITORIES

SUPPOSITORY	COMMERCIAL PRODUCT	ACTIVE CONSTITUENT	TYPE OF EFFECT	CATEGORY AND COMMENTS
Bisacodyl	Dulcolax (Boehringer-Ingelheim)	10 mg	Local	Cathartic. Base: hydrogenated vegetable oil
Hydrocortisone	Anusol-HC (Salix)	25 mg	Local	Pruritus ani, inflamed hemorrhoids, other inflammatory conditions of the anorectum. Base: hydrogenated glycerides
Indomethacin	Indocin	50 mg	Systemic	Anti-inflammatory: Base: polyethylene glycols


Pharmaceutical Technology Laboratory
Suspensions



- Suspensions are heterogeneous systems consisting of two phases: Continuous (external) phase and dispersed (internal) phase.
- The external phase is generally a liquid or semisolid and the internal phase is particulate matter (solid).
- The internal phase is insoluble but dispersed throughout the external phase.

- Some suspensions are available in ready to use form (e.g. metronidazole (Flagyl®)) and others are available as dry powders intended for suspension in liquid vehicles, most often purified water (e.g. amoxicillin (Amoxil®)).

- In suspension the vehicle is water and sometimes may be an organic or oily liquid.
- Suspensions can be used orally, parenterally, topically, rectally, ophthalmically, etc

◉ Stokes law:

$$v = \frac{D^2(d_1 - d_2)g}{18\eta}$$

v = velocity of the sedimentation.

D = particle diameter.

d_1 and d_2 = density of the particle and the liquid, respectively.

g = gravitational constant.

η = the viscosity of the medium.

Desired properties in the Pharmaceutical Suspension

- Settle down slowly (remain suspended long enough to withdraw an accurate dose).
- Readily redispersed upon gentle shaking of the container.
- The particle size should remain fairly constant throughout long periods of storage (no caking).
- Easily pourable from its container (not highly viscous).
- Suitable odour, colour, and taste. Stable and not decompose or support growth of moulds.

Why Suspensions?

- Solubility.
- Stability: Certain drugs are chemically unstable in solution but stable when suspended.
- Palatability: The disadvantage of a disagreeable taste of certain drugs in solution form is overcome when the drug is administered as undissolved particles of an oral suspension.

  For example, erythromycin estolate is a less water-soluble ester form of erythromycin and is used to prepare a palatable liquid dosage form of erythromycin.

Some Advantages of Suspensions

- Sterile suspensions are injected hypodermally or intramuscularly to produce **prolonged release** of medication than would a true solution of the same drug.

- The selection of the **flavouring agent** to be used in a given suspension may be based on taste preference rather than on a particular flavouring's ability to mask an unpleasant taste.

Some Disadvantages of Suspensions

- They must be well shaken prior to measuring a dose.
- The accuracy of the dose is likely to be less than with the equivalent solution.
- Conditions of storage may adversely affect the disperse system which might lead to aggregation and caking.

- ***Storage of suspension***

The physical stability of suspension is adversely effected by extreme variation in temperature suspension should be stored in cool place but not refrigeration . Freezing and very low temperature may cause the suspended particles to reaggregate.

Also should be stored in a wide mouth container that have a space to allow a good agitation before use.

Classification of Suspensions

1. Suspensions containing diffusible solid(s).

2. Suspensions containing non-diffusible solid(s).

3. Suspensions containing precipitate forming liquid.

4. Suspensions containing poorly wettable solid(s).

5. Suspensions prepared by chemical reaction.

6. Dispersions of oil in inhalation.

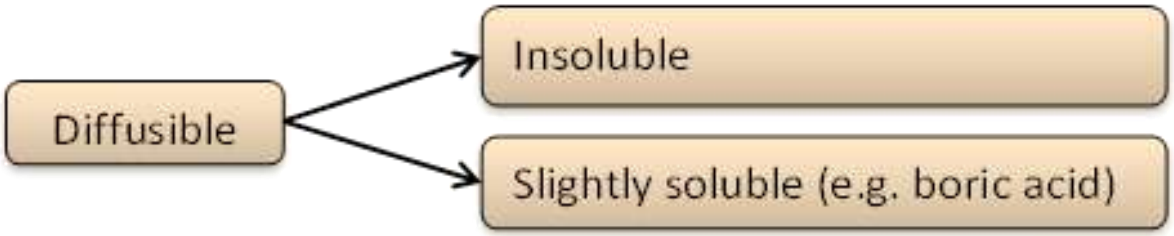
1. Suspensions containing diffusible solid(s)

- Diffusible solids are insoluble powders which are light and easily wettable and therefore readily mixed with water.
- Upon shaking, they diffuse evenly through the liquid for long period enough to ensure dosing consistency.

