Suppositories

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

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.

Suppository and Insert Shapes

Suppositories have various shapes and weights; the shape and size of a suppository must be such that:

- It can be easily inserted into the intended orifice without causing undue distension,
- Once inserted, it must be retained for the appropriate period.

Rectal suppositories

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

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

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.

Local Action

Once inserted, the suppository base melts, softens, or dissolves, distributing its medicaments to the tissues of the region. These medicaments may be intended for retention within the cavity for local effects, or they may be intended to be absorbed for systemic effects.

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

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.

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. Achievement of a rapid drug effect systemically.

Disadvantages of suppositories

1. Lack of flexibility regarding dosage of commercially available suppositories resulting in underuse and a lack of availability.

2. Suppositories as a dosage form are safe, but they exhibit variable effectiveness, depending upon many factors to be discussed later, including the pathology of the anorectal lesions.

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

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

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

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

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

1. Prochlorperazine and chlorpromazine for the relief of nausea and vomiting and as a tranquilizer;
2. Morphine and oxymorphone for analgesia;
3. Ergotamine tartrate for the relief of migraine;
4. Indomethacin, a nonsteroidal anti-inflammatory analgesic and antipyretic.

Factors Affecting Drug Absorption from Rectal Suppositories

The dose of a drug administered rectally may be greater than or less than the dose of the same drug given orally, depending on such factors as:

1. The constitution of the patient (Physiological factors)
2. The physicochemical nature of the drug and its ability to traverse the physiologic barriers to absorption, and
3. The nature of the suppository vehicle and its capacity to release the drug and make it available for absorption.

Some that are absorbed better orally as compared to rectally, and some cases where the oral and rectal doses are comparable. In some cases, the doses are different, for example, lincomycin, chloral hydrate requires four times the dose rectally as compared to orally and empirically, phenytoin requires about three times the dose rectally as compared to orally.

Physiological Factors:

➢ *Circulation Route*

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. Lymphatic circulation also assists in the absorption of rectally administered drugs.

➢ *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 have greater opportunity to make contact with the absorbing surface of the rectum and colon in the absence of fecal matter. 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.

Physicochemical Factors:

➢ *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.

Fatty base (e.g. cocoa butter) melts rapidly at body temperature but because of its immiscibility with rectal fluids, it fails to release fat-soluble drugs readily. Therefore, it is preferable to incorporate the ionized form (salt form) of the drug rather than the unionized (base form) of the drug to maximize bioavailability.

Water-soluble bases, for example, polyethylene glycols that dissolve in the anorectal fluids, release for absorption both water-soluble and oil-soluble drugs.

Generally, the more drug a base contains, the more drug will be available for potential absorption.

➢ *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. As indicated many times previously, **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.**

It is preferable to avoid a too fine particle size because of the high increase of the viscosity of the melted excipient that can result from the use of excessively small particles and possible difficulties in flow during production.

➢ *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 induce a bowel movement, eliminating the possibility of complete drug release and absorption. Long-acting or slow-release suppositories have also been prepared. Morphine sulfate in slow-release suppositories is prepared in a base that includes a material such as alginic acid, which will prolong the release of the drug over several hours.

Suppository Bases

Suppository bases play an important role in the release of the medication they hold and, therefore, in the availability of the drug.

One of the first 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. For instance, cocoa butter (theobroma oil) melts quickly at body temperature, but because it is immiscible with body fluids, 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. Fat-soluble drugs seem to be released more readily from bases of glycerinated gelatin or polyethylene glycol, both of which dissolve slowly in body fluids.

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.

Classification of Supp. Bases

1. Fatty or oleaginous bases,

2. Water-soluble or water-miscible bases, and

3. Miscellaneous bases, generally combinations of lipophilic and hydrophilic substances.

A suppository base should be:

1. Physically and chemically stable.
2. Nonirritating, nontoxic, nonsensitizing.
3. Chemically and physiologically inert.
4. Compatible with a variety of drugs.
5. Stable during storage, and esthetically acceptable.
6. It should contract slightly on cooling to release itself from the mold with requiring mold lubricants.
7. Has wetting and emulsifying properties.
8. Can be manufactured by molding by hand, machine, compression, or extrusion.
9. It should melt or dissolve in rectal fluids and should not bind or otherwise interfere with the release or absorption of drug substances.

Other desirable characteristics depend upon the drugs to be added. For example, bases with higher melting points can be used to incorporate drugs that generally lower the melting points of the base (e.g., camphor, chloral hydrate, menthol, phenol, thymol, and volatile oils) or to formulate suppositories for use in tropical climates.

Additionally, bases with lower melting points can be used when adding materials that will raise the melting points or when adding large amounts of solids.

Fatty or Oleaginous Bases

Fatty bases are the most frequently employed suppository bases, principally because cocoa butter is a member of this group of substances. Among the other fatty or oleaginous materials used in suppository bases are many hydrogenated fatty acids of vegetable oils, such as palm oil and cottonseed oil.

Also, fat-based compounds containing compounds of glycerin with the higher–molecular-weight fatty acids, such as palmitic and stearic acids, may be found in fatty bases. Such compounds, such as glyceryl monostearate and glyceryl monopalmitate, are examples of this type of agent.

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

Cocoa Butter, NF, 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.

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. Because of this, when cocoa butter is quickly or carelessly melted at a temperature greatly exceeding the minimum required temperature 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. However, because the crystalline form (alpha crystals) is a metastable condition, there is a slow transition to the more stable (beta form) of crystals having the greater stability and a higher melting point. This transition may require several days.

Consequently, if suppositories that have been prepared by melting cocoa butter for the base do not harden soon after molding, they will be useless to the patient and a loss of time, materials, and prestige to the pharmacist.

Cocoa butter must be slowly and evenly melted, preferably over a bath of warm water, to avoid formation of the unstable crystalline form.

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.

Other bases in this category include commercial products such as **Fattibase** (triglycerides from palm 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 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 present 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.

Polyethylene glycols 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 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.

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, 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

Are mixtures of the oleaginous and water-soluble or water-miscible materials.

They are emulsions, generally of w/o type. Mixtures of fatty bases (such as cocoa butter) with emulsifying agents capable of forming w/o emulsions have been prepared. These bases have the ability to hold water or aqueous solutions.