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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

Compounding Suppositories, Part I

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This is the first in a two-part series on the extemporaneous compounding of suppositories. Part I includes a general discussion, preparation methods and techniques involved. Part II includes selected aspects of physicochemical considerations, stability and calculation discussions.

INTRODUCTION

Suppositories are solid dosage forms intended for administration of medicine via the rectum, vagina or urethra that melt, soften, or dissolve in the body cavity. The definition of a suppository also depends upon one's point of view. For the *patient*, the suppository is a dosage form that can melt in the house or between the fingers, and a dosage form they find in the family medicine cabinet alongside the creams, tablets, capsules and bandages. Often used for children, it is a means of administering a medication with few complications. For the *doctor*, it is a means of treating the child or adult at a hospital or at home without using administration methods such as injections, especially when the patient cannot take a medication orally. It is also a useful method of avoiding intolerance and gastric rejection, and in some cases, a form of administration which is very effective because of its rapid onset of action. For the *pharmacist*, it is a homogenous, effective solid dosage form that can be prepared extemporaneously.

Suppositories have been used for several thousand years and are referred to in the early writings of the Egyptians, Greeks and Romans. Early suppositories consisted of pieces of cloth, plants, wood or other material used plain or soaked in a solution of a "medication" and administered.

Rectal suppositories are cylindrical or conical and tapered or pointed at one end. They generally weigh approximately 2 G and are about 1-1.5 inches long. Infant suppositories weigh approximately one-half that of adult rectal suppositories.

Vaginal suppositories, formerly called pessaries, are available in various shapes, e.g., ovoid or globular, and weigh approximately 3-5 G each. Extemporaneously prepared vaginal suppositories utilizing water-soluble bases, such as polyethylene glycol or glycerinated gelatin, are preferred as they will minimize leakage. Some vaginal suppositories are actually compressed tablets and are often called inserts.

Urethral suppositories, formerly called bougies, are usually about 5 mm in diameter and 50 mm in length for females and 125 mm in length for males, with weights being 2 G for female and 4 G for male.

APPLICATIONS/USES

Suppositories are indicated for administering drugs to infants/small children, to severely debilitated patients, to those who cannot take medications orally and to those for whom the parenteral route might be unsuitable.

Suppositories are used to administer drugs for either systemic or local application. Local applications include the treatment of hemorrhoids, itching and infections. Systemic application is used for a variety of drugs, including antinauseants, antiasthmatics, analgesics and hormones.

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BASES

A suppository base should be stable, nonirritating, chemically and physiologically inert, compatible with a variety of drugs, melt or dissolve in rectal fluids, stable during storage, not bind or otherwise interfere with the release or absorption of drug substances and be esthetically acceptable. Other desirable characteristics depend upon the drugs to be added. For example, higher melting point bases can be selected for incorporating drugs that generally lower the melting points of the base (e.g. camphor, chloral hydrate, menthol, phenol, thymol and volatile oils) or when formulating suppositories for use in tropical climates. Lower melting point bases can be used when adding materials that will raise the melting points or if adding large amounts of solids.