  Examples: Kaolin, pectin, magnesium carbonate, bismuth carbonate.
- Some substances are soluble at low concentrations only and at high concentration, they form suspensions. These are classified as diffusible solids as well.

  Example: Boric acid : ≤ 4% w/v: Soluble

  > 4% w/v: Not completely dissolved



General method to prepare suspension containing diffusible solid(s)

1. Using mortar and pestle, reduce the particle size of any ingredient having coarse particles to produce fine powders.

2. Mix insoluble powders in mortar by geometric dilution method.

3. After taking in consideration any liquid ingredients, measure ¾ of the vehicle and dissolve any soluble ingredients in it then use it as follows:
   - ❑ ¼ of the vehicle to prepare smooth paste.
   - ❑ ¼ of the vehicle for dilution to produce a pourable paste.
   - ❑ ¼ of the vehicle to wash the mortar.

¾ × final volume – (liquid ingredients)

General method to prepare suspension containing diffusible solid(s)

4. Transfer the mixture from the mortar to a measuring cylinder and rinse the mortar with ¼ of the vehicle.
5. Add any liquid ingredients and complete the volume with the vehicle.
6. Label: Shake before use.

General notes

- Soluble solids should be dissolved in the second ¼ of the vehicle (dilution part). e.g. sodium bicarbonate

- Volatile substances should be added to suspension before completing the volume to avoid their loss by volatilisation (e.g. chloroform, some tinctures, flavouring spirits, etc).

- Liquids with high viscosity such as syrup, glycerine, or propylene glycol are added to the dry powder in the mortar before formation of the smooth paste.

- Dyes are added to the smooth paste before dilution to allow penetration and distribution of the colour among insoluble particles (e.g. amaranth solution).

Rx

Boric acid		6.66 g
D.W.	qs.	20 ml
mitte		20 ml

- ¾ × final volume – (liquid ingredients)
- 10 g in 30 ml → 33.33 %w/v → suspension.
- ¾ × 20 – (0) = 15 ml → 3 parts each part 5 ml:
- mitte/qs. = 20/30 = 0.666.
- 5 ml for making smooth paste.
- 0.666 × 10 = 6.66 g.
- 5 ml for dissolving soluble solids and dilution.
- 0.666 × 30 = 20 ml.
- 5 ml for washing the mortar and pestle.

❖ Grind 6.66 g boric acid using mortar and pestle.

❖ Add 5 ml of D.W. and triturate to produce smooth paste.

❖ Add 5 ml of D.W. to produce pourable paste.

❖ Transfer to measuring cylinder and wash with 5 ml of D.W.

❖ Complete the volume to 20 ml with D.W.

❖ Transfer to suitable bottle and label.

Rx

Light magnesium carbonate		650 mg
Sodium bicarbonate		975 mg
Chloroform water	**qs.**	120 ml
mitte		120 ml

- Triturate light magnesium carbonate using mortar and pestle.
- Add 30 ml of chloroform water and triturate to produce smooth paste.
- Dissolve sodium bicarbonate in 30 ml of chloroform water and use this volume to dilute the paste to pourable one.
- Transfer to measuring cylinder and wash with 30 ml of chloroform water.
- Complete the volume to 120 ml with chloroform water.
- Transfer to suitable bottle and label.

Bismuth carbonate		585 mg
Compound powder of rhubarb		325 mg
Compound tincture of cardamom		0.9 ml
Syrup		1.8 ml
Peppermint water	qs.	30 ml

- Triturate 585 mg bismuth carbonate and 325 mg compound powder of rhubarb (1.8 g + 0.9 g = 2.7 g) in 3 parts method using mortar and pestle.
- Add 6.6 ml of peppermint water and triturate to produce smooth paste.
- Add 1.8 ml of syrup to the smooth paste and triturate.
- Add 6.6 ml of peppermint water for dilution to a pourable paste.
- Transfer to measuring cylinder and wash with 6.6 ml of peppermint water.
- Add 0.9 ml of compound tincture of cardamom and stir.
- Complete the volume to 30 ml with peppermint water.
- Transfer to suitable bottle and label.

