



# Secundum Artem

*Current & Practical Compounding  
Information for the Pharmacist.*

## Compounding Suppositories, Part II

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This is the second in a two-part series on the extemporaneous compounding of suppositories. Part I included preparation methods and techniques. This part includes physicochemical considerations, stability and calculations discussions.

Suppositories have the potential for enhanced utilization as a dosage form in today's pharmaceutical armamentarium. For example, extemporaneously compounded suppositories containing metoclopramide, haloperidol, dexamethasone, diphenhydramine and benzotropine can be administered prophylactically to effectively control severe nausea and vomiting; salbutamol can be administered rectally for long-term prophylactic treatment of asthma and a prolonged release morphine alkaloid suppository for chronic pain has been introduced. These, and other aspects of suppositories will be discussed here.

### PHYSICOCHEMICAL CONSIDERATIONS

In general, when formulating suppositories, the pharmacist should consider the following questions:

1. Is the desired effect to result from systemic or local use?
2. Is the route of administration rectal, vaginal or urethral?
3. Is a rapid or a slow and prolonged release of the medication desired?

Drugs for local effect may include the treatment of

hemorrhoids, local anesthetics, antiseptics, antibiotics and antifungals. Drugs for systemic effect include analgesics, antiasthmatics, antiemetics and others.

A drug that does not release its medication within six hours may not be completely utilized and may be expelled by the patient. The selection of a suppository base is dependent upon a number of physicochemical variables, including the solubility characteristics of the drug. To obtain maximum release of the drug from the base, a principle of opposite characteristics can be employed. For example, water soluble drugs can be placed in fat-soluble bases, fat-soluble drugs can be placed in water-soluble bases.

Fat soluble bases, e.g. cocoa butter, melt quickly in the rectum to release the drug whereas polyethylene glycol bases must dissolve in mucosal fluids, a process which may take longer. If higher molecular weight polyethylene glycols are used, the time for dissolution is extended. Moistening with warm water immediately prior to insertion facilitates not only insertion but also dissolution. Drug release rate requirements are important in the selection of the suppository base.

Factors such as the presence of water, hygroscopicity, viscosity, brittleness, density, volume contraction, special problems, incompatibilities, rate of drug release, pharmacokinetics and bioequivalence will be discussed here.

### Presence of Water

The presence of water, or using water to assist in incorporating an active drug, generally should be avoided in the preparation of suppositories. Water may accelerate the oxidation of fat, increase the degradation rate of many drugs, enhance reactions between the drug and other components in the

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suppository, support bacterial/fungal growth and require the addition of bacteriostatic agents. Further, if the water evaporates, the dissolved substances may crystallize.

## Hygroscopicity

Glycerin and polyethylene glycol-containing suppositories are hygroscopic. The rate of moisture change is dependent on the chain length of the molecule, as well as on the temperature and humidity of the environment. Polyethylene glycols with molecular weights greater than 4,000 have less tendency to be hygroscopic than the lower weight PEGs.

## Viscosity

Viscosity considerations are important in the preparation of the suppositories and in the release of the drug. If the viscosity of a base is low, it may be necessary to add a suspending agent such as silica gel to keep the drug uniformly dispersed until solidification. During preparation of the suppository, the melt should be handled at the lowest temperature possible to maintain high viscosity and should be stirred constantly. If the viscosity of the base, after administration and when in the body, is very high, the release rate of the drug may be slowed due to a decrease in the diffusion of the drug through the base to reach the mucosal membrane for absorption.

Approaches that have been utilized to increase viscosity would be to increase the fatty acid chain length of compounds in the base. For example, increased C-16 and C-18 mono- and di-glycerides can be added to the base. The addition of about 2% aluminum monostearate will also increase the viscosity of a fatty base; cetyl, stearyl and myristyl alcohols and stearic acid can also be used in concentrations of about 5%.

