Pharmaceutics 1

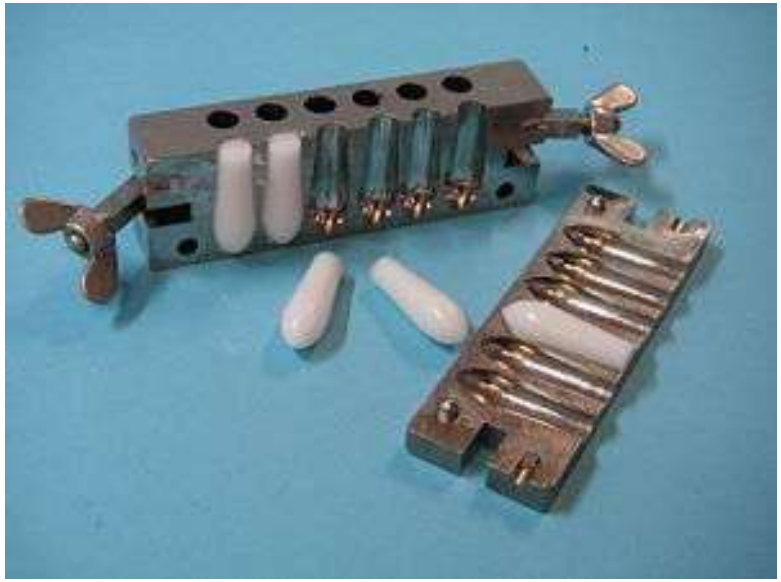
Chapter 6

Suppositries (1)

Lecture 10

By Mohammed Hussien Taleb

Suppositories



Rectal route

- Some drugs are administered rectally for **their local effects** and others for **their systemic effects**. Drugs given rectally may be administered as **solutions, suppositories, or ointments.**

- **Suppositories are** solid bodies of various weights **and** shapes intended for introduction into a body orifice **(usually** rectal, vaginal, or urethral**) where they** soften**,** melt**, or** dissolve**, release their medication, and exert their drug effects.**

- These effects simply may be locally as the promotion of laxation (as with glycerin suppositories), the soothing of inflamed tissues (as with various commercial suppositories used to relieve the discomfort of hemorrhoids), or systemically as the promotion of systemic effects (as antinausea or anti– motion sickness).
- The composition of the suppository base, or carrier, can greatly influence the degree and rate of drug release and should be selected on an individual basis for each drug.
- The use of rectal ointments is generally limited to the treatment of local conditions. Rectal solutions are usually employed as enemas or cleansing solutions.

- The rectum + the colon can absorb many soluble drugs. Rectal administration for systemic action may be preferred for drugs :

1-destroyed or inactivated by environments of stomach &intestines.

2-when the oral route is precluded because of vomiting

3- when the patient is unconscious or incapable of swallowing drugs safely without choking.

4- Approximately 50% of a dose of drug absorbed from rectal administration is likely to bypass the liver, an important factor when considering orally administered drugs that are rapidly destroyed in the liver by the first-pass effect.

- On the negative side, compared with oral administration, rectal administration of drugs is
- 1- inconvenient to some patients, and
- 2-the absorption of drugs from the rectum is frequently irregular and difficult to predict.

Suppositories

- ## A suppository:

- is **a solid dosage form in which one or more active ingredients are dispersed in a suitable base and molded or otherwise formed into suitable shape for insertion into the rectum to provide local or systemic effect.**

- **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)**

- **Local action:** rectal suppositories intended for localized action

  are most frequently used to relieve constipation or pain, irritation, itching, and inflammation associated with hemorrhoids.

- **Systemic action**: (e.g. Antiasthmatic, antirheumatic & analgesic drugs).

- **An insert**: is a solid dosage form that is inserted into a naturally occurring (nonsurgical) body cavity other than the mouth or rectum, including the vagina and urethra.

- 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 inserts (and tablets prepared by compression) may be inserted high in the tract with the aid of an appliance.

- **Rectal suppositories** are usually **about 32 mm** (1.5 inch) **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 inserts**, formerly called **suppositories or pessaries**, **are usually globular, oviform, or cone shaped and weigh about 5 g when cocoa butter is the base.**

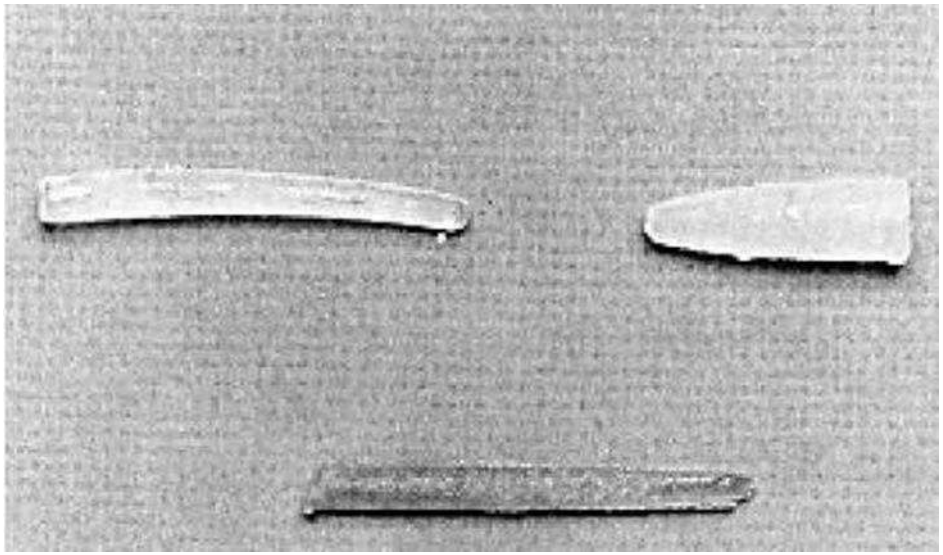
- **However, depending on the base and the manufacturer's product, the weights of vaginal inserts may vary widely.**

