**Suppositories**

They are solid dosage forms intended for insertion into the body cavity (rectum, vagina and urethra) where they melt, soften, or dissolve and exert localized or systemic effect.

- **Advantages of suppositories:**
  1. They offer a conventional means of administration for drugs, which:
     a. Irritate the G.I.T.
     b. Induce nausea and vomiting.
     c. Destroyed by the gastric acids and enzymes of the G.I.T.
  3. They can also be used for administration of drugs to unconscious patients.
  4. They can also be used for quick local action at the site of insertion.

Once inserted the supp., base melts, soften or dissolves, distributing the medicaments it carries it to the tissues of the region. These medicaments may be intended for retention within the cavity for either local or systemic action.

- **Local Action:** Rectal supp. intended for localized action are most frequently employed to relieve constipation, the pain, irritation, itching and inflammation associated with hemorrhoids.

Vaginal suppositories intended for localized effects are employed mainly as contraceptive, antiseptic…etc

- **Systemic Action:** For systemic effects, the mucous membranes of the rectum and vagina permit the absorption of many soluble drugs. Although the rectum utilized quite frequently as the site for the systemic absorption of drugs, the vagina is not as frequently used for this purpose.

Example of drugs administered rectally for their systemic effects include: prochlorperazine and chlorpromazine for the relief of nausea and vomiting and as a tranquilizers.
Some Factors Affecting on Drug Absorption from Rectal Suppositories

The factors affecting the rectal absorption of drug administered in the form of supps. may be divided into: 1-Physiological Factors. 2-Physicochemical Factors of the Drug and Supp. base.

1-Physiologic Factors:

The human rectum is approximately 15-20 cm in length. When empty of fecal material, the rectum contains only 2-3 ml of inert mucous fluid. There is abundant vascularization of the sub mucosal region of the rectum wall with blood and lymphatic vessels.

Among the physiologic factors affecting drug absorption from the rectum are the colonic contents, circulation route and the pH of the rectal fluids.

Colonic Content: When systemic effects are desired from the administration of a medicated supp., a drug will have greater opportunity to make contact with absorbing surface of the rectum and colon in the absence of fecal matter. Therefore, an evacuant enema may be administered and allowed to act before the administration of a supp..

Other conditions such as diarrhea, colonic obstruction due to tumorous growth, and tissue dehydration can all influence the rate and degree of drug absorption from the rectal site.

2-Physicochemical Factors of the Drug and Supp. Base:

a-Physico-chemical Factors Related to Drug: including

-Lipid-Water Solubility: The partition coefficient of a drug is an important consideration in the selection of the supp. base. A lipophilic drug that is distributed in a fatty supp. base in low conc. has less of tendency to escape to the surrounding aqueous fluids than would hydrophilic substance present in a fatty base to an extent approaching its saturation.

-Particle Size: For drugs present in the supp. in the undissolved state, the size of the drug particle will influence its of dissolution and its availability for absorption.
b-Physico-chemical Factors Related to the Base:

The base must be capable of melting, softening, or dissolving to release its drug components for absorption. If, the base interacts with the drug inhibiting its release, drug absorption will be impaired or even prevented. Also, if the base irritating to the mucous membranes of the rectum, it may initiate a colonic response and prompt a bowel movement negating the prospect of a drug release and absorption.

Suppositories Bases

Supp.base play an important role in the release of medication they hold and therefore the availability of the drug for absorption for systemic effect or for localized action

-**Ideal supp. Vehicles or bases:** The ideal supp. base should be

1. Melt at rectal temp.
2. Completely non-toxic & non irritant.
3. Compatible with a broad variety of a drug.
4. It has no other polymorph.
5. It shrink sufficiently on cooling (no need for lubricant)
6. It has wetting & emulsifying properties.
7. Water no. is high (i.e. high percentage of water can be incorporated in it).
8. Stable on storage. (color, odor or release ).

**A supp. Base – containing all of these properties has not been found.**

-Classification of Supp.Bases

Supp.bases can classified according to the physical characteristics into (1) Fatty bases.(2) Water-soluble or water miscible bases.(3) Miscellaneous bases, generally combinations of lipophilic and hydrophilic substances.
1-Fatty vehicles (the fatty vehicles in use nowadays are almost exclusively semi or fully synthetic ones).

A-Cocoa butter (theobroma oil).

Cocoa butter was the most widely used supp. base. It satisfies many of a requirement of an ideal supp. Since is non reactive and melts at body temp. Cocoa butter is a triglyceride with smells and tastes like chocolate. It's M.P. between 30°C and 35°C.

-Cocoa butter is no longer used because of its many disadvantages.