TABLE 1

EXAMPLE BASES, MOSTLY OF U.S. ORIGIN/AVAILABILITY

Base	Composition	Melting Range/Point
Cocoa Butter	Mixed triglycerides of oleic, palmitic, stearic acids	34-35
Cotomar	Partially hydrogenated cottonseed oil	35
Dehydag	Hydrogenated fatty alcohols and esters	
Base I		33-36
Base II		37-39
Base III	Glycerides of saturated fatty acids C_{12}-C_{18}	9 ranges
Fattibase	Triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostereate and polyoxyl stearate	35.5-37
Hexaride Base 95		33-35
Hydrokote 25	Higher melting fractions of coconut and palm kernel oil	33.6-36.3
Hydrokote 711		39.5-44.5
Hydrokote SP		31.1-32.3
Polybase	A homogenous blend of polyethylene glycols and polysorbate 80	60-71
S-70-XX95	Rearranged hydrogenated vegetable oils	34.4-35.6
S-070-XXA		38.2-39.3
Suppocire OSI	Eutectic mixtures of mono-, di-, tri-glycerides derived from natural vegetable oils. Each type having slightly different properties.	33-35
Suppocire OSIX		33-35
Suppocire A		35-36.5
Suppocire B		36-37.5
Suppocire C		38-40
Suppocire D		42-45
Suppocire DM		42-25
Suppocire H	As above but with addition of polyoxyethylated glycerides	36-37.5
Suppocire L		38-40
Tegester Triglyceride bases:	Specially prepared tryglycerides	
TG-95		32.2-34.5
TG-MA		34.5-36.0
TG-57	34.0-36.5	
Tween 61	Used alone or in combination Polyethylene glycol sorbitan monostearate	35-49
Wecobee FS	Triglycerides derived from coconut oil	39.4-40.5
Wecobee M		33.3-36
Wecobee R		33.9-35
Wecobee S		38-40.5
Wecobee SS		40-43
Wecobee W		31.7-32.8
Witepsol (Selected examples)	Triglycerides of saturated fatty acids C_{12}-C_{18} with varied portions of the corresponding partial glycerides	
H-5		35.2
H-12		32-33
H-15		33-35
H-19		34.8
H-85		42-44

Oil-Soluble Bases

Cocoa Butter, or Theobroma Oil, is an oleaginous base that softens at 30°C and melts at 34°C. It is a mixture of liquid triglycerides entrapped in a network of crystalline, solid triglycerides. Palmitic and stearic acids make up about half of the saturated fatty acids and oleic acid makes up the one unsaturated fatty acid. Cocoa butter contains four different forms, α, β, β', and γ with melting points of 22°, 34-35°, 28°, and 18°C, respectively. The β form is the most stable and is desired for suppositories. Cocoa butter will melt to form a

non-viscous, bland oil. However, it may leak from the body orifice as it is immiscible with body fluids. The lower melting point polymorphs eventually will convert to the more stable form over time. Chloral hydrate will decrease the melting point of cocoa butter. Cocoa butter suppositories will release best from molds if the molds are absolutely clean and dry and the cocoa butter has not been overheated. Otherwise, mold sticking may be a problem.

Hydrogenated Vegetable Oil Bases

Fattibase is a preblended suppository base that offers the advantages of a cocoa butter base with few of the drawbacks. It is composed of triglycerides derived from palm, palm kernel and coconut oils with self-emulsifying glyceryl monostearate and polyoxyl stearate used as emulsifying and suspending agents. It is stable with a low irritation profile, needs no special storage conditions, is uniform in composition and has a bland taste and controlled melting range. It exhibits excellent mold release characteristics and does not require mold lubrication. Fattibase is a solid with a melting point of 35-37°C, specific gravity of 0.890 at 37°C, is opaque-white and is free of suspended matter.

Wecobee bases are derived from palm kernel and coconut oils and the incorporation of glyceryl monostearate and propylene glycolmonostearate renders them emulsifiable. These bases exhibit most of the desirable features of cocoa butter but few of its shortcomings. They are stable and exhibit excellent mold release characteristics.

Witepsol bases number about 12 and are nearly white and almost odorless. Witepsol H 15 has a melting range and release characteristics similar to that of cocoa butter. They solidify rapidly in the mold and lubrication isn't necessary as the suppositories contract nicely. High melting point Witepsol bases can be mixed with low melting point Witepsol bases to provide a wide range of possible melting ranges, *i.e.*, 34-44°C. Since the Witepsol bases contain emulsifiers, they will absorb limited quantities of water. Examples of these and other bases are given in Table 1.

Water-Soluble Bases

The use of water soluble bases may result in some irritation because, as they take up water and dissolve, they may produce slight dehydration of the rectal mucosa. They are widely used, however, and release the drug by dissolving and mixing with the aqueous body fluids.

