Suppositories, inserts and sticks

Chapter 12

Textbook: Pharmaceutical Dosage Forms and Drug Delivery Systems by Howard A. Ansel; 11th edition, 2017

Learning Objectives

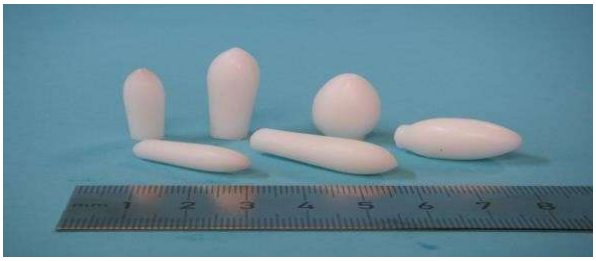
By the end of this lecture, students will be able to:

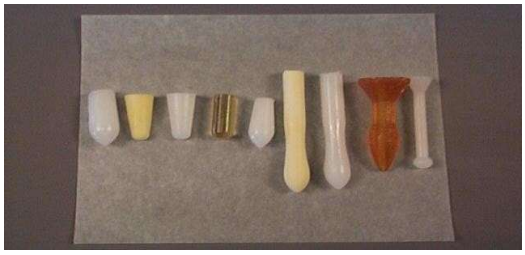
- Compare and contrast various suppositories and inserts, in terms of physical appearance, size, and shape
- Describe the advantages of suppositories and inserts.
- Identify and explain physiologic factors that influence the drug absorption from rectal suppository administration
- Identify and explain the physicochemical factors of the drug and suppository/insert base as these influence absorption
- Compare and contrast the various classes of suppository bases
- Describe the three methods of suppository preparation

Suppositories, definitions

Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert local or systemic effects.

Suppositories are commonly used rectally, vaginally, and occasionally urethrally.





They are used to deliver both systemically and locally acting medications. 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.

Uses and applications:

Suppositories generally have been employed for three reasons:

1. To promote defecation
2. To introduce drugs into the body
3. To treat anorectal diseases

<u>The advantages of rectal administration include the following:</u>

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 a 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 and the reasons for the infrequent use of suppositories include the following.

1. Lack of flexibility regarding the dosage of commercially available suppositories.
2. Variable effectiveness, depending upon many factors, including the pathology of the anorectal lesions.
3. Not suitable for drugs with a narrow therapeutic margin, such as aminophylline, (interchange can result in risk of toxicity).
4. Bowel movement may interrupt the absorption process of the drug; this may especially occur if the drug is irritating.
5. The absorbing surface area of the rectum is much smaller than that of the small intestine.
6. The fluid content of the rectum is much less than that of the small intestine, which may affect dissolution rate.
7. There is the possibility of degradation of some drugs by the microflora present in the rectum.

Local Action

Rectal suppositories intended for local action are most frequently used to relieve constipation or the pain, irritation, itching, and inflammation associated with hemorrhoids or other anorectal conditions. Anti-hemorrhoidal suppositories frequently contain a number of components, including local anesthetics, vasoconstrictors, astringents, analgesics, soothing emollients, and protective agents.

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.

Vaginal suppositories or inserts intended for local effects are employed mainly as contraceptives, antiseptics, antifungals to treat Candida albicans, and anti-antibiotics. Urethral suppositories may be antibacterial or a local anesthetic preparative for a urethral examination.

Systemic Action

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.

Examples of drugs administered rectally in the form of suppositories for their systemic effects include:

1. Drugs to treat nausea and vomiting
2. opioid analgesia
3. drugs for migraine syndrome
4. nonsteroidal anti-inflammatory analgesics
5. antipyretic;

The table below presents some examples for suppositories produced by Iraqi pharmaceutical companies.