- **Urethral inserts**, 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.

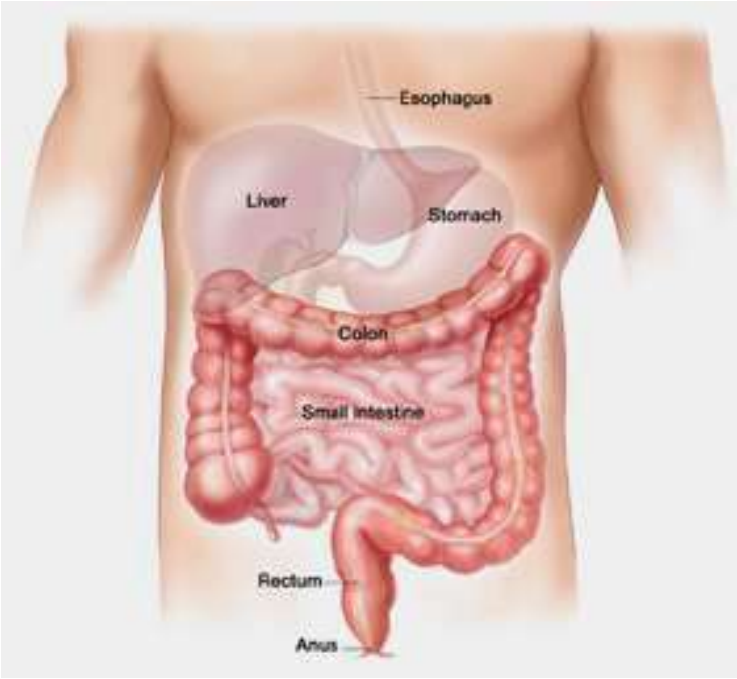
- **Female urethral suppositories** are about half the length and weight of the male urethral suppository, being about 70 mm long and weighing about 2 g when made of cocoa butter.