Polyethylene Glycol (PEG) suppository bases are the most popular in this class. They have the advantage in that the ratios of the low to the high molecular weight individual polythylene glycols can be altered to prepare a base with a specific melting point or one that will overcome the adverse characteristics of an excess of powder or liquid that must be incorporated into a suppository. Table 2 lists pertinent characteristics of various PEGs. PEG bases are listed as incompatible with silver salts, tannic acid, aminopyrine, quinine, ichthammol, aspirin, benzocaine, iodochlorhydroxyquin and sulfonamides. Sodium barbital, salicylic acid and camphor will crystallize out of polyethylene glycol suppositories. High concentrations of salicylic acid will soften polyethylene glycols and aspirin will complex with polyethylene glycols. Polyethylene glycol based suppositories may be irritating to some patients. Suppositories prepared with PEG should not be stored or dispensed in a polystyrene prescription vial as the polyethylene glycol will adversely interact with polystyrene. All PEG suppositories should be dispensed in glass or cardboard containers.

TABLE 2

CHARACTERISTICS OF SELECTED POLYETHYLENE GLYCOLS

Molecular in Weight Average (%)	Molecular Weight Range	Melting Range (°C)	Solubility water
300	285-315	-15- -8	100
400	380-420	4-8	100
600	570-630	20-25	100
1000	950-1050	37-40	80
1450	1300-1600	43-46	72
3350	3000-3700	54-58	67
4600	4400-4800	57-61	65
8000	7000-9000	60-63	63

Polybase is a pre-blended suppository base that is a white solid consisting of a homogeneous mixture of polyethylene glycols and polysorbate 80. It is a water-miscible base that is stable at room temperature, has a specific gravity of 1.177 at 25°C with an average molecular weight of 3440 and does not require mold lubrication.

Glycerin Bases: Glycerinated Gelatin suppositories, composed of 70% glycerin, 20% gelatin and 10% water, should be packaged in tight containers as they are hygroscopic. They are not recommended as a rectal suppository base as they may exert an osmotic effect and a defecation reflex. Glycerin base is now composed of glycerin (91%), sodium stearate (9%) and purified water (5%). These bases have been occassionally used for the preparation of vaginal suppositories.

PREPARATION METHODS/ TECHNIQUES

Suppositories can be prepared by hand molding, fusion, and compression. Extemporaneous preparation generally involves hand molding and fusion, even though compression could be used. Powders to be incorporated into suppositories should be in an impalpable form.

Hand molding requires considerable skill, but allows one to avoid heat, and is generally used with cocoa butter, which can easily be manipulated, shaped and handled at room temperature. The technique involves grating the cocoa butter, adding the active ingredient, mixing thoroughly utilizing either a mortar/pestle or a pill tile/spatula, pressing the mix together until it becomes solid again, shaping into a long cylinder the diameter of the suppository to be prepared, cutting into the desired length, rounding the tips, packaging and labeling. During the forming process with the hands, the material can be worked using plastic gloves, working through a filter paper or using corn starch or talc to decrease the tackiness of the cocoa butter.

Cold Compression is suitable for bases that can be formed into suppositories under pressure. It is especially appropriate for ingredients that are heat labile. Example bases that can be used for cold compression include a mixture of 6% hexanetriol-1,2,6 with polyethylene glycol 1450 and 12% polyethylene oxide polymer 4000.

Fusion involves the gentle heating of a base material followed by the addition of the active ingredients and any excipients with thorough mixing. The melt is poured into molds and the suppositories cooled. They are trimmed, packaged and labeled. Molds for urethral suppositories can be fashioned from straws, glass tubes, disposable plastic syringes or commercially available molds.

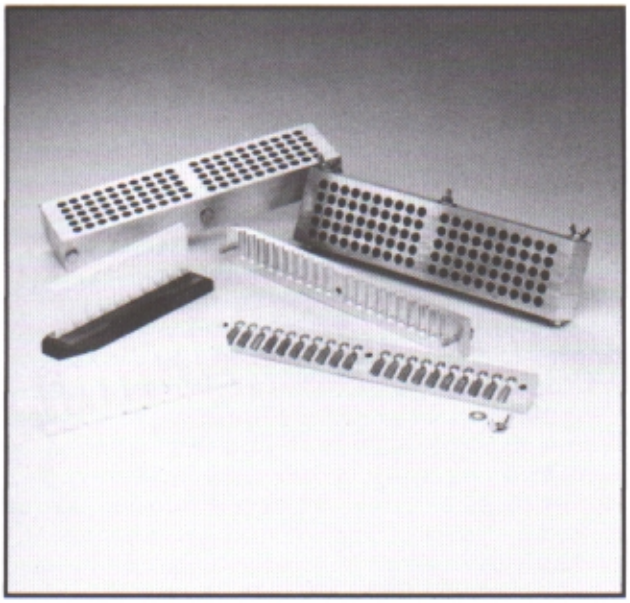
Mold Calibration (Preparation of blanks) for Fusion or Cold Compression