Suppository	Active ingredient	Type of Effect	Category and Comments
Voltadin®	Diclofenac	Systemic/rectal	Anti-inflammatory, analges
Mubek®	Meloxicam	Systemic/rectal	Anti-inflammatory
Safalax®	Bisacodyl	Local/ rectal	laxative.
Spasmo®	hyoscine butylbromide	Systemic /rectal	antispasmodic
Micazol®	Miconazole	Local/vaginal	Antifungal
Antipyrol®	Acetaminophen	Systemic/ rectal	antipyretic

Some factors of drug absorption from rectal suppositories

Some drugs are absorbed better rectally as compared to orally, some are absorbed better orally as compared to rectally, and some the oral and rectal doses are comparable. Therefore, the dose of a drug administered rectally may be greater than or less than the dose of the same drug given orally, depending on:

1. Physiological factors that affect drug ability to traverse the physiologic barriers to absorption
2. The physicochemical nature of the drug and the base: The nature of the suppository vehicle and its capacity to release the drug and make it available for absorption

1. Physiological factors:

1.1. Fluid volume and circulation:

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. 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

1.2. pH and buffering capacity:

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.

1.3. 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 evacuation 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.

2. Physicochemical factors and drug effect:

2.1. Physicochemical factors of the drug include such properties as:

a) The relative solubility of the drug in lipid and in water and

b) The particle size of a dispersed drug, and surface properties
c) Amount of drug
d) pKa of the drug

2.2. Physicochemical factors of the base include:

a) Its ability to melt, soften, or dissolve at body temperature
b) Its ability to release the drug substance
c) Its hydrophilic or hydrophobic character (composition of the base)
d) Rheological properties.

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

If a drug is readily soluble, the influence of particle size may be minimal.

For un-dissolved drugs in a suppository (suspension), 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.

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.

Properties of the ideal suppository base

- ✓ Non-toxic, non- irritating to sensitive and inflamed tissues.
- ✓ Inert and compatible with medicaments.
- ✓ Not deteriorated or contaminating the drug during storage.
- ✓ Easily manufactured by compression or molding.
- ✓ Dissolve or disintegrate in mucous secretions or melt quickly at body temperature

to allow the release of medicament.

- ✓ Remain molten for a sufficient period of time to allow pouring into molds.
- ✓ Solidify rapidly to minimize sedimentation of dispersed solids.
- ✓ Contract on cooling to allow easy withdrawal of the suppository from the mold.
- ✓ Has wetting and emulsifying properties.
- ✓ Stable on storage, keeps its shape during storage or handle (does not change color, odor and drug release pattern).

Main types of suppository bases:

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

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.

Miscellaneous bases, generally combinations of lipophilic and hydrophilic substances.

TABLE **12.5.** Melting Ranges of some Suppository Bases

Base	Composition	Melting Range (°C)
Cocoa butter	Mixed triglycerides of oleic, palmitic, and stearic acids	34–35
Fattibase	Triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostearate and polyoxyl stearate	35.5–37
Polybase	A homogeneous blend of PEGs and polysorbate 80	60–71
Suppocire OSI	Eutectic mixtures of mono-, di-, and triglycerides derived from natural vegetable oils, each type having slightly different properties	33–35
Wecobee W	Triglycerides derived from coconut oil	31.7–32.8
Witepsol H15	Triglycerides of saturated fatty acids C12–C18 with varied portions of the corresponding partial glycerides	33–35

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

Are 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 maintain in 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 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 (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.

Disadvantages of theobroma oil:

- 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 and quickly at high temperature then freezing or cooling it will form unstable γ form that melt at 15 °C.
- Adherence to the mold, this can be solved by using lubricant agent that is immiscible with the base.
- Low m.p, this can be solved by added medication, adding white bees wax.
- Low water absorbance (poor water-absorbing capacity), this can be solved by adding surface-active agent.
- Stability problem: slow deterioration during storage and chemical instability
- Not suitable for warm countries.
- 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),

Wecobee bases (triglycerides derived from coconut oil)

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 to maintain their shape and consistency.

2. Due to hygroscopic nature, they 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.

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. The numeric designations refer to the average molecular weight of each of the polymers.

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

PEG 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.