Rx

Light kaolin		10 g
Bismuth carbonate		10 g
Heavy magnesium oxide		10 g
Tincture of belladonna		4 ml
Peppermint water	qs.	30 ml

- Grind 10 g of each of light kaolin, bismuth carbonate and heavy magnesium oxide by geometrical dilution using mortar and pestle.
  - ¾ × final volume – (liquid ingredients).
  - ¾ × 30 – (4) = 18.5 ml → 3 parts each part 6.16 ml:
  - 6.16 ml for making smooth paste.
  - 6.16 ml for dilution.
  - 6.16 ml for washing the mortar and pestle.
- Add 6.16 ml of peppermint water and triturate to produce smooth paste.
- Add 6.16 ml of peppermint water to the mortar for dilution.
- Transfer to measuring cylinder and wash with 6.16 ml of peppermint water.
- Add 4 ml of tincture of belladonna and stir.
- Complete the volume to 30 ml with peppermint water.
- Transfer to suitable bottle and label.

2. Suspensions containing non-diffusible solid(s)

- They will not remain evenly distributed in the vehicle long enough to ensure uniformity of the measured dose.

- Examples: aspirin, phenobarbital, phenacetin, salicylic acid.
- The simplest way to solve this problem is to increase the viscosity of the vehicle by adding a thickening agent (suspending agent)

1. Decrease the sedimentation rate of particles.
2. Decrease the collisions of particles by each other which can lead to formation of aggregates that settle down rapidly..

- Some suspending agents for general use are:

1. Acacia Gum BP: Not commonly used alone because:

2. Suspensions containing non-diffusible solid(s)

2. Powdered Tragacanth BP: Used in a concentration of 0.2% w/v.

3. Compound Tragacanth Powder BP: Used in a concentration of 2% w/v.

Composed of powdered tragacanth 15%, acacia 20%, sucrose 45% and starch 20%. Also not to be used for suspension applied externally as it contains acacia.

4. Bentonite BP: Used in a concentration of 2-3% w/v.

5. Tragacanth mucilage: Used in a concentration of 25% v/v (¼ of the vehicle is displaced).

Composed of tragacanth powder (12.5 g) + alcohol (25 ml) + chloroform water (qs. 1000 ml). It is used when the vehicle is water or chloroform water.

General method to prepare suspension containing non-diffusible solid(s)

A) Using Powdered Tragacanth BP or Compound Tragacanth Powder BP:

- Using mortar and pestle, reduce the particle size of any ingredient having coarse particles to produce fine powders.
- Mix insoluble powders and suspending agent by geometrical dilution method.
- After taking in consideration any liquid ingredients, measure ¾ of the vehicle and add part of it (≅ ¼) to the mortar and triturate until smooth paste is formed.
- Dissolve any soluble solid ingredients in the other ¼ and add it to the mortar for diluting it to a pourable paste.
- Transfer the content to a measuring cylinder and rinse the mortar with ¼ of the vehicle.
- Add any liquid ingredients and complete the volume with the vehicle.
- Label: Shake before use.

General method to prepare suspension containing non-diffusible solid(s)

B) Using tragacanth mucilage (25% v/v):

- Using mortar and pestle, reduce the particle size of any ingredient having coarse particles to produce fine powders.
- Mix insoluble powders by geometrical dilution method.
- Triturate the powder mixture above with tragacanth mucilage (25 % v/v, i.e. ¼ of the final volume) to produce a smooth paste.
- After taking in consideration any liquid ingredients, measure ½ the vehicle and add part of it (≅ ¼) for dilution to produce pourable paste (soluble solids are dissolved in this portion).
- Transfer the content to a measuring cylinder and rinse the mortar with ¼ of the vehicle.
- Add any liquid ingredients and complete the volume with the vehicle.
- Label: Shake before use.

Rx

Phenacetin	1 g
Caffeine	0.5 g
Syrup of orange	2 ml
P.W. qs.	30 ml
mitte	30 ml

- Triturate 1.333 g of phenacetin and 0.166 g of caffeine by geometrical dilution in a mortar and pestle.
- 2.5% w/v (i.e. 2½ %) × 30 = 7.5 ml of mucilage will be used.
- Add 6.5 ml of mucilage (liquid ingredients) to the mortar and triturate until smooth paste is formed.
- 1% × 30 = 6(2) = 12 ml → 2 parts each part 6.5 ml:
- Add 6.5 ml of syrup to the smooth paste and triturate.
- Add 6.5 ml of P.W. in the mortar and pestle.
- Transfer to measuring cylinder and wash with 6.5 ml of P.W.
- Complete the volume to 30 ml with P.W.
- Transfer to suitable bottle and label.