## Brittleness

Brittle suppositories can be difficult to handle, wrap and use. Cocoa butter suppositories generally are not brittle unless there is a high percentage of solids present. When the percentage of nonbase materials exceeds about 30%, brittleness can result. Synthetic fat bases with high stearate concentrations or those that are highly hydrogenated are usually more brittle. Fracturing of fat and cocoa butter suppositories may also result from shock cooling, which may be prevented by ensuring that the temperature of the mold is as close to the melted base temperature as possible. Avoid placing suppositories in a freezer, which would also cause shock cooling. Also, the addition of a small quantity (usually less than 2%) of Tween 80, Tween 85, fatty acid monoglycerides, castor oil, glycerin or propylene glycol will make these bases more pliable and less brittle.

## Density

Density of the incorporated materials is important in the determination of the weight of the individual suppositories. This is covered in the section on dosage replacement. The density of insoluble powders is important because, if the density is too great, there will be a tendency for the suspended materials to settle and stratify in the molds, resulting in a poor appearance and portions of the suppository may be more brittle than the rest.

## Volume Contraction

Bases, excipients, and active ingredients generally will occupy less space at lower temperatures than at higher temperatures. When a hot suppository melt is placed in a mold it usually will have a tendency to contract in size during cooling. This can result in a good release of the suppository from the mold but may also result in formation of such a cavity at the back, or open end, of the suppository mold. The presence of such a cavity is undesirable and can be corrected by allowing the melt to approach its congealing temperature immediately prior to pouring into the molds. It is advisable to pour a small excess at

the open end of the mold to accommodate slight contraction during cooling. Scraping with a blade or spatula will remove the excess after solidification (be careful not to remove mold metal).

### Special Problems

*Vegetable extracts* can be moistened by levigation with a small amount of melted base prior to incorporation. This will make it easier to distribute the active drug throughout the base.

*Hard, crystalline materials* can be incorporated either by pulverizing to a very fine state of subdivision, or by dissolving in a small quantity of solvent and taking the solution up into the base. If the material is water-soluble, an aqueous solvent and polyethylene glycol base would be appropriate. Alternatively, if the material is oil-soluble and an oily solvent must be used, wool fat could be used to take up the solution for incorporation into the suppository base.

*Liquid ingredients*, when mixed with an inert powder such as starch, will be less fluid, making them easier to handle, and the subsequent suppository will hold together better.

*Excess powder* may be incorporated into a suppository base in different ways, depending upon the base used. For oil-miscible bases, a few drops of a bland oil like mineral oil may be used. When incorporating excess powder into water soluble bases, the ratio of low- to high-melting-point ingredients may be varied. For example, since the addition of extra powders will make the suppository harder, a higher percentage of low molecular weight polyethylene glycols would help prepare a suppository of the proper density.

### Incompatibilities

A number of ingredients are incompatible with polyethylene glycol bases, and include benzocaine, iodochlorhydroxyquin, sulfonamides, ichthammol, aspirin, silver salts and tannic acid. Other materials reported to have a tendency to crystallize out of polyethylene glycol include sodium barbital, salicylic acid and camphor.

### Rate of Drug Release

The time for liquefaction of a hydrogenated vegetable oil or cocoa butter based suppository is approximately 3-7 minutes, for a glycerinated gelatin suppository about 30-40 minutes and for a polyethylene glycol suppository 30-50 minutes.

The release of drug and onset of drug action is dependent upon:

1. liquefaction of the suppository base
2. dissolution of active drug
3. diffusion of drug through mucosal layers

The following table provides a general summary of the relationship of drug release, the drug and the suppository base.

