VOLUME 3 NUMBER 2

Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

Compounding Topical Dosage Forms: Ointments, Creams, Pastes and Lotions

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

INTRODUCTION

Topical dosage forms have been used throughout the history of man with ointments being mentioned numerous times in the Bible. Salves, ointments, pastes, compresses, etc. are examples of such dosage forms used primarily to deliver a drug topically to the skin for various disorders.

There are so many types of topicals that several issues of Secundem Artem will be required to discuss all of them. This issue will cover ointments, pastes and creams and some of the general attributes and preparation methods for each. Additional issues will be devoted to gels, medication sticks, suppositories, topical lotions (emulsions and suspensions), etc.

There are three main functions of topically applied pharmaceuticals. These are (1) to protect the injured areas from the environment and permit rejuvenation of the skin, (2) to provide skin hydration, or an emollient effect, and (3) to provide a means of conveying a medication to the skin for a specific effect, either topically or systemically.

From semisolid dosage forms, the amount of drug that penetrates into the skin is a function of the (a) amount of pressure and vigor of rubbing, (b) surface area covered, (c) condition of the skin, (d) base used, and (e) use of occlusive dressings.

DEFINITIONS AND CHARACTERISTICS

Ointments are semisolid preparations intended for external application to the skin or mucous membranes which soften or melt at body temperature; they should spread easily and be non-gritty.

Pastes are thick, stiff ointments that ordinarily do not flow at body temperature, and therefore serve as protective coatings over the areas to which they are applied; they usually contain at least 20% solids.

Creams are opaque, soft solids or thick liquids intended for external application, consisting of medicaments dissolved or suspended in water soluble or vanishing cream bases. They are of the water-in-oil or oil-in-water type. The term "cream" is most frequently applied to soft, cosmetically acceptable types of preparations.

Lotions are fluid emulsions or suspensions for external application. They include both suspension (Calamine Lotion) and oil-in-water emulsion dosage forms. This current discussion will apply to the oil-in-water emulsions.

The decision to use an ointment, paste, cream or lotion depends not only upon the considerations of degree of skin penetration of the medication that is desired, but also upon the characteristics of the skin to which the product is being applied. For example, ointments (oleaginous bases) are generally used on dry, scaly lesions as their emollient properties will aid in rehydrating the skin and they stay on longer. Pastes are generally applied to an area that is intended to be protected. Creams are usually applied to moist, weeping lesions as they have somewhat of a "drying" effect in that the fluids will be miscible with the aqueous external phase of the creams. Lotions are generally applied to intertriginous areas, *i.e.*, where skin rubbing occurs as between fingers, thighs, under

Salves, ointments, pastes and compresses are dosage forms used primarily to deliver a drug topically.

Skin penetration of a topically applied drug depends on many physical factors.

Loyd V. Allen, Jr., Ph.D., University of Oklahoma College of Pharmacy, Oklahoma City, OK 73190.

the arms, etc., as they have a lubricating effect. Based on these considerations, one should not substitute one form for the other without the consent of the prescribing physician.

Topical bases are classified according to two different methods: (1) the degree of skin penetration, and (2) the relationship of water to the composition of the base. These are both summarized in Tables 1 (below) and 2 (see next page).

TABLE 1

Classification based on skin penetration.

Base Type	Skin Penetration	Example Bases
Epidermic	None or very little	Oleaginous
Endodermic	Into the dermis	Absorption
Diadermic	Yes, into and through the skin	Emulsion, Water Soluble

Epidermic refers to the external layer of the skin or epidermis.
Endodermic refers to the internal layer of the skin or epidermis.
Diadermic refers to going through the skin.

Ingredients in topical preparations, in addition to the active drug, may include stiffeners, oleaginous components, aqueous components, emulsifying agents, humectants, preservatives and antioxidants.

PREPARATION

Most of the techniques discussed here will be directed towards the incorporation of ingredients into prepared bases. If a base must be prepared from individual ingredients, the principles previously discussed will apply as well as those discussed below.

Oleaginous Bases

White Petrolatum and White Ointment would be examples of bases in this category. An example of an extemporaneously prepared prescription using an oleaginous base would be 5% sulfur in white petrolatum.