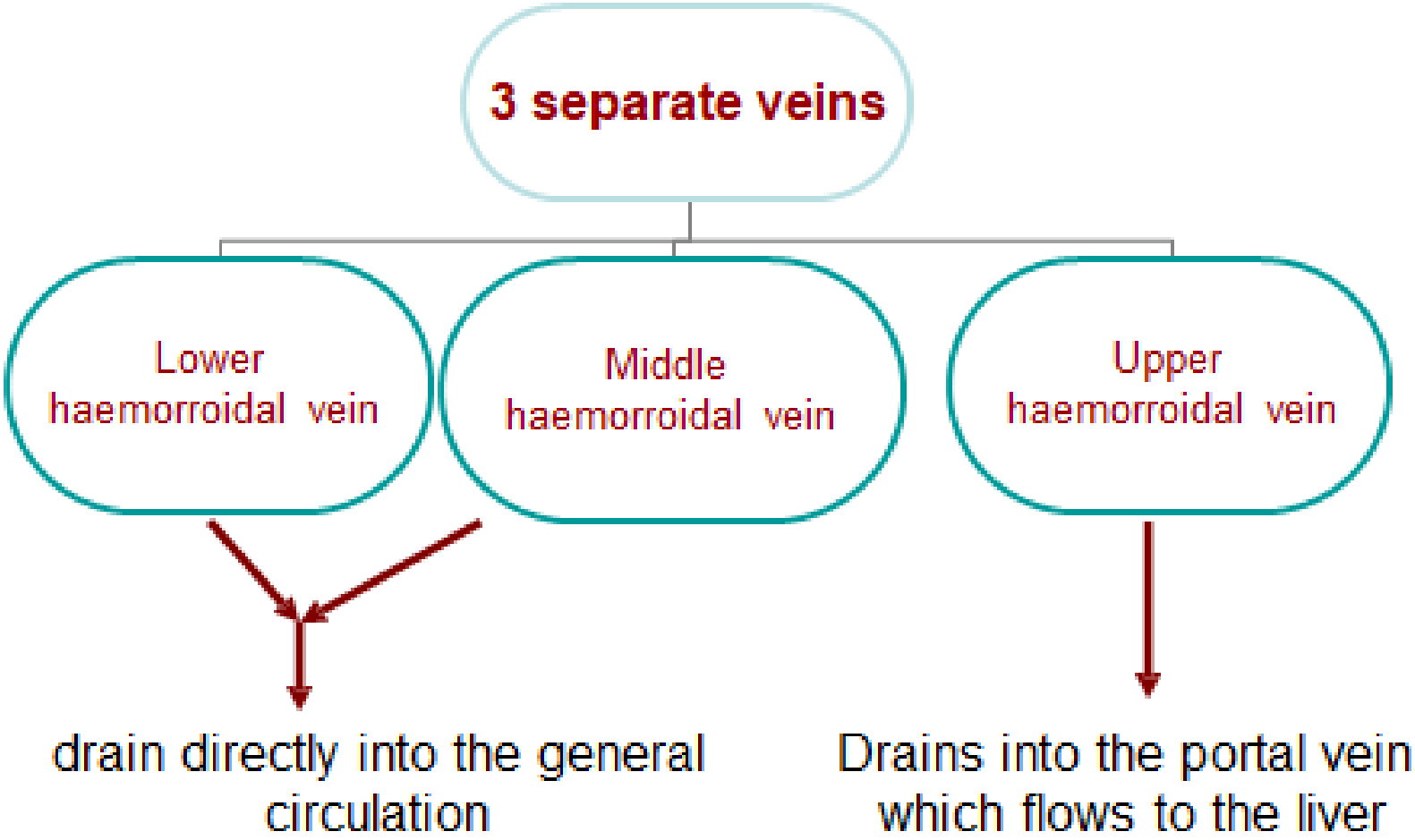

Cleocin® Vaginal Ovules
clindamycin phosphate vaginal suppositories
100 mg

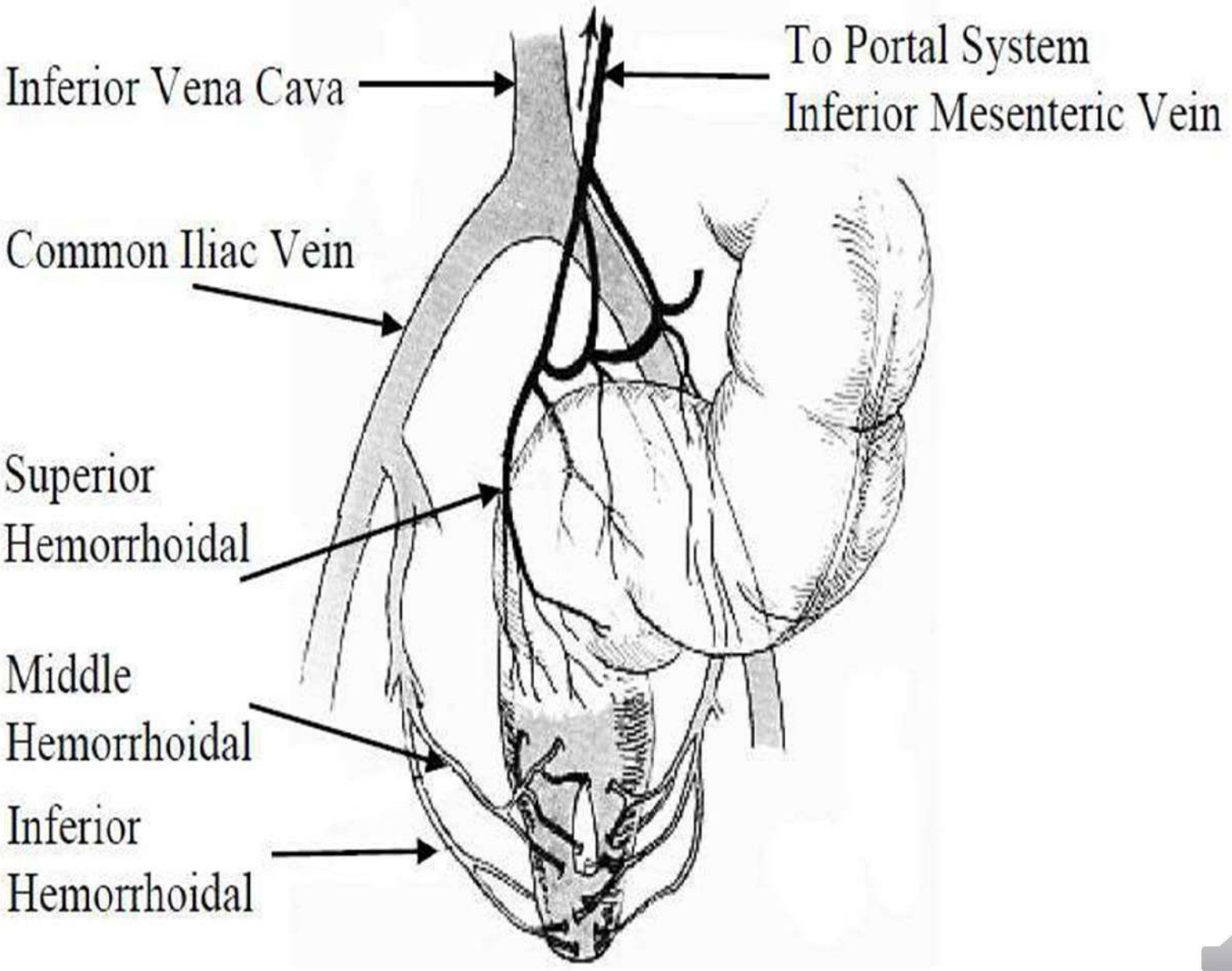
Anatomy of the rectum:

- The rectum is part of the colon, forming the last 15 – 20 cm of the GI tract.
- The rectum can be considered as a hollow organ with a relatively flat wall surface, without villi. It contains only 2 – 3 ml of inert mucous fluid with pH of 7.5 .



