EMULSIONS

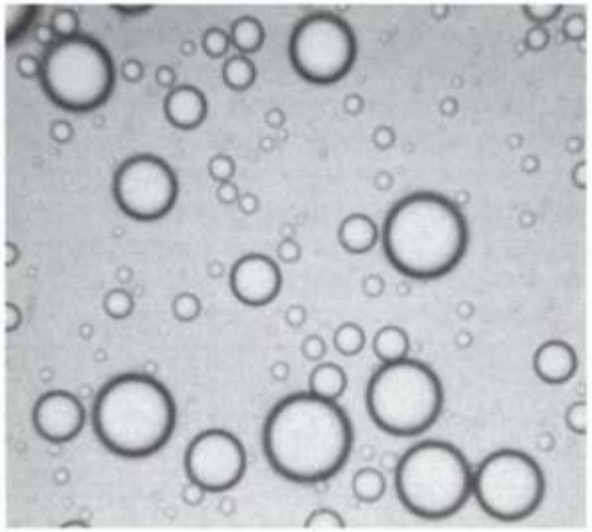
Ansel's

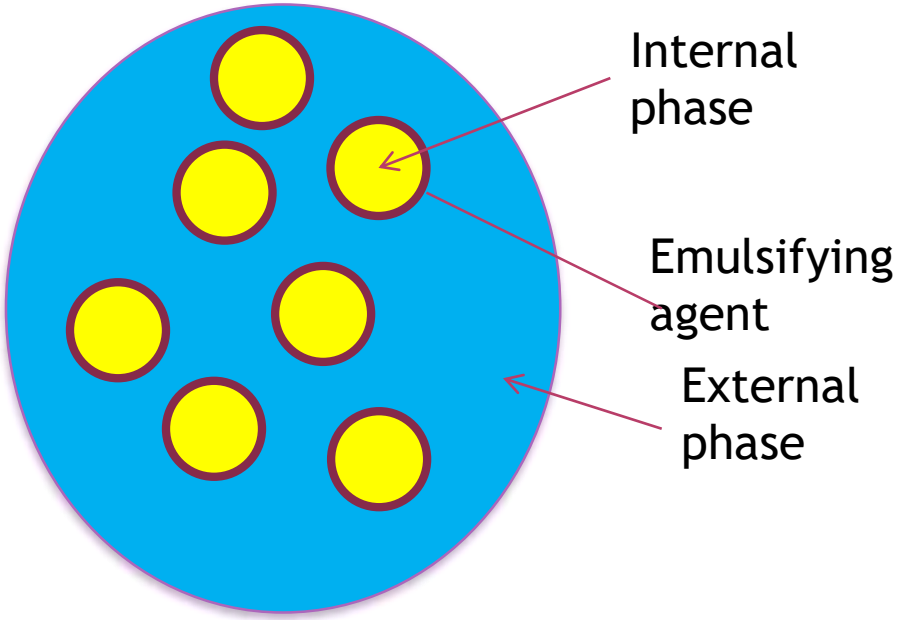
Pharmaceutical dosage forms and drug delivery systems

Chapter 14 and 10

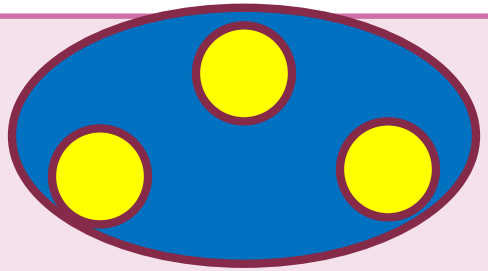
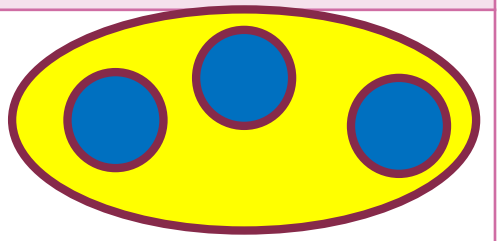
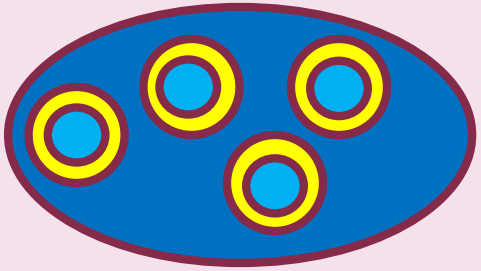
EMULSIONS

- Is a dispersion in which the dispersed phase is composed of small globules of liquid (internal phase) distributed throughout a vehicle(continuous phase) in which it is immiscible. Using an emulsifying agent





TERMINOLOGY

	Internal phase Dispersed phase	External phase Continuous phase
O/W Oil in water	Oil	Water 
W/O Water in oil	Water	Oil 
W/O/W or O/W/O	Multiple emulsion	

EMULSIONS

- Traditionally the term “emulsion” is restricted to pourable emulsions for internal use;
- Emulsions for external use are described by their pharmaceutical types as
- Liquid : **liniments**, **lotions (topical emulsions)**,
- Semisolid :**creams**.
- Which are the largest group of emulsions currently used in pharmacy and medicine are dermatological emulsions for external use.

Macro emulsion Coarse emulsions Ordinary emulsions	Micro emulsion
More than 500nm	20-200nm swollen micelle
White opaque appearance	Cloudy –Translucent or Transparent Homogeneous Tyndall effect
Thermodynamically unstable Kinetically stable	Thermodynamically stable Low Gibb's free energy
Needs large input of energy (high shear) for production Higher cost	Forms spontaneously Need a 2nd surfactant called Co-surfactant to lower the interfacial tension
High interfacial tension	Very low interfacial tension

TYPES OF EMULSIONS

DETERMINATION OF THE TYPE OF EMULSION

- The phase volumes

The larger the volume of the phase will be considered as the continuous phase

- (Rule of Bancroft)

The phase in which the emulsifying agent is more soluble will become the continuous or external phase of the emulsion

TESTS FOR IDENTIFICATION OF EMULSION TYPE

Oil in water emulsions	Water in oil emulsions
1-Miscibility test Miscible with water	Miscible with oil
2-Staining test by incorporation of an oil-soluble dye Macroscopic examination Paler color Microscopic examination Colored globules in a colorless background	Intense color Colorless globules against a colored background
3- Conductivity test The continuous phase is water It will conduct electricity throughout the system	The continuous phase is oil No conductance of electricity

CLASSIFICATION

- According to the (limited by its ultimate use and, constituents, route of administration.,)

Physical form	Route of administration	Examples	
Liquid	Oral	vitamin drops, castor oil emulsion	o/w
Liquid	Parenteral	I.V. o/w I.M. S.C. may be w/o	(non toxic EA, small droplets)
Liquid Semi solid	Topical	lotions, liniments, creams, ointments	Cosmetic effect, emollient, enhance penetration

ACCEPTABLE PHARMACEUTICAL EMULSIONS

- Physical stability (no phase separation).
- The flow properties of the emulsion/cream should enable the formulation to be easily removed from the container. Furthermore, if the formulation is designed for external application to, for example, the skin, the formulation must be easily spread over the affected area.
- The formulation must be aesthetically and texturally pleasing. If the emulsion is designed for oral application, the flavor must be suitable whereas if emulsions are to be externally applied, they must have the correct ‘feel’ (termed texture).

ORAL EMULSIONS

Oral emulsions are always of the **oil-in water** type.

- They provide a degree of taste masking as the aqueous external phase effectively isolates the oil from the tongue.
- The use of o/w emulsions as carriers for lipophilic drugs may improve oral bioavailability and efficacy.
- (Griseofulvin formulated as an o/w emulsion has enhanced gastrointestinal absorption when compared with suspensions, tablets, or capsule dosage forms.

ADVANTAGE OF ORAL EMULSIONS

- Prepare a relatively stable and homogeneous mixture of two immiscible liquids
- For orally emulsions o/w types permit palatable administration of distasteful oil by dispensing in a sweetened flavored aqueous vehicle
- An oil soluble drug can be dissolved in the dispersed phase
- Reduced oil globule diameter will make it more digestible, enhance its action (0.5μ)
- Introducing incompatible ingredients in different phases as a liquid dosage form

TOPICAL EMULSIONS

- Both oil-in-water and water-in-oil emulsions are extensively used for their therapeutic properties and/or as vehicles to deliver drugs and cosmetic agents to the skin.
- Emulsions applied to the skin may be o/w or w/o depending on

1. Nature of the drug
2. Need of emollient or tissue softening effect
3. The condition of the skin
4. Percutaneous absorption enhanced by **decreasing the particle size** of the internal phase, or by the use of **penetration enhancers**, or due to the **occlusive effects**

Irritant drugs are placed in the internal phase

Drugs are placed in the phase they are soluble in

TOPICAL EMULSIONS

- w/o emulsion

1. Easily applied to unbroken skin due to the thin film of sebum
2. Skin softening resist skin drying cannot be removed by washing

- o/w emulsion

- Easily removed by water

PARENTERAL EMULSIONS

- Sterile I.V. O/W emulsions are used for administration of foods and oil soluble vitamins, with droplet sizes similar to that of chylomicrons (approximately 0.5–2 *m*m), and for poorly soluble drugs (diazepam, amphotericin B)
- Special care in manufacture to produce uniform droplet size
- Oils used are Purified soybean, sesame, safflower, and cottonseed oils composed mainly of long-chain triglycerides have been used for many years as they are resistant to rancidity and show few clinical side effects.
- EA type
- Intravenous emulsions must be o/w
- Intramuscular emulsions, subcutaneous injections may be w/o

Drug action is prolonged in such oily emulsions because the drug has to diffuse from the aqueous dispersed phase through the oil-continuous environment to reach the tissue fluids.

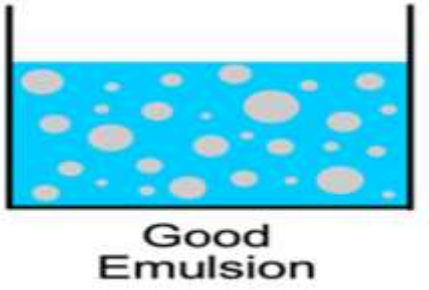
DISADVANTAGES OF EMULSIONS

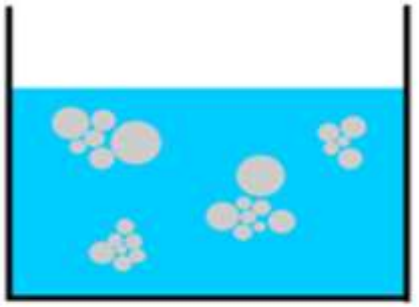
- Pharmaceutical emulsions are thermodynamically unstable and therefore must be formulated to stabilize the emulsion from separation of the two phases. This is by no means straightforward.

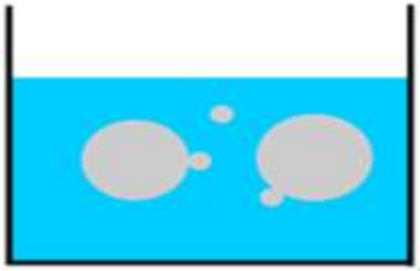
1. Must be shaken well prior to measuring a dose, even after efficient shaking the accuracy of the dose is likely to be less than solutions
2. Conditions of storage may effect the disperse system leading to creaming or cracking
3. Liable to microbial contamination which can lead to cracking
4. Liquid dosage forms are more bulky than solid dosage form
5. Pharmaceutical emulsions may be difficult to manufacture.

EMULSION INSTABILITY

- Emulsions are termed thermodynamically unstable systems.
- Following dispersion of an insoluble liquid, e.g. an oil into an aqueous phase, the oil phase will adopt a spherical (droplet) shape as this is the shape associated with the minimum surface area per unit volume.
- **Flocculation** describes a weak reversible association between emulsion globules separated by thin films of continuous phase
- If the droplet contacts a second droplet, **Coalescence** will occur to produce a single droplet of greater diameter and, in so doing, the surface area of the new droplet will be less than the surface areas of the two individual droplets prior to coalescence.
- This process will continue until there is complete **Phase separation**, i.e. two liquid layers occur.


Good Emulsion


ii. Flocculation


i. Coalescence


iv. Breaking

GIBBS FREE ENERGY IN AN EMULSION

- $\Delta G = \Delta A \gamma$
- A is the total surface area of dispersed particles
- γ is the interfacial tension,
- Stable emulsions must have a large “A” and a small “G” concurrently for consistent and uniform dosing. This is done by decreasing “γ,” which will decrease “G,” which will decrease self-attraction of dispersed phase particles.

GENERAL PRINCIPLES OF EMULSIFYING AGENTS

1. EA must be compatible with the other formula ingredients
2. Not interfere with the stability and efficacy of the drug
3. Non toxic
4. Little odor, taste, or color
5. Maintain the stability of the emulsion for the intended shelf life of the product
6. Select EA having the same HLB or close HLB as the oil depending on the type of emulsion desired

EMULSIFICATION

1. Immiscible liquid mixed together have high interfacial tension
2. All liquids assume the shape of the sphere having minimal surface area/ volume
   Smaller particles have large surface area thus larger interfacial tension and high surface free energy thermodynamically unstable system
3. Liquids tend to coalesce making larger drop so that the surface area is smaller to decrease the surface free energy

THEORIES OF EMULSIFICATION

- There are many theories of emulsification ; theory for the manner in which emulsions are stabilized

1. **Oriented- Wedge theory**
2. **Plastic and Interfacial Theory** . Adsorbed film and interfacial tension theory. This theory has been developed or rather extended from earlier theories.

At the present time it is probably the most universally accepted theory for the formation of emulsions.

1- ORIENTED- WEDGE THEORY

- This has been developed from the work of **Langmuir and of Harkins.**
- It is based upon the concept that the molecules of the emulsifier orient themselves in the interface between the dispersed and continuous phases, forming a wedge, the curvature of which determines the size of the dispersed phase
- EA surround the globules of the internal phase
- The EA is embedded more deeply in that phase than another

2- PLASTIC OR INTERFACIAL THEORY

- Emulsifying agent EA surround the globules of the internal phase as a thin layer of film adsorbed on the surface of the drops
- The tougher the film the greater the stability of the emulsion
- Enough EA must be present to cover the entire globules
- Provide protective sheath around the droplets and may impart a charge to the dispersed droplets
- They may swell causing an increase in viscosity of the system so the droplets coalesces are hindered

RULES OF BANCROFT

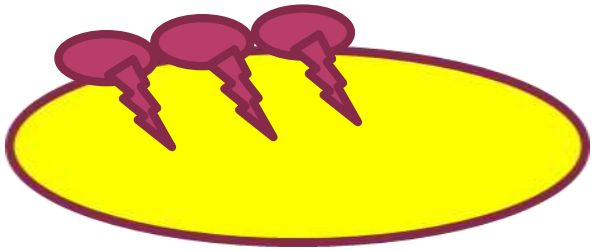
- “emulsification” is influenced by
- (1) the mass of the emulsifying agent present,
- (2) the ease with which this agent is adsorbed at the interfacial separating surface, and
- (3) the nature of the ions adsorbed by the resultant film."

OTHER THEORIES

- Emulsion formation can be explained by

1. Surface tension lowering
2. Repulsion
3. Viscosity modification

EMULSIFYING AGENTS
1- SURFACE ACTIVE AGENTS



- Wetting agents, These agents contain both hydrophilic and lipophilic groups, with the lipophilic protein of the molecule generally accounting for the surface activity of the molecule which may be
- 1- Anionic agents, this hydrophilic portion is negatively charged. Anionic emulsifiers include various monovalent, polyvalent, and organic soaps, such as sodium oleate, and sulfonates, such as sodium lauryl sulfate
- 2- Cationic, it is positively charged . Benzalkonium chloride, known primarily for its bactericidal properties, may be employed as a cationic emulsifier
- Owing to their opposing ionic charges, anionic and cationic agents tend to neutralize each other and are thus considered incompatible.
- 3-Nonionic emulsifiers show no inclination to ionize. Depending on their individual nature, certain of the members of these groups form o/w emulsions and others, w/o emulsions. Agents of the nonionic type include the sorbitan esters and the polyoxyethylene derivatives.
- The ionic nature of a surfactant is a prime consideration. Nonionic surfactants are effective over pH range of 3 to 10; cationic surfactants are effective over pH range of 3 to 7; and, anionic surfactants require a pH greater than 8.

SURFACE ACTIVE AGENTS

- Surface active agents will decrease the interfacial energy and facilitate the break down of the larger
- Depending on the nature of the EA (hydrophilic or hydrophobic) will promote the o/w or w/o emulsions

HLB VALUE OF SAA

ACTIVITY	ASSIGNED HLB
Antifoaming	1-3
Emulsifiers (w/o)	3-6
Wetting agents	7-9
Emulsifiers (o/w)	8-18
Solubilizers	15-20
Detergents	13-16

HLB OF SURFACTANT

- Wetting agents are surfactants with HLB values of 7 to 9. Wetting agents aid in attaining intimate contact between solid particles and liquids.
- Emulsifying agents are surfactants with HLB values of 3 to 6 or 8 to 18. Emulsifying agents reduce interfacial tension between oil and water, minimizing surface energy through the formation of globules.
- Detergents are surfactants with HLB values of 13 to 16. Detergents will reduce the surface tension and aid in wetting the surface and the dirt. The soil will be emulsified, and foaming generally occurs, and a washing away of the dirt.
- Solubilizing agents have HLB values of 15 to 20.

HYDROPHILIC-LIPOPHILIC BALANCE (HLB) VALUES OF SOME AMPHIPHILIC AGENTS

Substance	HLB	Substance	HLB
Oleic acid	1	Methyl cellulose (Methocel 15 cps)	10.5
Polyoxyethylene sorbitol beeswax derivative	2	Polyoxyethylene lauryl ether	10.8
Sorbitan tristearate	2.1	Polyoxyethylene monostearate (Myrj 45)	11.1
Glyceryl monostearate	3.8	Triethanolamine oleate	12
Sorbitan monooleate (Span 80)	4.3	Polyoxyethylene alkyl phenol	12.8
Diethylene glycol monostearate	4.7	Polyethylene glycol 400 monolaurate	13.1
Glyceryl monostearate, self-emulsifying (Tegin)	5.5	Polyoxyethylene sorbitan monooleate(Tween 80)	15
Diethylene glycol monolaurate	6.1	Polyoxyethylene sorbitan monolaurate(Tween 20)	16.7
Sorbitan monolaurate (Span 20)	8.6	Polyoxyethylene lauryl ether (Brij 35)	16.9
Polyethylene lauryl ether (Brij 30)	9.5	Sodium oleate	18
Gelatin (Pharmagel B)	9.8	Potassium oleate	20
		Sodium lauryl sulfate	40

REQUIRED HLB

- Certain emulsifying agents of a given HLB value appear to work best with a particular oil phase and this has given rise to the concept required HLB value for any oil or combination of oils.
- All oils, waxes and other materials likely to be incorporated into emulsions have an individual "Required HLB."
- However, this does not necessarily mean that every surfactant having the required HLB value will produce a good emulsion; specific surfactant may interact with the oil, with another component of the emulsion or even with each other.

SELECTION OF SAA REQUIRED HLB

- Mineral oil RHLB =4 w/o and
  RHLB=12 o/w
- Select EA having the same HLB or close HLB as the oil depending on the type of emulsion desired
- An emulsifier, or blend of emulsifiers, having an HLB of 12 will make a more stable fluid O/W mineral oil emulsion than emulsifiers of any other HLB value.