It is possible to prepare suppositories from PEG 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, PEG-based suppositories do not leak from the orifice, as 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

Miscellaneous Bases

The miscellaneous group of bases are mixtures of oleaginous and water- soluble or water-miscible materials. These materials may be chemical or physical mixtures.

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.

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.

Formulation Variables

Formulation variables that are generally considered include:

(a) The nature and form of the active principle (esters, salts, complexes, etc.); 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
- ✓ For liquids, it is necessary to take up the liquid into the suppository base as an emulsion, or by adding a drying powder, or adding a suitable thickening agent when the liquid is mixed with the suppository base.
- ✓ For the semisolids or paste-type drugs, 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.

(b) The physical state, particle dimensions, and the specific surface of the product: discussed earlier

(c) The solubility of the drug in various bases: discussed earlier

(d) The presence or absence of additives added to the active principle like the use of suspending agents to improve the viscosity of the base. A high viscosity base can slow drug release. This is because the viscosity causes the drug to diffuse more slowly through the base to reach the mucosal membrane for absorption. Non base materials exceeding 30% can increase Cocoa butter suppositories brittleness

(e) Pharmaceutical procedures used in the preparation of the dosage form. 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.

Preparation of suppositories

Suppositories are prepared on a small scale by two methods

a) Molding from a melt

b) 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:

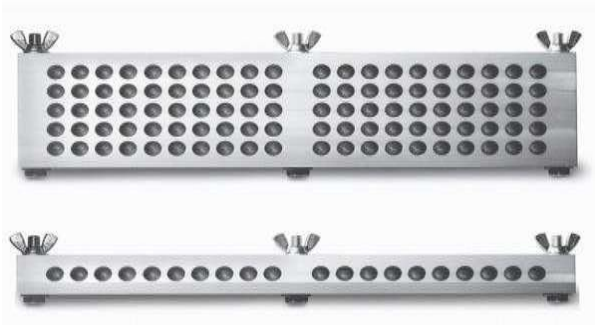
1. Melting the base,
2. Incorporating any required medicaments,
3. Pouring the melt into molds,
4. Allowing the melt to cool and congeal into suppositories,
5. Removing the formed suppositories from the mold.
6. Cocoa butter, glycerinated gelatin, polyethylene glycol, and most other bases are suitable 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.



Preparation by hand rolling and shaping

It is the oldest and simplest method of supp. Preparation. 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 (it requires considerable practice and skill).

Determination of the Amount of Base Required

Generally, in preparing suppositories, 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.

Because the volume of the mold is known (from 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.

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

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.

The three methods of calculating the quantity of base that the active medication will occupy and the quantities of ingredients required are:

1. Dosage replacement factor
2. Density factor
3. Occupied volume method

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.

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

Displacement value (D.V)

Displacement value is defined as the quantity of drug that displaces one part of the base (eg. 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 8 codeine phosphate suppositories (D.V=1.1) using mold of 1g size each suppository containing 60mg of codeine phosphate

Prepare 10 suppositories to compensate for any loss

60 X1 0 = 600mg = 0.6g of codeine phosphate

Supp. Base 1g X 10 = 10g total weight of pure base

Drug base

1.1 displace 1g base displaced = (1g X 0.6) / 1.1= 0.55 g

0.6 ?

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

Example: Calculate the quantities required to make 8 theobroma oil supp. (2g mold) each containing 400 mg of zinc oxide (DV= 4.7).

Calculate the total weight of zinc oxide required. 0.4 X10 = 4g

Calculate what weight of base would be required to prepare 10 unmedicated supp. 2g X10 = 20 g

Determine what weight of base would be displaced by the medicament. Replaced base = wt. of drug/ D.V = 4 / 4.7= 0.85

Calculate, therefore, the weight of base required to prepare the medicated supps.