ABSORPTION OF DRUGS FROM THE RECTUM




Inferior Vena Cava
To Portal System
Inferior Mesenteric Vein
Common Iliac Vein
Superior
Hemorrhoidal
Middle
Hemorrhoidal
Inferior
Hemorrhoidal

The advantages of rectal administration:

- 1. **First-pass effect**: Avoiding, at least partially, the first-pass effect that may result in higher blood levels for those drugs subject to extensive first-pass metabolism upon oral administration.

- 2. **Drug stability**: Avoiding the breakdown of certain drugs that are susceptible to gastric degradation.

- **3.Large dose drugs:** Ability to administer somewhat larger doses of drugs than using oral administration.

- 4. **Irritating drugs**: Ability to administer drugs that may have an irritating effect on the oral or gastrointestinal mucosa when administered orally.

- 5. **Unpleasant tasting or smelling drugs:** Ability to administer unpleasant tasting or smelling drugs whose oral administration is limited.

- 6. **In children**, the rectal route is especially useful. An ill child may refuse oral medication and may fear injections.
- 7. In patients experiencing **nausea and vomiting** or when the patient is **unconscious.**
- 8. The presence of **disease of the upper gastrointestinal** tract that may interfere with drug absorption.
- 9. **Objectionable taste or odor of a drug** (especially important in children).
- 10. Achievement of **a rapid drug effect systemically** (as an alternate to injection).

The disadvantages of suppositories:

1- Defecation may interrupt the absorption process of the drug; this may especially occur if the drug is irritating.

2- The absorbing surface area of the rectum is much smaller than that of the small intestine.

3- The fluid content of the rectum is much less than that of the small intestine, which may affect dissolution rate.

4- There is the possibility of degradation of some drugs by the microflora present in the rectum.

5- Drug with narrow therapeutic margin, can not be interchange without the risk of toxicity.

6- Cost-expensive.

Factors Affecting Drug Absorption From Rectal Suppositories

I- Physiological factors affecting rectal absorption:

- **A- Blood supply**

- Unlike drugs absorbed after oral administration, drugs absorbed rectally **can** bypass the portal circulation during their first pass into the general circulation. This enables drugs that are 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.

- There is also the possibility **of absorption into the lymphatic vessels that should not be dismissed, but may be minimal.**
- However, it **is generally accepted that** **at least 50% to 70% of the active ingredients administered rectally take the direct pathway**, thus **bypassing the liver and avoiding the first-pass effect**.

B- pH and Lack of Buffering Capacity of the Rectal Fluids

- **The pH of the rectal fluid is generally in the range of 7.2 to 7.4, and it has negligible buffer capacity.**
- The form in which the drug is **administered will not generally be chemically changed by the rectal environment;**
- Therefore, **the pH of the medium may be determined by the characteristics of the drug.**

C- Colonic Content

- When systemic effects are desired from the administration of a medicated suppository, 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 the absence of fecal matter.

- 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 rectal site.

II- Physicochemical Factors and Drug Effect

- **A- 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**.

-

- 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.**
- When drugs are highly soluble in the vehicle ,The tendency to leave the vehicle will be small and so the release rate into the rectal fluid will be low.

Solubility in		Choice of base
Fat	Water	
low	high	Fatty base
high	low	Aqueous base
low	low	Indeterminate

B- Particle Size

- For undissolved 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

- Whenever **the active principle has a limited water solubility, the use of finely divided products** (high SSA) often **leads to an appreciable absorption improvement.** The **rate of absorption is influenced by the solubilization rate, which in turn is related to the particle size of the active principle**.

C- Nature of the base:

- The **base must be capable of melting, softening, or dissolving to release its drug components for absorption.**

- If the(1) **base interacts with the drug inhibiting its release drug absorption will be impaired or even prevented.**
- Also,(2) if **the base is irritating to the mucous membranes of the rectum it may initiate a colonic response and a bowel movement incomplete drug release and absorption.**

D- Spreading Capacity:

- The **rapidity and intensity of the therapeutic effects of suppositories are related to the surface area of the rectal mucous membrane covered by the melted base** : **drug mixture (the spreading capacity of the suppositories).** **This spreading capacity may be related to the presence of surfactants in the base.**

Pharmaceutics 1

Chapter 6

Suppositries (2)

Lecture 11

By Mohammed Hussien Taleb

Suppository Bases

- **The properties of an ideal suppository base:**
- 1- Melts at body temperature or dissolves in body fluids.
- 2- Non-toxic and non-irritant.
- 3- Compatible with any medicament.
- 4- Releases any medicament readily.
- 5- Easily moulded and removed from the mould.
- 6- Stable to heating above the melting point.
- 7- Easy to handle.