Required HLB values for oil phase ingredients

	o/w	w/o
Cottonseed oil	6-7	—
Petrolatum	8	—
Beeswax	9-11	5
Paraffin wax	10	4
Mineral oil	10-12	5-6
Methyl silicone	11	—
Lanolin, anhydrous	12-14	8
Carnauba wax	12-14	—
Lauryl alcohol	14	—
Caster oil	14	
Cetyl alcohol	13-16	—
Stearyl alcohol	15-16	—
Lauric acid	16	—
Oleic acid	17	—
Stearic acid	17	—

BLENDING OF SURFACTANTS

- HLB values are additive, and often surfactants are blended. In practice usually a Tween and a Span are mixed to provide an emulsifier combination that has the RHLB required HLB to produce a stable emulsion
- The mixture contributes one or several action

1. It provide the proper hydrophilic- lipophilic nature
2. It establishes a stable film at the interface
3. Supplies the desired consistency to the product and also other features like emolliency, spreading, and flocculation.

CALCULATIONS FOR SINGLE OIL COMPONENT

- Prepare 100ml of a mineral oil 20% emulsion (RHLB=12) emulsified with a 5g mixture of Span 20 (HLB=8.6) and Tween 20 (HLB=16.7)
- $\% \, SAA \;\; HLBhigher = \frac{RHLB - HLB \; low}{HLB \; high - HLBlow}$
- $\% \, Tween \; 20 = \frac{12 - 8.6}{16.7 - 8.6} = 0.42 \; or \; 42\%$
- The product would require about 40% or 2g of Tween20 and 60% or 3g of Span20 in the emulsifier phase
- (8.6X0.6)+(16.7X0.4)=11.8
- Span Tween RHLB

CALCULATION OF HLB VALUE FOR OIL-IN-WATER EMULSIONS

Ingredient	Amount	RHLB (O/W)
1. Beeswax	15 g	9
2. Lanolin	10 g	12
3. Paraffin wax	20 g	10
4. Cetyl alcohol	5 g	15
5. Emulsifier	2 g	
6. Preservative	0.2 g	
7. Color	As required	
8. Water, purified q.s.	100 g	

Key: RHLB = required hydrophilic–lipophilic balance value.

RHLB CALCULATION

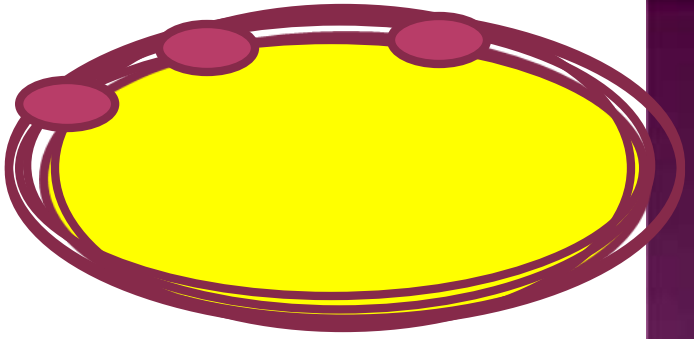
1-Calculate the overall RHLB of the emulsion by multiplying the RHLB of each oil-like component (items 1–4 in the formula) by the weight fraction that each oil-like component contributes to the oil phase.
The total weight of the oil phase is 50 g.

1	Beeswax	15/50 × 9 = 2.70
2	Lanolin	10/50 × 12 = 2.40
3	Paraffin	20/50 × 10 = 4.00
4	Cetyl alcohol	5/50 × 15 = 1.50
	Total RHLB for the emulsion	= 10.60

CALCULATION

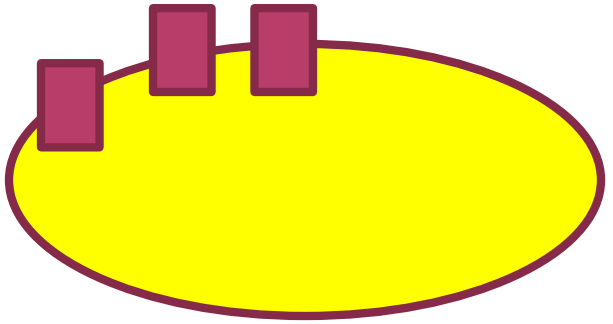
- 2-Choose a blend of two emulsifying agents, one with an HLB above and the other with an HLB below the required HLB of the emulsion (RHLB = 10.6 in this example).
- For example we choose Tween 80, with an HLB of 15, and Span 80, with an HLB of 4.3.
- The formula for calculating the weight percentage of Tween 80 (surfactant with the higher HLB) is
- $\%\ SAA\ \ HLBhigher = \frac{RHLB - HLB\ low}{HLB\ high - HLBlow}$
- $\%\ Tween80 = \frac{10.6-4.3}{15-4.3}$ =0.59 or 59%
- Two grams of emulsifier has been estimated as proper protection for the O/W emulsion.
- Therefore, 2.0 g × 0.59 = 1.18 g of Tween 80 is needed and the remainder, (2-1.18= 0.82 g), must be supplied by Span 80 for the 100-g emulsion.

EMULSIFYING AGENTS
2- MULTI MOLECULAR



- 1-Carbohydrate materials,
- A- naturally occurring agents like acacia, generally produce o/w emulsions.
- B- Semi- synthetic Microcrystalline cellulose
- 2- Protein substances, such as gelatin and casein. These substances produce o/w emulsions. The disadvantage of gelatin as an emulsifier is that the emulsion frequently is too fluid and becomes more fluid upon standing.
- 3-Fatty derivative, Cholesterol and cholesterol derivatives, egg yolk and Wool fat may also be employed in externally used emulsions to promote w/o emulsions..

EMULSIFYING AGENTS
3- SOLID PARTICLES



- Finely divided solids such as colloidal clays, including bentonite, magnesium hydroxide, and aluminum hydroxide.
- Generally, these form o/w emulsions when the insoluble material is added to the aqueous phase if there is a greater volume of the aqueous phase than of the oleaginous phase.
- However, if the powdered solid is added to the oil and the oleaginous phase volume predominates, a substance such as bentonite is capable of forming a w/o emulsion.

MECHANISM OF ACTION OF EA

Type of film	Example	Mechanism
Mono-molecular	Potassium laurate Tween 80	Coherent flexible film formed by SAA. (Lower **interfacial tension**)and stabilize the emulsion. Widely used especially the non-ionic type
Multi-molecular	Acacia Gelatin	Strong rigid film formed mostly by hydrocolloids, which produce O/W emulsions. Interfacial tension is not reduced, stability due mainly to strength of interfacial film (**mechanical barrier**)
Solid particles	Bentonite Magnesium hydroxide	Film formed by solid particles that are small in size compared to the droplets of the dispersed state Particles wetted by both phases to some extent in order to remain at the interface and form a stable film (**electrical barrier**)

AUXILIARY EMULSIFYING AGENT

- These are weak EA, always used in combination with others
- 1-lipohilic
- High-molecular-weight alcohols, such as stearyl alcohol, cetyl alcohol, and fatty esters like glyceryl monostearate, also fatty acids like stearic acid. These are employed primarily as thickening agents and stabilizers for o/w emulsions of certain lotions and ointments used externally.
- 2- hydrophilic
- Tragacanth and agar are commonly employed as thickening agents in acacia-emulsified products
- Chondrus, and pectin,
- Methyl cellulose and sodiumcarboxymethylcellulose

METHODS OF PREPARATION SMALL SCALE

- On a small scale, in the laboratory or pharmacy, emulsions may be prepared using
- 1- wood or porcelain mortar and pestle,(A mortar with a rough rather than smooth inner surface must be used to ensure proper grinding action and reduction of the globule size. A glass mortar is too smooth to produce the proper reduction of the internal phase)
- 2- a mechanical blender or mixer, such as a milkshake mixer, a hand homogenizer , a bench-type homogenizer
- 3-a simple prescription bottle.

METHOD OF PREPARATION LARGE SCALE

- On a large scale, large mixing tanks provided with jackets that permit heating and cooling of the ingredients and emulsion formed by the action of a high-speed impeller.
- As desired, the product may be rendered finer by passage through a
- colloid mill, in which the particles are sheared between the small gap separating a high-speed rotor and the stator, this is favored when the emulsion is too viscous for homogenization or when suspended solids are present in the mixture.
- or by passage through a large homogenizer, in which the liquid is forced under great pressure through a small valve opening. Industrial homogenizers have the capacity to handle as much as 100,000 L of product per hour

EMULSIFICATION

- Prior to mixing, all the water soluble ingredients are dissolved in the aqueous phase and all the oil-soluble components are dissolved in the oil
- In case of o/w emulsion the EA is water soluble so it is dissolved in the aqueous phase
- If a blend of surfactants are used, dissolve each EA in the appropriate phase
- If fats waxes or SAA that are solids or semisolid at room temperature are needed, warm the 2 phases, the aqueous phase temperature is raised 2-3ºC above that of oil phase, so that no local crystallization of waxes takes place upon mixing of the 2 phases
- If the o/w emulsion formula contains strong electrolyte, this must added after the emulsion is formed, to minimize any interaction with the emulsifier.

1- ADDITION OF INTERNAL PHASE TO THE EXTERNAL PHASE

- The internal phase added gradually to the external phase with continuous mixing.
- In this way, the external phase is always in excess

2- ADDITION OF EXTERNAL PHASE TO THE INTERNAL PHASE

- Using SAA
- If we formulate o/w emulsion
- A portion of the aqueous phase (external) is added to the oil (internal phase) forming w/o
- Add sufficient water all at once suddenly with adequate agitation, which should invert the w/o into o/w
- The remaining water is added with stirring to bring the product up to the final volume.

SPECIAL POINTS

- Other liquid formula ingredients that are soluble in or miscible with the external phase may then be mixed into the primary emulsion.
- Solid substances such as preservatives, stabilizers, colorants, and any flavoring material are usually dissolved in a suitable volume of water (assuming water is the external phase) and added as a solution to the primary emulsion.
- Any substances that might interfere with the stability of the emulsion or the emulsifying agent are added as near last as is practical.
- alcohol has a precipitating action on gums such as acacia, thus no alcohol or solution containing alcohol should be added directly to the primary emulsion, because the total alcoholic concentration of the mixture would be greater at that point than after other diluents were added.
- When all necessary agents have been added, the emulsion is transferred to a graduate and made to volume with water previously swirled about in the mortar to remove the last portion of emulsion.

BOTTLE OR FORBES BOTTLE METHOD

- The bottle method is useful for the extemporaneous preparation of emulsions from volatile oils or oleaginous substances of low viscosities.
- Powdered acacia is placed in a dry bottle, two parts of oil are added, and the mixture is thoroughly shaken in the capped container.
- A volume of water approximately equal to that of the oil is then added in portions and the mixture thoroughly shaken after each addition.
- When all of the water has been added, the primary emulsion thus formed may be diluted to the proper volume with water or an aqueous solution of other formula agents.
- This method is not suited for viscous oils because they cannot be thoroughly agitated in the bottle when mixed with the emulsifying agent.
- When the intended dispersed phase is a mixture of fixed oil and volatile oil, the dry gum method is generally employed

NASCENT SOAP METHOD

- The two types of soaps developed by this method are calcium soaps and soft soaps
- Oil containing sufficient free fatty acids such as linseed or olive oil, placed in a suitable container, an equal volume of alkali such as calcium hydroxide. Forming w/o emulsions
- The soap is formed in –situ therefore it is called nascent soap method
- If we use sodium hydroxide o/w emulsion is formed.

CALCIUM SOAPS

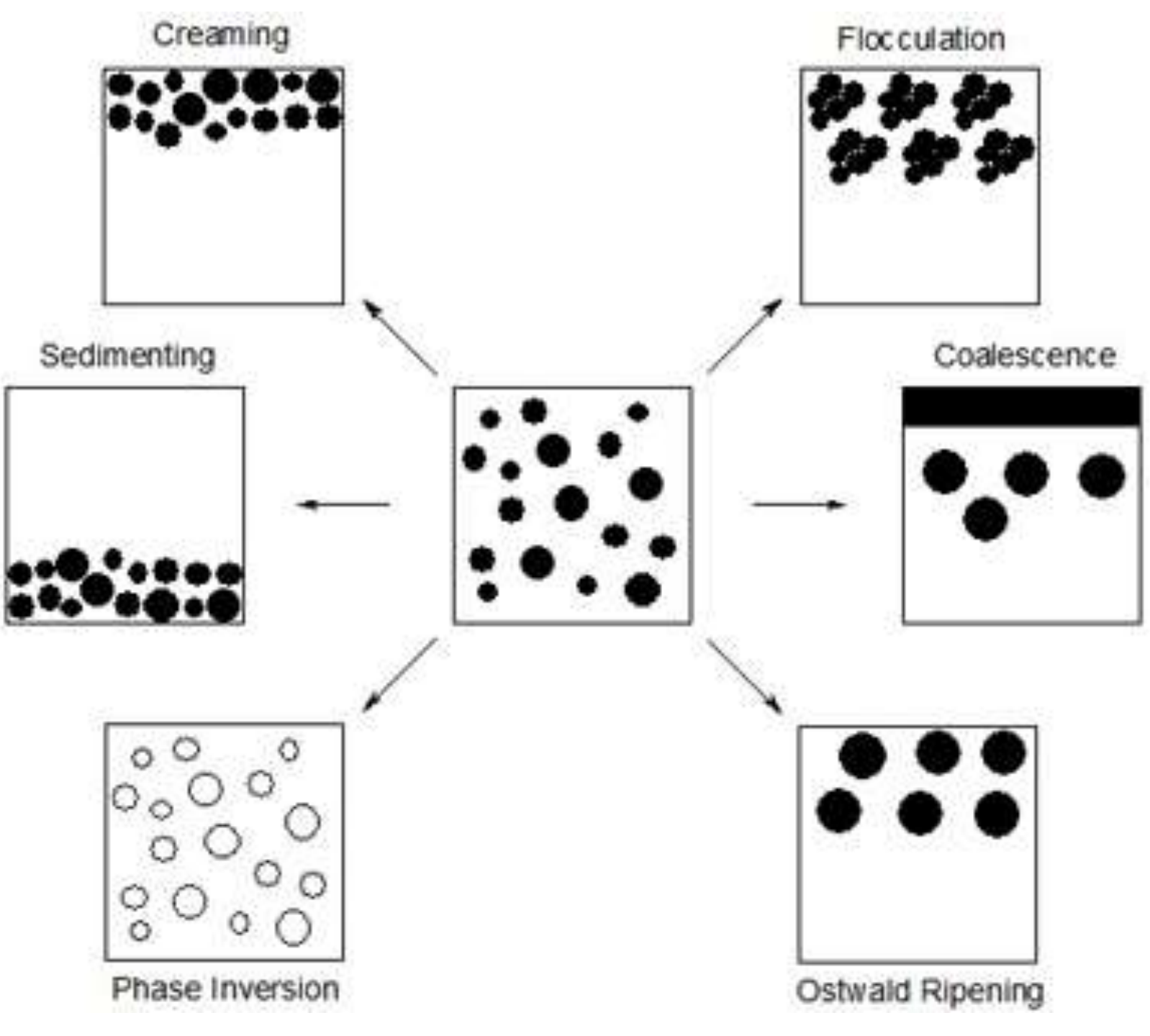
- Calcium soaps are w/o emulsions that contain certain vegetable oils, such as oleic acid, in combination with limewater (Calcium Hydroxide Solution, USP).
- They are prepared simply by mixing equal volumes of the oil and limewater. The emulsifying agent in this instance is the calcium salt of the free fatty acid formed from the combination of the two entities. In the case of olive oil, the free fatty acid is oleic acid and the resultant emulsifying agent is calcium oleate.
- A difficulty that sometimes arises when preparing this self-emulsifying product is that the amount of free fatty acids in the oil may be insufficient on a 1:1 basis with calcium hydroxide. Typically, to make up for this deficiency a little excess of the olive oil, or even a small amount of oleic acid, is needed to ensure a nice, homogeneous emulsion. Otherwise, tiny droplets of water form on the surface of the preparation.
- Because the oil phase is the external phase, this formulation is ideal where occlusion and skin softening are desired, such as for itchy, dry skin or sunburned skin.

Calamine liniment

- calamine,
- zinc oxide aa 80g
- Olive oil
- Calcium hydroxide solution aa qs ad 1000ml

TERMS ASSOCIATED WITH EMULSIONS

- Flocculation describes a weak reversible association between emulsion globules separated by thin films of continuous phase.
- Creaming or sedimentation occurs when the dispersed droplets or floccules separate under the influence of gravity to form a layer of more concentrated emulsion, the cream. Creaming or sedimentations are reversible weak association of internal phase droplets, creamed emulsion can be restored to its original state by gentle agitation
- Coalesces cohesions of like droplets to produce larger globules to reduce the surface free energy
- Ostwald ripening, where droplet sizes increase due to large droplets growing at the expense of smaller ones
- Cracking or breaking is irreversible coalesces of the internal phase droplets


Creaming
Flocculation
Sedimenting
Coalescence
Phase Inversion
Ostwald Ripening

STABILITY OF EMULSIONS

- Emulsions can break down through cracking, creaming, or phase inversion

1. Cracking happens if the oil turns rancid during storage, the acid formed denatures the emulsifying agent, causing the two phases to separate
2. Creaming Undesirable, poor appearance, patient may not obtain correct dose due to insufficient shaking. Increase viscosity of the continuous phase will decrease creaming(the principles apply as in suspension according to Stork's law)
3. Phase inversion o/w change into w/o and vice versa occurs when the dispersed phase exceed a theoretical maximum of 74% of the total volume.

CREAMING

- According to Stokes' equation the rate of separation of the dispersed phase of an emulsion may be related to such factors as:
- the particle size of the dispersed phase,
- the difference in density between the phases,
- and the viscosity of the external phase.
- It is important to recall that the rate of separation is increased by increased particle size of the internal phase, larger density difference between the two phases, and decreased viscosity of the external phase.
- Therefore, to increase the stability of an emulsion, the globule or particle size should be reduced as fine as is practically possible, the density difference between the internal and external phases should be minimal, and the viscosity of the external phase should be reasonably high.
- Thickeners such as Tragacanth and microcrystalline cellulose are frequently added to emulsions to increase the viscosity of the external phase.
- Upward creaming takes place in unstable emulsions of the o/w or the w/o type in which the internal phase has a lesser density than the external phase.
- Downward creaming takes place in unstable emulsions in which the opposite is true

STORAGE

- Generally, care must be taken to protect emulsions against extremes of cold and heat. Freezing and thawing coarsen an emulsion and sometimes break it. Excessive heat has the same effect. Because emulsion products may be transported to and used in locations with climates of extremely high or low temperature, manufacturers must know their emulsions' stability before they may be shipped. For most emulsions, the industry performs tests at 5°C, 40°C, and 50°C to determine the product's stability. Stability at both 5°C and 40°C for 3 months is considered minimal. Shorter exposure periods at 50°C may be used as an alternative test.
- Because other environmental conditions, such as the presence of light, air, and contaminating microorganisms can adversely affect the stability of an emulsion, appropriate formulative and packaging steps are usually taken to minimize such hazards to stability.
- For light-sensitive emulsions, light-resistant containers are used. For emulsions susceptible to oxidative decomposition, antioxidants may be included in the formulation and adequate label warning provided to ensure that the container is tightly closed to air after each use.

PRESERVATION

- Many molds, yeasts, and bacteria can decompose the emulsifying agent, disrupting the system. Even if the emulsifier is not affected by the microbes, the product can be rendered unsightly by their presence and growth and will of course not be efficacious from a pharmaceutical or therapeutic standpoint.
- Because fungi (molds and yeasts) are more likely to contaminate emulsions than are bacteria, fungistatic preservatives, commonly combinations of methylparaben and propylparaben, are generally included in the aqueous phase of an o/w emulsion.
- Alcohol in the amount of 12% to 15% based on the external phase volume is frequently added to oral o/w emulsions for preservation.