Oil soluble drug—oily base
<i>Slow release, poor escaping tendency</i>
Water soluble drug—oily base
<i>Rapid release</i>
Oil soluble drug—water miscible base
<i>Moderate release rate</i>
Water miscible drug—water miscible base
<i>Rapid release. . . based on diffusion. . . all water soluble</i>

A recent study described the evaluation of a Novata BBC-based, prolonged-release morphine alkaloid suppository that maintains plasma morphine levels for at least 7 hours.<sup>1</sup> This formulation is useful for patients who cannot tolerate oral morphine and for those where a longer-acting preparation is advisable. In this study comparing different morphine forms and bases, the release of morphine HCl from a polyethylene glycol base was very rapid, as expected, and is consistent with the high water solubility of morphine hydrochloride and PEG. The low water solubility of morphine alkaloid did not influence the release of morphine from a morphine alkaloid/PEG suppository, which is consistent with the release behavior of other lipophilic drugs in a hydrophilic base. The release of a water-insoluble drug from a lipid base depends on diffusion through the lipid to the lipid-water interface whereas release of a water-soluble (suspended) drug will depend on mechanical transportation (e.g. sedimentation) to the lipid-water interface. The latter rate will increase with particle size of the drug. It is thought that the release of a water-soluble drug from an oily base is primarily dependent on the dissolution rate of the drug in water.

### Pharmacokinetics

Factors affecting absorption include, among other things, anorectal or vaginal physiology, suppository vehicle, absorption site pH, drug pKa, degree of ionization and lipid solubility. In some instances, suppositories have been demonstrated to be advantageous over orally administered medications. For example, in a study of rectally administered salbutamol [albuterol-Ed.] using a Witepsol H15 base, significantly higher salbutamol concentrations were obtained soon after dosing as compared with oral administration.<sup>2</sup> The  $C_{max}$  following rectal administration was 17.9 ng/mL (17.0 ng/mL for oral administration), the  $t_{max}$  0.67 h (1.5 h for oral administration) and the AUC 98.2 ng/mL/h (100 ng/ml/h for oral administration). An advantage to rectally administered salbutamol is that of reducing first-pass metabolism. The authors conclude that rectal administration of salbutamol may be a useful method for long-term prophylactic treatment of asthma. At equivalent doses, it gives almost the same salbutamol level in serum but rather

stronger effects compared with oral administration.

### Bioequivalence Examples

The influence of administration route on the biopharmaceutical behavior of etodolac, a nonsteroidal agent with anti-inflammatory and analgesic activity, has been studied. The blood levels obtained when the same dose of etodolac was administered orally (tablets) and rectally (suppositories) were determined. The results indicated that the two routes of administration are bioequivalent and that the rectal route is an alternative administration route for etodolac.<sup>3</sup>

Some prodrugs may degrade before absorption through the gastrointestinal tract. The use of cyclodextrins to improve the pharmaceutical properties of drugs has been well-documented in the pharmaceutical literature.<sup>4</sup> The rectal bioavailability of selected prodrugs has been enhanced by incorporating the prodrug with a cyclodextrin in a suppository dosage form.

Single dosing of fluconazole has been demonstrated to be equivalent to once-daily dosing for 3 days of terconazole (80 mg each). In the case of late evaluation of the infection, the cure rates for the oral and vaginal administration was 75 and 100% respectively. The terconazole was contained in a cocoa butter base.<sup>5</sup>

### STABILITY

Suppositories prepared without the aid of water are reasonably stable. The USP description of stability considerations for suppositories includes observations for excessive softening and evidence of oil stains on packaging materials. It may be necessary for the pharmacist to examine individual suppositories closely by removing any wrappers used for their packaging.

The variation in weight in prepared suppositories should be within  $\pm 5\%$ . According to the USP, excessive softening is the major indication of instability in suppositories. Some suppositories may dry out, harden or shrivel. As a general rule, the USP recommends storage in a refrigerator, unless otherwise indicated.

Cocoa butter instability during preparation may be manifest as the formation of polymorphs which may be liquid at room temperature. This is most easily avoided by substituting an appropriate hydrogenated vegetable oil base for the cocoa butter [see *Secundum Artem, Compounding Suppositories, Part I*, Vol. 3, No. 3 - Ed.]. If necessary, fatty materials of higher melting points such as white wax or paraffin can be added to low melting point fatty bases or cocoa butter to increase formulation melting points. However, caution must be observed to prepare a suppository that will melt when administered. Melting point can be checked easily by placing a sample suppository into a beaker of water that has been heated to 37°C. If

it doesn't melt, the formulation should not be used for patient therapy.

