Compounding

Chapter Outline

- Compounding
- Compounding Regulations
- Compounding Considerations
- Stability and Beyond-Use Dates
- Equipment
- Using a Balance
- Volumetric Equipment
- Mixing Solids and Semisolids
- Select Dosage Forms

Compounding

- Extemporaneous compounding
  - On-demand preparation of a drug product.
  - According to a physician's prescription.
  - Meets the unique needs of an individual patient.
- Manufacturing
  - The production or processing of a drug in a LARGE quantity by various mechanisms.

Why Compound?

- **Pediatric patients** requiring diluted strengths.
- Patients **needing an oral solution** or suspension of a product that is only available in another form.
- Patients with **sensitivity to dyes**, preservatives, or flavoring agents found in commercial formulations.
- **Dermatological formulations** with strengthened or diluted concentrations of commercially available products.
- **Specialized dosages for therapeutic drug monitoring.**
- Care for **hospice patients** in pain management.
- Compounding for **animals.**

The U.S. Pharmacopeia (USP)

- Established in the 1906 Pure Food and Drugs Act.
- Has the federal authority to set standards pertaining to pharmacy compounding.
- Develops **STANDARDS** where various topics are grouped into **“CHAPTERS.”**
- Publishes its standards in the resource book called the **USP/NF.**

The USP

- Chapters are assigned numbers.
  - Chapters numbered below **1000 are legally enforceable by the FDA.**
- The USP/NF has over 60 chapters.
- The USP also publishes **MONOGRAPHS** of the most commonly compounded preparations used in practice.

Chapters

- **Chapters <795>** - called **Pharmaceutical Compounding - Nonsterile Preparations**
  - Published in 2000
  - Enforceable
- **Chapter <797>** - called **Pharmaceutical Compounding - Sterile Preparations,**
  - Became official in 2004.
- **Other Chapters**
  - Containers <661>
  - Good Compounding Practices <1075>
  - Pharmaceutical Stability <1150>
  - Pharmaceutical Dosage Forms <1151>

Compounding Regulations Applies

- Personnel
- Facilities and Equipment
- Ingredient Standards
- Quality Assurance and Quality Control
- Packaging and Storage
- Documentation and Record Keeping

Ingredient Standards

- **USP/NF**
  - Meets standards set by the USP/NF.
- **ACS reagent**
  - High purity: meets specifications of the American Chemical Society.
- **AR (analytical reagent)**
  - Very high purity.
- **HPLC**
  - Very high purity.
  - Used in high pressure chromatography.

Record Keeping

- **Formulation Record**
  - Formulas and procedures (i.e., recipes) for what should happen when a formulation is compounded.
- **Compounding Record**
  - A record of what actually happened when the formulation was compounded.
- **Standard Operating Procedures (SOPs)**
  - Equipment maintenance, equipment calibration, handling and disposal of supplies, etc.
- **Material Safety Data Sheets MSDSs**
  - Ingredients records with certificates of purity.

Storage Temperature Definitions

- Freezer: -20°C to -10°C
- Protect from Freezing: Store above 0°C
- Cold: Any temperature not exceeding 8°C
- Refrigerator: Between 2°C and 8°C
- Cool: Between 8°C and 15°C
- Room Temperature (RT): Temp. in the work area
- Controlled RT: Thermostatically controlled at 20°C to 25°C
- Warm: Between 30° and 40°C
- Excessive Heat: Any temperature above 40°C

Stability

- **Stability**
  - The extent to which a dosage form retains the same properties and characteristics that it possessed at the time of its manufacture.
- **Expiration date**
  - The date until which the manufacturer can guarantee the safety and potency of a drug-product's stability.
- **Beyond-use dates**
  - Used for compounded preparations, generally in the order of "days" or "months."
- **Shelf life**
  - Length of time a packaged drug will last without deteriorating

Assigning a Beyond-Use Date

- **Non-aqueous liquids and solid formulations**
  - If the source the active drug is a manufactured drug product, the beyond-use date is not later than 25% of the time remaining until the drug product's expiration date, or 6 months, whichever is earlier.

  - If the source of the active drug is a USP or NF substance, the beyond-use date is not later than 6 months.

Assigning a Beyond-Use Date

- **Water containing formulations**
  - When prepared from ingredients in solid form, the beyond-use date should be not later than 14 days when stored at cold temperature.
- **For all other formulations**
  - The beyond-use date is not later than the intended duration of therapy or 30 days, whichever is earlier.

Types of Equipment

- **Measuring**
  - Balance, weights, weighing containers, volumetric glassware (graduates, pipets, flasks, syringes).
- **Mixing**
  - Beakers, Erlenmeyer flasks, spatulas, funnels, sieves, mortar and pestle.
- **Molding**
  - Hot plates, suppository molds, capsule shells, ointment slabs.
- **Packaging**
  - Prescription bottles, capsule vials, suppository boxes, ointment jars.

