Formulation Variables

Formulation variables that are generally considered include:

1. The nature and form of the active principle (esters, salts, complexes).
2. The physical state, particle dimensions, and the specific surface of the product.
3. The solubility of the drug in various bases.
4. The presence or absence of adjuvants added to the active principle.
5. The nature and type of base in which the active principle is incorporated.
6. Pharmaceutical procedures used in the preparation of the dosage form.

Physical State

An active drug can be a solid, liquid or semisolid in nature. For solids, the drug's particle size may be very important, especially if the drug is not very water soluble; the increase in surface area resulting from decreased particle size can serve to enhance its activity.

For liquids, it is necessary to take up the liquid into the suppository base using one of several techniques such as forming an emulsion, adding a drying powder or adding a suitable thickening agent when the liquid is mixed with the suppository base.

For the semisolids or paste-type drugs, it can be either mixed with a solid that will serve to thicken the drug prior to mixing with the base or mixed with the base to which a thickener is added.

Particle Size

If a drug is readily soluble, the influence of particle size may be minimal. For highly water-soluble drugs, the tendency will be to dissolve and migrate to the rectal barrier. For poorly water-soluble drugs, the dissolution rate will be slower, and a reduction in particle size may increase the rate of dissolution by exposing a greater surface area.

Solubility

Increased solubility of the active in the base can improve product homogeneity; however, it may also delay the release of the active if there is too great affinity of the drug for the suppository base.

Viscosity

If the viscosity of a base is low, it may be necessary to add a suspending agent such as silica gel to ensure that the drug is uniformly dispersed until solidification occurs. When preparing the suppository, the pharmacist should stir the melt constantly and keep it at the lowest possible temperature to maintain a high viscosity.

After the suppository has been administered, the release rate of the drug may be slowed if the viscosity of the base is very high. This is because the viscosity causes the drug to diffuse more slowly through the base to reach the mucosal membrane for absorption.

Brittleness

Brittle suppositories can be difficult to handle, wrap, and use. Cocoa butter suppositories are usually not brittle unless the percentage of solids present is high. In general, brittleness results when the percentage of non-base materials exceeds about 30%. Synthetic fat bases with high stearate concentrations are typically more brittle. Shock cooling also causes fat and cocoa butter suppositories to crack.

This condition can be prevented by ensuring that the temperature of the mold is as close to the temperature of the melted base as possible. Suppositories should not be placed in a freezer, which also causes shock cooling.

Volume contraction

Bases, excipients, and active ingredients generally occupy less space at lower temperatures than at higher temperatures. When preparing a suppository, the pharmacist pours hot melt into a mold and allows the melt to cool. During this cooling process, the melt has a tendency to contract in size. This makes it easier to release the suppository from the mold, but it may also produce a cavity at the back, or open end of the mold. Such a cavity is undesirable and can be prevented if the melt is permitted to approach its congealing temperature immediately before it is poured into the mold.

Preparation of suppositories

Suppositories are prepared by two methods:

1. Molding from a melt.
2. Hand rolling and shaping.

The method most frequently employed both on a small scale and on an industrial scale is “**molding**”.

Molding

The steps in molding include:

a) Melting the base,

b) Incorporating any required medicaments,

c) Pouring the melt into molds,

d) Allowing the melt to cool and congeal into suppositories, and

e) Removing the formed suppositories from the mold.

Cocoa butter, glycerinated gelatin, polyethylene glycol, and most other bases are suitable for preparation by molding.

Suppository Molds

Commercially available molds can produce individual or large numbers of suppositories of various shapes and sizes. Individual plastic molds may be obtained to form a single suppository. Other molds, such as those most commonly found in the community pharmacy, are capable of producing 6, 12, or more suppositories in a single operation. Industrial molds produce hundreds of suppositories from a single batch.

Molds in common use today are made from stainless steel, aluminum, brass, or plastic. The molds, which separate into sections, generally longitudinally, are opened for cleaning before and after preparation of a batch of suppositories, closed when the melt is poured, and opened again to remove the cold, molded suppositories.

Care must be taken in cleaning the molds, as any scratches on the molding surfaces will take away from the desired smoothness of the suppositories. Plastic molds are especially prone to scratching.

Lubrication of the Mold

Depending on the formulation, suppository molds may require lubrication before the melt is poured to facilitate clean and easy removal of the molded suppositories. Lubrication is seldom necessary when the base is cocoa butter or polyethylene glycol, as these materials contract sufficiently on cooling to separate from the inner surfaces and allow easy removal.

Lubrication is usually necessary with glycerinated gelatin. A thin coating of mineral oil applied with the finger to the molding surfaces usually suffices. However, no material that might irritate the mucous membranes should be employed as a mold lubricant.