Suppository Bases

➢ **Classification of Bases**: For most purposes, it is convenient to classify suppository bases according to **their physical characteristics :**

a- Fatty or oleaginous bases,

b- Water-soluble or water miscible bases,

c- Miscellaneous bases, generally combinations of lipophilic and hydrophilic substances.

Some bases are prepared with the fatty materials emulsified or with an emulsifying agent present to prompt emulsification when the suppository makes contact with the aqueous body fluids.

Fatty or Oleaginous Bases

- **Fatty bases are perhaps the most frequently employed suppository bases, principally because cocoa butter is a member of this group of substances.**
- **Fatty bases** are predominantly composed of **naturally occurring or semisynthetic/synthetic fatty acid esters of glycerol**.
- These systems are designed to **melt** **within the rectum thereby facilitating drug release and subsequent dissolution.**

Cocoa Butter

- **1- Cocoa Butter (theobroma oil)** is the **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, it is a triglyceride** (combination of glycerin and one or different fatty acids) primarily of oleopalmitostearin and oleodistearin.

- **The presence of unsaturated (e.g. oleic acid) esters contributes to the low melting point of cocoa butter (30–36C**), thereby **facilitating cocoa butter melting following insertion within the rectum.**

- **Because cocoa butter melts at 30°C to 36°C** (86°F to 97°F), 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 exists in four polymorphic forms: (1) alpha (α, melting point circa 20°C); (2) beta (β , melting point circa 34–35C); (3) beta prime (, melting point circa 28C); and (4) gamma (, melting point circa 15-18C).

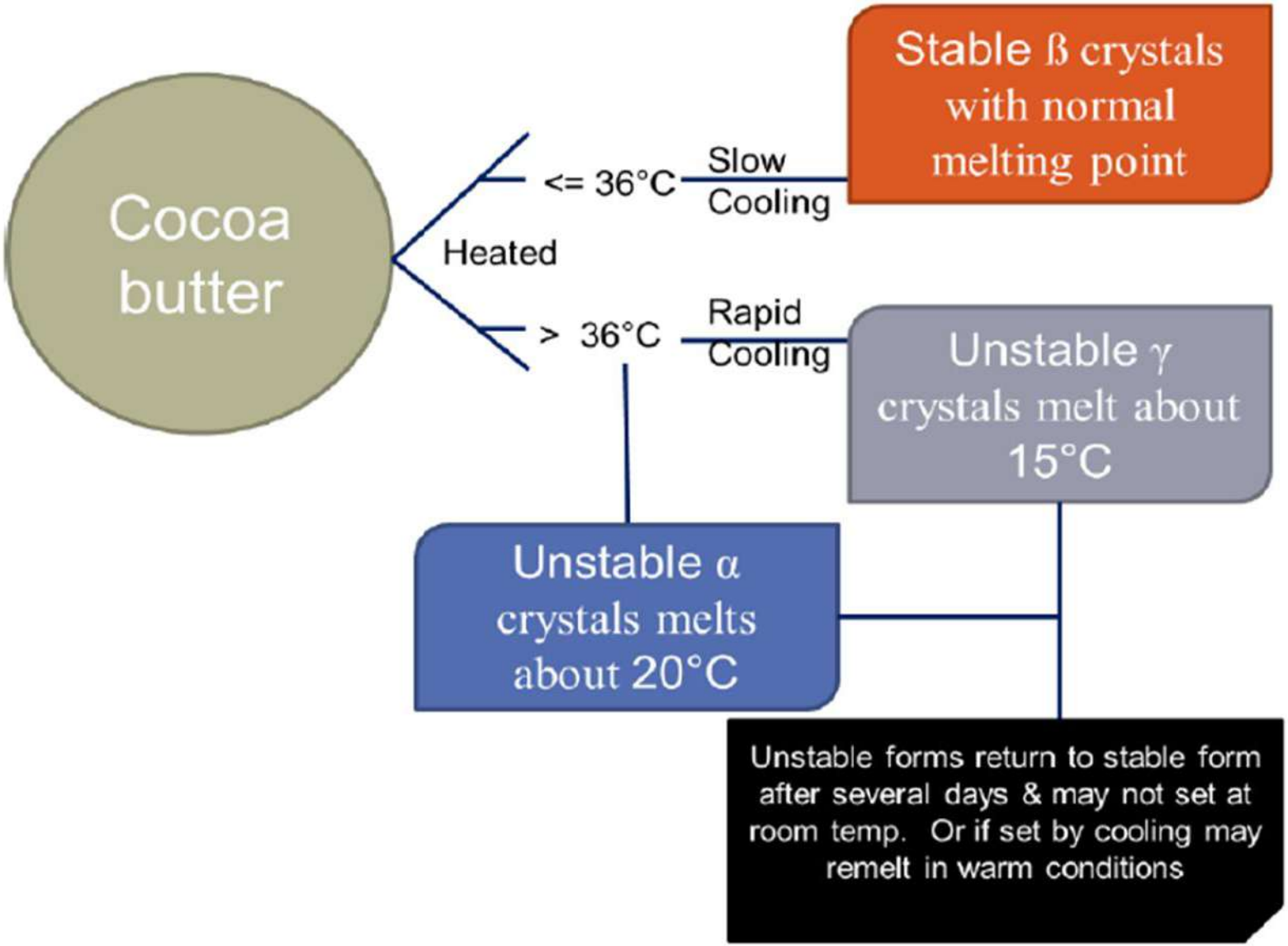
- If cocoa butter is melted at temperature 36C and allowed to solidify slowly, the stable (β)polymorph will form.