Class “A” Balance Scale

- A two pan torsion balance that uses both internal and external weights.
- Weights go on the right pan and powder on the left pan.
- Sensitivity: up to 6mg
- Capacity: 120mg to 60gms
- Degree of error: 5%
- Weights: 1gm to 50gms
  - fraction weights 10mg to 500mg
- Electronic or Analytical Balance
- How do you weigh something less than 120 mg?

Using a Balance

1. Place on a level surface in a draft free area.
2. Use clean weighting papers or boats.
3. Must be readjusted after a new paper or boat has been placed on the pan.
4. Arrest the balance before adding or removing weight.
5. Use a spatula.
6. Clean the balance.

Using an Electronic Balance

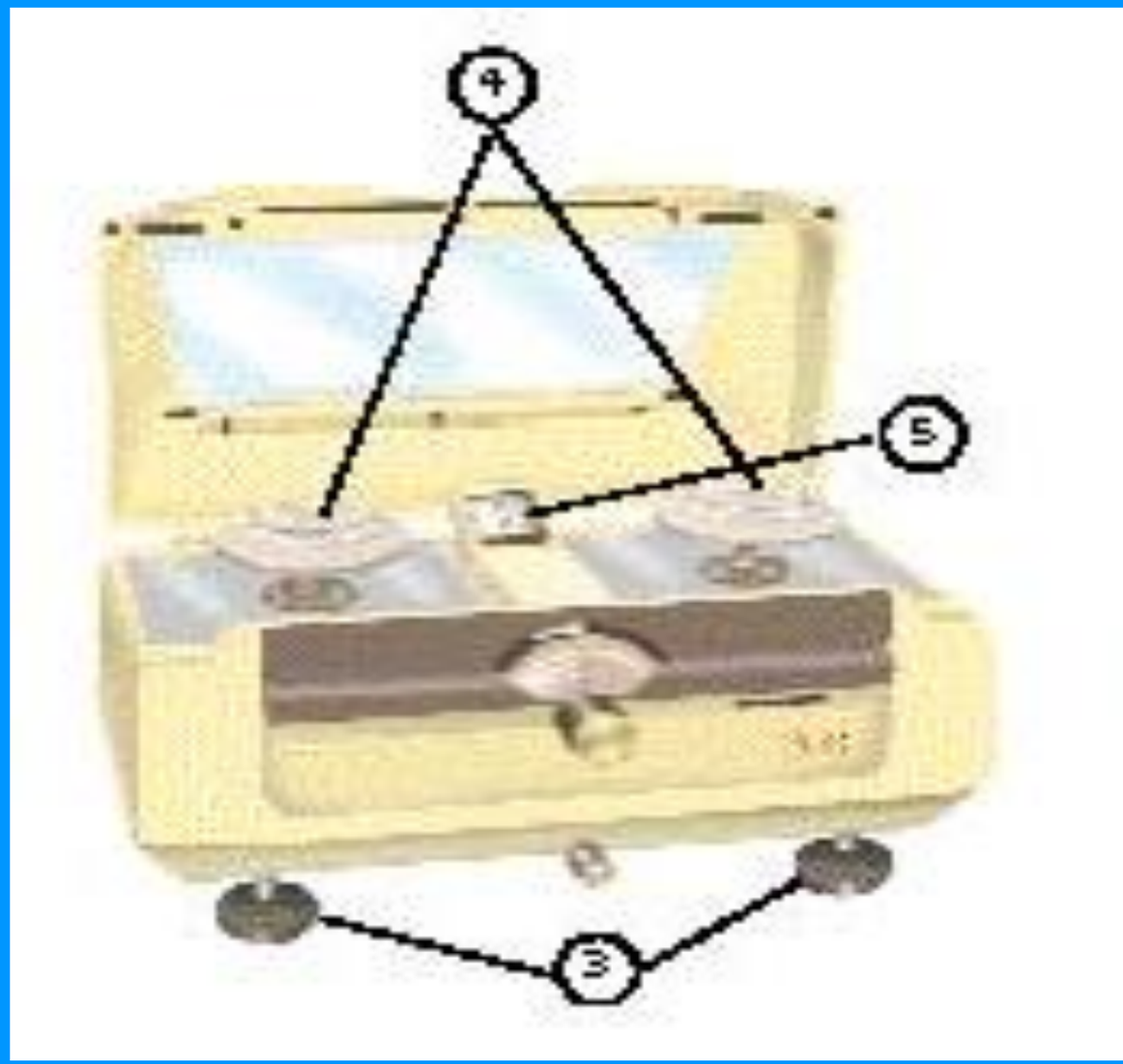
1. Keep balance where it will not be moved.
2. Turn the leveling feet.
3. Turn on the balance.
4. First use of the day, check internal weight calibration.
5. Removed top ring of the draft shield. Place weighing boat in the center.
6. Add ingredients
7. Clean spills with a lint-free towelette.
8. Turn off balance at the end of the day.

