Lecture 2.

Lipid-Water Solubility of drug

- 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.

Drug solubility and suppository formulation

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

Amount of drug

- 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.

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

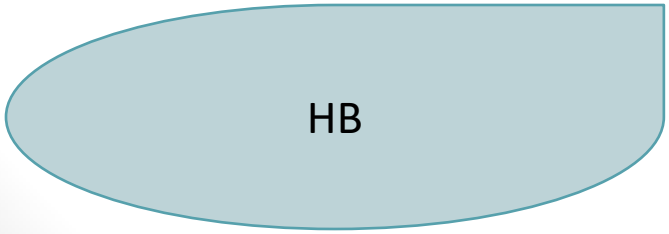
- **Requisites for a suppository base is that it should remain solid at room temperature but soften, melt, or dissolve readily at body temperature so that the drug is fully available soon after insertion. Certain bases are more efficient in drug release than others.**

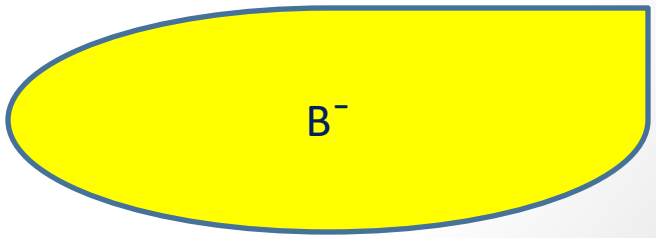
1. **Fatty bases or oleaginous bases, Cocoa butter (theobroma oil) melts quickly at body temperature, but is immiscible with body fluids as for fat-soluble drugs tend to remain in the oil and have little tendency to enter the aqueous physiologic fluids. For water-soluble drugs in cocoa butter, the reverse is usually true and good release results. Also, when irritation or inflammation is to be relieved, as in the treatment of anorectal 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.**

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.**





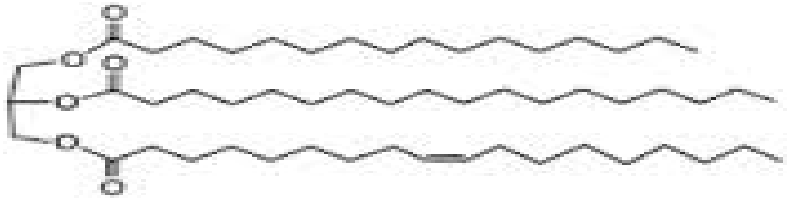
Fatty or Oleaginous Bases

1. Cocoa butter
2. hydrogenated fatty acids of vegetable oils, such as palm kernel oil and cotton seed 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 (naturally occurring comp.)
- Chemically, the main constituent of cocoa butter is the triglyceride derived from palmitic acid, stearic acid, and oleic acid, primarily of oleo-palmito-stearin and oleo-distearin



- 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 temperature.
- 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.
- 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 °C 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 °C, it may form α form that melt at 20 °C.**
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 (PEG)

- 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	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.

THANK YOU