Calibration of the Mold

Each individual mold is capable of holding a specific volume of material in each of its openings. Because of the difference in the densities of the materials, if the base is cocoa butter, the weight of the suppositories will differ from the weight of suppositories prepared in the same mold with a base of polyethylene glycols. Similarly, any added medicinal agent alters the density of the base, and the weight of the resulting suppository differs from that of those prepared with base material alone.

Preparing and Pouring the Melt

Using the least possible heat, the weighed suppository base material is melted, generally over a water bath. A porcelain casserole, that is, a dish with a pouring lip and a handle, is perhaps the best utensil, because it later permits convenient pouring of the melt into the cavities of the mold.

Usually, medicinal substances are incorporated into a portion of the melted base by mixing with a spatula. After incorporation, this material is stirred into the remaining base and poured to the mold and allowed to cool to its congealing point.

Any volatile materials or heat-labile substances should be incorporated at this point with stirring. The melt is poured carefully and continuously into each cavity of the mold.

If any undissolved or suspended materials in the mixture are denser than the base, so that they have a tendency to settle and constant stirring, even during pouring, is required.

The solid materials remain suspended if the pouring is performed just above the congealing point and not when the base is too fluid. If the melt is not near the congealing point when poured, the solids may settle within each cavity of the mold to reside at the tips of the suppositories, with the result that the suppositories may be broken when removed from the mold. Alternatively, a small quantity of silica gel (about 25 mg per suppository) can be incorporated into the formula to aid in keeping the active drug suspended.

In filling each suppository cavity, the pouring must be continuous to prevent layering, which may lead to a product easily broken on handling. To ensure a completely filled mold upon congealing, the melt is poured excessively over each opening, actually rising above the level of the mold. This use of extra suppository material prevents formation of recessed dips in the ends of the suppositories and justifies preparation of extra melt.

When solidified, the excess material is evenly scraped off of the top of the mold with a spatula warmed by dipping into a beaker of warm water; this will make a smooth surface on the back of the suppository during trimming.

Manufacturing suppositories

In large scale, manufactured suppositories are generally prepared by the melt fusion method. Commercially automated equipment for melt fusion is available to continually produce large quantities of finished suppositories per hour.

The automated equipment for preparing suppositories has provided an efficient method for manufacturing large quantities of suppositories in a relatively short time. This equipment allows for a single continuous manufacturing process. The stages of manufacturing process are completed in a continuous process, at rates that can reach 30,000 suppositories per hour.

Vaginal inserts

These preparations are employed principally to combat infections in the female genitourinary tract, to restore the vaginal mucosa to its normal state, and for contraception.

The most commonly used base for vaginal inserts consists of combinations of the various molecular weight polyethylene glycols. To this base is frequently added surfactants and preservative agents, commonly the parabens.

Many vaginal inserts and other types of vaginal dosage forms are buffered to an acid pH usually about 4.5, consistent with the normal vagina. This acidity discourages pathogenic organisms and provides a favorable environment for the acid-producing bacilli normally found in the vagina.

The polyethylene glycol vaginal suppositories are water miscible and are generally sufficiently firm for the patient to handle and insert without great difficulty. However, to make the task easier, many manufacturers provide plastic insertion devices that are used to hold the suppository or tablet for proper placement within the vagina.

Vaginal inserts (Tablets)

Vaginal inserts (tablets) are widely used today as they are easy to manufacture, more stable, and less messy to handle. They are usually ovoid and are accompanied in their packaging with a plastic inserter, a device for easy placement of the tablet within the vagina.

They are prepared by tablet compression and are commonly formulated to contain lactose as the base or filler, a disintegrating agent such as starch, a dispersing agent such as polyvinylpyrrolidone, and a tablet lubricant such as magnesium stearate. They are intended to disintegrate within the vagina, releasing their medication.

Quality Control

Quality control procedures listed in the USP 36 – NF 31 for manufactured suppositories and inserts include identification, assay, loss on drying, disintegration, dissolution, physical and chemical stability.

Packaging and Storage

Glycerin and glycerinated gelatin suppositories are packaged in tightly closed containers to prevent a change in moisture content. Suppositories prepared from a cocoa butter base are usually individually wrapped or otherwise separated in compartmented boxes to prevent contact and adhesion.

Suppositories containing light sensitive drugs are individually wrapped in an opaque material such as a metallic foil. In fact, most commercial suppositories are individually wrapped in either foil or plastic material.

Because suppositories are adversely affected by heat, it is necessary to maintain them in a cool place. Cocoa butter suppositories must be stored below 30°C and preferably in a refrigerator (2°C to 8°C).

Glycerinated gelatin suppositories can be stored at controlled room temperature (20°C to 25°C).

Suppositories made from a base of polyethylene glycol may be stored at usual room temperatures. Suppositories stored in high humidity may absorb moisture and tend to become spongy, whereas suppositories stored in places of extreme dryness may lose moisture and become brittle.