Using a Prescription Balance

1. Lock the Balance by turning the **arrest knob**.
2. Set the internal weights to zero.

Using a Prescription Balance

3. Unlock the balance and level it *left* to *right*.
4. Lock the balance. Place a weighing boat or paper.
5. Unlock the balance by releasing the arrest knob.

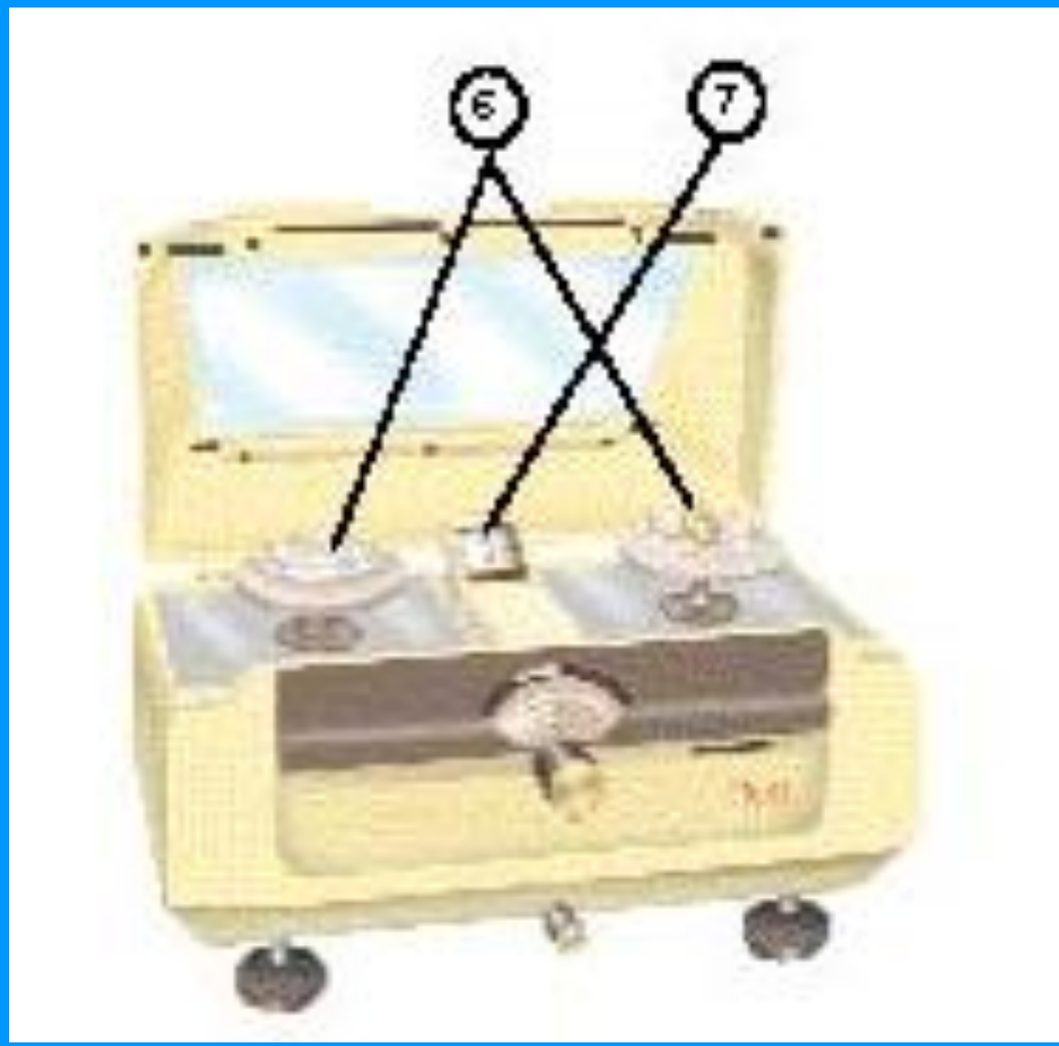


Using a Prescription Balance

6. Lock the balance and place the required weights in the boat.

7. Unlock the balance and note the shift of the pointer.

After an accurate measurement is made, check your work.



Reason for Accurate Weighing

- Weighing of the product is an essential part of the compounding process.
- Weighing the exact amount is essential in compounding for several reasons:
  - The product cannot be “checked” for content once mixed.
  - The quantities weighed out are often very small, and a slight overage could mean a serious overdose for the patient.