If water is incorporated into an oily base using an emulsifying agent (nonionic surfactant, wool fat, etc.), the product may become rancid and will not be as stable as the same drug added to a PEG-based suppository containing water.

If the stability of a product is unknown, an arbitrary expiration date of 30 days has been suggested and it is best to recommend refrigeration of extemporaneously compounded suppositories to optimize both drug and base stability.

### Packaging

Suppositories are best individually wrapped or dispensed in the disposable molds 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 suppositories are usually placed in wide-mouth containers or in 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 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. . .".

### CALCULATIONS

#### Dosage Replacement

It has been stated that if the quantity of active drug is less than 100 mg, then the volume occupied by the powder is insignificant and need not be considered. This is usually based on a 2 gram suppository weight. Obviously, if a suppository mold less than 2

gram weight is used, the powder volume may need to be considered. 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. Density factors for a selected number of ingredients are shown in Table 1.

Alum . . . . .	1.7	Morphine HC1 . . . . .	1.6
Aminophylline . . . . .	1.1	Opium . . . . .	1.4
Aspirin . . . . .	1.3	Paraffin . . . . .	1.0
Barbital . . . . .	1.2	Peruvian Balsam . . . . .	1.1
Belladonna extract . . . . .	1.3	Phenobarbital . . . . .	1.2
Benzoic Acid . . . . .	1.5	Phenol . . . . .	0.9
Bismuth carbonate . . . . .	4.5	Potassium bromide . . . . .	2.2
Bismuth salicylate . . . . .	4.5	Potassium iodide . . . . .	4.5
Bismuth subgallate . . . . .	2.7	Procaine . . . . .	1.2
Bismuth subnitrate . . . . .	6.0	Quinine HC1 . . . . .	1.2
Boric Acid . . . . .	1.5	Resorcinol . . . . .	1.4
Castor oil . . . . .	1.0	Sodium bromide . . . . .	2.3
Chloral hydrate . . . . .	1.3	Spermaceti . . . . .	1.0
Cocaine HC1 . . . . .	1.3	Sulfathiazole . . . . .	1.6
Digitalis leaf . . . . .	1.6	Tannic acid . . . . .	1.6
Glycerin . . . . .	1.6	White wax . . . . .	1.0
Ichthammol . . . . .	1.1	Witch hazel fluidextract . . . . .	1.1
Iodoform . . . . .	4.0	Zinc oxide . . . . .	4.0
Menthol . . . . .	0.7	Zinc sulfate . . . . .	2.8

Two different methods of calculating the quantity of base that the active medication will occupy will be illustrated here: (1) Dosage Replacement Factor, and (2) Density Factor-Paddock Method.

#### Determination of the Dosage Replacement Factor<sup>6</sup>

$$f = \frac{100 (E - G) + 1}{(G)(X)}$$



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where E = the weight of the pure base suppositories  
 G = the weight of suppositories with X% of the active ingredient

Cocoa butter is arbitrarily assigned a value of 1 as the standard base. Examples of other dosage replacement factors are shown in Table 2.

TABLE 2	
Dosage replacement factors for selected drugs.	
Boric Acid . . . . .	0.67
Phenobarbital . . . . .	0.81
Mild silver protein . . . . .	0.61
Balsam Peru . . . . .	0.83
Bismuth subgallate . . . . .	0.37
Bismuth subnitrate . . . . .	0.33
Camphor . . . . .	1.49
White/yellow wax . . . . .	1.0
Spermaceti . . . . .	1.0
Chloral hydrate . . . . .	1.67
Quinine HC1 . . . . .	0.83
Ichthammol . . . . .	0.91
Castor oil . . . . .	1.0
Phenol . . . . .	0.9
Procaine HC1 . . . . .	0.8
Resorcin . . . . .	0.71
Zinc oxide . . . . .	0.15-0.25

The dosage replacement factor equation can be used both for calculating the dosage replacement factor (see Table 2) and for calculating the weight of the prepared suppositories as illustrated here.