CASTOR OIL EMULSION

- Castor oil emulsion is used as a laxative for isolated bouts of constipation and in preparation of the colon for radiography and endoscopic examination.
- The castor oil in the emulsion works directly on the small intestine to promote bowel movement. This and other laxatives should not be used regularly or excessively, as they can lead to dependence for bowel movement. Overuse of castor oil may cause excessive loss of water and body electrolytes, which can have a debilitating effect. Laxatives should not be used when nausea, vomiting, or abdominal pain is present, because these symptoms may indicate appendicitis, and use of a laxative in this instance could promote rupturing of the appendix.
- The amount of castor oil in commercial emulsions varies from about 35% to 67%. The amount of oil influences the dose required. Generally, for an emulsion containing about two-thirds oil, the adult dose is 45 mL, about three tablespoonful. For children 2 to 6 years of age, 15 mL is usually sufficient, and for children less than 2 years of age, 5 mL may be given.
- Castor oil is best taken on an empty stomach, followed with one full glass of water.

Suppositories and Inserts

Chapter 12

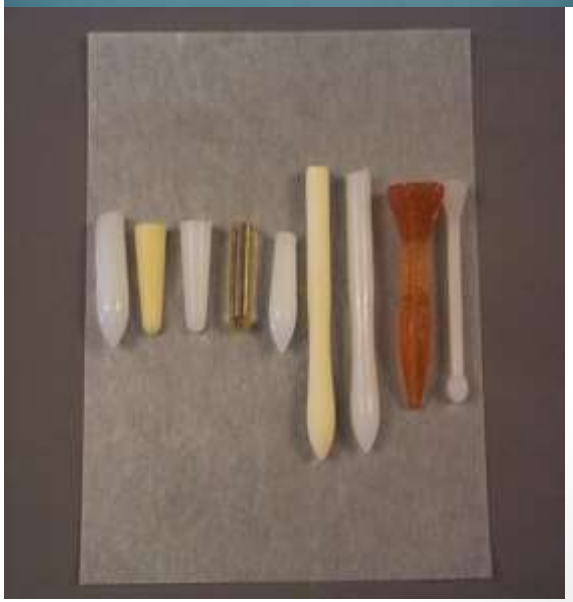
Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 9th Edition

SUPPOSITORIES

- Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert local or systemic effects.
- The derivation of the word suppository is from the Latin supponere, meaning “to place under,” as derived from sub (under) and ponere (to place).
- Thus, suppositories are meant both linguistically and therapeutically to be placed under the body, as into the rectum
- Suppositories are commonly used rectally and vaginally and occasionally urethrally
- They are used to deliver both systemically and locally acting medications

SUPPOSITORIES SHAPES

- Suppositories have various shapes and weights.
- The shape and size of a suppository must be such that it can be easily inserted into the intended orifice without causing undue distension, and once inserted, it must be retained for the appropriate period.
- Rectal suppositories are inserted with the fingers, but certain vaginal suppositories, particularly the inserts, or tablets prepared by compression, may be inserted high in the tract with the aid of an appliance.



Rectal suppositories

- Rectal suppositories are usually about 32 mm (1.5 in.) long, are cylindrical, and have one or both ends tapered. Some rectal suppositories are shaped like a bullet, a torpedo, or the little finger.
- Depending on the density of the base and the medicaments in the suppository, the weight may vary.
- Adult rectal suppositories weigh about 2 g when cocoa butter (theobroma oil) is employed as the base.
- Rectal suppositories for use by infants and children are about half the weight and size of the adult suppositories and assume a more pencil-like shape.

Vaginal suppositories

- Vaginal suppositories, also called pessaries, are usually globular, oviform, or cone-shaped and weigh about 5 g when cocoa butter is the base.
- However, depending on the base and the manufacturer's product, the weights of vaginal suppositories may vary widely.

Urethral suppositories

- Urethral suppositories, also called **bougies,** are slender, pencil-shaped suppositories intended for insertion into the male or female urethra.
- Male urethral suppositories may be 3 to 6 mm in diameter and approximately 140 mm long, although this may vary. When cocoa butter is employed as the base, these suppositories weigh about 4 g.
- Female urethral suppositories are about half the length and weight of the male urethral suppository, being about 70 mm long and weighing about 2 g when made of cocoa butter
- Urethral suppositories may be
- antibacterial or
- a local anesthetic preparative for a urethral examination.

Fate of the suppository

- Once inserted, the suppository base melts, softens, or dissolves, distributing its medicaments to the tissues of the region.
- These medicaments may be intended for retention within the cavity for local effects, or they may be intended to be absorbed for systemic effects.
- They may exhibit the effect immediately or sustain the release of the drug such as Long-acting or slow-release suppositories are also prepared.
- Morphine sulfate in slow-release suppositories is prepared by compounding pharmacists. The base includes a material such as alginic acid, which will prolong the release of the drug over several hours

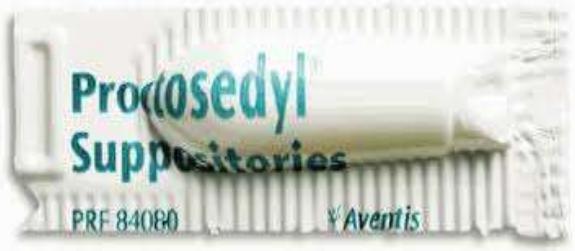
Local rectal suppositories

- Rectal suppositories intended for local action are most frequently used to relieve

1- constipation

A popular laxative, glycerin suppositories promote laxation by local irritation of the mucous membranes, probably by the dehydrating effect of the glycerin on those membranes.

2- the pain, irritation, itching, and inflammation associated with hemorrhoids or other ano-rectal conditions.



Anti-hemorrhoidal suppositories frequently contain a number of components, including local anesthetics, vasoconstrictors, astringents, analgesics, soothing emollients, and protective agents.

Local vaginal suppositories

- Vaginal suppositories or inserts intended for local effects are employed mainly as

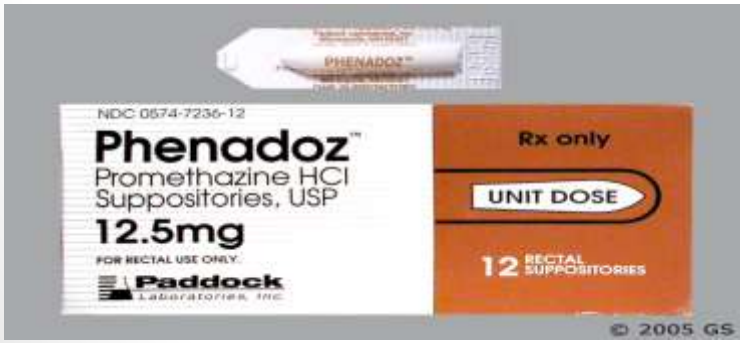
1. contraceptives, the drugs used are nonoxynol-9
2. antiseptics in feminine hygiene, trichomonacides to combat vaginitis caused by Trichomonas vaginalis
3. specific agents to combat an invading pathogen. Most commonly, antifungals to treat Candida (Monilia) albicans, and anti-infectives/antibiotics directed at other microorganisms

Systemic effect of rectal suppositories

- For systemic effects, the mucous membranes of the rectum and vagina permit the absorption of many soluble drugs.
- Although the rectum is used frequently as the site for the systemic absorption of drugs, the vagina is not as frequently used for this purpose.
- Among the advantages over oral therapy of the rectal route for systemic effects are these:
- (a) Drugs destroyed or inactivated by the pH or enzymatic activity of the stomach or intestines need not be exposed to these destructive environment
- (b) Drugs irritating to the stomach may be given without causing such irritation.
- (c) Drugs destroyed by portal circulation may bypass the liver after rectal absorption (drugs enter the portal circulation after oral administration and absorption).
- (d) The route is convenient for administration of drugs to patients who are unable or unwilling to swallow medication.
- (e) It is an effective route in the treatment of patients with vomiting.

Examples of drugs administered rectally for systemic effect

- (a) prochlorperazine and chlorpromazine for the relief of nausea and vomiting and as a tranquilizer;
- (b) oxymorphone HCl for opioid analgesia;
- (c) ergotamine tartrate for the relief of migraine syndrome;
- (d) indomethacin, a nonsteroidal anti-inflammatory analgesic and antipyretic; and
- (e) ondansetron for the relief of nausea and vomiting



SOME FACTORS OF DRUG ABSORPTION FROM RECTAL SUPPOSITORIES

- The dose of a drug administered rectally may be greater than or less than the dose of the same drug given orally, depending on such factors as
- the physicochemical nature of the drug and
- its ability to traverse the physiologic barriers to absorption,
- and the nature of the suppository vehicle and its capacity to release the drug and make it available for absorption.

Rectal absorption

- The factors that affect rectal absorption of a drug may be divided into two main groups:
- (a) physiologic factors and
- (b) physicochemical factors of the drug and the base

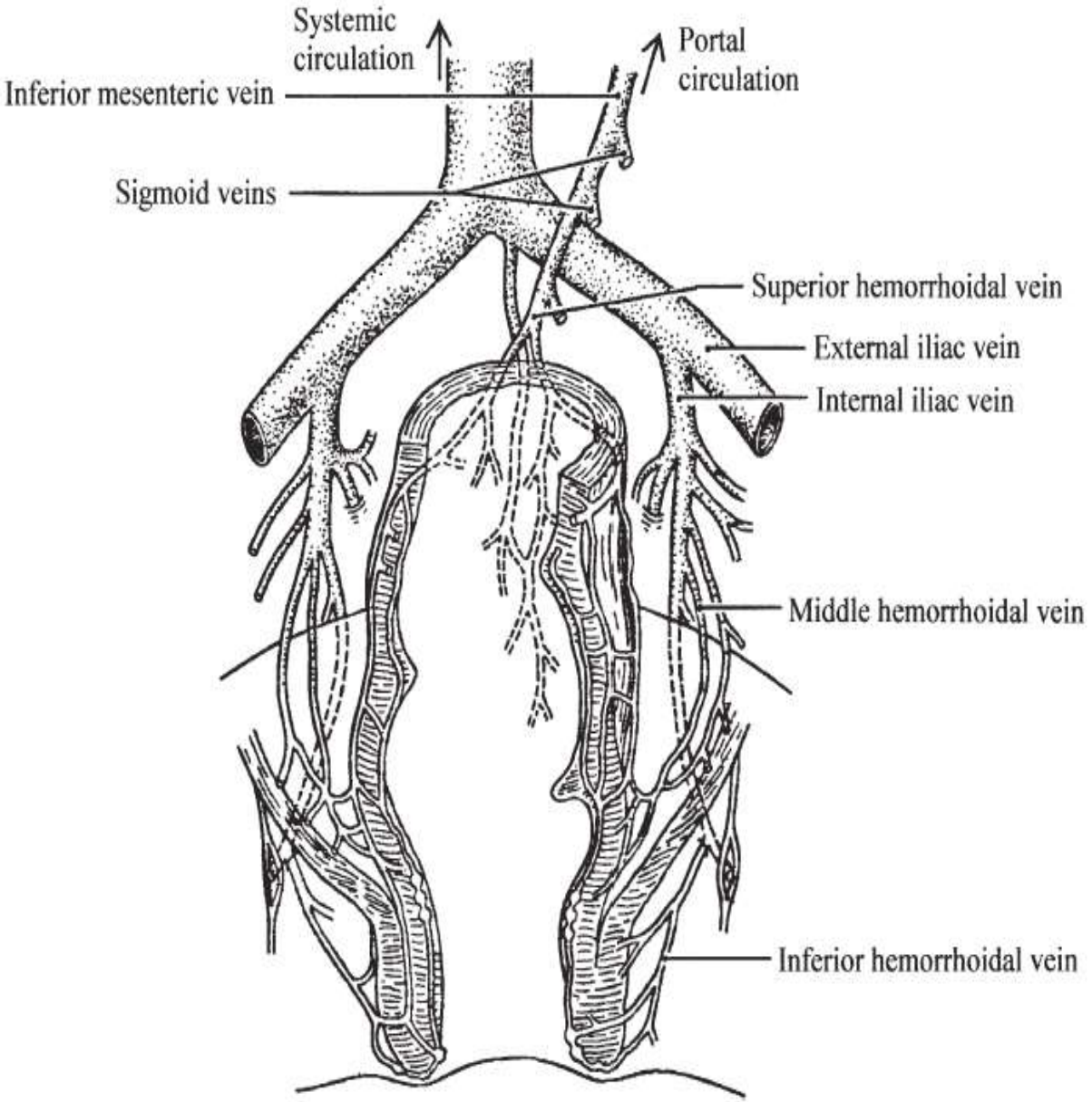


Figure 10. Anatomy of colonal and hemorrhoidal veins.

PHYSIOLOGIC FACTORS

- The human rectum is approximately 15 to 20 cm long.
- When empty of fecal material, the rectum contains only 2 to 3 mL of inert mucous fluid. (low volume of fluid available)
- In the resting state, the rectum is not motile; there are no villi or microvilli on the rectal mucosa .
- However, there is abundant vascularization of the submucosal region of the rectum wall with blood and lymphatic vessels.
- Among the physiologic factors that affect drug absorption from the rectum are the colonic contents,
- and the pH and lack of buffering capacity of the rectal fluids.

Colonic Content

- When systemic effects are desired, greater absorption may be expected from a rectum that is void than from one that is distended with fecal matter.
- A drug will obviously have greater opportunity to make contact with the absorbing surface of the rectum and colon in an empty rectum.
- Therefore, when deemed desirable, an evacuant enema may be administered and allowed to act before the administration of a suppository of a drug to be absorbed.
- Other conditions, such as diarrhea, colonic obstruction due to tumorous growths, and tissue dehydration can all influence the rate and degree of drug absorption from the rectum

Circulation Route

- Drugs absorbed rectally, unlike those absorbed after oral administration, bypass the portal circulation during their first pass into the general circulation, thereby enabling drugs otherwise destroyed in the liver to exert systemic effects.
- The lower hemorrhoidal veins surrounding the colon receive the absorbed drug and initiate its circulation throughout the body, bypassing the liver.
- Lymphatic circulation also assists in the absorption of rectally administered drugs

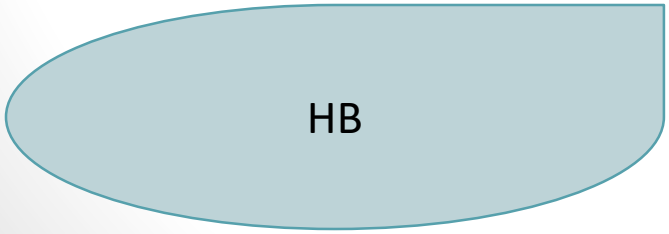
pH and Lack of Buffering Capacity of the Rectal Fluids

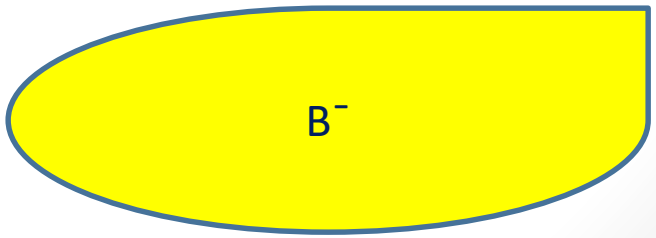
- Because rectal fluids are essentially neutral in pH (7) and have no effective buffer capacity, the form in which the drug is administered will not generally be chemically changed by the environment.
- The suppository base has a marked influence on the release of active constituents. While cocoa butter melts rapidly at body temperature, because of its immiscibility with fluids, it fails to release fat-soluble drugs readily.

Effect of drug ionization and suppository base on release

- Un-ionized drug
- Although un-ionized drugs more readily partition out of water-miscible bases such as glycerinated gelatin and polyethylene glycol, the bases themselves tend to dissolve slowly and thus retard release of the drug

- Ionized drug
- For systemic drug action using a cocoa butter base, it is preferable to incorporate the ionized (salt) form rather than the un-ionized (base) form of a drug to maximize bioavailability.





PHYSICOCHEMICAL FACTORS OF THE DRUG AND SUPPOSITORY BASE

- Physicochemical factors of **the drug** include such properties as:

1. the relative solubility of the drug in lipid and in water and
2. the particle size of a dispersed drug, and surface properties
3. Amount of drug
4. pKa of the drug

- Physicochemical factors **of the base** include :

1. its ability to melt, soften, or dissolve at body temperature,
2. its ability to release the drug substance, and
3. its hydrophilic or hydrophobic character(composition of the base)
4. Rheological properties

Lipid-Water Solubility

- The lipid-water partition coefficient of a drug is an important consideration in the selection of the suppository base and in anticipating drug release from that base.
- A lipophilic drug that is distributed in a fatty suppository base in low concentration has less tendency to escape to the surrounding aqueous fluids than a hydrophilic substance in a fatty base.
- Water soluble bases—for example, polyethylene glycols—that dissolve in the anorectal fluids release for absorption water-soluble and oil-soluble drugs.
- Naturally, the more drug a base contains, the more drug will be available for absorption. However, if the concentration of a drug in the intestinal lumen is above a particular amount, which varies with the drug, the rate of absorption is not changed by a further increase in the concentration of the drug

Drug solubility and suppository formulation

Solubility in		
Fat	Water	Choice of base
Low	High	Fatty base
High	Low	Aqueous base
Low	Low	Intermediate

Particle Size

- For un-dissolved drugs in a suppository, the size of the drug particle will influence its rate of dissolution and its availability for absorption.
- The smaller the particle, the greater the surface area, the more readily the dissolution of the particle and the greater the chance for rapid absorption.

Nature of the Base

- The base must be capable of melting, softening, or dissolving to release its drug for absorption. If the base interacts with the drug to inhibit its release, drug absorption will be impaired or even prevented. Also, if the base irritates the mucous membranes of the rectum, it may initiate a colonic response and prompt a bowel movement, eliminating the prospect of complete drug release and absorption.
- Because of the possibility of chemical and/or physical interactions between the medicinal agent and the suppository base, which may affect the stability and/or bioavailability of the drug, the absence of any drug interaction between the two agents should be ascertained before or during formulation.

Properties of the ideal suppository base

1. **Non-toxic**, **non- irritating** to sensitive and inflamed tissues.
2. **Inert** and **compatible** with medicaments.
3. **Not deteriorated** or **contaminating** the drug during storage.
4. **Easily manufactured** by compression or molding.
5. **Dissolve** or **disintegrate** in mucous secretions or **melt** quickly at body temperature to allow the release of medicament.
6. **Remain molten** for a sufficient period of time to allow pouring into molds.
7. **Solidify rapidly** to minimize sedimentation of dispersed solids.
8. **Contract on cooling** to allow easy withdrawal of the suppository from the mold.
9. Has **wetting** and **emulsifying** properties.
10. **Stable on storage**, keeps its shape during storage or handle does **not change color, odor** and **drug release** pattern.

SUPPOSITORY BASES

- Requisites for a suppository base is that it *should remain solid at room temperature but soften, melt, or dissolve readily at body temperature so that the drug is fully available soon after insertion.* Certain bases are more efficient in drug release than others.

1. **Fatty bases or oleaginous bases** Cocoa butter (theobroma oil) melts quickly at body temperature, but is immiscible with body fluids As for fat-soluble drugs tend to remain in the oil and have little tendency to enter the aqueous physiologic fluids. For water-soluble drugs in cocoa butter, the reverse is usually true and good release results. Also, when irritation or inflammation is to be relieved, as in the treatment of ano-rectal disorders, cocoa butter appears to be the superior base because of its emollient or soothing, spreading action
2. **Water soluble or water miscible bases** glycerinated gelatin or polyethylene glycol, Fat-soluble drugs seem to be released more readily from these bases, but, both of which dissolve slowly in body fluids.
3. **Miscellaneous bases**, generally combinations of lipophilic and hydrophilic substances.