1. Prepare the suppository molds and confirm that the cavities are clean and dry.
2. Obtain and melt sufficient suppository base to fill 6-12 molds.
3. Pour the molds, cool and trim.
4. Remove the suppositories and weigh.
5. Divide the total weight by the number of blank suppositories prepared to obtain the average weight of each suppository for this

particular base.

6. Use this weight as the calibrated value for that specific mold using that specific lot of suppository base.

Five different steps involved in the preparation of suppositories include (1) mold preparation, (2) base preparation, (3) preparation of the active drug, (4) mixing and pouring, and (5) cooling and finishing.



Disposable and Reusable Suppository Molds.

1. Mold Preparation:

Molds should be CLEAN AND DRY at the start. Good suppository bases, if prepared and heated properly and if the mold is clean and dry, should require no lubricants. However, if it is absolutely necessary to use a lubricant, the molds should be lubricated properly. If a water soluble base is used, light mineral oil is a good lubricant. If an oil soluble base is used, glycerin or propylene glycol is a good lubricant. It is critical to use only enough lubricant to provide a very thin layer on the walls of the mold. Excessive lubricant will pool at the tip of the mold and result in deformed suppositories. Inadequate lubricant will result in suppositories that are difficult to remove. The lubricant can be applied by spraying or by using a cloth to which the lubricant has been added and wiping the molds. Some pharmacists have reported satisfactorily using a commercial vegetable spray for mold lubrication. The mold should be equilibrated at room temperature for the pouring procedure.

2. Base Preparation

The preparation of the base will be determined by the type of base that will be used. Cocoa butter must be grated for hand molding and may be grated if desired for the fusion method for melting on a water bath. If fusion is used, caution must be observed to not exceed about 34-35°C to prevent the formation of an unstable polymorph of the cocoa butter base, which may result in formation of the α form resulting in a low melting point suppository that would melt at room temperature and may stick to the mold. Cocoa butter should be melted only to form a fluid, mixable, pourable liquid that is still creamy-hazy in appearance. It should not be melted to a clear yellow state.

Polyethylene glycol bases can be melted using a water bath or the judicious use of direct heat to a temperature of approximately 60°C. PEG bases are very heat stable, but should not be heated excessively. They should be gently heated to just a few degrees above their melting range.

3. Preparation of the Active Drug

The drug should be comminuted to a uniform, small particle size to ensure even distribution of the drug throughout the base and to minimize settling in the melt. The best source of ingredients for the extemporaneous compounding of suppositories is the pure drug powder. If pure powder is unavailable, commercial dosage forms such as injections, tablets, capsules, etc. can be used. If these dosage forms are used, the presence of any excipients must be

considered as to the influence they might have on the physico-chemical properties and stability of the finished product, since it is rarely feasible to extract the active drug from the dosage forms. In many cases, depending upon the solubility of the drug and the excipients, it may be possible simply to mix the dosage form with a solvent (Alcohol 95%) and filter, collect the filtrate, dry and use the resulting active drug powder.

In general, a maximum quantity of excipient to be incorporated is about 30% of the blank weight of the suppository. For example, for a 2 mL disposable mold, the maximum excipient would be about 600 mg.

Liquids may occupy too much volume to be easily incorporated and the vehicles may not be compatible with selected suppository bases. Tablets and capsules may contain excessive powder that may result in suppositories that are too brittle. If a large quantity of liquid is to be incorporated into an oily suppository base, it may be necessary to prepare a water-in-oil emulsion. This can be done by incorporating 10% wool fat or 2% cholesterol in up to 15% aqueous solutions in cocoa butter, or utilizing one of the modern triglyceride vegetable oil bases like Fattibase, Wecobee, Witepsol, etc. For PEG bases, a higher percent of the higher molecular weight PEGs can be used to accommodate the liquid.