These ointments can be prepared very nicely on a pill tile with a spatula. The preparation of an oleaginous-based ointment is rather simple. After obtaining the desired quantities of the individual ingredients, the powders are finely pulverized. This may include levigation[1] with a small quantity of the base. It may be advantageous to melt this small quantity of base to make levigation easier or to use mineral oil. The remainder of the ointment vehicle is added by geometric dilution.[2]

When preparing a base containing some high melting point ingredients, it is necessary to use heat. Generally, water baths or direct heat are employed. Water baths are used for low temperature applications and direct heat for preparations requiring higher temperatures. The use of direct heat (hot plate) requires caution to prevent scorching the product. Microwaves can be used to heat the product directly or to heat the hot water for making a water bath. If heating the product, a microwave with a carousel should be used to minimize "hot spots" that normally occur. These "hot spots" are due to uneven heating and can result in areas of very high temperatures. The materials with the highest melting points are added to a container placed on a heat source and heated until melting occurs. The ingredients are then added in order

1. Levigation is "to make smooth": it is the process of first preparing a paste by the addition of a suitable nonsolvent to the solid material-See Remington's Practice of Pharmacy.
2. Geometric dilution involves the addition of a portion of base approximately equal to that of the active drug/levigating agent and mixing. This is followed by adding an amount of base that is equivalent to the already-mixed portion and increasing the quantity of base similarly with each addition.

of decreasing melting point and thoroughly mixed. The product is cooled with occasional stirring and packaged and labeled. While cooling, it is best not to cool it too rapidly as the product may become lumpy.

Pastes are often prepared utilizing oleaginous bases and are more easily prepared using heat. This allows for an easier introduction of the high percentage of powders into the base but it is imperative that the product be thoroughly stirred during the cooling process to prevent settling of the solids.

Absorption Bases

If a water-in-oil emulsifying agent is added to an oleaginous base, then an absorption base is formed. These bases can absorb water and examples include Hydrophilic Petrolatum, Aquabase™[1] and Aquaphor™[2]. Example prescriptions include one percent hydrocortisone incorporated into Aquabase and 3% crude coal tar/3% Polysorbate 80 in Aquabase.

The preparation of ointments using an absorption base can use the same techniques as with an oleaginous base, *i.e.*, incorporation directly into the base or with the use of heat, but there are other options, depending upon the material(s) to be incorporated. For example, if incorporating a water-insoluble powder, levigation as described above can be used. If a water-soluble ingredient is added, it can first be dissolved in a minimal quantity of water and the water incorporated into the base using either a pill tile and spatula or a mortar and pestle. If large quantities of water or an aqueous solution are to be incorporated, it may be best to use heat. Also, it may be necessary to add additional emulsifying agent and a preservative. The preservative would be necessary as the presence of water usually will support microbial growth. The alternative would be to assign a short expiration date, such as two weeks. The base can be melted using a water-bath and then the aqueous phase added, with stirring. Cooling with continued stirring will complete the preparation of the water-in-oil emulsion final product.

Emulsion Bases: Water-In-Oil

Water-in-oil emulsion bases can be prepared by adding water to an absorption base. Commercial preparations are also available and include Hydrocream™[1], Eucerin™[2], Nivea™[2] and Cold Cream. An extemporaneous preparation example would be 2% miconazole in Hydrocream.

Oils and insoluble powders can be incorporated directly using a pill tile and spatula or mortar and pestle. If large amounts of insoluble powders are required, it may be necessary to use a levigating agent. In many of the water-in-oil emulsion bases, there is sufficient agent further to emulsify a reasonable quantity of an aqueous solution of a drug which can be incorporated on a pill tile with a spatula, mortar and pestle, or by gentle heat using a water bath. If heat is used, the preparation should not be held at a high temperature very long as loss of some water may occur resulting in a thicker ointment (cream).

Emulsion Bases: Oil-In-Water

Oil-in-water emulsion bases are the "vanishing cream" type preparations as they disappear, or vanish, upon application. These are usually elegant preparations and bases include Dermabase™[1], Velvachol™[3] and Hydrophilic Ointment™[4]. Various concentrations of triamcinolone or retinoic acid have been included in these bases as extemporaneous preparations.