-Disadvantages:
1. A major disadvantage of theobroma oil is its tendency to form low melting points polymorphic forms on over-heating. On normal melting at 36°C and slow cooling, it forms stable beta crystals with normal melting point but if overheated, it may form, on cooling, unstable gamma crystals with a melting point of 15°C or alpha crystals with a melting point of 20°C.
2. It shrinks only slightly on solidification and hence a mould lubricant is required.
3. It has a low absorptive capacity for water.
4. Chemical instability (It is prone to air oxidation and may become rancid on storage).
5. The melting point of theobroma oil is usually reduced by addition of drugs such as volatile oils.
**B- The semi synthetic type of fatty vehicles**

They have few or none of the problem mentioned with cocoa butter, the general composition is mixed triglyceride with C\textsubscript{12} – C\textsubscript{18} acids. These acids are saturated, with lauric acid being predominant; the common base in this group is witepsol bases.

Witepsol H 15 disintegrates in the rectum as fast as theobroma oil. The melting times were 4 mins. For cocoa butter while 6 mins. for witepsol.

The higher melting time of witepsol enables supp to ascend more in the rectum before disintegration while C.B supp melt at lower temperature more rapidly and more likely to cause leakage. The witepsols are not subject to structural change at a temp. above their M.P..

They absorb water due to their high hydroxyl no. which refers directly to presence of mono and diglyceride in fatty bases.

A high numbers means that power to absorb water is high, this may lead to increase the rate of decomposition for drugs that are easily hydrolyzed, as aspirin. This capacity of absorbing could lead to the formation of a w/o emulsion in the rectum which is generally to be avoided because of its very low drug release rate.

Witepsols contracts more upon solidification than cocoa butter, thus eliminating the need for lubricating the mold. Witepsol H15 can be mixed with other witepsols.

Witepsols solidify rapidly after being poured at their melting temp. into mold.

**II-Water soluble vehicle**

Water soluble or (miscible) vehicle are much less in use because of their disadvantages. They comprise a classical glycerin gelatin or soap bases which are used exclusively for laxative purposes or in vaginal therapy.

The most popular water soluble vehicles are the PEG. The PEG supp base termed carbowaxes; they exist in a M. wt range from 200 to 20000.

At room temp, the lower members of the series are liquid, PEG1000 is a soft solid and the higher members are wax like, they melt between 37°C and 63°C and are easily shaped into a supp.
- Disadvantages of Macrogols Bases:

1. They are hygroscopic and may cause dehydration and subsequent irritation of the rectal mucosa. Such irritant effects can however be reduced by immersing the supp. in water before insertion, this can help to reduce this problem.

2. They may be brittle unless the molten base is poured into the mould at as low a temperature as possible. Britteness can however be reduced by the addition of surfactants or plasticizers such as castor oil or propylene glycol.

3. The good solvent properties of macrogols may retard the release of certain drugs.

4. Crystal growth of suspended or partially dissolved drugs may occur in these bases. Such crystals may make the base brittle and may show delayed dissolution and irritant effects.

5. These bases are incompatible with a number of medicaments and materials such as benzocaine, penicillins, phenols, salicylic acid, sulphonamides, tannic acid, sorbitol and some plastics.

- Several combinations of PEGs have been prepared for supp bases having different physical characteristics e.g.

  PEG 1000 96%
  PEG 400 4%

This base is low melting and may require refrigeration during the summer months. It is useful when rapid disintegration is required.

III- Water dispersible bases

Several non ionic surfactants related chemically to PEGs, have been developed as a supp vehicle. Many of these bases can be used for formulating both water soluble and oil soluble drugs.

These bases offer additional advantages of storage and handling at elevated temp., with broad drug compatibility, non support of microbial growth, non toxicity and non sensitivity.

The most widely used are the polyoxy ethylene sorbitan fatty acid esters (tween), the polyoxy ethylene stearate (Myrj) and the sorbitan fatty acid esters (span). These bases may increase the rate of drug absorption, so should be use with caution.
-Compressed tablet supp

Rectal supp usually are not compressed as tablets, because the amount of liquid in the rectal cavity is inadequate for tablet disintegration.

Effervescent base tablets have been described as a carbon dioxide releasing laxative supp. Compressed tablets weighing about 3g are used as a vaginal supp.

Fat base vaginal supp are sometimes rejected because of the discomfort resulting from the seepage obtained from the supp with water insoluble bases.

The compressed tablet for vaginal use is usually almond shaped to ease insertion and to provide maximum surface area, which facilitates tablet disintegration and hasten dispersion of the drug on the vaginal wall.