Other considerations in the formulation of extemporaneously prepared suppositories will be discussed in Part II.

4. Mixing and pouring

The drug is either mixed directly into the base or is "wetted" prior to incorporation. Mixing can be done using a stirring rod or a magnetic stirring setup. Sufficient time is utilized for the mixing process to obtain a uniform distribution of the drug but not too long to result in either drug or base deterioration. When the melt is ready, it may be poured into the mold, which has been brought to room temperature and situated with the openings on top. A cold or frozen mold should not be used as fractures and fissures may occur throughout the suppository. Starting at one end of the mold, each cavity is slowly filled, being careful not to incorporate air bubbles into the suppository, and a small excess of material allowed to "build up" on the top of the mold and the next cavity is filled, etc. Once pouring is initiated, do not stop the pouring process until all the molds have been filled; this will prevent layering in the suppositories. A 10 mL syringe, or other suitable size, can be filled with the melt and used to fill the molds if one is careful not to let the melt cool too rapidly. The mold should be at room temperature so the melt does not prematurely solidify as it is poured down the sides of the mold cavity. Premature solidification could result in unfilled mold tips and deformed suppositories. If disposable molds are used, PEG melts should be poured at a minimum temperature since some molds may collapse at about 70°C. If the melt is poured around 60°C, this should not occur. Other bases should be kept near their respective melting temperatures.

5. Cooling and finishing

The molds can be allowed to set for 15-30 minutes at room temperature followed by refrigeration for an additional 30 minutes, if necessary. Excess material is removed from the top of the mold (the back of the suppository). This can be easily accomplished by dipping the blade of a stainless steel spatula in a beaker of warm water and using it to cut off the excess material. This will also serve to place a nice smooth surface on the suppository. Alternatively, a razor blade works very well. Suppositories can be removed carefully from the molds, packaged and labeled. If the suppository mold is still cool, the suppositories should be slightly contracted which will effect easier removal from the mold. Individual suppositories can be wrapped using foil wrappers, if desired. Wrapping, though not necessary, does present an elegant product to the patient.

PACKAGING

Suppositories are best individually wrapped or dispensed in a disposable mold in which they are prepared. If suppositories are not packaged properly, they may become deformed, stained, broken or chipped. Foil suppository wrappers are available in various colors for the compounding pharmacist. Wrapped

(Continued on page 6)

suppositories are usually placed in a wide-mouth container, slide, folding or partitioned boxes for dispensing to the patient. Suppositories that are dispensed in disposable molds are often placed in cardboard sleeves or plastic bags, labeled and dispensed.

STORAGE/LABELING

Suppositories must be protected from heat and may be stored in a refrigerator. They generally should not be frozen. Glycerin and polyethylene glycol-based suppositories should be protected from moisture, as they tend to be hygroscopic.

It is usually a good idea, if the suppositories are wrapped, to add to the label, "Unwrap, moisten and insert. . ." or "Unwrap and insert. . .".

Administration of medication rectally affords an opportunity for the pharmacist to provide pharmaceutical care for patients, who often have an aversion to this dosage form. This includes education of patients in proper storage, handling, preparation, and use of suppositories.

EQUIPMENT REQUIRED

Suppository molds, reusable or disposable
Water bath, electric heater
Thermometer
Beakers
Heat-resistant gloves
Stirring rods
Tongs
Grater
Suppository foil wraps

CONSIDERATIONS IN PREPARING SUPPOSITORIES

1. Calibrate the suppository mold to be used before calculating for the total batch.
2. Calculate a 10% overage of materials to allow for loss during preparation and over-pouring.
3. The molds should be CLEAN AND DRY before use.
4. Determine whether or not lubricants should be used: this is generally dictated by the characteristics of the base.
5. Suppositories or suppository molds should not be placed in a refrigerator or freezer prior to pouring.
6. Slightly overfill each cavity in a suppository mold to allow for contraction upon cooling. When using some disposable molds, it is necessary to determine the extent of fill from the blank. Some molds are also marked with lines for reproducible filling.
7. Once pouring is initiated, do not stop.
8. The molds should be at room temperature during the pouring process.

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