Insoluble powders and aqueous solutions can be incorporated using a pill tile and spatula or mortar and pestle. Water soluble materials can be added by dissolving in the powder in a small quantity of water and incorporating the solution into the base. A small quantity of an oil may be incorporated directly into the base as there is usually an excess of emulsifying agent, but, it may also be necessary to add a small quantity of an oil-in-water surfactant to assist in uniformly dispersing the oil in the vehicle if larger amounts of an oil must be added.

If heat is used while incorporating an ingredient into an oil-in-water vehicle, it is important to work quickly as water may be lost rather rapidly from the product. If this occurs, oftentimes the product becomes stiff and "waxy" and loses its elegant character.

Water-Soluble Bases

Polyethylene Glycol Ointment (PEG 400-600 G, PEG 3350-400 G) is an example in this class and the incorporation of 20% benzocaine in this base yields a very nice ointment that can easily be removed by washing.

Water-soluble ingredients can be dissolved in a small quantity of water and mixed with the base using a pill tile and spatula or mortar and pestle. Insoluble powders can be levigated with a small quantity of PEG 400, glycerin, or propylene glycol and mixed with the base. Oils may need to be mixed with an intermediate solvent, *e.g.*, glycerin or propylene glycol, prior

TABLE 2

Classification based on relationship to water

Base Type	Characteristic	Example
Oleaginous	—Insoluble in water —Not water-washable —Will not absorb water —Emollient —Occlusive —Greasy	White Petrolatum White Ointment
Absorption	—Insoluble in water —Not water-washable —Anhydrous —Can absorb water —Emollient —Occlusive —Greasy	Hydrophilic Petrolatum Aquabase Aquaphor Polysorbate
Emulsion: Water-in-Oil	—Insoluble in water —Not water-washable —Will absorb water —Contains water —Emollient Nivea —Occlusive —Greasy	Cold Cream Lanolin, Hydrous Hydrocream Eucerin
Emulsion: Oil-in-Water	—Insoluble in water —Water washable —Will absorb water —Contains water —Nonocclusive —Nongreasy	Hydrophilic Ointment Dermabase Velvachol Unibase™[5]
Water Soluble	—Water soluble —Water washable —Will absorb water —Anhydrous or hydrous —Nonocclusive —Nongreasy —Lipid-free	Polyethylene Glycol Ointment

1. Paddock; 2. Beiersdorf; 3. Owen/Galderma; 4. Rugby; 5. Warner-Chilcott

to mixing with a water-soluble base to enhance stability. If large quantities of water or aqueous solutions are to be added, it may be easier to use gentle heat on a water bath to prepare the product.

Manual Methods

Manual methods primarily use a pill tile and spatula or a mortar and pestle. Ointment pads and various hard, clean surfaces have also been used for ointment preparation. Ointment pads, however, may absorb moisture and tear. The surface used must be clean and should be non-shedding, and provide for ease of mixing of the components. The advantage of a pill tile is that it can be used for some particle size reduction as well as for mixing the ointment. It is also easy to clean and there should be no carryover of any of the materials from one preparation to the next.

Mechanical Methods

If one is preparing large quantities of ointments, it may be advisable to invest in mixers, which range from hand-held propeller types to kitchen type mixers with paddles/blades or "kitchen center" types. In fact, if the regular supply sources do not have the specific type of equipment you might need, gourmet shops are excellent sources of unusual equipment for compounding pharmacists.

PROBLEMS

Problems in ointment preparation include separation of ointment components, drug degradation, discoloration, and the development of a rancid odor. It is a good idea to check with a good source for incompatibility information such as Remington's, Martindale's, dispensing pharmacy texts or with product suppliers if unsure about the occurrence of an incompatibility. This is especially true as very potent products are being used topically and it is rather expensive to try something and find out it doesn't work.

One interesting potential problem involves Plastibase (Squibb). If compounding a product that uses Plastibase, it should NOT be heated, as it will not regain its viscosity upon cooling. Plastibase is a shock-cooled product consisting of mineral oil jelled with polyethylene.