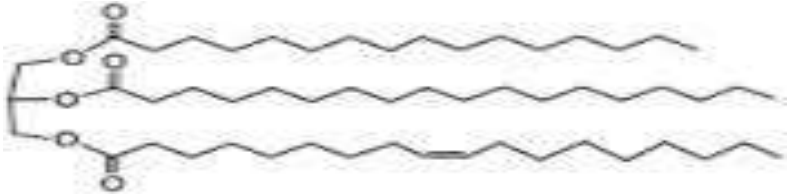
Fatty or Oleaginous Bases

1. Cocoa butter
2. hydrogenated fatty acids of vegetable oils, such as palm kernel oil and cottonseed oil.
3. fat-based compounds ,esters of glycerin with the higher-molecular-weight fatty acids, such as palmitic and stearic acids, such as glyceryl monostearate and glyceryl monopalmitate.

- The bases in many commercial products employ varied combinations of these types of materials to achieve the desired hardness under conditions of shipment and storage and the desired quality of submitting to the temperature of the body to release their medicaments.

Cocoa Butter, NF

- Fat obtained from the roasted seed of Theobroma cacao.
- At room temperature, it is a yellowish-white solid having a faint, agreeable chocolate-like odor.
- Chemically, the main constituent of cocoa butter is the triglyceride derived from palmitic acid, stearic acid, and oleic acid, primarily of oleopalmitostearin and oleodistearin



- Cocoa butter melts at 30°C to 36°C it is an ideal suppository base, melting just below body temperature and yet maintaining its solidity at usual room temperatures.
- However, because of its triglyceride content, cocoa butter exhibits marked polymorphism, or existence in several crystalline forms

Cocoa Butter polymorphism

- When cocoa butter is hastily or carelessly melted at a temperature greatly exceeding the minimum required temperature (about 35°C) and is then quickly chilled, the result is a metastable crystalline form (alpha crystals) with a melting point much lower than that of the original cocoa butter. In fact, the melting point may be so low that the cocoa butter will not solidify at room temperature. (melts at 22°C)
- However, because the crystalline form is a metastable condition, there is a slow transition to the more stable beta form of crystals having the greater stability and a higher melting point. This transition may require several days.
- Consequently, if suppositories that have been prepared by melting cocoa butter for the base do not harden soon after molding, they will be useless to the patient and a loss of time, materials, and prestige to the pharmacist.
- Cocoa butter must be slowly and evenly melted, preferably over a bath of warm water, to avoid formation of the unstable crystalline form and ensure retention in the liquid of the more stable beta crystals that will constitute nuclei upon which the congealing may occur during chilling of the liquid.

Melting point lowering

- Substances such as phenol and chloral hydrate have a tendency to lower the melting point of cocoa butter. If the melting point is low enough that it is not feasible to prepare a solid suppository using cocoa butter alone as the base, solidifying agents like cetyl esters wax (about 20%) or beeswax (about 4%) may be melted with the cocoa butter to compensate for the softening effect of the added substance.
- However, the addition of hardening agents must not be so excessive as to prevent the base from melting in the body, nor must the waxy material interfere with the therapeutic agent in any way so as to alter the efficacy of the product.

Disadvantages of theobroma oil:

1. **Polymorphism**: when melt &solidify it form **different crystal form** depending on the **temperature** if its melt at low temp, not exceed 36 ºC it will form β-polymorph form which is stable form, if melted suddenly &quickly at high temperature then freezing or cooling it will form unstable γ form that melt at 15 ºC, it may form α form that melt at 20 ºC.
2. **Adherence to the mold**, this can be solved by using lubricant agent that is immiscible with the base.
3. **Low m.p**, this can be solved by added medication, adding **white bees wax.**
4. **Low water absorbance (poor water-absorbing capacity)**, this can be solved by adding **surface active agent**.
5. **Stability** problem (slow deterioration during storage, chemical instability).
6. Not suitable for **warm countries**, m.p can be raised by adding white bees wax or a synthetic fatty base such as **Witepsol**.
7. Relatively high cost.

Other fatty bases

- Other bases in this category include commercial products such as
- Fattibase (triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostearate and polyoxyl stearate),
- the Wecobee bases (triglycerides derived from coconut oil) and Witepsol bases (triglycerides of saturated fatty acids C12-C18 with varied portions of the corresponding partial glycerides).

Water-Soluble and Water-Miscible Bases

- The main members of this group are glycerinated gelatin and polyethylene glycols.
- Glycerinated gelatin suppositories may be prepared by dissolving granular gelatin (20%) in glycerin (70%) and adding water or a solution or suspension of the medication (10%).
- A glycerinated gelatin base is most frequently used in preparation of vaginal suppositories, with which prolonged local action of the medicinal agent is usually desired. The glycerinated gelatin base is slower to soften and mix with the physiologic fluids than is cocoa butter and therefore provides a slower release.

Glycerinated gelatin suppositories disadvantages

1. Because glycerinated gelatin-based suppositories have a tendency to **absorb moisture** as a result of the hygroscopic nature of glycerin, they must be protected from atmospheric moisture if they are to maintain their shape and consistency, **difficult to prepare and handle**.
2. These suppositories may have a dehydrating effect and irritate the tissues upon insertion, exerting **a laxative effect**. The water in the formula for the suppositories minimizes this action; however, if necessary, the suppositories may be moistened with water prior to insertion to reduce the initial tendency of the base to draw water from the mucous membranes and irritate the tissues
3. Gelatin is incompatible with protein precipitants such as tannic acid.

Urethral Glycerinated gelatin suppositories

- Urethral suppositories may be prepared from a glycerinated gelatin base of a formula somewhat different from the one indicated earlier.
- For urethral suppositories, the gelatin constitutes about 60% of the weight of the formula, the glycerin about 20%, and the medicated aqueous portion about 20%.
- Urethral suppositories of glycerinated gelatin are much more easily inserted than those with a cocoa butter base owing to the brittleness of cocoa butter and its rapid softening at body temperature

Polyethylene glycols

- Polyethylene glycols are polymers of ethylene oxide and water prepared to various chain lengths, molecular weights, and physical states, the most commonly used being polyethylene glycol 300, 400, 600, 1,000, 1,500, 1,540, 3,350, 4,000, 6,000, and 8,000. Various combinations of these polyethylene glycols may be combined by fusion, using two or more of the various types to achieve a suppository base of the desired consistency and characteristics

PEG	Melting range	PEG	Melting range
300	-15°C -18°C	3350	54°C -58°C
400	4°C -8°C	4600	57°C -61°C
600	20°C -25°C	6000	56°C -63°C
1000	37°C -40°C	8000	60°C -63°C
1450	43°C -46°C		

Polyethylene glycol suppositories

- Polyethylene glycol suppositories do not melt at body temperature but rather dissolve slowly in the body's fluids. Therefore, the base need not be formulated to melt at body temperature.
- Thus, it is possible, in fact routine, to prepare suppositories from polyethylene glycol mixtures having melting points considerably higher than body temperature.
- This property permits a slower release of the medication from the base once the suppository has been inserted,
- and permits convenient storage of these suppositories without need for refrigeration and without danger of their softening excessively in warm weather.
- Further, their solid nature permits slow insertion without fear that they will melt in the fingertips (as cocoa butter suppositories sometimes do).
- Because they do not melt at body temperature but mix with mucous secretions upon dissolution, polyethylene glycol-based suppositories do not leak from the orifice, as do many cocoa butter-based suppositories.
- Polyethylene glycol suppositories that do not contain at least 20% water should be dipped in water just before use to avoid irritation of the mucous membranes after insertion. This procedure prevents moisture being drawn from the tissues after insertion and the stinging sensation

Miscellaneous Bases

- In the miscellaneous group of bases are mixtures of oleaginous and water-soluble or water-miscible materials. These materials may be chemical or physical mixtures.
- Some are preformed emulsions, generally of the water-in-oil type, or they may be capable of dispersing in aqueous fluids, these emulsions prompt emulsification when the suppository makes contact with the aqueous body fluids.
- 1- Polyoxyl 40 stearate, a surface-active agent that is employed in a number of commercial suppository bases. Polyoxyl 40 stearate is a mixture of the monostearate and distearate esters of mixed polyoxyethylene diols and the free glycols, the average polymer length being equivalent to about 40 oxyethylene units. The substance is a white to light tan waxy solid that is water soluble. Its melting point is generally 39°C to 45°C.
- 2-Other surface-active agents useful in the preparation of suppository bases also fall into this broad grouping. Mixtures of many fatty bases (including cocoa butter) with emulsifying agents capable of forming water-in-oil emulsions have been prepared. These bases hold water or aqueous solutions and are said to be hydrophilic.

PREPARATION OF SUPPOSITORIES

- Suppositories are prepared by three methods:
- (a) molding from a melt,
- (b) compression, and
- (c) hand rolling and shaping.
- The method most frequently employed both on a small scale and on an industrial scale is molding.

PREPARATION BY 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,
- (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

- 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 exercised 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.

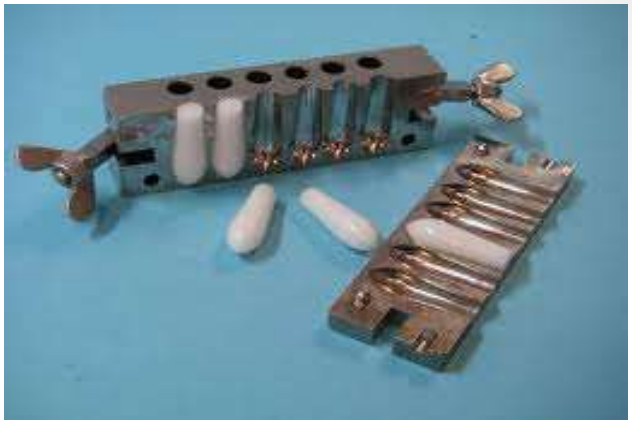
Preparing and Pouring the Melt

- 1-Using the least possible heat, the weighed suppository base material is melted, generally over a water bath, because not a great deal of heat is required. 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.
- 2-Usually, medicinal substances are incorporated into a portion of the melted base by mixing on a glass or porcelain tile with a spatula.
- 3- After incorporation, this material is stirred into the remaining base, which has been allowed to cool almost to its congealing point. Any volatile materials or heat-labile substances should be incorporated at this point with thorough stirring

Molding from the melt

- 3-The melt is poured carefully and continuously into each cavity of the mold, which has been previously equilibrated to room temperature.
- If any un-dissolved or suspended materials in the mixture are denser than the base, so that they have a tendency to settle, constant stirring, even during pouring, is required, else the last filled cavity will contain a disproportionate share of the un-dissolved materials.
- 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.

Molding from the melt



- 4-To ensure a completely filled mold upon congealing, the melt is poured excessively over each opening, actually rising above the level of the mold. The excessive material may form a continuous ribbon along the top of the mold above the cavities. 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.
- The mold is usually placed in the refrigerator to hasten hardening.

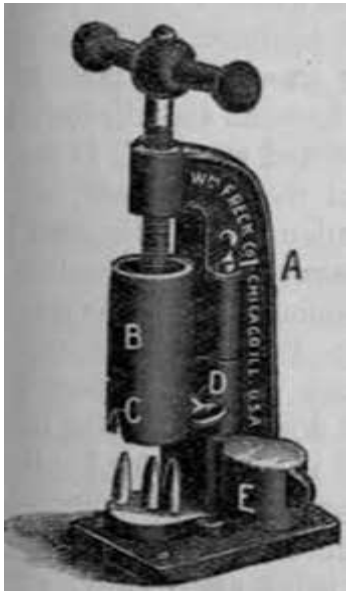
- 5-When the suppositories are hard, the mold is removed from the refrigerator and allowed to come to room temperature. Then the sections of the mold are separated, and the suppositories are dislodged, with pressure being exerted principally on their ends and only if needed on the tips. Generally, little or no pressure is required, and the suppositories simply fall out of the mold when it is opened.

PREPARATION BY COMPRESSION

- Suppositories may be prepared by forcing the mixed mass of the base and the medicaments into special molds using suppository-making machines. In preparation for compression into the molds, the base and the other formula ingredients are combined by thorough mixing, the friction of the process softening the base into a paste-like consistency.
- On a small scale, a mortar and pestle may be used. Heating the mortar in warm water (then drying it) greatly facilitates the softening of the base and the mixing.
- On a large scale, a similar process may be used, employing mechanical kneading mixers and a warm mixing vessel

Compression

- Compression is especially suited for making suppositories that contain heat-labile medicinal substances or a great deal of substances that are insoluble in the base.
- In contrast to the molding method, compression permits no likelihood of insoluble matter settling during manufacture.
- The disadvantage to compression is that the special suppository machine is required and there is some limitation as to the shapes of suppositories that can be made



Compression

- In preparing suppositories with the compression machine, the suppository mass is placed in a cylinder; the cylinder is closed; pressure is applied from one end, mechanically or by turning a wheel; and the mass is forced out of the other end into the mold or die. When the die is filled with the mass, a movable end plate at the back of the die is removed, and when additional pressure is applied to the mass in the cylinder, the formed suppositories are ejected.
- The end plate is returned and the process is repeated until all of the mass has been used. Various sizes and shapes of dies are available.
- It is possible to prepare suppositories of uniform circumference by extrusion through a perforated plate and by cutting the extruded mass to the desired length

PREPARATION BY HAND ROLLING AND SHAPING

- With ready availability of suppository molds of accommodating shapes and sizes, there is little requirement for today's pharmacist to shape suppositories by hand.
- Hand rolling and shaping is a historic part of the art of the pharmacist

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,(density =1) the weight of the suppositories will differ from the weight of suppositories prepared in the same mold with a base of polyethylene glycols. (density =1.2)
- 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.
- The pharmacist should calibrate each suppository mold for the usual base (generally cocoa butter and a polyethylene glycol base) so as to prepare medicated suppositories each having the proper quantity of medicaments.

Calibration of the mold

- The first step in calibration of a mold is to
- prepare molded suppositories from base material alone.
- After removal from the mold,
- the suppositories are weighed and the total weight and average weight of each suppository are recorded (for the particular base used).
- To determine the volume of the mold, the suppositories are carefully melted in a calibrated beaker, and the volume of the melt is determined for the total number as well as for the average of one suppository.

Determination of the Amount of Base Required

- Calculate the amounts of materials needed for the preparation of one or two more suppositories than the number prescribed to compensate for the inevitable loss of some material and to ensure having enough material (prepare an extra 1 or 2 supp.)
- Verify the required amount of drug is provided in each suppository. Because the volume of the mold is known (from **mold calibration** the determined volume of the melted suppositories formed from the base),
- the volume of the drug substances subtracted from the total volume of the mold will give the volume of base required.
- The total volume of these materials is subtracted from the volume of the mold,
- and the appropriate amount of base is added.

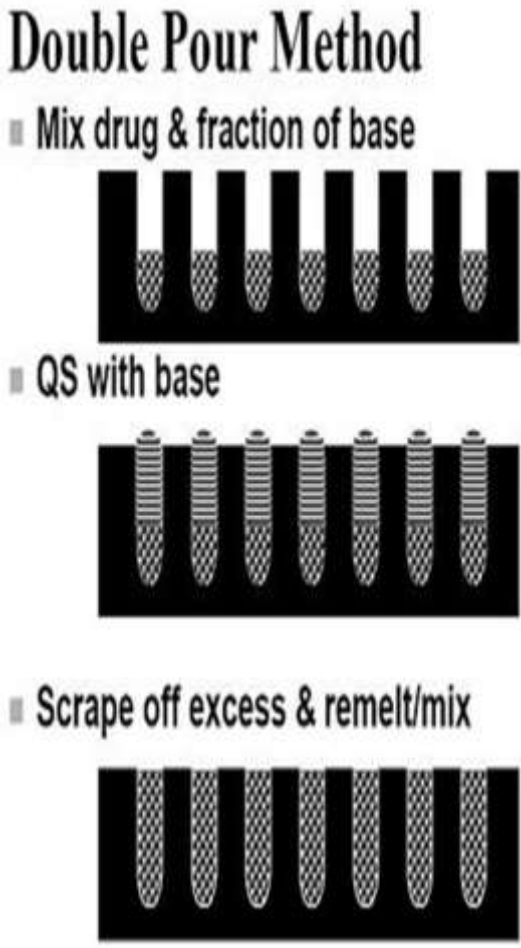
Because the bases are solid at room temperature, the volume of base may be converted to weight from the density of the material

Medicated suppositories

- If the added amounts of medicaments are slight, they may be considered to be negligible, and no deduction from the total volume of base may be deemed necessary. In preparation of suppositories, it is generally assumed that if the quantity of active drug is less than 100 mg,/ 2-g suppository weight then the volume occupied by the powder is insignificant and need not be considered
- Obviously, if a suppository mold of less than 2 g is used, the powder volume may need to be considered.
- However, if considerable quantities of other substances are to be used, the volumes of these materials are important and should be used to calculate the amount of base actually required to fill the mold.

Other calibration method

- Another method for determination of the amount of base is called the **double pour method** in the preparation of medicated suppositories requires the following steps:
- (a) weigh the active ingredient for the preparation of a single suppository;
- (b) dissolve it or mix it (depending on its solubility in the base) with a portion of melted base insufficient to fill one cavity of the mold, and add the mixture to a cavity;
- (c) add additional melted base to the cavity to fill it completely;
- (d) allow the suppository to congeal and harden; and
- (e) remove the suppository from the mold and weigh it.
- The weight of the active ingredients subtracted from the weight of the suppository yields the weight of the base. This amount of base multiplied by the number of suppositories to be prepared in the mold is the total amount of base required



Example

- For example, if 12 mL of cocoa butter is required to fill a suppository mold and if the medicaments in the formula have a collective volume of 2.8 mL, 9.2 mL of cocoa butter will be required. By multiplying 9.2 mL times the density of cocoa butter, 0.86 g/ mL, it may be calculated that 7.9 g of cocoa butter will be required. After adjusting for the preparation of an extra suppository or two, the calculated amount is weighed.

Displacement value DV

- Displacement value is defined as the
- The quantity of drug that displaces one part of the base
- Ex hydrocortisone has a displacement value of 1.5
- Means 1.5g hydrocortisone displaces 1g the suppository base
- If the density of the drug equals the density of the base. The drug will displace the same amount of base
- If the density of the drug is more than the density of the base the drug will displace low amount of base
- if the density of the drug is less than the density of the base the drug will displaces high amount of base
- DV for liquids equals 1

Calculations using displacement values

- Prepare six codeine phosphate suppositories (D.V=1.1)using mold of 1g size each supp. Containing 60mg /supp.
- prepare 10 supp. to compensate for any loss
- 60X10=600mg=0.6g codeine phosphate
- Supp. Base 1gX10=10g total wt. of pure base

- Drug base
- 1.1 displace 1g base replaced=(1gX0.6)/1.1=0.55
- 0.6 ?