Using compound powder of tragacanth

- Grind 0.333 g of phenacetin, 0.166 g of caffeine and 0.6 g of compound tragacanth powder by geometrical dilution using mortar and pestle.
- Add 6.83 ml of vehicle to the mortar and triturate until smooth paste is formed.
- Add 2 ml of syrup to the smooth paste and triturate.
- Add 6.83 ml of the vehicle for dilution.
- Transfer to measuring cylinder and wash with 6.83 ml of the vehicle.
- Complete the volume to 30 ml with the vehicle.
- Transfer to suitable bottle and label.

℞

Aspirin	500 mg	(non-diffusible solid)
Ammonium bromide	65 mg	(water soluble solid)
Syrup of orange	1 ml	(thick liquid)
Conc. chloroform water	0.25 ml	(volatile liquid)
P.W. qs.	20 ml	(vehicle)

- Vehicle is water → use tragacanth and triturate.
- 25% v/v (i.e. ¼ × 20 = 5 ml) of tragacanth will be used.
- Final volume – (liquid ingredients)
- 20 – (1 + 0.25) = 18.75 ml → 2 parts each part 9.375 ml:
- 9.375 ml for making ammonium bromide and 9.375 ml for syrup.
- 4.375 ml for washing the mortar and pestle.

- Grind 500 mg aspirin using mortar and pestle.
- Add 5 ml (i.e. ¼ × 20 = 5 ml) of tragacanh and triturate to produce smooth paste.
- ½ × 20 = 10 ml → this volume of tragacanth will be used.
- ½ × 18.75 = 9.375 ml → this volume of ammonium bromide and syrup.
- Dissolve 65 mg of ammonium bromide in 4.375 ml of P.W.
- Add this P.W. for dilution to the mortar and pestle.
- Transfer to measuring cylinder and wash with 4.375 ml of P.W.
- Add 0.25 ml of concentrated chloroform water and stir.
- Complete the volume to 20 ml with P.W.
- Transfer to suitable bottle and label.

℞

Aspirin gr ii

Potassium citrate gr X

Cpd tr. Of camphor ℥ V

P.W q.s f℥ i

- Note: aspirin in the presence of sodium or potassium citrate or acetate (except caffeine citrate) it will be react with these salts and form a soluble complex but the amount of salts should be double the amount of aspirin in order to form soluble complex

3. Suspensions containing precipitate forming liquid(s)

- Some liquid preparations may contain resinous material that is precipitated upon addition of water.

- Resins are insoluble in water and form non-diffusible masses particularly when salts are present.

- Examples on precipitate forming liquids:

  - Compound benzoin tincture.
  - Myrrh tincture.
  - Tolu tincture.
  - Podophyllum tincture.

3. Suspensions containing precipitate forming liquid(s)

- The precipitated resinous materials may adhere to the sides of the bottle or form a clotted precipitate which will not re-suspended upon shaking.
- To prevent this, it is necessary to add suspending agent as Compound Tragacanth Powder BP or tragacanth mucilage (in the same percentages used for suspensions containing non-diffusible solids).