- However, if the temperature is markedly elevated above 36C and allowed to cool, the other polymorphic forms will be produced. Being unstable, the α β and polymorphs will slowly revert to the stable b polymorph.

Cocoa butter molded

- 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.


Cocoa butter
Heated
<= 36°C
Slow Cooling
Stable ß crystals with normal melting point
> 36°C
Rapid Cooling
Unstable γ crystals melt about 15°C
Unstable α crystals melts about 20°C
Unstable forms return to stable form after several days & may not set at room temp. Or if set by cooling may remelt in warm conditions

Melting Range :

- Suppository bases don't have a sharp melting point, their melting characteristics are expressed as ranges, indicating the temperature at which the fats start to melt and the temperature at which completely melted.

- Melting range is usually determination by " Wiley melting point", "Capillary melting point",

Solidification Point:

- This test allow to determine the time required for solidifying the base, when it is chilled in the mold if the interval between the melting point and solidifying point is 10° C or more.
- Time required for solidification may have to be shortened for amore efficient manufacturing procedure by refrigeration, if melting point 33° C and solidifying point 20° C then it will be liquid for 13° C, then the drug will sediment and the apex of the suppository will contain all the drug

Saponification Value:

- The number of milligrams of KOH (Potassium hydroxide) required to neutralize the free fatty acids and saponify the ester contained in 1 g of a fat.
- From saponification value we can know the type of glyceride present (mono-, di- or tri-) and also amount present.
- Acid Value:
- It is the number of milligrams of KOH (Potassium hydroxide) required neutralizing the free fatty acids in I g substance (fat). Low acid value or absence of acid value is important for good suppository bases.

- **Iodine Value:**
- It is the number of grams of Iodine that reacts with l00 g of fat or other unsaturated material.
- The possibility of decomposition by moisture, acids, oxygen (which leads to rancidity of fats) increases with higher iodine value.

- **Water Number:**
- It is the amount of water in grams that can be incorporated in l00g of fat. The "water number" can be increased by the addition of surface- active agents.

- **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.**

2- Semisynthetic/synthetic triglycerides

- The **main problems associated with cocoa butter** (**polymorphism and variation in composition)** led to the development and use of suppository bases that were based on synthetic/semisynthetic glycerides.

- Typically these systems are **composed of mixtures of triglycerides of higher saturated fatty acids**

Semisynthetic/synthetic triglyceride bases

safe

non-toxic

non-irritating

unlike cocoa butter, can be reheated during processing (whilst not affecting the solidification temperature)

exhibit low batch-to-batch variability.

Synthetic Fats

- To overcome **the disadvantages of Theobroma oil synthetic substitutes** .

. It is obtained from **hydrogenation and heat treatment to vegetable oils such as palm kernel and arachis.**

- **Most synthetic fat bases are made by first hydrolyzing the vegetable oil, then hydrogenating the resulting fatty acids and finally esterifying the acids by heating with glycerol.**
- For example: **Whitepsol , Massa Estarinum**

Advantages:

a- Their **solidifying points are** unaffected by overheating.

b- They have good resistance to oxidation because of the lower content of unsaturated fatty acids.

c- The **difference** between melting and setting points is small.

Hence they set **quickly, the risk of sedimentation of suspended ingredients is low.**

d- **They are marketed in a series of grades with different melting point ranges, which can be chosen to suit particular products and climatic condition.**

e- They contain a **proportion of w/o emulsifying agents, and therefore, their water-absorbing capacities are good**.

f- **No mould lubricant is necessary because they contract significantly on cooling**.

Disadvantages:

a- Brittle if cooled rapidly, avoid refrigeration during preparation.

b- The melted fats are less viscous than theobroma oil.

As a result greater risk of drug particles to sediment during preparation lack of uniform drug distribution give localized irritancy.

B) Water-Soluble and Water-Miscible Bases

- The main members of this group are glycerin , **glycerinated gelatin, and polyethylene glycols.**

1- Glycerin suppositry

- Glycerine 91 g
- Sodium stearate 4g
- Purified water 5g

2- Glycerinated gelatin:

- **S**uppositories may be prepared by dissolving granular gelatin (20%) in glycerin (70%) and adding water or a solution or suspension of the medication (10%).
- **USP: Glycerin 70%, Gelatin 20% + water 10%**
- **BP : Glycerin 70%, Gelatin 14% + water 16%**
- A glycerinated gelatin base is most frequently used in the 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.**

- **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.
- Also as a result of the hygroscopicity of the glycerin, the suppository may have a dehydrating effect and irritate the tissues upon insertion.
- 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.**

- 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.