- Amount of base needed is 10g-0.55= 9.45g

Displacement values D.V. of some common drugs incorporated into suppositories

Drug	D.V.	Drug	D.V.
Aminophylline	1.3	Morphine sulphate	1.6
Aspirin	1.1	Paracetamol	1.5
Bismuth subgallate	2.7	Phenobarbital	1.1
Castor oil	1	Phenobarbital Sod.	1.2
Chloral hydrate	1.4	Resorcinal	1.5
Codeine phosphate	1.1	Sulfur	1.6
Diphenhydramine HCl	1.3	Theophylline sodium acetate	1.7
Hydrocortisone	1.5	Zinc oxide	4.7
Metronidazole	1.7	Zinc sulphate	2.4
Morphine HCl	1.6		

Density (Dose Replacement) Calculations for Suppositories

- 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
- Three methods of calculating the quantity of base that the active medication will occupy and the quantities of ingredients required are illustrated here:
- (a) dosage replacement factor,
- (b) density factor, and
- (c) occupied volume methods

DETERMINATION OF THE DOSAGE REPLACEMENT FACTOR METHOD

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

- where
- E is the weight of the pure base suppositories, and
- G is the weight of suppositories with X% of the active ingredient.
- Cocoa butter is arbitrarily assigned a value of 1 as the standard base

DOSAGE REPLACEMENT FACTORS FOR SELECTED DRUGS

Balsam of peru	0.83	Phenol	0.9
Bismuth subgallate	0.37	Procaine HCl	0.8
Bismuth subnitrate	0.33	Quinine HCl	0.83
Boric acid	0.67	Resorcin	0.71
Camphor	1.49	Silver protein, mild	0.61
Castor oil	1.00	Spermaceti	1.0
Chloral hydrate	0.67	White or yellow wax	1.0
Ichthammol	0.91	Zinc oxide	0.15-0.25
Phenobarbital	0.81		

Example 1

- 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 g. What will be the total weight of each suppository?
- Because 100 mg of phenobarbital is to be contained in an approximately 2.0-g suppository, it will be about 5% phenobarbital.
- $f = \frac{[100(E-G)]}{[(G)(X)]} + 1$
- $0.81 = \frac{[100(2-G)]}{[(G)(5)]} + 1$
- G= 2.015g weight of the medicated suppository

DETERMINATION OF DENSITY FACTOR 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 g of medication. The weight of medication per suppository, B, is equal to 1 g/10 supp = 0.1 g/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:

$$density\ factor = \frac{B}{A - C + B}$$

- A is the average weight of blank,
- B is the weight of medication per suppository, and
- C is the average weight of medicated suppository

DENSITY FACTORS FOR COCOA BUTTER SUPPOSITORIES

Alum	1.7	Digitalis Leaf	1.6	Quinine HCl	1.2
Aminophylline	1.1	Glycerin	1.6	Resorcinol	1.4
Aspirin	1.3	Ichthammol	1.1	Sodium bromide	2.3
Barbital	1.2	Iodoform	4.0	Spermaceti	1.0
Belladonna Extract	1.3	Menthol	0.7	Sulfathiazole	1.6
Benzoic Acid	1.5	Morphine HCl	1.6	Tannic acid	1.6
Bismuth Carbonate	4.5	Opium	1.4	White wax	1.0
Bismuth Salicylate	4.5	Paraffin	1.0	Witch hazel fluid extract	1.1
Bismuth Subgallate	2.7	Peruvian Balsam	1.1	Zinc oxide	4.0
Bismuth Subnitrate	6.0	Phenobarbital	1.2	Zinc sulfate	2.8
Boric Acid	1.5	Phenol	0.9		
Castor Oil	1.0	Potassium Bromide	2.2		
Chloral Hydrate	1.3	Potassium Iodide	4.5		
Cocaine HCl	1.3	Procaine	1.2		

Example 2

- **Prepare 12 acetaminophen 300 mg suppositories using cocoa butter. The average weight of the cocoa butter blank is 2 g and the average weight of the medicated suppository is 1.8 g.**
- Take the weight of the medication required for each suppository and divide by the density factor of the medication to find the replacement value of the suppository base
- $density\ factor\ D.F\ = \frac{B}{A-C+B} = \frac{0.3}{2-1.8+0.3} = 0.6$
- Replacement value =B/D.F=0.3/0.6=0.5
- Subtract this quantity from the blank suppository weight
- 2-0.5=1.5
- Multiply by the number of suppositories required to obtain the quantity of base and the drug required for the prescription
- 12X1.5= 18 g of cocoa butter required
- 12X0.3= 3.6g of the drug required

DETERMINATION OF OCCUPIED VOLUME METHOD

1. Determine the average weight per mold (blank) using the designated base.
2. Weigh out enough base for 12 suppositories.
3. Divide the density of the active drug by the density of the 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 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 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

Example 3

- **Prepare 10 suppositories, each containing 200 mg of a drug with a density of 3.0. The base has a density of 0.9, and a prepared blank weighs 2.0 g. Using the determination of occupied volume method, prepare the requested suppositories.**
- From step 1: The average weight per mold is 2.0 g.
- From step 2: The quantity required for 10 suppositories is 2 g× 10 = 20 g.
- From step 3: The density ratio is 3.0/0.9 = 3.3.
- From step 4: The amount of suppository base displaced by the active drug is 2.0 g/3.3 = 0.6 g.
- From step 5: The weight of the base required is 20 - 0.6 g = 19.4 g.
- From step 6: The quantity of active drug required is 0.2 × 10 g = 2.0 g.
- The required weight of the base is 19.4 g, and the weight of the active drug is 2 g

Practical examples

- **Example: Calculate the quantities required to make 10 theobroma oil supp. (2g mold) each containing 400 mg of zinc oxide (DV= 4.7).**

1. Calculate the total weight of zinc oxide required. 0.4X10=4g
2. Calculate what weight of base would be required to prepare10 un medicated supp. 2gX10=20g
3. Determine what weight of base would be displaced by the medicament. Replaced base =drug/DV = 4/4.7=0.85
4. Calculate, therefore, the weight of base required to prepare the medicated supps. 20-0.85= 19.15g wt of base required

- **Glycero-gelatin base** has a **density 1.2 times greater than theobroma oil**. Therefore, a 1 g supp. mold will produce a 1 g theobroma oil supp., but a 1.2 g glycero-gelatin supp. This factor must be taken into account in displacement value calculations.

Example

- **Calculate the quantities required to make six glycero gelatin supp. (4 g mold), each containing100 mg aminophylline (Displacement value = 1.3)**
- **Drug 6X100=0.6g**
- **glycerin gelatin Base 6X4gX1.2 =28.8g**
- **glycerin gelatin Base replaced = 0.6/1.3=0.46X1.2=0.55g**

- **Base required 28.8-0.55g=28.25g of the base required**

Example

- **prepare 10 supp. non-medicated (only theobroma oil) weight 12 gm. Then prepare 10 medicated supps weighted 14 g, the weight of drug incorporated =4.2 gm, calculate the replacement value?**
- 14 - 4.2= 9.8 g
- 12 - 9.8 = 2.2 g the amount of theobroma oil displace by the drug
- Base Drug
- 2.2 gm 4.2 gm
- 1 x = 1.909≈ 1.91 D.V

Example

- **what quantities are required to prepare 8 theobroma oil supps, in a 4 g mold, containing 1% w/w lignocaine hydrochloride?**
- **Base required 8 X 4= 32g**
- Calculate the total weight of the drug required (1% of the total weight). 1%of 32g=0.32g drug

EXAMPLES OF RECTAL SUPPOSITORIES

SUPPOSITORY	COMMERCIAL PRODUCT	ACTIVE CONSTITUENT	TYPE OF EFFECT	CATEGORY AND COMMENTS
Bisacodyl	Dulcolax (Boehringer-Ingelheim)	10 mg	Local	Cathartic. Base: hydrogenated vegetable oil
Hydrocortisone	Anusol-HC (Salix)	25 mg	Local	Pruritus ani, inflamed hemorrhoids, other inflammatory conditions of the anorectum. Base: hydrogenated glycerides
Indomethacin	Indocin	50 mg	Systemic	Anti-inflammatory: Base: polyethylene glycols

Semi- solid dosage forms

Chapter 10

Ointments, Creams, and Gels

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 9th Edition

Semi solid dosage form

- Ointments, creams, and gels are semisolid dosage forms intended for topical application.
- They may be applied to the

1. skin,
2. placed on the surface of the eye,
3. or used nasally,
4. vaginally,
5. or rectally.

Most of these preparations are used for the effects of the therapeutic agents they contain.

The un-medicated ones are used for their physical effects as protectants or lubricants

Local vs. systemic

Topical applications can be designed for either local effects or systemic absorption. The following distinction is an important one with regard to dermatologic applications.

1) Local : A topical dermatological product is designed to deliver drug into the skin in treating dermal disorders, with the skin as the target organ
2) Systemic effects. Systemic drug absorption should always be considered when using topical products if the patient is pregnant or nursing, because drugs can enter the fetal blood supply and breast milk and be transferred to the fetus or nursing infant.

- A transdermal product is designed to deliver drugs through the skin (percutaneous absorption) to the general circulation for systemic effects, with the skin not being the target organ

OINTMENTS

- Ointments are semisolid preparations intended for external application to the skin or mucous membranes.
- Ointments according to the BP :
  - *Ointments are formulated to provide preparations that are immiscible, miscible, or emulsifiable with skin secretion.*
- Ointments may be medicated or not.
- Un-medicated ointments are used for the physical effects they provide as protectants, emollients, or lubricants. Ointment bases, as described, may by used for their physical effects or as vehicles for medicated ointments

Ideal ointment base

- In terms of physiochemical properties as:

1. Stable
2. Neutral in reaction
3. Compatible with all medication (water or fat soluble)
4. Free from objection odor
5. Non-staining
6. Melt or soften at body temperature

OINTMENT BASES

Ointment bases are generally classified by the USP into four groups

- (a) oleaginous bases
- (b) absorption bases,
- (c) water-removable bases
- (d) water-soluble bases

A-Oleaginous Bases (hydrocarbon base)

- Oleaginous bases are also termed hydrocarbon bases. On application to the skin,

1. they have an emollient effect,
2. protect against the escape of moisture, useful in treatment of dry scaly conditions.
3. are effective as occlusive dressings
4. can remain on the skin for long periods without drying out, they are not absorbed by the skin.
5. and because of their immiscibility with water are difficult to wash off.

- Water and aqueous preparations may be incorporated, but only in small amounts and with some difficulty.
- When powdered substances are to be incorporated into hydrocarbon bases, liquid petrolatum (mineral oil) may be used as the levigating agent

Hydrocarbon ointment bases

Petrolatum USP

- is a purified mixture of semisolid hydrocarbons obtained from petroleum. It is an unctuous mass, varying in color from yellowish to light amber. It melts at 38°C to 60°C and may be used alone or in combination with other agents as an ointment base. Petrolatum is also known as yellow petrolatum and petroleum jelly. A commercial product is Vaseline

White Petrolatum, USP

- is a purified mixture of semisolid hydrocarbons from petroleum that has been wholly or nearly decolorized. It is used for the same purpose as petrolatum, but because of its lighter color, it is considered more esthetically pleasing by some pharmacists and patients. White petrolatum is also known as white petroleum jelly. A commercial product is White Vaseline

Yellow Ointment, USP

contains 50g yellow wax (bees wax) in 950 g petrolatum, called simple ointment, has slightly greater viscosity than petrolatum

White Ointment, USP.

- This ointment differs from yellow ointment by substitution of white wax (bleached and purified yellow wax) and white petrolatum in the formula.

B- Absorption Bases

- Absorption bases are of two types:
- (a) those that permit the incorporation of aqueous solutions resulting in the formation of water-in-oil (W/O) emulsions (e.g., hydrophilic petrolatum), they consist of a hydrocarbon base combined with a water-in-oil emulsifier such as wool alcohol or wool fat
- (b) those that are W/O emulsions (syn: emulsion bases) that permit the incorporation of additional quantities of aqueous solutions (e.g., lanolin).

1. These bases may be used as emollients, although they do not provide the degree of occlusion afforded by the oleaginous bases.
2. Absorption bases are not easily removed from the skin with water washing, because the external phase of the emulsion is oleaginous.
3. Absorption bases are useful as pharmaceutical adjuncts to incorporate small volumes of aqueous solutions into hydrocarbon bases.

- This is accomplished by incorporating the aqueous solution into the absorption base and then incorporating this mixture into the hydrocarbon base.

1-Hydrophilic Petrolatum, USP

- Hydrophilic Petrolatum has the following formula for the preparation of 1000 g

Cholesterol	30 g
Stearyl alcohol	30 g
White wax	80 g
White petrolatum	860 g

- It is prepared by melting the stearyl alcohol and white wax on a steam bath, adding the cholesterol with stirring until dissolved, adding the white petrolatum, and allowing the mixture to cool while stirring until congealed.

2- Aquaphor

- A commercial product, Aquaphor, a variation of hydrophilic petrolatum, has the capacity to absorb up to three times its weight in water and useful to help incorporate a water-soluble drug, e.g., tobramycin sulfate, into a oleaginous ointment base.
- **Aquaphor** is a petrolatum based ointment manufactured by Eucerin, . It is available in two forms
- 1-The Original Ointment contains mineral oil and ceresin,(derived from earth wax) and lanolin alcohol.
- 2-The Healing Ointment contains mineral oil, ceresin, lanolin alcohol, panthenol, glycerin, and bisabolol, known as levomenol, is a natural alcohol. It is the primary constituent of the essential oil from German chamomile)
- This concept is used in the preparation of ophthalmic ointments. Eucerin is a 50% W/O emulsion.

3-Lanolin, USP (Anhydrous lanolin)

- Lanolin, obtained from the wool of sheep, is a purified wax-like substance that has been cleaned, deodorized, and decolorized.
- It contains not more than 0.25% water. Additional water may be incorporated into lanolin by mixing.
- Modified Lanolin, USP, is lanolin processed to reduce the contents of free lanolin alcohols and any detergent and pesticide residues.

C-Water-Removable Bases

1. Water-removable bases are oil-in-water emulsions resembling creams.
2. Because the external phase of the emulsion is aqueous, they are easily washed from skin and are often called water-washable bases.
3. They may be diluted with water or aqueous solutions.
4. They can absorb serous discharges.
5. Hydrophilic Ointment, USP, is an example of this type of base.

Hydrophilic Ointment, USP,

Ingredient	Amount (grams)	use
Methylparaben	0.25	Preservative
Propylparaben	0.15	Preservative
Sodium lauryl sulfate	10.00	Emulsifying agent
Propylene glycol	120.00	
Stearyl alcohol	250.00	Oil phase
White petrolatum	250.00	Oil phase
Purified water	370.00	

- The formula is used for the preparation of about 1000 g. The stearyl alcohol and white petrolatum are melted together at about 75°C.
- The other agents, dissolved in the purified water, are added with stirring until the mixture congeals.

D-Water-Soluble Bases

1. Water-soluble bases do not contain oleaginous components.
2. They are completely water washable and often referred to as greaseless.
3. Because they soften greatly with the addition of water, large amounts of aqueous solutions are not effectively incorporated into these bases.
4. They mostly are used for incorporation of solid substances.

Polyethylene glycol (PEG) ointment, NF, is the prototype example of a water-soluble base.

Polyethylene Glycol, PEG

- PEG is a polymer of ethylene oxide and water represented by the formula H(OCH2CH2)n OH, in which n represents the average number of oxyethylene groups. The numeric designations associated with PEGs refer to the average molecular weight of the polymer. PEGs having average molecular weight

Molecular weight	Physical state
below 600	clear, colorless liquids
Above 600 and lower than 1000	semisolids
above 1,000	wax-like white materials

- The greater the molecular weight, the greater the viscosity.

Polyethylene Glycol Ointment NF

The general formula for preparation of 1,000 g of PEG ointment is

PEG 3350	400 g
PEG 400	600 g

- Combining PEG 3350, a solid, with PEG 400, a liquid, results in a very pliable semisolid ointment.
- If a firmer ointment is desired, the formula may be altered to contain up to equal parts of the two ingredients.
- When aqueous solutions are to be incorporated into the base, substitution of 50 g of PEG 3350 with an equal amount of stearyl alcohol is advantageous in rendering the final product firmer.

Classification and properties of USP ointment bases

Hydrocarbon base	Absorption base	Water removable base	Water soluble base
White petrolatum USP White ointment USP	Hydrophilic petrolatum USP Lanolin USP	Hydrophilic ointment USP	Polyethylene Glycol ointment NF
Hydrocarbons	Anhydrous or W/O emulsion	O/W emulsion	Water soluble
Highly occlusive	Moderate to high	Low to moderate	Minimal
Maintain prolonged contact with application site	Allows incorporation of aqueous solutions	Water-washable; may be diluted with water	Water- washable; no water-insoluble residue
Emollient effect	Emollient effect	Allows absorption of serous discharge	

SELECTION OF THE APPROPRIATE BASE

- Selection of the base to use in the formulation of an ointment depends on careful assessment of a number of factors, including the following:

1. Desired release rate of the drug substance from the ointment base
2. Desirability of topical or percutaneous drug absorption
3. Desirability of occlusion of moisture from the skin
4. Stability of the drug in the ointment base
5. Effect, if any, of the drug on the consistency or other features of the ointment base
6. Desire for a base easily removed by washing with water
7. Characteristics of the surface to which it is applied
   an **ointment** is generally applied to dry, scaly skin; a **cream** is applied to weeping or oozing surfaces, and a **topical emulsion** is applied to intertriginous areas or where friction may occur, as between the thighs or under the armpit. The base which provides the best combination of the most desired attributes should be selected.

Effect of skin delivery system on the horny layer hydration and skin permeability

Delivery system	Examples/constituents	Effect on skin hydration	Effect on skin permeability
Occlusive dressing	Plastic film, unperforated waterproof plaster	Prevents water loss; full hydration	Marked increase
Occlusive patch	Most transdermal patches	Prevents water loss; full hydration	Marked increase
Lipophilic material	Paraffins, oils, fats, waxes, fatty acids and alcohols, esters, silicones	Prevents water loss; may produce full hydration	Marked increase
Absorption base	Anhydrous lipid material plus water/oil emulsifiers	Prevents water loss; marked hydration	Marked increase
Emulsifying base	Anhydrous lipid material plus oil/water emulsifiers	Prevents water loss; marked hydration	Marked increase
Water/oil emulsion	Oily creams	Retards water loss; raised hydration	Increase
Oil/water emulsion	Aqueous creams	May donate water; slight hydration increase	Slight increase?
Humectant	Water-soluble bases, glycerol, glycols	May withdraw water, decreased hydration	Can decrease or act as penetration enhancer
Powder	Clays, organics, inorganics, 'shake' lotions	Aid water evaporation, decreased excess hydration	Little effect on stratum corneum

PREPARATION OF OINTMENTS

Ointments are prepared by two general methods,

(a) incorporation

(b) fusion,

depending primarily on the nature of the ingredients

1- Incorporation

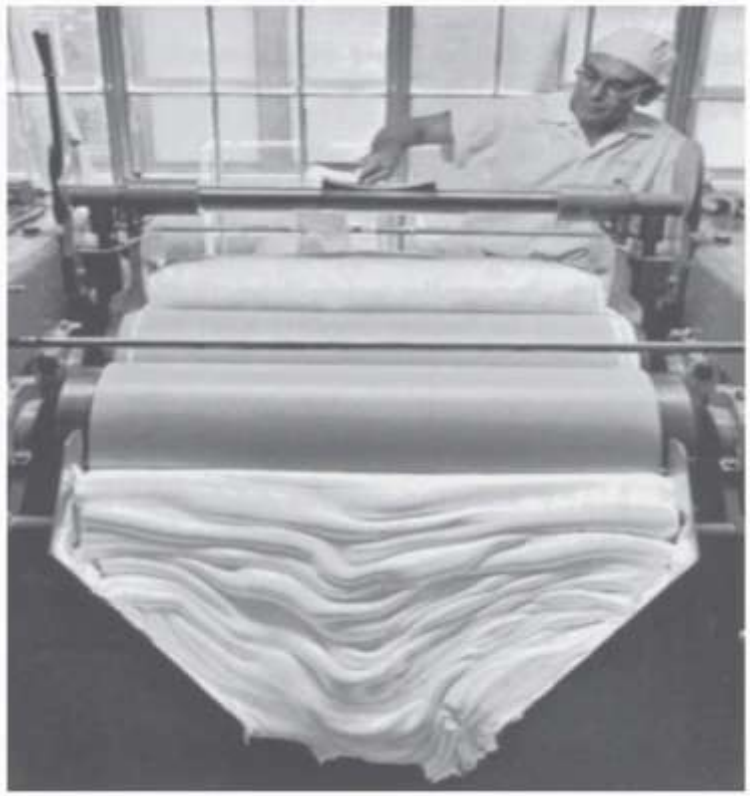
- The components are mixed until a uniform preparation is attained
- On a small scale, as in extemporaneous compounding, the pharmacist may mix the components using
- a mortar and pestle,
- or a spatula may be used to rub the ingredients together on an ointment slab
- (a large glass or porcelain plate or pill tile).
- Some pharmacists use nonabsorbent parchment paper to cover the working surface; being disposable, the paper eliminates cleaning the ointment slab. If using an ointment parchment pad, it is best to not allow too long a contact of the ointment with the parchment, as it may soften and tear.