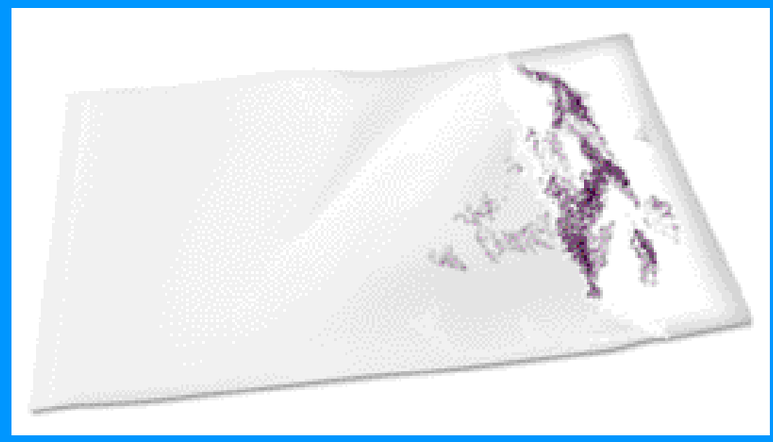
Spatulas

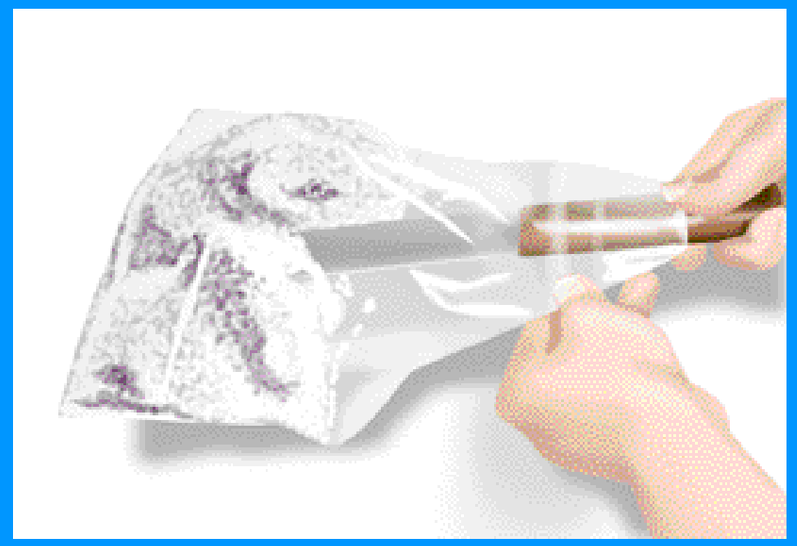
- **Spatulas**
  - Used to transfer solid ingredients or prepare ointments and creams or loosening material from the surfaces of a mortar and pestle.
- **Types**
  - Stainless steel
  - Hard rubber
  - Plastic

Spatulation

- Mixes powders using a spatula.

- Mixing can be done in a mortar, on an ointment slab, or in a plastic bag.





Mortar and Pestle

Mortar and Pestle

- The coarser the surface of the mortar and pestle, the finer the triturating, or grinding, that can be done.