3- Macrogols (polyethylene glycols):

- **PEG are polymers of ethylene oxide and water prepared to various chain lengths, molecular weights, and physical states.**
- They are **available in a number of molecular weight ranges, the most commonly used being PEG 300, 400, 600, 1,000, 1,500, 1,540, 3,350, 4,000, 6,000, and 8,000.**
- The numeric **designations refer to the average molecular weight of each of the polymers.**

- **Polyethylene glycols having average molecular weights of 300, 400, and 600 are clear, colorless liquids.**

- Those having **average molecular weights of greater than 1,000 are waxlike white solids whose hardness increases with an increase in the molecular weight.**

- Melting ranges, for example, polyethylene glycols, are PEG 300 (–15°C to 18°C), PEG 1000 (37°C to 40°C), PEG 3350 (54°C to 58°C), and PEG 8000 (60°C to 63°C).
- 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.
- Polyethylene glycol suppositories do not melt at body temperature but rather dissolve slowly in the body's fluids

- **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.**

- 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.

- PEG 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.

Pharmaceutics 1

Chapter 6

Suppositries (3)

Lectures (12)

By Mohammed Hussien Taleb

Formulation Variables

- Formulation variables that are generally considered include:

1- The nature and form of the active principle (esters, salts, complexes, etc).

2- The physical state, particle dimensions, and the specific surface of the product.

3- The solubility of the drug in various bases.

4- The presence or absence of adjuvants added to the active principle.

5- The nature and type of dosage form in which the active principle is incorporated.

6- Pharmaceutical procedures used in the preparation of the dosage form.

- Active drugs have a number of physical characteristics.
- In suppositories, those of interest involve the drug's physical state, including physical state, particle size, solubility, dielectric constant, and bulk density.

Physical State:

- An active drug can be a solid, liquid, or semisolid in nature.
- For solids, the drug's particle size may be very important, especially if the drug is not very water soluble; the increase in surface area resulting from decreased particle size can serve to enhance its activity.
- For liquids, it is **necessary to take up the liquid into the suppository base using one of several techniques such as forming an emulsion** For the semisolids , **it can be either mixed with a solid that will serve to thicken the drug prior to mixing with the base or mixed with the base to which a thickener is added**.

➢ Particle Size:

- If a **drug** is readily soluble, the influence of particle size may be minimal.
- For highly water-soluble drugs, the **tendency will be** to dissolve and migrate to the rectal barrier.
- For poorly water-soluble drugs, the dissolution rate will be slower, **and a reduction in particle size may increase the rate of dissolution by exposing a greater surface area.**

Solubility

- Increased solubility of the active in the base can improve product homogeneity; however, it may also delay the release of the active if there is too great an affinity of the drug for the suppository vehicle.

- If the active ingredient is insoluble in the base, as is the case when a "suspension" or "emulsion" is formed, this poses different problems.

- It is necessary to maintain homogeneity of the total mixture; this can usually be obtained by constant agitation of the mixture during processing and filling.

- Oftentimes, it is best to select a temperature just above the melting point of the suppository mixture where the mixture is thick but still pourable.

Viscosity

- Viscosity **considerations are important in the preparation of the suppositories and the release of the drug.**

- If the viscosity of a base is low, it may be necessary to add a suspending agent such as silica gel to ensure that the drug is uniformly dispersed until solidification occurs.

- When preparing the suppository, the pharmacist should stir the melt constantly and keep it at the lowest possible temperature to maintain a high viscosity.
- After the suppository has been administered, the release rate of the drug may be slowed if the viscosity of the base is very high.
- This is because the viscosity causes the drug to diffuse more slowly through the base to reach the mucosal membrane for absorption.

Brittleness

- **Brittle suppositories can be difficult to handle, wrap, and use.**
- **Cocoa butter suppositories are usually not brittle unless the percentage of solids present is high.**
- In general, **brittleness results when the percentage of non base materials exceeds about 30%.**
- **Synthetic fat bases with high stearate concentrations** or those that are **highly hydrogenated are typically more brittle.**

- **Shock cooling also causes fat and cocoa butter suppositories to crack.**
- This condition can be prevented by ensuring that the temperature of the mold is as close to the temperature of the melted base as possible.
- **Suppositories should not be placed in a freezer, which also causes shock cooling.**

Volume Contraction:

- **Bases, excipients, and active ingredients generally** occupy less space at lower temperatures than at higher temperatures.
- When **preparing a suppository,** the pharmacist pours hot melt into a mold and allows the melt to cool.
- **During this** cooling process, the melt has a tendency to contract in size.
- This makes it easier to release the suppository from the mold, but it may also produce a cavity at the back, or open end, of the mold.

- Such a cavity is undesirable and can be prevented if the melt is permitted to approach its congealing temperature immediately before it is poured into the mold.
- It is advisable to pour a small amount of excess melt at the open end of the mold to allow for the slight contraction during cooling.
- Scraping with a blade or spatula dipped in warm water will remove the excess after solidification, but care must be taken not to remove the metal from the mold.
- The heated instrument can also be used to smooth out the back of the suppository.