Incorporation

- Others will use an ointment mill, an electronic mortar and pestle, or a device called an “Unguator” which allows a pharmacist to place the ingredients in a plastic ointment jar with a special lid that allows for a mixing blade to be used to mix the ingredients in the dispensing container. These devices can be controlled manually or via computer software.

Incorporation

- Ointment or roller mills can be used to force coarsely formed ointments through stainless steel or ceramic rollers to produce ointments uniform in composition and smooth in texture
- Small ointment mills also find use in product development laboratories and in small batch manufacture or compounding.



Incorporation of Solids.

- When preparing an ointment by spatulation, the pharmacist works the ointment with a stainless steel spatula having a long, broad blade and periodically removes the accumulation of ointment on the large spatula with a smaller one.
- If the components of an ointment react with metal (as does iodine), hard rubber spatulas may be used.
- The ointment is prepared by thoroughly rubbing and working the components together on the hard surface until the product is smooth and uniform.
- The ointment base is placed on one side of the working surface and the powdered components, previously reduced to fine powders and thoroughly blended in a mortar, on the other side.
- A small portion of the powder is mixed with a portion of the base until uniform.
- Geometric dilution is continued until all portions of the powder and base are combined thoroughly and uniformly blended.

Levigating

- It often is desirable to reduce the particle size of a powder or crystalline material before incorporation into the ointment base so the final product will not be gritty.
- This may be done by levigating, or mixing the solid material in a vehicle in which it is insoluble to make a smooth dispersion. The levigating agent (e.g., mineral oil for bases in which oils are the external phase, or glycerin for bases in which water is the external phase) should be physically and chemically compatible with the drug and base.
- The levigating agent should be about equal in volume to the solid material.
- A mortar and pestle are used for levigation. This allows both reduction of particle size and dispersion of the substance in the vehicle.
- After levigation, the dispersion is incorporated into the ointment base by spatulation or with the mortar and pestle until the product is uniform.

Incorporation of soluble solids

- Solids soluble in a common solvent that will affect neither the stability of the drug nor the efficacy of the product may first be dissolved in that solvent (e.g., water or alcohol) and the solution added to the ointment base by spatulation or in a mortar and pestle.
- The mortar and pestle method is preferred when large volumes of liquid are added, because the liquid is more captive than on an ointment slab.

Incorporation of gummy material

- For incorporating a gummy material, such as camphor, pulverization by intervention can be used. The material is dissolved in a solvent and spread out on the pill tile. The solvent is allowed to evaporate, leaving a thin film of the material onto which the other ingredient or ingredients are spread. The material is then worked into the ingredients by trituration with a spatula.

Incorporation of liquids

- Liquid substances or solutions of drugs, are added to an ointment only after due consideration of an ointment base's capacity to accept the volume required.
- Only very small amounts of an aqueous solution may be incorporated into an oleaginous ointment, whereas hydrophilic ointment bases readily accept aqueous solutions.
- When it is necessary to add an aqueous preparation to a hydrophobic base, the solution first may be incorporated into a minimum amount of a hydrophilic base and then that mixture added to the hydrophobic base. However, all bases, even if hydrophilic, have their limits to retain liquids, beyond which they become too soft or semiliquid.
- Alcoholic solutions of small volume may be added easily to oleaginous vehicles or emulsion bases.
- Natural balsams, such as Peru balsam, are usually mixed with an equal portion of castor oil before incorporation into a base. This reduces the surface tension of the balsam and allows even distribution of the balsam throughout the base

2-Fusion

- By the fusion method, all or some of the components of an ointment are combined by being melted together and cooled with constant stirring until congealed.
- Components not melted are added to the congealing mixture as it is being cooled and stirred.
- Naturally, heat-labile substances and any volatile components are added last, when the temperature of the mixture is low enough not to cause decomposition or volatilization of the components.
- Substances may be added to the congealing mixture as solutions or as insoluble powders levigated with a portion of the base.
- On a small scale, fusion may be conducted in a porcelain dish or glass beaker.
- On a large scale, it is carried out in large steam-jacketed kettles. Once congealed, the ointment may be passed through an ointment mill (in large-scale manufacture) or rubbed with a spatula or in a mortar to ensure a uniform texture.

Fusion

- Medicated ointments and ointment bases containing components such as beeswax, paraffin, stearyl alcohol, and high-molecular-weight PEGs, which do not lend themselves well to mixture by incorporation, are prepared by fusion.
- By this general process, the materials with the highest melting points are heated to the lowest required temperature to produce a melt.
- The additional materials are added with constant stirring during cooling of the melt until the mixture is congealed.
- In this way, not all of the components are subjected to the highest temperature.
- Alternative methods entail melting the component with the lowest melting point first and adding the remaining components in order of their melting points or simply melting all of the components together under slowly increasing temperature.
- By these methods, a lower temperature is usually sufficient to achieve fusion because of the solvent action exerted by the first melted components on the others.

Fusion

- In preparation of ointments having an emulsion base, the method of manufacture often involves both melting and emulsification. The water-immiscible components such as the oil and waxes are melted together in a steam bath to about 70°C to 75°C.
- Meantime, an aqueous solution of the heat-stable, water-soluble components is prepared and heated to the same temperature as the oleaginous components.
- Then the aqueous solution is slowly added, with mechanical stirring, to the melted oleaginous mixture.
- The temperature is maintained for 5 to 10 minutes and the mixture is slowly cooled and stirred until congealed. If the aqueous solution is not at the same temperature as the oleaginous melt, some of the waxes will solidify on addition of the colder aqueous solution to the melted mixture

COMPENDIAL REQUIREMENTS FOR OINTMENTS

- Ointments and other semisolid dosage forms must meet USP tests for

1. Microbial content,
2. Minimum fill,
3. Packaging, storage, and labeling.

- Ophthalmic ointments must also meet tests for sterility and metal particles content

MICROBIAL CONTENT

- Usually topical applications are not required to be sterile. They must, however, meet acceptable standards for microbial content, and preparations prone to microbial growth must contain antimicrobial preservatives.
- Preparations that contain water tend to support microbial growth to a greater extent than water-free preparations.
- Among the antimicrobial preservatives used to inhibit microbial growth in topical preparations are methylparaben, propylparaben, phenols, benzoic acid, sorbic acid, and quaternary ammonium salts.
- Microbial limits are stated for certain articles in the USP. For example, Betamethasone Valerate Ointment, USP, must meet the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.
- These particular microbes have special importance in dermatologic preparations because of their capacity to infect the skin, which for patients being treated for a skin condition, is already compromised.

Approx. minimum water activity required for growth of selected M.O.

M.O.	**Water activity a_w**
Most bacteria	0.9
Pseudomonas spp.	0.96
Enterobacteraceae spp.	0.93
Staphylococcus aureus	0.86
Most spoilage yeast	0.7
Most spoilage moulds	0.6

pH of the formulation

pH	
Below 3	Hostile for yeast
5	Favor moulds and yeasts proliferation but not support bacterial growth
9	Hostile for some MO

MINIMUM FILL

- The USP's minimum fill test is determination of the net weight or volume of the contents of filled containers to ensure proper contents compared with the labeled amount

“Microbiological Attributes of Non-sterile Pharmaceutical Products” USP

Strict adherence to environmental control and application of good manufacturing practices to minimize both the type and the number of microorganisms in unsterilized pharmaceutical products. This involves

1. the testing of raw materials,
2. use of acceptable water,
3. in-process controls, and
4. final product testing.

The USP states certain products should be routinely tested for microorganisms because of the way they are used.

Thus, dermatologic products should be examined for P. aeruginosa and S. aureus, and those intended for rectal, urethral, or vaginal use should be tested for yeasts and molds, common offenders at these sites of application

PACKAGING, STORAGE, AND LABELING

- Ointments and other semisolid preparations are packaged either in large-mouth ointment jars or in metal or plastic tubes.
- Semisolid preparations must be stored in well-closed containers to protect against contamination and in a cool place to protect against product separation in heat.
- When required, light-sensitive preparations are packaged in opaque or light-resistant containers.
- In addition to the usual labeling requirements for pharmaceutical products, the USP directs the labeling for certain ointments and creams include the type of base used (e.g., water soluble or water insoluble).

Ophthalmic applications

- The ointment base selected for an ophthalmic ointment must not be irritating to the eye and must permit the diffusion of the medicinal substance throughout the secretions bathing the eye.
- Ointment bases used for ophthalmics should have a softening point close to body temperature, both for comfort and for drug release.
- Most often, mixtures of white petrolatum and liquid petrolatum (mineral oil) are used as the base in medicated and un-medicated (lubricating) ophthalmic ointments.
- Sometimes a water-miscible agent such as lanolin is added.
- Medicinal agents are added to an ointment base either as a solution or as a finely micronized powder. The ointment is made uniform and smooth by fine milling

Residence time

- In general, ocular ophthalmic drug penetration is limited by the short residence time on the surface of the eye because of rapid removal by tearing and other natural mechanisms, the small surface area of the cornea for drug absorption, and the cornea's natural resistance to drug penetration .
- Compared with ophthalmic solutions, ophthalmic ointments and gels provide extended residence time on the surface of the eye, increasing the duration of their surface effects and bioavailability for absorption into the ocular tissues.
- Ophthalmic ointments are cleared from the eye as slowly as 0.5% per minute, compared with solutions, which can lose up to 16% of their volume per minute .

Sterility

- In addition to the previously stated quality standards for ointments, ophthalmic ointments must meet the USP sterility tests and the test for metal particles in ophthalmic ointments.
- Rendering an ophthalmic ointment sterile requires special technique and processing. For a number of reasons, the terminal sterilization of a finished ointment by standard methods may be problematic. Steam sterilization or ethylene oxide methods are ineffective because neither is capable of penetrating the ointment base.
- Although dry heat sterilization can penetrate the ointment base, the high heat required may pose a threat to the stability of the drug substance and introduces the possibility of separating the ointment base from the other components .
- Because of these difficulties, terminal sterilization generally is not undertaken. Rather, strict methods of aseptic processing are employed as each drug and nondrug component is rendered sterile and then aseptically weighed and incorporated in a final product that meets the sterility requirement . When an antimicrobial preservative is needed, among those used are methylparaben (0.05%) and propylparaben (0.01%) combinations, phenylmercuric acetate (0.0008%), chlorobutanol (0.5%), and benzalkonium chloride (0.008%).

EXAMPLES OF OPHTHALMIC OINTMENTS

CATEGORY	OINTMENT	ACTIVE INGREDIENT	USE
Anti bacterial	Chloramphenicol ophthalmic	1%	Ophthalmic bacterial infection
Adrenocortical steroid	Dexamethasone sodium phosphate ophthalmic	0.05%	Anti-inflammatory

CREAMS

- Pharmaceutical creams are semisolid preparations containing one or more medicinal agents dissolved or dispersed in either a W/O emulsion or an oil-in-water emulsion or in another type of water-washable base for external application
- The definition eliminates thick liquids (lotions or emulsion lotions)
- Creams are pharmaceutically and cosmetically appealing.
- They are soft, easy to apply, cooling to the skin, and many are water- removable.

Creams vanishing creams

- The so-called vanishing creams are oil-in-water emulsions containing large percentages of water and stearic acid or other oleaginous components.
- Vanishing creams get their name from the fact that they seemed to disappear when spread onto the skin.
- After application of the cream, the water evaporates, leaving behind a thin residue film of the stearic acid or other oleaginous component.

Creams

- Creams find primary application in topical skin products and in products used rectally and vaginally.
- Many patients and physicians prefer creams to ointments because they are easier to spread and remove.
- Pharmaceutical manufacturers frequently manufacture topical preparations of a drug in both cream and ointment bases to satisfy the preference of the patient and physician.

ADRENOCORTICAL STEROIDS OINTMENTS AND CREAMS

Potency	PREPARATION Ointment , creams	USUAL STRENGTH OF ACTIVE INGREDIENT	Use
ointments> creams	Clobetasol propionate	0.05%	Relief of dermatitis Anal itching Psoriasis Eczema Skin rash Urticara
	Betamethasone dipropionate	0.05%	
	Mometasone furoate	0.1%	
	Triamcinolone acetonide	0.1%	
	Fluocinolone acetonide	0.03%	
	Hydrocortisone acetate	0.5% and 1%	

ANTIFUNGAL OINTMENTS AND CREAMS

Condition	Topical Medication
Oral Thrush	Nystatin Clotrimazole Miconazole Metronidazole
Vaginal Yeast Infection	Miconazole nitrate cream 2% Clotrimazole
Jock Itch	Whitefield ointment Terbinafine ointment 1% Clotrimazole Cream 1% Miconazole Cream 2% Econazole cream 1% Ketocanazole Tolnaftate
Ringworm	
Athlete's Foot	

PASTES

- Pastes are semisolid preparations intended for application to the skin.
- They generally contain a larger proportion of solid material (such as 25%) than ointments and therefore are stiffer.
- They consist of finely powdered medicaments combined with white soft paraffin or liquid paraffin or with a non greasy base made from glycerol, mucilage or soaps
- Pastes can be prepared in the same manner as ointments, by direct mixing or the use of heat to soften the base prior to incorporating the solids, which have been comminuted and sieved. However, when a levigating agent is to be used to render the powdered component smooth, a portion of the base is often used rather than a liquid, which would soften the paste.

Pastes

- Because of the stiffness of pastes, they remain in place after application and are effectively employed to absorb serous secretions.
- They are used for local effect on a discrete skin area for corrosive skin materials like salicylic acid thereby not compromising the healthy skin
- Because of their stiffness and impenetrability, pastes are not suited for application to hairy parts of the body.
- They can be used to adsorb wound exudates
- Used for babies nappy products
- Also may be used as a sun filter

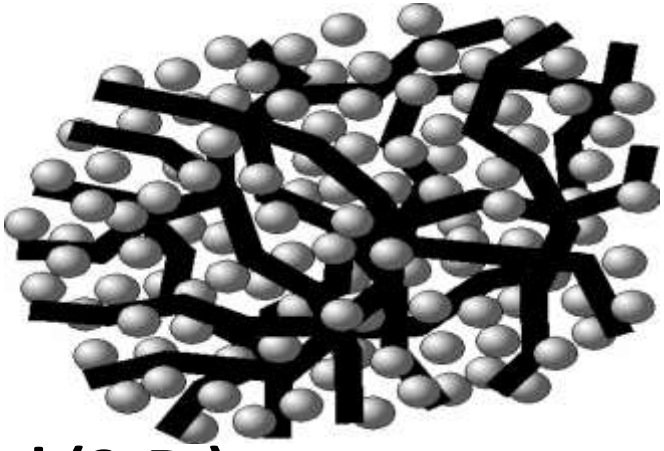
Zinc oxide paste (Lassar's Plain Zinc Paste),

- Among the few pastes in use today is which is prepared by mixing 25% each of zinc oxide and starch with white petrolatum. The product is very firm and is better able to protect the skin and absorb secretions than is zinc oxide ointment

DERMATOLOGIC PASTES

Category	PREPARATION	USUAL STRENGTH OF ACTIVE INGREDIENT	Use
Astringent, protectant	Zinc oxide ointment	40%	Topical astringent, protective in skin conditions such as diaper rash

GEL



- Gels are semisolid **three dimensional (3-D)**systems consisting of **colloidal** dispersions of small or large molecules in an aqueous liquid vehicle rendered jellylike by the addition of a gelling agent.
- Solid – like properties sustain sheer, mechanical characters of solids
- Undergo liquid –solid transition(sol-gel)

Gel point transition from liquid colloidal dispersion (S/L) into 3-D semisolid gel (L/S)

Pharmaceutical Gels

- Gels have good appearance usually translucent or transparent
- Medicated gels may be prepared for administration by various routes, including the skin, and to mucous membranes of the eye, the nose, the vagina, and the rectum, giving high rates of release of the medicament and rapid absorption

Classification of gels

- According to the fluid entrapped in the 3-D three dimensional structure

1. Hydrogel (highly adsorbent, degree of fluidity)
2. Organogels (non crystalline, non greasy, thermoplastic)
3. Xerogel

According to the nature of the bond involved in the 3 dimensional structure

Lyophobic (Two-phase gel)

- Type I flocculated solids
- Type II card house floc
- mass consisting of floccules of small distinct particles is termed a two-phase system, often referred to as a magma.

Lyophilic (Single-phase gels)

- Type 1 chemical
- Type 2 physical
- are gels in which the macromolecules are uniformly distributed throughout a liquid with no apparent boundaries between the dispersed macromolecules and the liquid.

Gel preparation (Main Procedure)

- Hydrophilic gelling agent is dispersed in water with continuous stirring (at the appropriate temperature for the gelling agent)
- Drug is dissolved in a suitable solvent with the preservatives, and other additives
- This solution is added to the gelling agent dispersion

Gel formulation

- In addition to the gelling agent and water, gels may be formulated to contain a drug substance,
- solvents, such as alcohol and/or propylene glycol;
- humectants as glycerin (30%) or propylene glycol (15%) also
- antimicrobial preservatives, such as methylparaben and propyl paraben or chlorhexidine gluconate; and
- stabilizers, such as edetate disodium.

Gelation methods

1-Phase separation (Temperature effect)

2-Effect of Solvent addition

3- Addition of Electrolytes

4-Chemical Reaction

Antiacne Creams and Gels

Category	Medication	Dosage form	Use
Affects keratin formation	Tretinoin Isotretinoin Adapalene	Solution, cream, gel	Derivative of vitamin A for topical treatment of acne vulgaris
Antibiotic	Erythromycin Clindamycin		
Antiseptic Kertolytic	Benzoyl Peroxide Azelaic acid		

Collodion and aerosols and foams

Collodion

- **Collodion** is a flammable, syrupy solution of pyroxylin (a.k.a. "nitrocellulose", "cellulose nitrate", "flash paper", and "gun cotton") in ether and alcohol.
- Collodion (pyroxylin solution USP), is a clear or slightly opalescent viscous liquid prepared by dissolving pyroxylin (4% w/v) in a 3:1 mixture of ether and alcohol.
- The resulting solution is highly volatile and flammable and should be preserved in a tight container remote from fire at a temperature not exceeding 30°C.

Collodion types

- There are two basic types: flexible; non-flexible.
- The flexible type is often used as a surgical dressing or to hold dressings in place. When painted on the skin, collodion dries to form a flexible nitrocellulose film. While it is initially colorless, it discolors over time.

Non-flexible collodion

- The product is capable of forming a protective film on application to the skin and the volatilization of the solvent.
- The film is useful in holding the edges of an incised wound together.
- However, its presence on the skin is uncomfortable because of its inflexible nature.
- Non-flexible collodion is often used in theatrical make-up.
- Liquid bandage
- Physicians frequently apply the coating over bandages or stitched incisions to make them waterproof and to protect them from external stress.

Flexible Collodion

- This product, which is flexible, has a greater appeal when a pliable film is acceptable.
- Flexible collodion is prepared by adding
- 2% camphor and
- 3% castor oil to collodion.
- The castor oil renders the product flexible, permitting its comfortable use over skin areas that are normally moved, such as joints, fingers, and toes.
- The camphor makes the product waterproof.
- Because the medicinal use of a collodion depends on the formation of a protective film, the film should be durable, tenacious in adherence, flexible, and occlusive

Salicylic Acid Collodion

- Many wart-remover preparations consist of acetic acid and salicylic acid in an acetone collodion base used in the treatment of warts by keratolysis. especially in the removal of corns from the toes.
- Salicylic acid collodion is a 10% solution of salicylic acid in flexible collodion.
- As the volatile solvents evaporate, a dry celluloid-like film is left on the skin.
- Patients who use such products should be advised about their proper use. The product should be applied one drop at a time on the corn or wart, allowing time to dry before the next drop is added. Because salicylic acid can irritate normal, healthy skin, every attempt must be made to ensure application directly on the corn or wart.
- A useful preventive measure is to line the adjacent healthy skin with some white petrolatum prior to application of the product. Proper tightening and storage of the product after use are absolutely necessary because of the volatility of the vehicle.