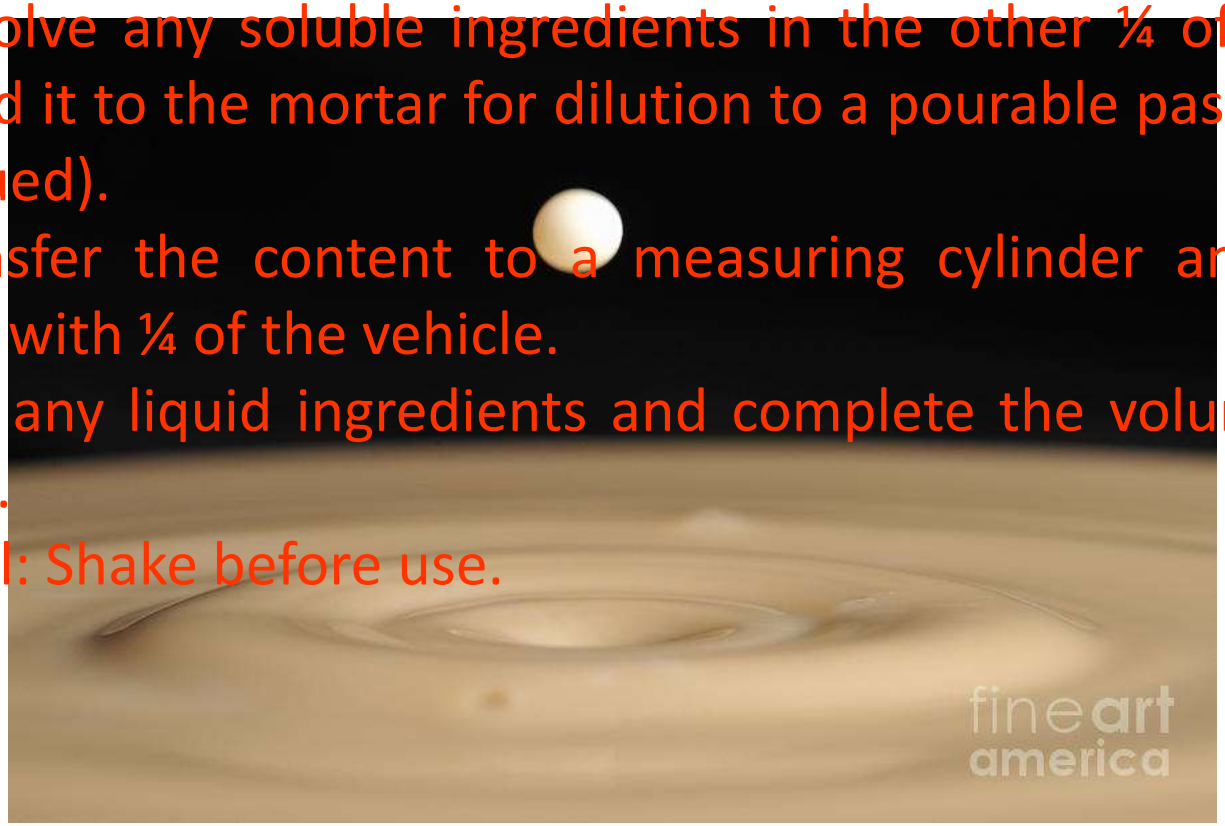
Method of preparing suspension containing precipitate forming liquid(s)

- This method is suitable when diffusible or non-diffusible solids are also present in the mixture.
- **A\\ compound powder of tragacanth**

1. Using mortar and pestle, reduce the particle size of insoluble solids to produce fine powders.
2. Mix insoluble powders and suspending agent by geometrical dilution method (if there is no insoluble solid ingredient in the prescription, put the suspending agent alone in the mortar).
3. After taking in consideration any liquid ingredients, measure ¾ of the vehicle and add part of it (≅ ¼) to the mortar and triturate until smooth paste is formed.

Method of preparing suspension containing precipitate forming liquid(s)

4. Measure the precipitate forming liquid in a **dry** measuring cylinder and add it **gradually** and **slowly** in the **centre** of the smooth paste with rapid stirring.
5. Dissolve any soluble ingredients in the other ¼ of the vehicle and add it to the mortar for dilution to a pourable paste (stirring is continued).
6. Transfer the content to a measuring cylinder and rinse the mortar with ¼ of the vehicle.
7. Add any liquid ingredients and complete the volume with the vehicle.
8. Label: Shake before use.



- The precipitate forming liquids are adsorbed on the hydrocolloid (acacia, tragacanth or starch) which offers hydrophilic properties and prevents aggregation into clots.

B\\ using tragacanth mucilage

1-mix the mucilage with equal volume of aqueous vehicle (¼+¼)

2- measure the ppt forming liquid and pour it slowly into the center of the mixture with constant stirring

3- The electrolyte added after dilution and dissolving in part of the vehicle.

℞

Tincture of tolu balsam		5 ml	(precipitate forming liquid)
Syrup of orange		2 ml	(thick liquid)
Peppermint water	qs.	30 ml	(vehicle)

4. Suspensions containing poorly wettable solid(s)

◉ Some substances as sulphur, calamine, zinc oxide, and hydrocortisone are insoluble in water and poorly wetted by it. Upon preparing simple aqueous dispersions, it is difficult to disperse clumps and the foam produced upon shaking will not rapidly subside because it is stabilised by a film of a non-wettable solid at the liquid-air interface.

