Compounding Suppositories, Part I

By Loyd V. Allen, Jr., Ph.D., R.Ph.

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 homogeneous, 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 pesaries, are available in various shapes, e.g., ovoid oglobular, and weigh approximately 3-5 G each. Extemporeously prepared vaginal suppositories utilizing water-soluble bases, such as polyethylene glycol or glycérinated 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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TABLE 1

<table>
<thead>
<tr>
<th>Base</th>
<th>Composition</th>
<th>Melting Range/Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocoa Butter</td>
<td>Mixed triglycerides of oleic, palmitic, stearic acids</td>
<td>34-35</td>
</tr>
<tr>
<td>Cotonol</td>
<td>Partially hydrogenated cottonseed oil</td>
<td>35</td>
</tr>
<tr>
<td>Dehydridge Base I</td>
<td>Hydrogenated fatty alcohols and esters</td>
<td>35-36</td>
</tr>
<tr>
<td>Dehydridge Base II</td>
<td></td>
<td>37-39</td>
</tr>
<tr>
<td>Dehydridge Base III</td>
<td>Glycerides of saturated fatty acids C16-C18</td>
<td>9 ranges</td>
</tr>
<tr>
<td>Fattibase</td>
<td>Triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostearate and polyoxyethylene glycol</td>
<td>35.5-37</td>
</tr>
<tr>
<td>Hexaride Base 95</td>
<td></td>
<td>35-35</td>
</tr>
<tr>
<td>Hydrokote Z5</td>
<td>Higher melting fractions of coconut and palm</td>
<td>33.6-38.5</td>
</tr>
<tr>
<td>Hydrokote 711</td>
<td>kernel oil</td>
<td>35.5-44.5</td>
</tr>
<tr>
<td>Hydrokote SP</td>
<td></td>
<td>31.1-32.3</td>
</tr>
<tr>
<td>Polybase</td>
<td>A homogenous blend of polyethylene glycols and polyoxyethylene glycol</td>
<td>60-71</td>
</tr>
<tr>
<td>S-70-X395</td>
<td>Rearranged hydrogenated vegetable oils</td>
<td>34.4-35.6</td>
</tr>
<tr>
<td>S-GID-K-XA</td>
<td></td>
<td>38.2-39.9</td>
</tr>
<tr>
<td>Suppocire OSI</td>
<td>Eutectic mixtures of mono-, di-, tri-glycerides derived from natural vegetable oils. Each type having slightly different properties.</td>
<td>36-35</td>
</tr>
<tr>
<td>Suppocire GBX</td>
<td></td>
<td>36-37.5</td>
</tr>
<tr>
<td>Suppocire A</td>
<td></td>
<td>36-40</td>
</tr>
<tr>
<td>Suppocire B</td>
<td></td>
<td>42-44</td>
</tr>
<tr>
<td>Suppocire C</td>
<td></td>
<td>42-25</td>
</tr>
<tr>
<td>Suppocire D</td>
<td></td>
<td>36-37.5</td>
</tr>
<tr>
<td>Suppocire DM</td>
<td></td>
<td>36-40</td>
</tr>
<tr>
<td>Suppocire H</td>
<td>As above but with addition of polyoxyethylated</td>
<td>36-37.5</td>
</tr>
<tr>
<td>Suppocire L</td>
<td>glycerides</td>
<td>36-40</td>
</tr>
<tr>
<td>Tegester Triglycerides bases</td>
<td></td>
<td>36-37.5</td>
</tr>
<tr>
<td>TG-95</td>
<td>Specially prepared triglycerides</td>
<td>36-40</td>
</tr>
<tr>
<td>TG-MA</td>
<td></td>
<td>34.0-36.5</td>
</tr>
<tr>
<td>TG-57</td>
<td>Used alone or in combination</td>
<td>34.0-36.5</td>
</tr>
<tr>
<td>Tween 81</td>
<td>Polyethylene glycol with sorbitan monostearate</td>
<td>36.4-40.5</td>
</tr>
<tr>
<td>Wecobee FS</td>
<td>Triglycerides derived from coconut oil</td>
<td>36.4-40.5</td>
</tr>
<tr>
<td>Wecobee M</td>
<td></td>
<td>33.3-36</td>
</tr>
<tr>
<td>Wecobee R</td>
<td></td>
<td>33.9-35</td>
</tr>
<tr>
<td>Wecobee S</td>
<td></td>
<td>38-40</td>
</tr>
<tr>
<td>Wecobee SS</td>
<td></td>
<td>40-43</td>
</tr>
<tr>
<td>Wecobee W</td>
<td></td>
<td>31.7-32.8</td>
</tr>
<tr>
<td>Witexos ()</td>
<td>Triglycerides of saturated fatty acids C16-C18 with</td>
<td></td>
</tr>
<tr>
<td>(Selected examples)</td>
<td>varied portions of the corresponding partial</td>
<td>34.0-44.4</td>
</tr>
<tr>
<td>H-5</td>
<td></td>
<td>34.0-44.4</td>
</tr>
<tr>
<td>H-12</td>
<td></td>
<td>34.0-44.4</td>
</tr>
<tr>
<td>H-15</td>
<td></td>
<td>34.0-44.4</td>
</tr>
<tr>
<td>H-19</td>
<td></td>
<td>34.0-44.4</td>
</tr>
<tr>
<td>H-85</td>
<td></td>
<td>34.0-44.4</td>
</tr>
</tbody>
</table>

Oil-Soluble Bases

Cocoa Butter, or Theobroma Oli, 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 monoestersate and polyoxyx steareate 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 monoestersate 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.

**Polystyrene 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 polyethylene 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, benzoic acid, 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.

**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 occasionally 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 grasping the cocoa butter, adding the active ingredient, mixing thoroughly utilizing either a mortar/pestle or a pill tile/epistula, 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% hexaneol-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. Rods 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

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

**TABLE 2**

**CHARACTERISTICS OF SELECTED POLYETHYLENE GLYCOLS**
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.

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 Fatibase, Wecooee, Witresol,
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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