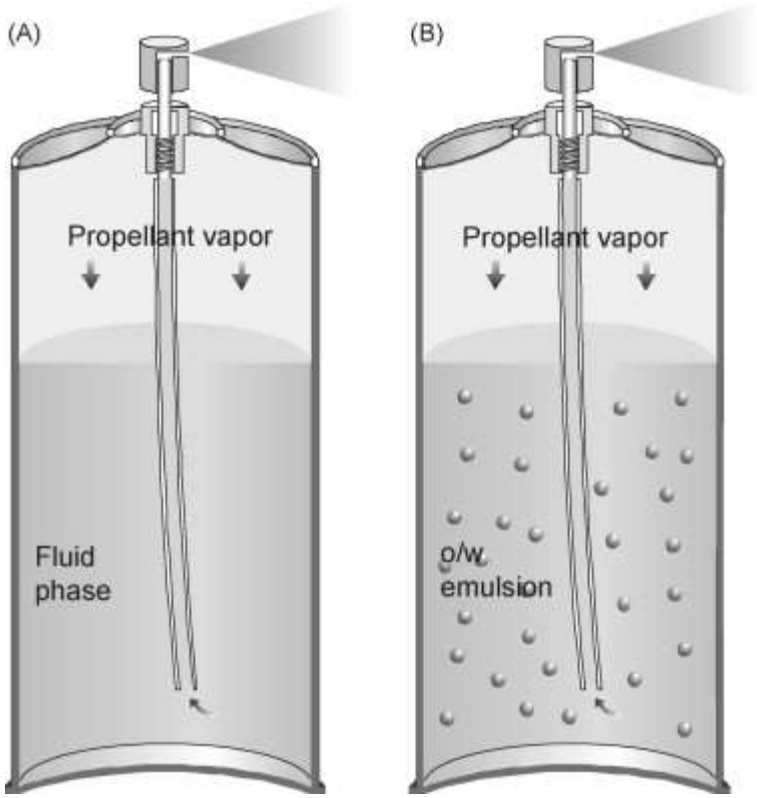
Salicylic acid Collodion

Pharmaceutical Aerosols

- Aerosols Pressurized dosage forms containing one or more active ingredients that, upon valve actuation, emit a fine dispersion of liquid and/or solid materials **in a gaseous medium**.
- An aerosol formulation consists of two components:

1. The **product concentrate** is the active drug combined with additional ingredients or co-solvents required to make a stable and efficacious product. The concentrate can be a solution, suspension, emulsion, semisolid, or powder.
2. The **propellant** provides the force that expels the product concentrate from the container and additionally is responsible for the delivery of the formulation in the proper form. When the propellant is a liquefied gas or a mixture of liquefied gases, it can also serve as the **solvent** or vehicle for the product concentrate. When the **propellant** is in the **external phase ,** foams are not created but sprays or wet streams result.

Aerosols


(A)
Propellant vapor
Fluid
phase
(B)
Propellant vapor
o/w
emulsion

Pharmaceutical Foams

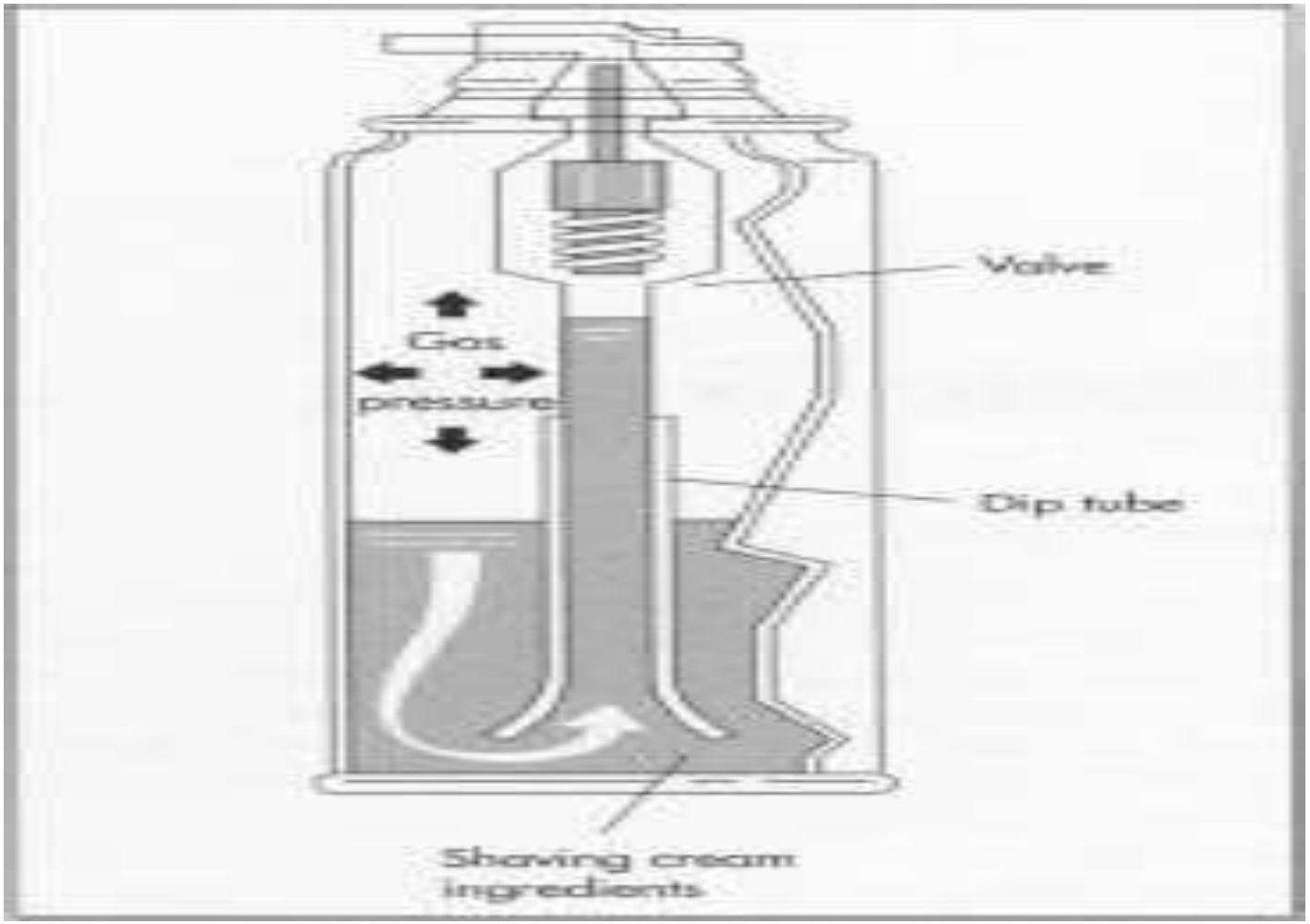
A foam is a coarse dispersion of a **gas in a liquid**

Foams are emulsified systems packaged in special dispensing devices that contain dispersed gas bubbles, usually in a liquid continuous phase, that when dispensed has a fluffy, semisolid consistency.

The product concentrate in an emulsion consists of the active ingredient, aqueous and/or non-aqueous vehicles, and a surfactant.

Foams are produced when the product concentrate is dispersed throughout the propellant and the **gas** is in the **internal phase**; i.e., the emulsion behaves like o/w emulsions.

Foams



Advantage of foams and aerosols

- Probably the most convincing argument for the use of foams is ease of use by the patient, and consumer acceptance.
- Foam formulations are generally easier to apply, are less dense, and spread more easily than other topical dosage forms. Used for vagina, rectal and for burn dressing
- Foams may be formulated in various ways to provide emollient or drying functions to the skin, depending on the formulation constituents.
- The use of topical aerosols provides the patient a means of applying the drug in a convenient manner, to the desired surface area without the use of the fingertips, making the procedure less messy than with most other types of topical preparations.

Disadvantages

- Among the disadvantages to the use of topical aerosols are the difficulty in applying the medication to a small area and the greater expense associated with the aerosol package.
- However, only a few pharmaceutical foams are commercially available.

Topical aerosols

Class	Examples	
Anti-infective agents	Povidone iodine Tolnaftate Terbinafine	Lamisil®
Adrenocortical steroids	Betamethasone dipropionate and valerate, Dexamethasone, and Triamcinolone acetonide	
Local anesthetic	Dibucaine hydrochloride.	
Hair growth	Minoxidil	

Foam types

- Depending on the components, the emitted product can be a **stable foam** (shaving cream type)
- A quick **breaking foam** creates a foam when emitted from the container but the foam collapses in a relatively short time.
- This type of foam is used to apply the product concentrate to a large area without having to manually rub or spread the product. Also, the active drug is more rapidly available because the foam quickly collapses.

Topical Breaking Foams

Antifungal

1. Ketoconazole 2% foam
2. Undecylenate 10%

Topical Breaking Foams

Adrenocortical steroids

- Betamethasone valerate 0.12%
- Clobetasol propionate 0.05%

Stable foams

- Stable foams are produced when surfactants are used that have limited solubility in both the organic and aqueous phases.
- Surfactants concentrate at the interface between the propellant and the aqueous phase forming a thin film referred to as the "lamella." It is the specific composition of this lamella that dictates the structural strength and general characteristics of the foam.
- Thick and tightly layered lamellae produce very structured foams which are capable of supporting their own weight

Surfactants used

1. Anionic surfactants: Fatty acids saponified with triethanolamine,
2. Nonionic surfactants: such as the polyoxyethylene fatty esters, polyoxyethylene sorbitan esters, alkyl phenoxy ethanols, and alkanolamides.

The nonionic surfactants are present fewer compatibility problems because they charge no electronic charge

VAGINAL FOAMS

- Aerosol foams containing **estrogenic** substances and **contraceptive agents** are commercially available. The foams are used intravaginally in the same manner as for creams.
- The aerosol package contains an inserter that is filled with foam and the contents placed in the vagina through activation of the plunger.
- The foams are generally o/w emulsions resembling light creams. They are water miscible and non-greasy.

RECTAL FOAMS

- Some commercial rectal foams use inserters, to relieve inflammatory anorectal disorders
- **ProctoFoam** (Schwartz),
- pramoxine hydrochloride 1% and hydrocortisone 1%

CAPSULES

Chapter 7

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 9th Edition

Capsules

- Capsules are solid dosage forms in which medicinal agents and/or inert substances are enclosed in a small shell of gelatin. Gelatin capsule shells may be hard or soft, depending on their composition.

Hard and soft gelatin capsules

These differ in both their

- 1 **Mechanical properties** Hard gelatin capsules are less flexible, whereas soft gelatin capsules are more flexible
- 2 **Capsule design**. Hard gelatin capsules are composed of two pieces, termed the caps and the body, and soft gelatin capsules are composed of a one piece capsule shell.
- 3 **Capsule Fill.** A wide range of formulation types may be included within the interior of the capsule. For example, powders, tablets, semisolids and nonaqueous liquids/gels may be filled into *hard* capsules, with powders being the most common formulation option. Soft gelatin capsules are usually filled with non-aqueous liquids containing the therapeutic agent either dispersed or dissolved within this carrier

Advantages of capsules

Elegant and Attractive (colored) and readily identified

Conveniently **Carried (resist mechanical stress)**,

Easily swallowed There is no need for spoons or other measuring devices,(shell is inert and easily digested in the GIT)

Are **Tasteless** and **Odorless** when swallowed (cover the taste and odor of unpleasant drugs)

Available for many medications in a **variety of dosage** strengths, providing flexibility to the prescriber and **accurate** individualized dosage for the patient.

They are packaged and shipped by manufacturers at **lower cost** and with less breakage

They are also **more stable** and have a longer shelf life than their liquid counterparts. (can be made as light resistant)

Disadvantages

- The disadvantages of capsule formulations include:
- ■ the requirement for specialized manufacturing equipment
- ■ potential stability problems associated with capsules
- containing liquid fills
- ■ problems regarding the homogeneity of fill weight and
- content may be associated with capsule formulations.

Types of gelatin capsules

- 1- Hard Gelatin Capsule
- Hard gelatin capsule shells are used in most commercial medicated capsules.
- The community pharmacist also uses hard gelatin capsules in the extemporaneous compounding of prescriptions.

Hard Gelatin Capsules

- The empty capsule shells are made of gelatin, sugar, and water. As such, they can be clear, colorless, and essentially tasteless.
- They may be colored with various FD&C and D&C dyes and made opaque by adding agents such as titanium dioxide.
- Most commercially available medicated capsules contain combinations of colorants and opaquants to make them distinctive, many with caps and bodies of different colors

Gelatin

- Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals.
- It is available in the form of a fine powder, a coarse powder, shreds, flakes, or sheets.
- **Normally, hard gelatin capsules contain 13% to 16% of moisture**.
- Type A
- Acid treated collagen
- Type B
- Alkali treated collagen

Storage conditions of gelatin

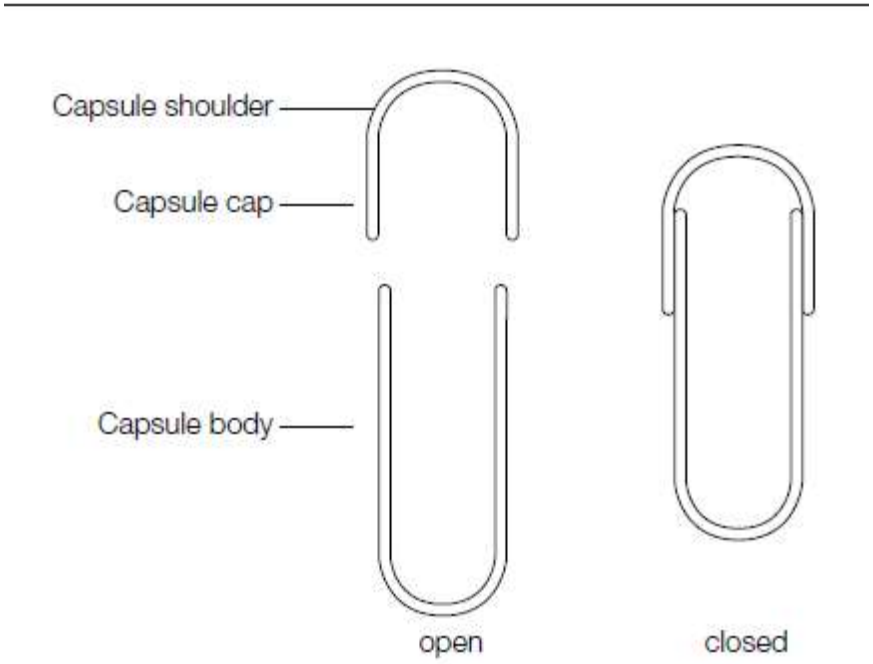
- Gelatin is stable in air when dry but is subject to **microbial decomposition** when it becomes moist.
- Gelatin if stored in an environment of high humidity, additional moisture is absorbed by the capsules, and they may become **distorted and lose their rigid shape**.
- In an environment of extreme dryness, some of the moisture normally present in the gelatin capsules is lost, and the capsules may become **brittle and crumble when handled**.
- Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excessive humidity or dryness
- Because moisture may be absorbed by gelatin capsules and may affect hygroscopic agents within, many capsules are packaged along with a small packet of a **desiccant material** to protect against the absorption of atmospheric moisture.
- The desiccant materials most often used are **dried silica gel, clay, and activated charcoal.**

Gelatin after administration

- Although gelatin is insoluble, it does soften in cold water through the absorption of water up to 10 times its weight of water.
- Some patients prefer to swallow a capsule wetted with water or saliva because a wetted capsule slides down the throat more readily than a dry capsule.
- Gelatin is soluble in hot water and in warm gastric fluid; a gelatin capsule rapidly dissolves and exposes its contents.
- Gelatin, being a protein, is digested by proteolytic enzymes and absorbed.

THE MANUFACTURE OF HARD GELATIN CAPSULE SHELLS

- Hard gelatin capsule shells are manufactured in two sections, the capsule body and a shorter cap.
- The two parts overlap when joined, with the cap fitting snugly over the open end of the capsule body.



1. **Dipping and Spinning** The shells are produced industrially by the mechanical **dipping** of pins or pegs of the desired shape and diameter into a temperature-controlled reservoir of melted gelatin mixture. The pegs, made of manganese bronze, are affixed to plates, each capable of holding up to about 500 pegs. Each plate is mechanically lowered to the gelatin bath, the pegs submerged to the desired depth and maintained for the desired period to achieve the proper length and thickness of coating.
2. **Drying** Then the plate and the pegs are slowly lifted from the bath and the gelatin is **dried** by a gentle flow of temperature- and humidity-controlled air.
3. **Trimming and Stripping** When dried, each capsule part is **trimmed** mechanically to the proper length and **removed** from the pegs,
4. **Joining** Then the capsule bodies and caps are **joined** together.

Capsule identification

- Capsules and tablets also may be imprinted with the names or monograms of the manufacturer, the assigned national drug code number, and other markings making the product identifiable and distinguishable from other products.

Large scale processing of gelatin

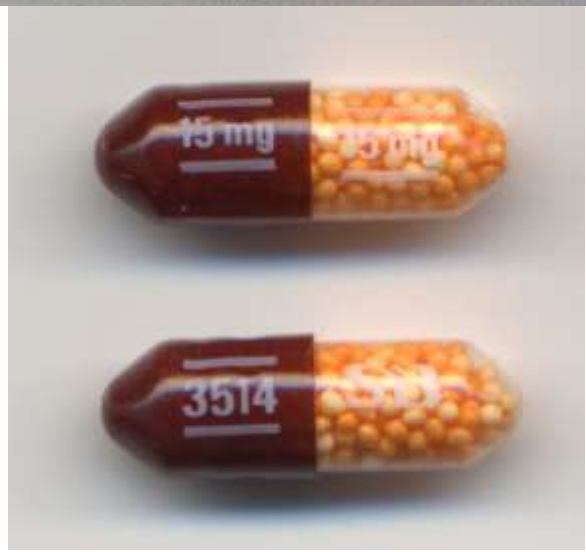
A- Hard gelatin capsules

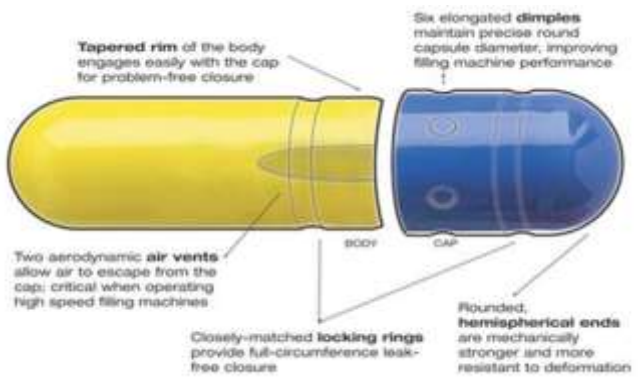
- It is important that the thickness of the gelatin walls be strictly controlled so that the capsule's body and cap fit snugly to prevent disengagement.
- The pegs on which the caps are formed are slightly larger in diameter than the pegs on which the bodies are formed, allowing the telescoping of the caps over the bodies.
- In capsule shell production, there is a continuous dipping, drying, removing, and joining of capsules as the peg-containing plates rotate in and out of the gelatin bath.

Capsule shapes and designs

- A manufacturer also may prepare distinctive-looking capsules by altering the usual rounded shape of the capsule-making pegs.