-Choice of vehicle

The points which are important for the choice of a suppository base

*Composition
*Melting behavior
*Rheological properties

One interesting parameter can be added to this list, i.e. the volume of the suppository.

Usually suppositories for adults are 2ml and for children 1 ml. It has been suggested that the larger volume may provoke a reaction of the rectal wall, thus helping to spread the melt over a larger area. The increase of volume of, for example, paracetamol suppositories, resulted in faster and more complete absorption of the drug.

-The drug

The factors related to the drug substance are listed which are of possible consequence for the quality of suppositories:

Solubility in water and vehicle, Surface properties, Particle size, Amount, and PKa.
-Drug solubility in vehicle

The drug solubility in the vehicle is of especial interest from the biopharmaceutical point of view. It determines directly the type of product, i.e. solution suppository or suspension suppository.

The drug solubility in the rectal fluid determines the maximum attainable concentration and thus the driving force for absorption.

When a drug has a high vehicle to water partition coefficient, it is likely to be in solution to an appreciable extent (or completely) in the vehicle.

This generally means that the tendency to leave the vehicle will be small and thus the release rate into the rectal fluid will be low. This is obviously unfavorable for rapid absorption.

On the other hand certain lipid solubility is required for penetration through the rectal membranes.

The optimal balance between these two requirements is usually found using these rules listed in this table.

Table shows the Drug solubility and suppository formulation

<table>
<thead>
<tr>
<th>Solubility in fat</th>
<th>Solubility in water</th>
<th>Choice of base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>Fatty base (rule 1)</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>Aqueous base (rule 2)</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>

This table assumes that the release from the dosage form is considered as the rate-limiting step. Thus the tendency to remain in the base should be lowered as much as possible (rules 1 and 2).

When the solubility in fat and water are both low no definite rule can be given. It may well be that the dissolution rate will become the controlling step and thus it seems advisable to use micronized drug particles.
It should be stated as a general rule that emulsion-type suppositories (w/o) are strongly discouraged. The transfer of drug molecules present in dissolved state in the inner phase will be very slow and thus the absorption will be very much retarded. It seems logical therefore that the first choice of a formulation would be a readily water-soluble form of the drug dispersed in a fatty base. This lays special emphasis on the water solubility of drugs and the methods to improve this.

**-Surface properties:**

The surface properties of drug particles are also important as these particles will be transferred from one phase to another. This happens first when the drug is brought into contact with the vehicle and air has to be displaced from its surface. When this is not achieved particles may form agglomerates. This adversely affects final content uniformity by an increased tendency to separate.

If wetting by the vehicle has taken place displacement by rectal fluid will be required to let the drug go into solution, which is the prerequisite for absorption. This is the underlying reason why people have tried the addition of surfactants to their formulation.

**-Particle size**

The particle size of the drug is an important parameter, both technologically and biopharmaceutical. To prevent undue sedimentation during or after preparation the particle size should be limited.

The smaller the particles the less the possible mechanical irritation to the patient (esp. < 50 µm) and the higher the dissolution rate and therefore drugs with a low water solubility will be dispensed in small, preferably micronized particles.

One should be aware of the increased tendency of these particles to agglomerate due to strongly increased van der Waals forces in that case, however. Also an unnecessary size reduction operation should be avoided when possible.

There are good indications that size reduction is not a good decision for all drugs. It has been shown, especially for readily water-soluble drugs, that large particles give blood levels which are higher than small particles. This would lead to the suggestion to use particles in the size range 50-100 µm in that case. The lower limit of 50 µm to increase transport
through the molten vehicle. and the upper limit of 100 µm is a safe protection against undue sedimentation during preparation.

**Amount of drug**

A complicating factor is the amount of drug present in a suppository. If the number of particles increases, this would also increase the rate to form agglomerates. This will very much depend on the particle size and on the presence of additives.

**Other additives:**

For several widely varying reasons formulators of suppositories make use of additives to improve their product. Formulations for specific drugs which affect the melting point of the suppository; it may become depressed (by a soluble liquid compound) or increased (by a high amount of soluble high melting active compound).

The important point to consider in these situations is the possible influence of formulation changes on the release characteristics. The addition of viscosity increasing additives e.g. colloidal silicon oxide or aluminum monostearate, both approximately 1-2% will create a gel-like system with a slower release rate of the drug. The addition of surface-active agents has been extensively practiced but still remains a source of great uncertainty. When these compounds are used to create an emulsion system (thus w/o) this must certainly be discouraged, as the release will be unacceptably slow. It may well be, however, that surfactants act as wetting agents, so this can influence the release in a positive sense.

There are good indications that the presence of surfactants in a concentration higher than the critical micelle concentration can retard the release from the suppositories