Types

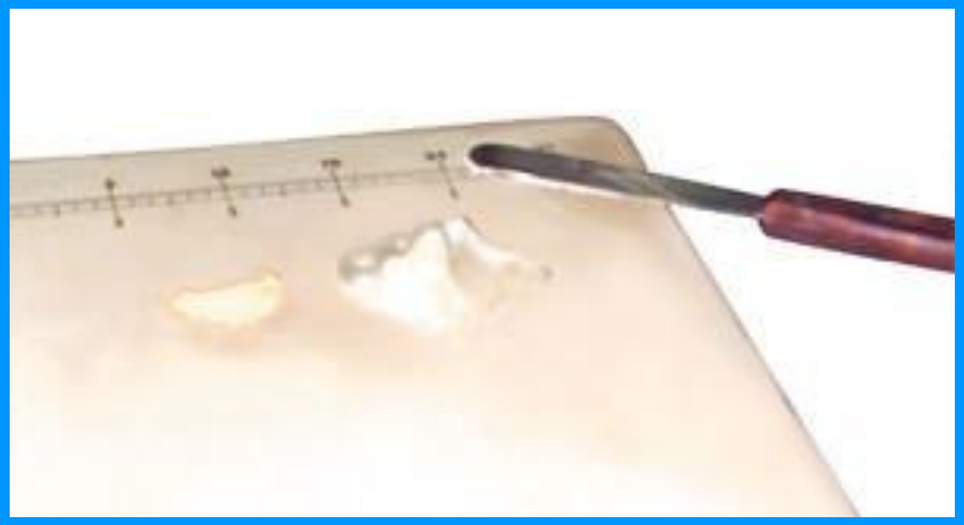
- Glass
- Wedgwood
- Porcelain

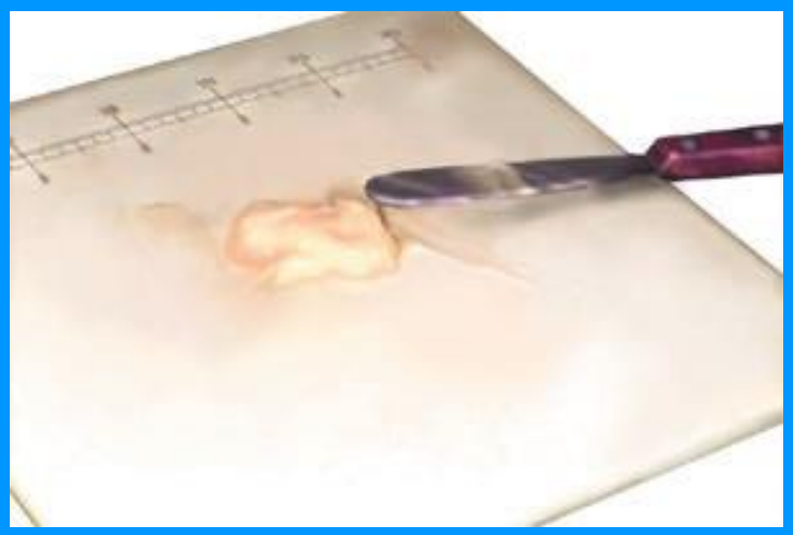
Trituration

- The process of grinding powders to reduce the particle size.

Compounding Slab

- This is an ideal surface for mixing compounds because of its nonabsorbent surface.
- **Levigation**
  - Technique used to reduce the particle size of a powder drug by triturating it with a solvent in which the drug is insoluble.





Volumetric Equipment

- Graduates
- Flasks
- Pipets
- Syringes
- Droppers
- Oral syringes

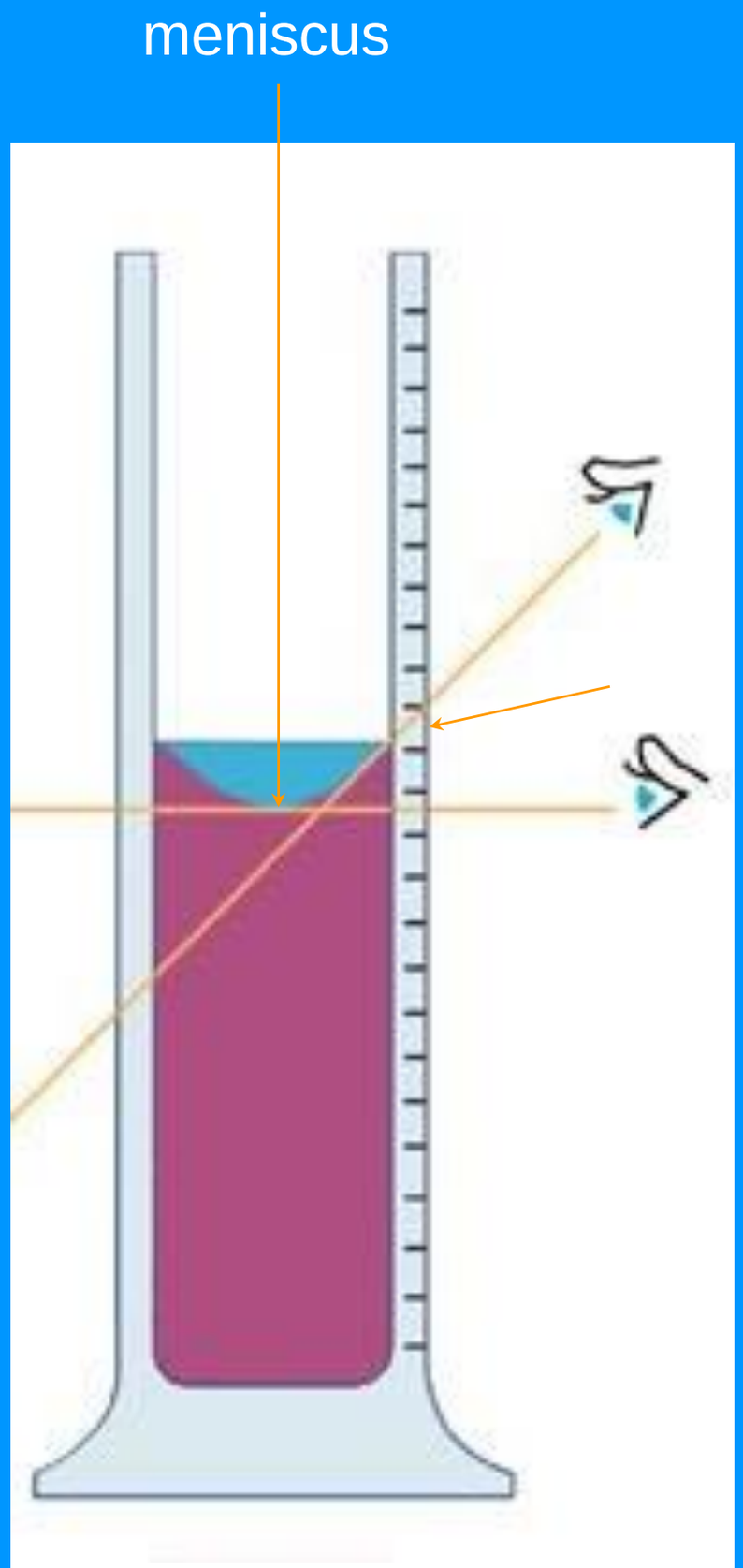
Volumetric Equipment Graduated Cylinders