20 – 0.85 = 19.15 g 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 **four** glycero gelatin supp. (4 g mold), each containing100 mg aminophylline (Displacement value = 1.3)

Drug 6 X 100 = 0.6 g

Glycerin gelatin Base 6 X4g X1.2 = 28.8 g

Glycerin gelatin Base replaced = 0.6 / 1.3 = 0.46 (by theobroma oil base)

0.46 X 1.2 = 0.55 g base displaced by the base (glycero gelatin) Base required
28.8 – 0.55 =28.25g of the base required

Manufacturing suppositories

Manufactured suppositories are generally prepared by the melt fusion method. Commercially automated equipment for melt fusion is available to continually produce large quantities of finished suppositories per hour.

The automated equipment for preparing suppositories has provided an efficient method for manufacturing large quantities of suppositories in a relatively short time. This equipment allows for a single continuous manufacturing process.

The process starts with two main components: The packaging shell material and the molten bulk drug product.

The empty shells are aligned with the nozzles of the dosing pump, and the molten product is dosed into the empty shells. For high-speed machines, multiple cavities can be dosed at one time.

Filled shells are moved to the cooling tunnels. The cooling tunnels reduce temperature of the molten mass in the shells. This allows the product to solidify in the shells. Cooling tunnels blow chilled air around the molds. The cooling is controlled by the time the suppositories spend in the tunnels and the temperature of the tunnels.

Once the solidified suppositories leave the cooling tunnel, they move to the *sealing* area where the open top of the mold is closed.

Quality Control

Quality control procedures listed in the USP /NF for manufactured

- Suppositories and inserts include
- Identification assay
- Loss on drying
- Disintegration,
- Dissolution.
- Stability considerations in dispensing practice for suppositories include observation for excessive softening and oil stains on packaging

Packaging and Storage

Most commercial supps are individually wrapped in either foil or plastic. Some are packaged in a continuous strip, separated by tearing along perforations or otherwise separated in compartmented boxes to prevent contact and adhesion.

Suppositories containing light-sensitive drugs are individually wrapped in an opaque material such as a metallic foil. Because supps. are adversely affected by heat, it is necessary to maintain them in a cool place.

Cocoa butter suppositories must be stored below 30°C and preferably in a refrigerator (2°C to 8°C).

Glycerinated gelatin suppositories can be stored at controlled room temperature (20°C to 25°C).

Suppositories made from a base of PEG may be stored at usual room temperatures. Suppositories stored in high humidity may absorb moisture and tend to become spongy, whereas suppositories stored in places of extreme dryness may lose moisture and become brittle.

Stability

Physical Stability

Physical observation can generally detect physical stability problems, including softening, hardening, drying, cracking, separation, polymorphs when melting range is affected, and one can often detect the odor of rancidity.

Chemical Stability

In working with suppositories, the majority will be anhydrous, so the presence of water is not really an issue. However, in some cases, water may be present to help incorporate the drug into the base, or it may be present as part of the hydrated form of the drug components' crystalline structure. Also, if emulsions or suspensions are incorporated into suppositories, water may be present. Some suppositories may be hygroscopic and absorb **water from** the atmosphere.

In suppositories, the following reactions and conditions can result in loss of active drug content and may not provide obvious visual or olfactory evidence of their occurrence: hydrolysis, epimerization, decarboxylation, dehydration, oxidation, photochemical decomposition, pH effect, solid state stability, temperature, and microbiological considerations.

Microbiological Stability

Most suppository formulations do not contain preservatives or antioxidants because water is usually excluded from the formulations. However, in the event water is present or the formulation may support the growth of microorganisms, an appropriate preservative may be indicated

Rectal suppositories

Used for local and systemic administration of drugs. The rectal route of administration is especially useful if the patient is unwilling or unable to take medication by mouth. Cathartic suppositories are more rapid acting than orally administered medication

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.

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 .

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

Vaginal inserts and suppositories

Vaginal suppositories, also called (in past) **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.

The most commonly used base for vaginal inserts consists of combinations of the various molecular weight polyethylene glycols. To this base is frequently added surfactants and preservative agents, commonly the parabens. Many vaginal suppositories and other types of vaginal dosage forms are buffered to an acid pH usually about 4.5, consistent with the normal vagina. This acidity discourages pathogenic organisms and provides a favorable environment for eventual recolonization by the acid- producing bacilli normally found in the vagina.