DRUG SOURCES

The best source of active ingredients for ointments is the pure drug. However, it is often difficult to obtain the drug in a pure form so other dosage forms must suffice. Injectable forms of drugs are excellent sources since they contain few excipients which are potential sources of compounding problems. Tablets and capsules are a last resort because of the high excipient content.

PRESERVATION

The selection of a preservative for ointments and the concentration required to preserve the product is beyond the scope of this discussion and will be covered in future editions.

PACKAGING

Ointments are best packaged in tubes or in syringes if feasible. The reason for this is that there is minimal air space in the package and the product is kept clean during the administration process. Ointment jars, although widely used, expose the preparation to air and to microbial contamination when opened and when ointment is removed using the fingers. An implement similar to a tongue depressor could be used to remove the required quantity of ointment from a jar for application. Pharmacies that prepare large quantities of ointments often use plastic tubes and a tube sealer.

STORAGE/STABILITY

Ointments should generally be kept at room temperature and away from excess heat. They are relatively stable, especially if in an oleaginous, anhydrous absorption or anhydrous water-soluble base. If water is present, as in the emulsion bases, the stability is often not quite as good. Both physical stability (appearance, feel, odor, color, etc.) and chemical stability (both the active drug and the base ingredients) must be considered. Generally, the base ingredients are relatively stable so the stability of the active drug is a determining factor in the overall stability of the product. In projecting an expiration period, one can usually look at commercial products containing the active drug and get a reasonable idea. It is best always to be very conservative when determining the

expiration period for an extemporaneously-prepared product, especially if water is present as it supports microbial growth. Generally only a two-week supply should be dispensed if no preservative is present in preparations containing water.

ABSORPTION ENHANCERS

This class of additives deserves brief mention here, but will be covered in depth in a future issue. Absorption enhancers have attracted attention in the popular and scientific literature, particularly since the transdermal route of administration has become more widely used. These substances facilitate absorption of drugs through the skin. It appears that some materials have a direct effect on the permeability of the skin and others augment percutaneous absorption by increasing the thermodynamic activity of the penetrant, thus creating a greater concentration gradient across the skin.

Direct-effect absorption enhancers include common as well as not-so-common chemicals, including solvents, surfactants, and chemicals such as urea and N, N-diethyl-m-toluamide.

Water is the most prevalent absorption enhancer, even in "anhydrous" systems because of their occlusive nature. The classic absorption enhancer is dimethylsulfoxide (DMSO), which has lost popularity due to adverse side effects. However, other solvents such as laurocapram (Azone) have been shown to be very effective, even in concentrations below 5%, because they are retained in the stratum corneum for a period of time, which prolongs their effect.

Surfactants have functioned as absorption enhancers, but they do cause irritation, which limits their usefulness.

Examples of absorption enhancers are shown in Table 3.

TABLE 3

Absorption Enhancers

Solvents
- Water
- Alcohols (Methanol, Ethanol, 2-propanol)
- Alkyl methyl sulfoxides (Dimethyl sulfoxide, Decylmethyl sulfoxide, Tetradecyl methyl sulfoxide)
- Pyrrolidones (2-Pyrrolidone, N-Methyl-2-pyrrolidone, N-(2-Hydroxyethyl) pyrrolidone
- Laurocapram
- Miscellaneous: (Acetone, Dimethyl acetamide, Dimethyl formamide, Tetrahydrofurfuryl alochol)

Amphiphiles
- Anionic surfactants (docusate sodium, sodium lauryl sulfate)
- Cationic surfactants (quaternary ammonium salts)
- Amphoteric surfactants (lecithins, cephalins, alkylbetamines)
- Nonionic surfactants (mono-, di-, and triglycerides)
- Fatty acids and alcohols (lauryl, cetyl, and stearyl alcohols; sucrose, sorbitan, PEG)

Miscellaneous
- Urea
- N, N-Diethyl-m-toluamide

EXAMPLE CALCULATION

Numerous examples could be given here but one example calculation that can be involved includes the following:

Rx	Clotrimazole powder		1%
	Dermabase	qs	30 G

Solution:

The quantities of the ingredients would be calculated as follows:

Clotrimazole:	30 G * 0.01 = 0.3 G or 300 mg
Dermabase:	30 G - 0.3 G = 29.7 G

GENERAL CONSIDERATIONS:

1. Powders need to be in a very fine state of subdivision prior

to incorporation into the base. This can be accomplished using a mortar and pestle, mechanical grinder or pill tile and spatula. The rationales for this are that a gritty preparation may injure the skin further and impede the healing process and the more finely divided powders increase the medication surface area thereby increasing the potential availability for therapeutic activity.