- Cylindrical and cone shaped.
- Used for measuring and transferring liquids.
- Available in sizes ranging from 5 ml to 4,000 ml.
- Selecting a graduated cylinder.
  - Choose the smallest one capable of containing the volume to be measured.
  - Rule: Avoid measurements of volumes that are below 20 percent of the capacity of the graduated cylinder.
    - Example, a 100 ml graduated cylinder cannot accurately measure volumes below 20 ml.
- When measuring small volumes, such as 20 ml and less, use a syringe or pipet.

Graduates

conical graduate

cylindrical graduate



reading a graduate

Small Volumetric Equipment

Calibrated pipette

Single volume pipettes

Syringe

Measure volume to edge of stopper.

Volumetric Equipment Syringes

- **Range** from 0.5 ml to 60 ml and in a variety of materials and styles.
- Contain **graduation marks** on the barrel for measuring partial volumes.
- A **disposable hypodermic syringe** or an oral syringe made of plastic is used for most compounding tasks involving small volumes.
- Always **choose the smallest syringe** capable of containing the volume to be measured.

Liquid Measurement Droppers

- Used to deliver small doses of liquid medication.
- Medicine dropper must first be calibrated because
  - The drop size will vary from dropper to dropper.
  - Personal factors can also contribute to the inaccuracy of droppers.

Measuring Liquid Volumes

- Pour the liquid to be measured slowly into the graduate, watching the level of the liquid in the graduate as you do so.
- If the liquid is viscous, or thick, then you should attempt to pour it toward the center of the graduate to avoid having some of the liquid cling to the sides.

Liquid Measurement Oral Syringes

- Available for accurately administering liquid medication to the patient.
- Have tips that are larger than tips on hypodermic syringes so needles cannot be placed on these syringes.
- After the dose is drawn into the syringe, a cap is placed on the tip to prevent leakage and prevent contamination.
- Oral syringes can be used with a device called an **Adapt-a-Cap®**
  - An example of an oral syringe cap that screws onto the bottle containing the liquid, and the oral syringe is fitted into the other side of the cap.

- Adapt-a-Cap®

Mixing Powders – Geometric Dilution

When mixing powders of unequal size, the smaller volume is mixed *(triturated)* with an equal volume of the other. That mixture is then mixed with an equal volume of the larger volume of powder. This process is repeated until the mixture is completed.

Solutions

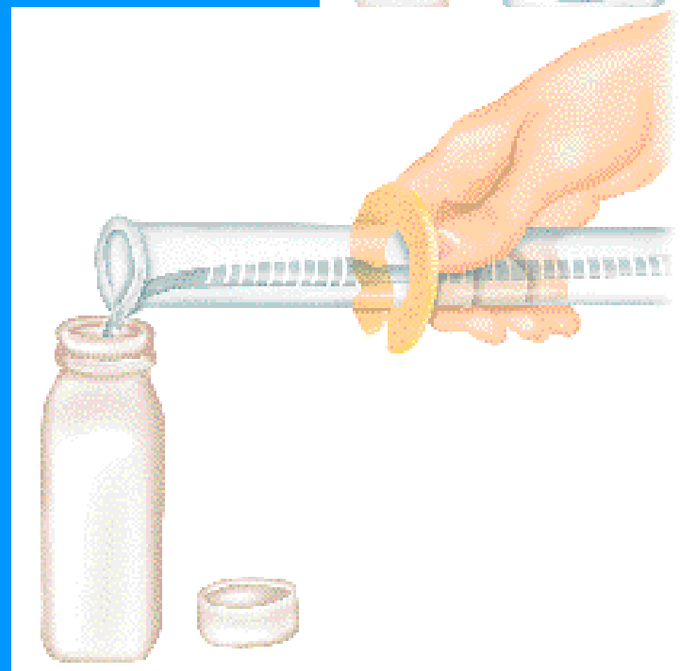
- The most commonly compounded products.
- C**lear** (but not necessarily colorless) **liquids** in which the drug is completely dissolved.
- The **solubility** of the drug must be known before attempting to dissolve it in a solution. If a drug is not soluble in a vehicle, then no amount of mixing will help.
- Some solids need to be **triturated** before mixing in a solution.