Rx

Progesterone, micronized powder q.s.

Polyethylene glycol 400 60%

Polyethylene glycol 8000 40%

Vaginal inserts (tablets)

Vaginal tablets are more widely used nowadays than are commercial vaginal suppositories. The tablets are easier to manufacture, more stable, and less messy.

Vaginal tablets, frequently referred as vaginal inserts, are usually ovoid and are accompanied in their packaging with a plastic inserter, a device for easy placement of

the tablet within the vagina. Vaginal tablets contain the same types of anti-infective and hormonal substances as vaginal supps.

They are prepared by tablet compression and are commonly formulated to contain lactose as the base or filler, a disintegrating agent such as starch, a dispersing agent such as polyvinylpyrrolidone, and a tablet lubricant such as magnesium stearate. The tablets are intended to disintegrate within the vagina, releasing their medication.

Some vaginal inserts are capsules of gelatin containing medication to be released intravaginally.

Capsules may also be used rectally, especially to administer medication to children unwilling or unable to tolerate the drug orally. Capsule insertion into the rectum can be facilitated by first lightly wetting the capsule with water. Holes may be punched into these capsules before moistening and insertion to facilitate fluid movement into the capsule if desired. Drugs are absorbed from the rectum, but frequently at unpredictable rates and in varying amounts, as previously noted. Drugs that do not dissolve rapidly and that irritate mucous membranes should not be placed in direct contact with such membranes.

Special Types of Suppositories

There has been a lot of work done in the development of altered release suppository dosage forms, both long-acting and slow-release suppositories (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.

Various coatings, emulsions, hydrogels, layering, matrices of different substances, hollow-type suppositories, nanoparticles, osmotic release, micellar solutions, thermoreversible liquid suppositories, xerogel suppositories, and technologies have been used to later drug release rate from suppositories.

Medication Sticks

The medication stick, a fairly recent preparation, is used for both cosmetic and medical purposes. Examples include lip balm sticks (ChapStick).

Medication sticks are prepared similar to suppositories except that the melt is poured into the administering device, or tube. For application, the stick is pushed up from the bottom or using a screw-type device to raise the stick.

These bases, which will soften and melt at body temperatures, include cocoa butter, petrolatum, waxes, and PEGs. Active drugs can include any agent that can be applied directly to a specific skin site or over a larger area of skin to relieve such discomforts as muscle sprains and arthritis. Using waxes, oils, or plain polymers such as PEGs alone achieves a topical effect. Penetration enhancers (e.g., glycerin, propylene glycol, alcohol, and surfactants) can increase the amount of transdermal drug delivery. Melting bases can be further divided into opaque and clear. Opaque bases include waxes, oils, PEGs, and the like, whereas clear bases include sodium stearate/glycerin mixtures.

Medications and other ingredients that have been incorporated into sticks include local anesthetics, sunscreens, antivirals, and antibiotics.

The medication in a soft stick is applied by raising the stick above the tube level and simply rubbing it onto the skin, where it softens and flows easily onto the affected area. The medication usually cannot be seen on the skin. When a hard stick is applied, the tip of the stick is moistened and then touched to the affected area. The crystalline powder used to prepare the stick can leave a white residue on the skin.

The surface of the stick should be cleaned with a clean tissue after each use, and, to avoid transmitting infection, the product should not be shared with others.

Acyclovir Lip Balm

Acyclovir (200 mg capsules) #6

Polyethylene glycol base (Polybase) 25 g

These formulas can be modified by incorporating lidocaine, PABA, or other ingredients as needed.

Clinical Considerations

The pharmacist should instruct the patient on:

- Proper storage of the suppository
- Proper insertion of the suppository: whether to moisten it prior to insertion, how far to insert it, and how long to remain inactive after insertion.
- The patient should be advised to rub cocoa butter suppositories gently with the fingers to melt the surface to provide lubrication for insertion.
- When the patient is instructed to use one-half suppository, the patient should be told to cut the suppository in half lengthwise with clean razor blade.