Drug Release Rates

- General approximate drug release rates as they relate to the drug and base characteristics are summarized as follows:

Drug Characteristics	Base Characteristics	Approximate Drug Release Rate
Oil-soluble drug	Oily base	Slow release; poor escaping tendency
Water-soluble drug	Oily base	Rapid release
Oil-soluble drug	Water-miscible base	Moderate release
Water-miscible drug	Water-miscible base	Moderate release; based on diffusion; all water soluble

Preparation Of Suppositories

- Suppositories are prepared by two methods:

(a) **Hand rolling.**

(b) **Compression molding.**

(c) **Pour molding.**

(d) **Automatic Moulding machine.**

- The method most frequently employed both on a small scale and on an industrial scale is molding.

- It is the oldest and simplest method of suppository preparation and may be used when only a few suppositories are to be prepared in a cocoa butter base
- It is suitable for thermo labile drugs.
- It is more economical methods.
- It is more time consuming and not uniformity process.
- Steps:
- 1. The drug is made into a fine powder.
- 2. It is incorporated into the suppository base by kneading with it or by trituration in a mortar.
- 3. The kneaded mass is rolled between fingers into rod shaped
- 4. The rods are cut into pieces and then one end is pointed

2- Compression molding:

- The cold mass of the base containing the drug is compressed into suppositories using a hand operated machine.

- Advantages:
- 1. It is a simple method.
- 2. It gives suppositories that are more elegant than hand moulded suppositories.
- 3. In this method sedimentation of solids in the base is prevented.
- 4. Suitable for heat labile medicaments.

- Disadvantages:
- 1.Air entrapment may take place.
- 2.This air may cause weight variation.
- 3.The drug and/or the base may be oxidized by this air.

Suppository moulds

- Commercially available moulds can produce individual or large numbers of suppositories of various shapes and sizes.
- Individual plastic moulds may be obtained to form a single suppository.
- Other molds, such as those most commonly found in the community pharmacy, are capable of producing 6, 12, or more suppositories in a single operation.
- Industrial molds produce hundreds of suppositories from a single batch.

- Molds in common use today are made from stainless steel, AL+3, 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.

- Lubricants for use with suppository bases:
- Lubricating the cavities of the mould is helpful in producing elegant suppositories and free from surface depression.
- 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.
- The **lubricant must be different in nature from the suppository base, otherwise it will be become absorbed and will fail to provide a buffer film between the mass & the metal.**

- However, no material that might irritate the mucous membranes should be employed as a mold lubricant.
- The water soluble lubricant is useful for fatty bases while the oily lubricant is useful for water soluble bases.
- The lubricant should be applied on a pledget of gauze or with fairly stiff brush.

Synthetic fat or macrogol base	Glycero-gelatin base	Theobroma oil
Contract significantly on cooling	Sticky nature	Oily lubricant cannot be used
Lubrication is not needed	Oily lubricant – liquid paraffin or arachis oil	Soft soap -10 g Glycerol – 10 ml Alcohol (90%) – 50 ml

- 3- Pour moulding (fusion method):
- Using a suppository mould which is made of metal or plastic.Traditional metal moulds are in two halves which are clamped together with a screw.
- Steps:
- **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**

- **Preparing and Pouring the Melt**
- **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.** Usually, medicinal substances are incorporated into a portion of the melted base by mixing on a glass or porcelain tile with a spatula.
- **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.**
- The melt is poured carefully and continuously into each cavity of the mold, which has been previously equilibrated to RT.
- **If any undissolved or suspended materials in the mixture are dense 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 undissolved 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.

- In filling each suppository cavity, the pouring must be continuous to prevent layering, which may lead to a product easily broken on handling.
- 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 filled mold is usually placed in the refrigerator to hasten hardening.

- 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.

Determination of the Amount of Base Required

- Generally, in preparing such prescriptions, the pharmacist calculates 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.

- In determining the amount of base to be incorporated with the medicaments, the pharmacist must be certain that the required amount of drug is provided in each suppository.

Density (Dose Replacement) Calculations for Suppositories

- In preparation of suppositories, it is generally assumed that if the quantity of active drug is less than 100 mg, then the volume occupied by the powder is insignificant and need not be considered. This is usually based on a 2-g suppository weight.

- Obviously, if a suppository mold of less than 2 g is used, the powder volume may need to be considered.

➢ **Displacement value**: The displacement value may be defined as , the number of parts by weight of medicament that displaces one part by weight of the base.

- The volume of suppositories from a particular mould will be constant but the weight will vary because the densities of the medicaments usually differ from the density of the base, and hence the density of the medicament will affect the amount of the base required for each suppository

The end of chapter

- **Medicinal powders** are intimate mixtures of medicinal substances usually in an inert base such as talcum powder or starch.
- Depending on the particle size of the resulting blend, the powder will have varying dusting and covering capabilities.
- In any case, the particle should be small enough to ensure against grittiness and consequent skin irritation.
- Powders are most frequently applied topically to relieve such conditions as diaper rash, chafing, and athlete's foot.

Lotion

- When topical application is desired in liquid form other than solution, lotions are most frequently employed.
- **Lotions** are emulsions or suspensions generally in an aqueous vehicle, although certain solutions have been designated as lotions because of either their appearance or application.
- Lotions may be preferred over semisolid preparations because of their nongreasy character and their increased spreadability overlarge areas of skin.