2. Levigating agents must be compatible with the vehicle used. For oleaginous bases, a small quantity of the base (melted or at room temperature) or mineral oil works fine. For absorption bases, such as Aquabase, it depends on where the drug should be, *i.e.*, in the external or internal phase if water is going to be added to the base. Generally water, glycerin, alcohol or propylene glycol can be used and should be taken up into the internal phase of the finished product. Mineral oil can be used if the ingredient should stay in the continuous phase of the product. For emulsion bases, the levigating agent should generally be selected based upon the external phase of the emulsion. For example, if an oil-in-water emulsion base is used, such as Dermabase, the levigating agent should be water, glycerin, propylene glycol, PEG 400, alcohol, or some liquid that is miscible with water. If a water-in-oil emulsion base is used, such as Hydrocream, the levigating agent should be miscible with the oil phase, *i.e.*, mineral oil. For water soluble bases, such as polyethylene glycol ointment, water, glycerin or propylene glycol are commonly used.

3. When incorporating insoluble powders using a levigating agent, the technique of geometric dilution should be followed to ensure thorough mixing of the active ingredient with the vehicle. For example, a few drops of mineral oil can be used to levigate sulfur prior to mixing with white petrolatum. The sulfur-mineral oil mixture would be mixed with an equal quantity of white petrolatum. Then, another quantity of white petrolatum equal to the new mixture is added and the process repeated until all the white petrolatum has been added.

4. When incorporating soluble powders, use solvents that have low vapor pressure, *i.e.*, water, glycerin, propylene glycol. The reason volatile solvents should not generally be used, especially in oleaginous bases, is that if the solvent evaporates, the drug may be crystallized out in the base and cause irritation upon application to the skin.

5. When preparing ointments, generally heat the aqueous phase a few degrees higher than the oil phase. The reason for this is that the aqueous phase will cool faster than the oil phase and, if cooler in the beginning, may cause some of the higher melting point ingredients to solidify prematurely.

6. When adding volatile ingredients, *i.e.*, flavors and active drugs, cool the product a little prior to adding. The melt should still be fluid, but not hot, to allow uniform mixing without evaporative loss of ingredients. Temperatures less than 78°C work well with many bases but lower temperatures would be required if alcohol and volatile materials are present.

7. Lotions often can be prepared from creams (oil-in-water emulsions) by diluting with water or an aromatic water such as Rose Water. To do this successfully usually requires the slow addition of the water to the cream with continuous stirring. This will result in the dilution of the preservative and bacterial contamination may occur. Therefore, a short expiration date should be assigned.

8. If an oil-in-water emulsion dries too rapidly on the skin, a humectant such as glycerin, propylene glycol, 70% sorbitol or PEG 400 can be included in the formulation in approximately a 2-5% concentration.

9. When preparing a base, melt the ingredient with the highest melting point first and gradually reduce the heat, while adding the ingredient with the next lowest melting point, then the next, etc. until a uniform mixture is obtained. This is to insure that the ingredients will be exposed to the lowest possible temperature during the preparation process and thus enhance the stability of the final product.

10. When working with aqueous systems, use heat for as short a time and as low a temperature as feasible. This will minimize the quantity of water lost through evaporation.

11. When preparing pastes, which are characterized by relatively high percentages of solids, levigating agents generally are not used. The easiest method of preparing pastes involves the fusion technique (heat).

12. When packaging products prepared using fusion, cool them prior to filling into tubes or jars. If poured in while they are hot, they may tend to separate upon cooling. They may be cooled to the temperature where they are viscous fluids and then poured into the containers.

13. If a product is too stiff and difficult to apply, try decreasing the concentration of the waxy components.

Paddock
Laboratories, Inc.
3940 Quebec Avenue North
Minneapolis, MN 55427