◉ The interfacial energy between the solid and liquid must be reduced. This could be achieved by adding a suitable wetting agent which is adsorbed at the solid-liquid interface to increase the affinity of solid particles to the surrounding medium and reduce the interparticle forces.

- Examples on wetting agents: Alcohol, glycerine and propylene glycol. Polysorbate (Tween) and sorbitan ester (Span) are SAA used as wetting agent for internal preparation. While sodium lauryl sulphate (SLS) and quillia tincture are used in external preparation.
- ◉ However, in lotions the compound preferred for oral and parenteral suspensions are nontoxic non-ionic surface active agents known as polysorbates (spans and tweens).
- ◉ Lotions are liquid or semiliquid preparations containing one or more pharmaceutically active ingredient intended for external application to the unbroken skin without friction. They usually contain suspended particles or emulsified liquid droplets which may be diffusible or non-diffusible. A suspending or emulsifying agent is needed if non-diffusible material is present (suspending agent: solid–liquid, emulsifying agent: liquid–liquid).

℞

Calamine 150 g (poorly wettable solid)

Zinc oxide 50 g (poorly wettable solid)

Bentonite 30 g (suspending agent)

Sodium citrate 5 g (convert bentonite from gel to solution)

Liquefied phenol 5 ml (preservative, antiseptic)

Glycerol 50 ml (thick liquid)

P.W. qs. 1000 ml (vehicle)

mitte 25 ml

- Used as antipruritic (e.g. for chickenpox).

◉ Special procedure: Triturate the calamine, the zinc oxide and the bentonite with a solution of the sodium citrate in about 700 ml of the purified water and add the liquefied phenol, the glycerol and sufficient purified water to produce 1000 ml.

Rx compound sulphur lotion

Precipitated sulphur 40 g (poorly wettable solid)

Alcohol (95%) 60 ml (wetting agent)

Glycerol 20 ml (wetting agent)

Quillaia tincture 0.5 % v/v (wetting agent – saponin)

Calcium hydroxide solution qs. 1000 ml (vehicle)

mitte 25 ml

- Used for scabies.

◉ Calcium hydroxide solution also known as lime water.

5. Dispersions of oil in inhalation

◉ Inhalations are liquid products that contain volatile ingredients intended to be released and brought into contact with the respiratory lining.

◉ Here, the volatile ingredient is adsorbed onto a carrier powder (a diffusible solid) and formulated as suspension.

◉ When used, an accurate dose of the suspension is added to hot (about 65 °C) but not boiling water, so that the volatile ingredient is released and inhaled by the patient.

◉ Example: A volatile oil is suspended in water after being adsorbed on light magnesium carbonate powder. If the quantity of light magnesium carbonate is not included in the formula, 1 g of it is added to each 2 ml of oil (e.g. eucalyptus and pumilio pine oil) or 2 g of volatile solid (e.g. menthol and thymol)

6. Suspensions prepared by chemical reaction

◉ Here, the insoluble active constituent of the suspension is formed by chemical reaction.

◉ Example: White lotion is prepared by mixing dilute solutions of zinc sulphate and sulphureted potash. The mixing must be slowly with continuous stirring so that a finely divided precipitate will be formed in the reaction.

$ZnSO_4 + K_2S \rightarrow K_2SO_4 + ZnS \downarrow$ (insoluble diffusible)

◉ White lotion is used in the treatment of number of dermatological diseases.

Syrup

Syrups are sweet, viscous, aqueous liquid with a relative high specific gravity.

Medicinally syrup is divided to:

1) Flavoring syrup (non-medicated) which is used as vehicle to prepare medicated syrup
2) Medicated syrup which contain ingredients that give them a therapeutic value

Pharmaceutically classified: the syrup may be grouped according to their basic formula to:

1) Sugar based syrup, which are concentrated aqueous solution of sugar (Sucrose, dextrose)
2) Sugar free syrup (non-nutritive) which are formulated with artificial sweetening agent and viscosity builder

Sugar based syrup

Sucrose is one of the purest commercially available substance and the perfect carbohydrate for syrup, because:

- Purity
- Degree of sweetness
- Lack of color
- Ease of handling
- Inert
- Its availability

Stability of sucrose based syrup

Sucrose is subjected to 2 degradative pathways in aquous solutions

1) Fermentation 2) Hydrolysis

Fermentation: as a carbohydrate, sucrose in diluted aqueous solution provides a nutrient media which will support the growth of many micro-organisms especially yeast and mold.