Solutions

• Very soluble	<1
• Freely soluble	1 - 10
• Soluble	10 - 30
• Sparingly soluble	30 - 100
• Slightly soluble	100 - 1000
• Very slightly soluble	1,000 - 10,000
• Practically insoluble	>10,000

Suspension

- A two phase system consisting of a finely divided solid dispersed in a liquid.
- **Flocculating Agent**
  - Electrolytes used in the preparation of suspensions to form particles that can be easily redispersed.
- **Thickening Agent**
  - Ingredient used in the preparation of suspensions to increase the viscosity of the liquid.



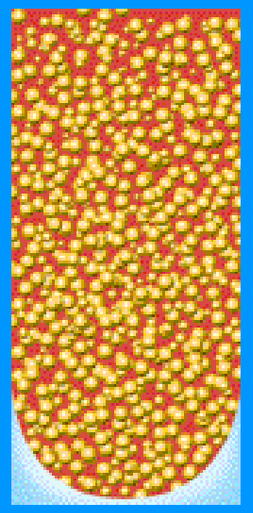
Additives

- **Flavoring**
  - The human tongue contains about 10,000 taste buds which distinguish salty, bitter, sour, and sweet tastes.
- **Sweeteners**
  - Colorless, odorless, soluble in water, pleasant with no “after-taste,” and stable over a wide pH range.
- **Coloring**
  - Not required in every formulation.
  - Contraindicated in all sterile solutions.
  - Dark colors, such as dark purple, navy, black, and brown may also be rejected because they are often associated with poisons.

Emulsions

- Unstable system consisting of at least two **immiscible liquids**.
  - One is dispersed in the form of small droplets throughout the other.
  - The other is a stabilizing agent.

- **Types**
  - Oil-in-water (o/w) emulsion
  - Water-in-oil (w/o) emulsion

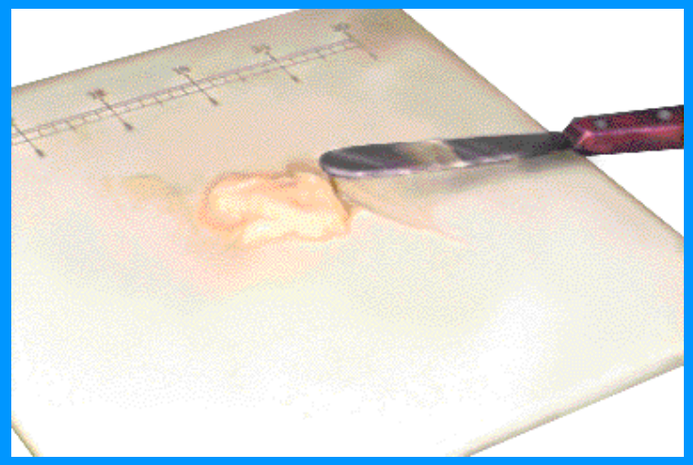


Emulsions

- **Emulsifier -** a stabilizing agent in emulsions.
  - commonly used emulsifying agents include tragacanth, sodium lauryl sulfate, sodium dioctyl sulfosuccinate, and polymers known as the Spans® and Tweens®.
- **Primary emulsion** the initial emulsion to which ingredients are added to create the final product.
- **Mucilage** a wet, slimy liquid formed as an initial step in the wet gum method.

Ointments

- Used for many different purposes, e.g., as protectants, antiseptics, emollients, antipruritics, kerotolytics, and astrigents.



Ointments are generally compounded
on an ointment slab.

Transferring ointment into an ointment jar.

Suppositories

Mold

Three types of bases:

Oleaginous: primarily synthetic triglycerides.

Water soluble: containing glycerinated gelatin or polyethylene glycols (PEGs).

Hydrophyllic: mixtures of oleaginous and water soluble bases.