Ex. Prepare a suppository containing 100 mg of phenobarbital (f=0.81) using cocoa butter as the base. The weight of the pure cocoa butter suppository is 2.0 gm. Since 100 mg of phenobarbital is to be contained in an approximately 2.0 gm suppository, it will be about 5% phenobarbital. What will be the total weight of each suppository?

$$0.81 = \frac{100(2 - G) + 1}{(G)(5)}$$

$$G = 2.019 \text{ gm}$$

*Determination of Density Factor—Paddock Method*

1. Determine the average blank weight, A, per mold using the suppository base of interest.
2. Weigh the quantity of suppository base necessary for 10 suppositories.
3. Weigh 1.0 gm of medication.  
The weight of medication per suppository, B, is then equal to 1 gm/10 supp = 0.1 gm/supp.
4. Melt the suppository base and incorporate the medication, mix, pour into molds, cool, trim and remove from the molds.
5. Weigh the 10 suppositories and determine the average weight C.
6. Determine the Density Factor as follows:

$$\text{Density Factor} = \frac{B}{A - C + B}$$

where A=average weight of blank.  
 B=weight of medication per suppository.  
 C=average weight of medicated suppository.

7. Take the weight of the medication that is required for each suppository and divide by the density factor of the medication to find the replacement value of the suppository base.
8. Subtract this quantity from the blank suppository weight.
9. Multiply by the number of suppositories required to obtain the quantity of suppository base required for the prescription.
10. Multiply the weight of drug per suppository by the number of suppositories required to obtain the quantity of active drug required for the prescription.

Ex: Prepare twelve acetaminophen 300 mg suppositories using cocoa butter where the average weight of the cocoa butter blank is 2 gm and the average weight of the medicated suppository is 1.8 gm.

$$DF = \frac{0.3}{2 - 1.8 + 0.3} = 0.6$$

Step 7: (0.3 gm)/0.6 = 0.5 (the replacement value of the base)

Step 8: 2.0 gm - 0.5 gm = 1.5 gm



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Step 9: #12 X 1.5 gm = 18 gm cocoa butter required

Step 10: #12 X 0.3 gm = 3.6 gm acetaminophen

Determination of occupied volume:

1. Determine the average weight per mold (blank) using the suppository base of interest.
2. Weigh the quantity of suppository base necessary for 10 suppositories.
3. Divide the density of the active drug by the density of the suppository base to obtain a ratio.
4. Divide the total weight of active drug required for the total number of suppositories by the ratio obtained in step 3. This will give the amount of suppository base displaced by the active drug.
5. Subtract the amount obtained in step 4 from the total weight of the prescription (number of suppositories multiplied by the weight of the blanks) to obtain the weight of suppository base required.
6. Multiply the weight of active drug per suppository times the number of suppositories to be prepared to obtain the quantity of active drug required.

Ex: Prepare ten suppositories each containing 200 mg of a drug with a density of 3.0. The suppository base has a density of 0.9 and a

prepared blank weighs 2.0 gm. Using the "determination of occupied volume" method, how would you prepare the requested suppositories?

These steps refer to those outlined above:

1. The average weight per mold is 2.0 gm.
2. The quantity required for 10 suppositories would be 2 gm X 10 supp = 20 gm.
3. The density ratio is 3.0/0.9 = 3.3.
4. The amount of suppository base displaced by the active drug is 2.0 gm./3.3 = 0.6 gm.
5. The weight of the suppository base required is 20 gm. - 0.6 gm. = 19.4 gm.
6. The quantity of active drug required is 0.2 gm. X 10 = 2.0 gm.

The required weight of the suppository base is 19.4 gm. and the active drug is 2 gm.

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