The consequences of their growth are turbidity, fermentation and change in taste.

The ability of these micro-organisms to grow is decreased as the concentration of sucrose is increased, therefor syrup should contain enough sucrose to approach saturation.

Nearly saturated (66.7% w/w) solution of sucrose, if stored properly is self-preservative, because it does not contain free water H2O so they behave as anhydrous medium with respect to the growth of micro-organisms.

So to prevent Fermentation we should:

- Add preservative
- Saturate the solution

Many of the official syrups do not contain any preservative other than adequate sucrose concentration to prevent fermentation or the growth of other micro-organisms, a few syrups contain 0.1-0.2% W/V of sodium benzoate or benzoic acid which is efficient for its purpose.

Hydrolysis: in the presence of water and strong acid sucrose is a disaccharide, it undergo hydrolysis to give a molecule each of Monosaccharide, dextrose(glucose) and levulose(fructose).

This reaction is called inversion because a solution of sucrose rotate polarized light to the right while the same solution after hydrolysis rotate the light to the left because the levulose has a greater rotating power than dextrose.

This reaction is interfering for 3 reasons:

1) Solution of inverted syrup or sugar are more subjected to fermentation than solution of sucrose
2) After inversion the solution is sweeter, if sucrose is rated with sweetness of 100 dextrose is rated 74 while levulose is 173

The levulose formed by inversion seems to be responsible for brown discoloration which develop in some colorless syrups, this change is called caramelization and it take place in syrups

1) containing strong acid because hydrogen catalyzes the inversion of sucrose

   To eliminate this discoloration of certain colorless syrup containing acid dextrose is used in place of sucrose

Storage of syrup

1) Syrup is stored at room temperature in a tightly stoppered and well filled bottle to avoid the presence of micro-organisms
2) Refrigeration inhibits both fermentation and hydrolysis but cooler than 4^{o}C cause crystallization of sugar which result the formation of large crystals which are difficult to re-dissolve, this proceeds sufficiently to yield a sucrose concentration greatly below saturation.

Dextrose based syrup

Dextrose may be used as a substitute in syrup containing strong acid in order to eliminate the discoloration associated with caramelization.

The formula in which dextrose is used in place of sucrose syrup:

1)Hypophosphite

2)Compound syrup of hypophosphite.

3)hydroiodic acid (HI) syrup was the only the official syrup using dextrose.

4)Ferrous iodide syrup containing dextrose has been formulated.

Dextrose based syrup do not become brown in the acidic solution but other difficulties are introduced

***The differences between dextrose and sucrose are*:**

1)Dextrose formulated a saturated solution in water at 70% w/v which is less viscous than simple syrup.

2)Dextrose dissolve more slowly than sucrose

3)Dextrose is less sweet than sucrose its sweetness 74% as sweet as sucrose

4) The saturated solution of dextrose readily support the growth of microorganism consequently its more easily fermented while the saturated solution of sucrose is self preservative, so they need preservative to prevent the fermentation of dextrose based syrup.

Glycerin is used in concentration of 30-40% v/v to act as

1- preservative 2-sweetener and viscosity builder.

Prescriptions

Rx1 Simple Syrup B.P (66.7% w/w)

Sucrose 667gm

D.W.q.s to 1000gm

Mitt 100g

100-66.7=33.3 gm of water

Procedure:

- Weigh the beaker only (empty) and weigh 66.7gm of sucrose in it
- Add about (20ml) D.W. and stir to dissolve with gentle heating by using water bath
- Weigh again and complete the weight by hot water to 100gm (adjustment of weight)
- Put in clear, dry, bottle and label it.

Rx2 Simple syrup U.S.P (85% w/v)

Sucrose 850gm

P.W. qs 1000ml

Mitt 20ml

Prepared by simple solution

Note: use purified boiling water

Rx4 Acacia syrup

Acacia granulated or powder		100g
Sodium benzoate		1g
Tr. of vanilla	5ml	
Sucrose		800g
D.W	Q.s	1000ml

Fit mist

Mitt 20ml

Procedure

- Mix acacia sodium benzoate and sucrose
- Add about 10 ml of p.w mix well by stirrer
- Heat mixture on water bath until solubility is complete
- Cool, add Tr. of vanilla and sufficient D.W to complete the volume to 20 ml
- Strain if necessary

This syrup has higher viscosity than simple syrup
Sodium benzoate is used as preservative instead of benzoic acid because of its greater solubility in H2O.
Use of acacia syrup(Home work).