Suppository box

Suppositories

- **Cocoa butter (Theobroma Oil) USP**
  - A well-known oleaginous base.
  - At room temperature, cocoa butter is a solid.
  - At body temperature, it melts to a bland, non-irritating oil. (melting point 30 - 35 C)
  - No longer the base of choice because preparing suppositories with it is difficult, and the suppositories require refrigeration.

Suppositories

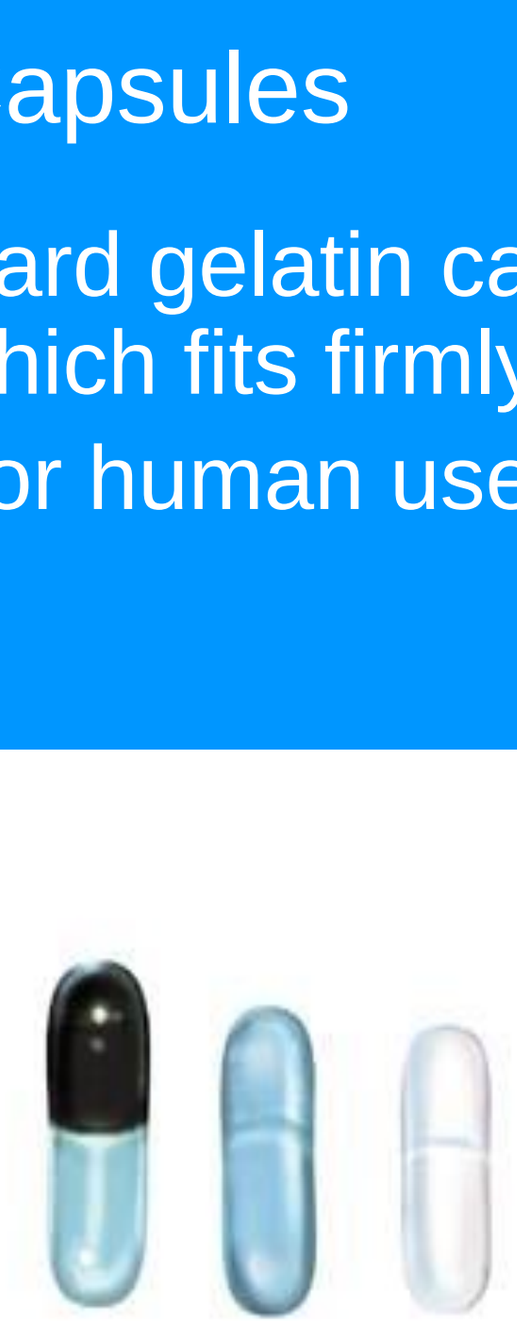
- Synthetic triglycerides can be used that do not have the formulation difficulties of cocoa butter, but they are more expensive.
- There are newer bases composed of mixtures of fatty acids that do not have the formulation problems or the expense (e.g., FattiBase®, Witepsol®).

Water Soluble or Miscible Bases

- Glycerinated gelatin or polyethylene glycol (PEG) polymers.
  - Useful for vaginal suppositories.
  - Dissolve slowly to provide prolonged release of active ingredients.
  - Can be formulated by molding or compression in a wide range of hardness and melting points.
  - Do not melt at body temperature, but dissolve slowly to provide a prolonged release of drugs.
- Available in **various molecular weight ranges.**
  - 200, 400, or 600 molecular weight are liquids.
  - Molecular weights over 1,000 are solids.

Capsules

- Hard gelatin capsules consist of a **body** and a **cap** which fits firmly over the body of the capsule.
- For human use, **eight sizes** of capsules are available.



Sizes	Volume ml
000	1.37
00	0.95
0	0.68
1	0.50
2	0.37
3	0.30
4	0.20
5	0.13

Punch Method

Used when filling a small number of capsules.

Labeling, Record Keeping, & Cleanup

- After compounding
  - The product **must be labeled** with a prescription label, and **a careful record** of the compounding operation should be kept.
- Once the compounding operation is finished
  - The **equipment and area should be cleaned.**
  - Everything should be returned to their proper places in storage.
- Compounding should never be rushed.

Labeling, Record Keeping, & Cleanup

- Regardless of their apparent stability, all **suspensions** should be dispensed with an auxiliary label reading **“Shake Well.”**
- The **qs** abbreviation means to add **“a sufficient quantity”** to the specified amount.
  - JCAHO recommends using text words rather than abbreviations to minimize a medication error.
- Refer to a standard reference work on the subject.
  - Example: ***Remington: The Science and Practice of Pharmacy***

Terms to Remember

1. Aliquot
2. Arrest knob
3. Beyond-use date
4. Calibrate
5. Chapter <795>
6. Chapter <797>
7. Compounding record
8. Compression molding
9. Emulsifier
10. Finger cots
11. Flocculating agent
12. Formulation record
13. Fusion molding

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