Rx5 ferrous sulfate syrup (hematinic syrup)

Ferrous sulfate 1 gm
Citric acid 0.5 gm
Peppermint oil 0.02ml
Alcohol 0.1ml
Water 10 ml
Syrup qs to 25ml
Sig. ʒIItida.c
Mitt 25 ml

Procedure:

- Dissolve ferrous + citric acid in 10 ml DW
- Dissolve the oil in alcohol
- Then add aq. to the alcoholic solution and complete the volume to 25ml

Procedure:

- Dissolve ferrous + citric acid in 10 ml DW
- Dissolve the oil in alcohol
- Then add aq. to the alcohol Solution and complete the volume to 25ml
- Care must be taken in preparing aq. Solution of ferrous sulfate since Fe++will precipitate as basic ferric salt, discoloring the solution, so citric acid prevent discoloration of syrup from green to reddish brown it does this by chelating Fe+++(Stabilizing agent ,reducing agent inhibit the oxidation)

Rx1 Hypophosphite syrup

Ca^{+2} hypophosphite 35 g

Na^{+} hypophosphite 18g

K^{+} hypophosphite 18g

Hypophosphorous acid 1ml

Dextrose 250g

Glycerin 300ml

P.W Q.S 1000ml

Ft.Mist

Mitt 25 ml

Sig:One tablespoonful tid

Nutritive syrup for element supplement

Method

1-Dissolve Ca,Na ,K hypophosphite in 500 ml pf P.W

2-Filter to reagent bottle containing acid dextrose and glycerol

3- Mix acid dextrose and acid

4-Shake from time to time until solubility is completed

5-Complete the volume to 1000 ml with P.W.

Sugar free syrup(Non nutritive syrup)

Several formula are intended as a substitutes for syrup which are administered to person who are suffering from diabetes mellitus .Some early formula included glycerin inorder to take advantages of its sweetness and viscosity. However glycerin as well as alcohol and propylene glycol are glycogenitic substances i.e materials which are converted directly or indirectly to glucose in body.

Substances to be used in non nutritive syrup should be non glycogenetic.

General formula of non nutritive syrup

Viscosity builder Q.S

Sweetening agent Q.S

Preservative Q.S(sodium benzoate ,or benzoic acid)

P.w Q.S

Viscosity builder

Natural gum like acacia and tragacanth are used as viscosity builder. However syrup prepared from these gum are not colorless and tend to change their characteristics upon aging. Sodium alginate ,methyl cellulose and sodium carboxymethylcellose has been used as the base of sugar free syrup these substances are non glycogentic and produce clear and colorless syrup.

Sweetening agent

Saccharin sodium : rated 300- 550 time as sweet as sucrose (has excellent acid and heatstability).It may be used in concentration of 0.1-0.2% but itcharacterize by bitter after taste.

Sodium cyclamate :is 30-40 times as sweet as sucrose, has less after taste than saccharinbut its carcinogenic substance.

New synthetic sweetener had been developed example aspartylphenylalanin methyl ester (aspartame) which is about 160 times as sweet as sucrose in aqueous solution

Sorbitol based syrup

Sorbitol is a hexahdric alcohol (C6H1406) made by hydrogenation of glucose.

Sorbitol properties

1-It is used in a concentration of 70% w/w aqueous solution which not support the growth of microorganism.

Preservative should be used in solution containing less than 60% w/w of sorbitol.

2-Sorbitol is not irritating to the membrane of the mouth and throat, unlike sucrose it's not contributing to the formation of dental carries.

3-sorbitol metabolized and converted to glucose, however it's not absorbed from the GIT as rapidly as sugar .No significant hyperglycemia has been found .

And consequently its may be used as component of non –nutritive syrup.

4-The ingestion of excessive quantity of sorbitol may have alaxative effect.

5-sorbitol solution is about 60% as sweet as sucrose and half as viscous as simple syrup.

6-Sorbitol solution show no crystallization around the mouth bottle found in high concentration of sucrose

Chloral hydrate syrup (non-official)

Chloral hydrate 0.5g

Sorbitol 25g

P.W 100ml

Fit mist

Mitt 25ml

Sig : tsf o.n

Rx

Acacia		1g
Saccharin		0.2 g
Na. benzoate		0.1 g
D.W	Q.S	100 ml
Mitt.	25 ml	