1. By **tapering the end** of the body-producing peg while leaving the cap-making peg rounded, one manufacturer prepares capsules differentiated from those of other manufacturers (Pulvules, Eli Lilly). Another manufacturer uses capsules with the ends of both the bodies and caps highly tapered (Spansule Capsules, SmithKline Beecham).
2. **Snap-fit** . The original Snap-fit construction enables the two halves of the capsule shells to be positively joined through locking grooves in the shell walls. The two grooves fit into each other and thus ensure reliable closing of the filled capsule.





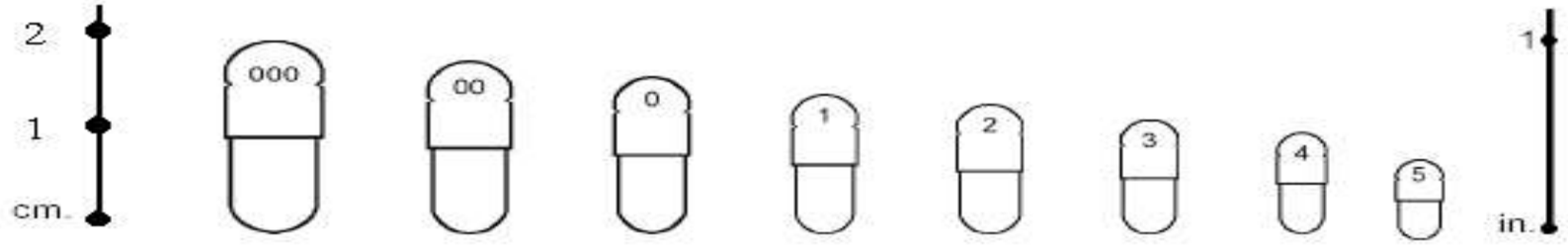
CAPSULE SIZES

- Empty gelatin capsules are manufactured in various lengths, diameters, and capacities.
- The size selected for use is determined by
  - The amount of fill material to be encapsulated.
  - The density and compressibility of the fill will largely determine to what extent it may be packed into a capsule shell
- For estimation, a comparison may be made with powders of well known features and an initial judgment made as to the approximate capsule size needed to hold a specific amount of material.
- However, the final determination may be largely the result of trial and error.
- For human use, empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available
- Larger capsules are available for veterinary use.
- For prescriptions requiring extemporaneous compounding, hard gelatin capsules permit a wide number of options for the physician.
- The pharmacist may compound capsules of a single medicinal agent or combination of agents at the precise dosage prescribed for the individual patient

APPROXIMATE CAPACITY OF EMPTY GELATIN CAPSULES

	Capsule size							
	000	00	0	1	2	3	4	5
Volume (mL)	**1.40**	**0.95**	**0.68**	**0.50**	**0.37**	**0.30**	**0.21**	**0.13**
Drug substance (mg)[a]								
Quinine sulfate	650	390	325	227	195	130	97	65
Sodium bicarbonate	1430	975	715	510	390	325	260	130
Aspirin	1040	650	520	325	260	195	162	97

[a] Amount may vary with the degree of pressure used in filling the capsules



THE CAPSULE SIZE

- An easy method to select the proper capsule size is to

1. Weigh the ingredients for the required number of capsules to be prepared
2. Place the powdered in a graduated cylinder , then tap the cylinder until no change in volume is obtained (tapped density) and obtain the volume occupied by the powder
3. Divide the volume by the number of capsules to be prepared

Selecting the capsule size

- To determine the capsule size to be used
- Capsule fill weight =tapped density of formulation X capsule volume

- Example
- Formulation of capsule has a fill weight of 450mg and tapped density of 0.8g/ml
- Volume occupied =0.45g/0.8g/ml=0.56ml
- So the size 0 capsule is appropriate (0.54ml)

PREPARATION OF FILLED HARD GELATIN CAPSULES

- The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps.

1. Developing and preparing the formulation and selecting the capsule size
2. Filling the capsule shells
3. Capsule sealing (optional)
4. Cleaning and polishing the filled capsules

1- DEVELOPING THE CAPSULE FORMULATION

- In dry formulations, the active and inactive components must be blended thoroughly to ensure a **uniform powder mix** for the fill.
- Care in blending is especially important for **low-dose drugs**, since lack of homogeneity in blending may result in significant therapeutic consequences.
- Preformulation studies are performed to determine whether all of the formulation's bulk powders may be effectively blended together as such or require **reduction of particle size** or any other processing to achieve homogeneity.

Particle size of capsule fill

- To achieve uniform drug distribution, it is advantageous if the density and particle size of the drug and nondrug components are similar.
- This is particularly important when a drug of low dosage is blended with other drugs or nondrug fill .
- When necessary, particle size may be reduced by milling to produce particles ranging from about **50 to 1,000 µm.**
- Milled powders may be blended effectively for uniform distribution throughout a powder mix when the drug's dosage is **10 mg or greater.**
- For drugs of lower dose or when smaller particles are required, micronization is employed. Depending on the materials and equipment used, micronization produces particles ranging from about **1 to 20 µm.**

Formulation Ingredients

- A **diluent or filler** may be added to the formulation to produce the proper capsule fill volume. **Lactose, microcrystalline cellulose, and starch** are commonly used for this purpose. In addition to providing bulk, these materials often provide cohesion to the powders, which is beneficial in the transfer of the powder blend into capsule shells.
- **Disintegrants** are frequently included in a capsule formulation to assist the breakup and distribution of the capsule's contents in the stomach. Among the disintegrants used are pregelatinized starch, croscarmellose, and sodium starch glycolate

Large Scale Production, Lubricants

- The powder mix or granules must be free-flowing to allow steady passage of the capsule fill from the hopper through the encapsulating equipment and into the capsule shells.
- The addition of a **lubricant or glidant** such as fumed silicon dioxide, magnesium stearate, calcium stearate, stearic acid, or talc (about 0.25% to 1%) to the powder mix enhances flow properties
- When magnesium stearate(water insoluble) is used as a lubricant, it can retard penetration of GIT fluids and delay drug dissolution and absorption
- A surface active agent such as sodium lauryl sulfate to facilitate wetting by GIT fluids

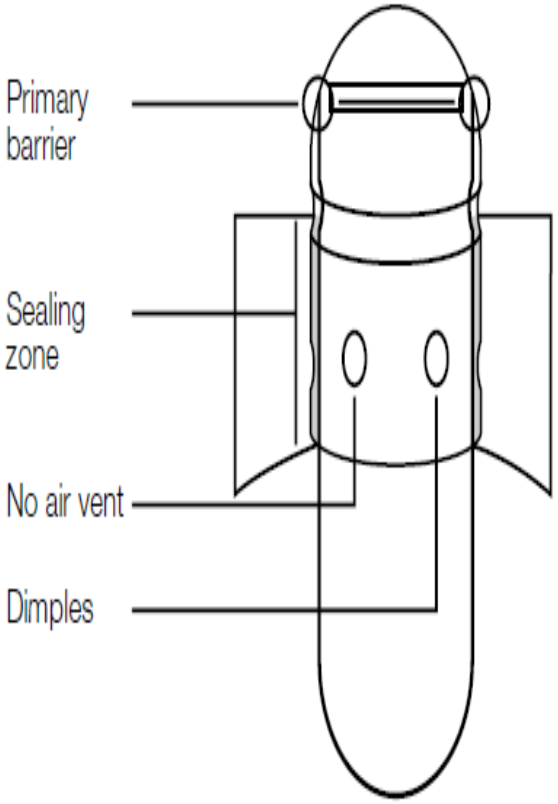
Encapsulation of different ingredients

1. Inserting tablets or small capsules into capsules is sometimes useful in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules This may be done to **separate chemically incompatible** agents or to add premeasured amounts of **potent** drug substances. Rather than weighing a potent drug, a pharmacist may choose to insert a prefabricated tablet of the desired strength in each capsule. Other less potent agents and diluents may then be weighed and added.
2. On an industrial scale, coated pellets designed for modified-release drug delivery are also commonly placed in capsule shells.

Examples of fill in hard gelatin capsules.
1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet

Liquid fill

- Gelatin capsules are unsuitable for aqueous liquids because water softens gelatin and distorts the capsules, resulting in leakage of the contents.
- However, some **liquids**, such as **fixed or volatile** oils, that do not interfere with the stability of the gelatin shells may be placed in locking gelatin capsules (or the capsules may be sealed with a solution of gelatin thinly coating the interface of the cap and body) to ensure retention of the liquid.
- Rather than placing a liquid as such in a capsule, the liquid may be mixed with an inert powder to make a wet mass or paste, which may then be placed in capsules in the usual manner.
- **Eutectic mixtures** of drugs, or mixtures of agents that have a propensity to liquefy when admixed, may be mixed with a diluent or absorbent such as magnesium carbonate, kaolin, or light magnesium oxide to separate the interacting agents and to absorb any liquefied material that may form.



Extemporaneous compounding of prescriptions

1. Calculate for the preparation of one or two more capsules than required to fill the prescription, to compensate a slight loss of powder
2. Selection of the capsule size, If the dose of the drug is inadequate to fill the volume of the capsule body, a diluent is added. A properly filled capsule should have its body filled with the drug mixture, not the cap. The cap is intended to fit snugly over the body to retain the contents.
3. When the usual dose of the drug is too large for a single capsule, 2 or more capsules may be required.

FILLING HARD CAPSULE SHELLS

- When filling a small number of capsules in the pharmacy, the pharmacist may use the **punch method**.
- The pharmacist takes the precise number of empty capsules to be filled from the stock container. By counting the capsules as the initial step rather than taking a capsule from stock as each one is filled,

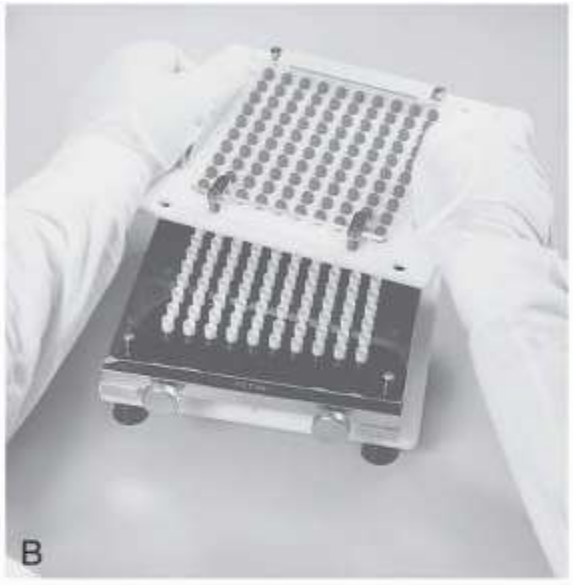
1. the pharmacist guards against filling the wrong number of capsules and
2. avoids contaminating the stock container with drug powder.

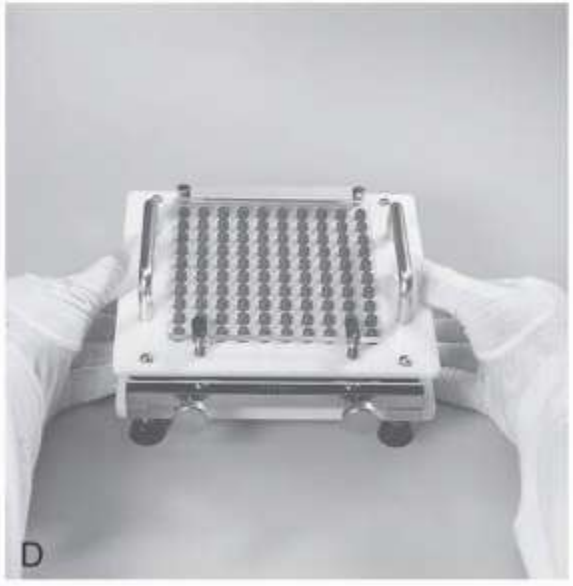
The powder to be encapsulated is placed on a sheet of clean paper or on a glass or porcelain plate. Using the spatula, the powder mix is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body.

Then an empty capsule body is held between the thumb and forefinger and punched vertically into the powder cake repeatedly until filled. Some pharmacists wear surgical gloves or latex finger cots to avoid handling the capsules with bare fingers. Because the amount of powder packed into a capsule depends on the degree of compression, the pharmacist should punch each capsule in the same manner and weigh the product after capping

2- Filling of capsules

- . When **non-potent** materials are placed in capsules, the first filled capsule should be weighed (using an empty capsule of the same size on the opposite balance pan to counter the weight of the shell) to determine the capsule size to use and the degree of compaction to be used. After this determination, the other capsules should be prepared and weighed periodically to check the uniformity of the process.
- When **potent drugs** are being used, each capsule should be weighed after filling to ensure accuracy. Such weighings protect against uneven filling of capsules and premature exhaustion or underuse of the powder. After the body of a capsule has been filled and the cap placed on the body, the body may be squeezed or tapped gently to distribute some powder to the cap end to give the capsule a full appearance.
- Granular material that does not lend itself to the punch method of filling capsules may be poured into each capsule from the powder paper on which it is weighed.





The Feton capsule-filling machine.

A. With empty capsules in the loader tray, the tray placed on top of the filler unit.

B. The loader inserts the capsules into the filling unit and is removed, and the top plate is lifted to separate the caps from the bodies.

C. The powder is placed on the unit and the capsule bodies are filled.

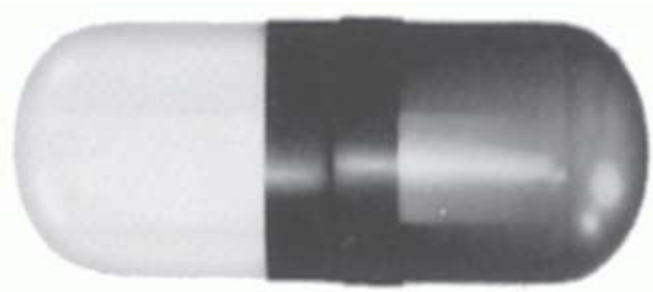
D. The top plate is returned to the unit and the caps are placed on filled capsule bodies.

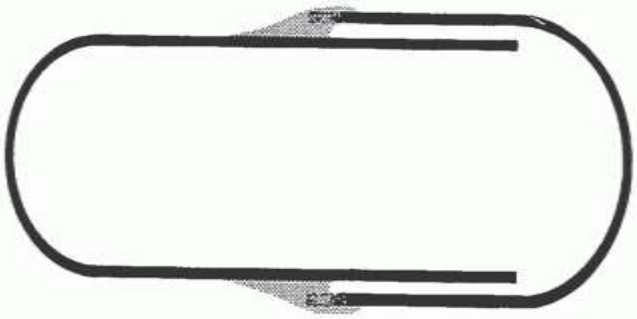
(Courtesy of Chemical and Pharmaceutical Industry Company.)

3- CAPSULE SEALING

1. Some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. One manufacturer makes distinctive-looking capsules by sealing them with a **colored band** of gelatin (Kapseals, Parke-Davis). If removed, the **band** cannot be restored without expert resealing with gelatin.
2. Capsules may also be sealed through a **heat-welding process** that fuses the capsule cap to the body through the double wall thickness at their juncture . The process results in a distinctive ring around the capsule where heat welded.
3. Still another process uses a **liquid wetting agent** that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40°C-45°C) .

Industrial capsule sealing machines are capable of producing 60,000 to 150,000 gelatin-banded, heat-welded, or thermally coupled capsules per hour

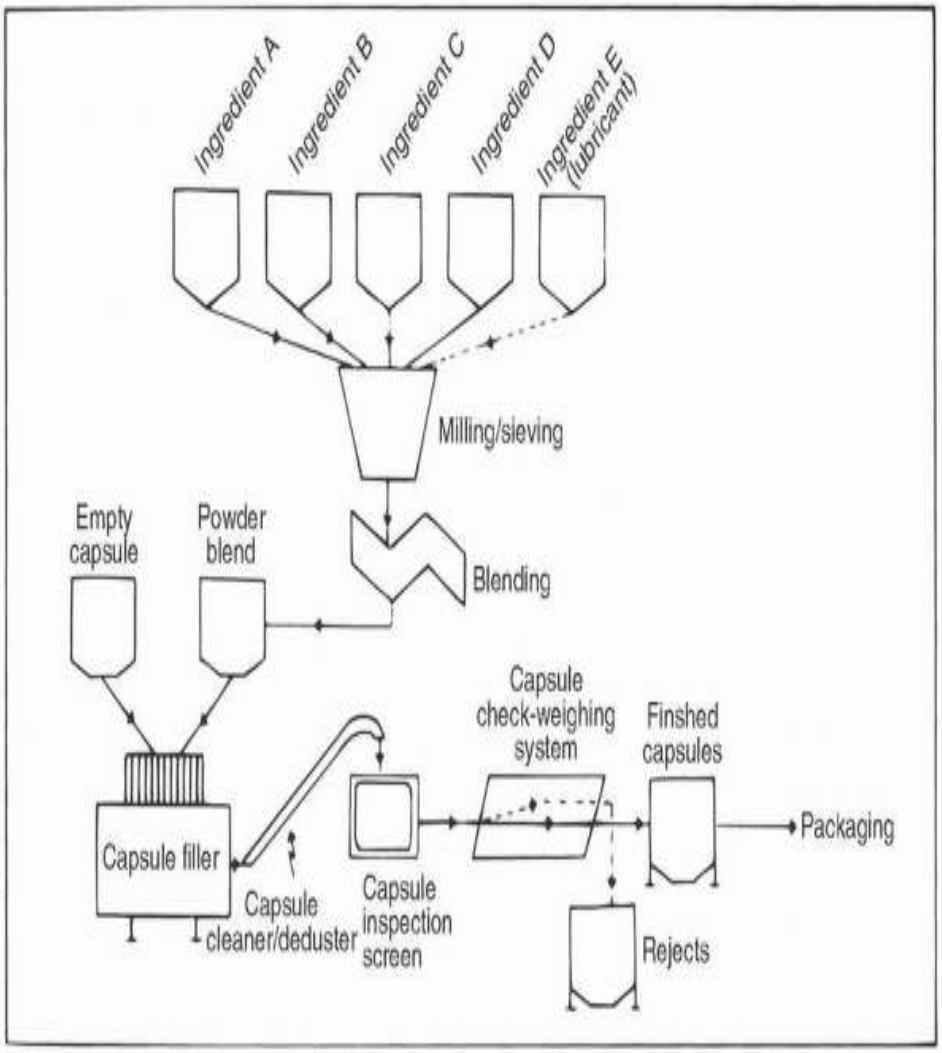




4- CLEANING AND POLISHING CAPSULES

- Small amounts of powder may adhere to the outside of capsules after filling. The powder may be bitter or otherwise unpalatable and should be removed before packaging or dispensing. On a small scale, capsules may be cleaned individually or in small numbers by rubbing them with a clean gauze or cloth.
- On a large scale, many capsule-filling machines are affixed with a cleaning vacuum that removes any extraneous material from the capsules as they exit the equipment, using the Accela-Cota apparatus

Process flow diagram for automated capsule filling



B- Soft gelatin capsule

1. Soft gelatin capsules are pharmaceutically **elegant**
2. and are easily swallowed
3. Soft gelatin capsules are used to encapsulate and hermetically **seal**

a) liquids,
b) suspensions, pasty materials,
c) dry powders, granules and pellets
d) preformed tablets.

SOFT GELATIN CAPSULES

- Soft gelatin capsules are made of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added.
- Soft gelatin capsules, which contain more moisture than hard capsules, may have a preservative, such as methylparaben and/or propylparaben, to retard microbial growth.
- Soft gelatin capsules may be oblong, oval, or round.
- They may be single colored or two-toned and may be imprinted with identifying markings. As with hard gelatin capsules, they may be prepared with opaquants to reduce transparency and render characteristic features to the capsule shell.

PREPARATION OF SOFT GELATIN CAPSULES

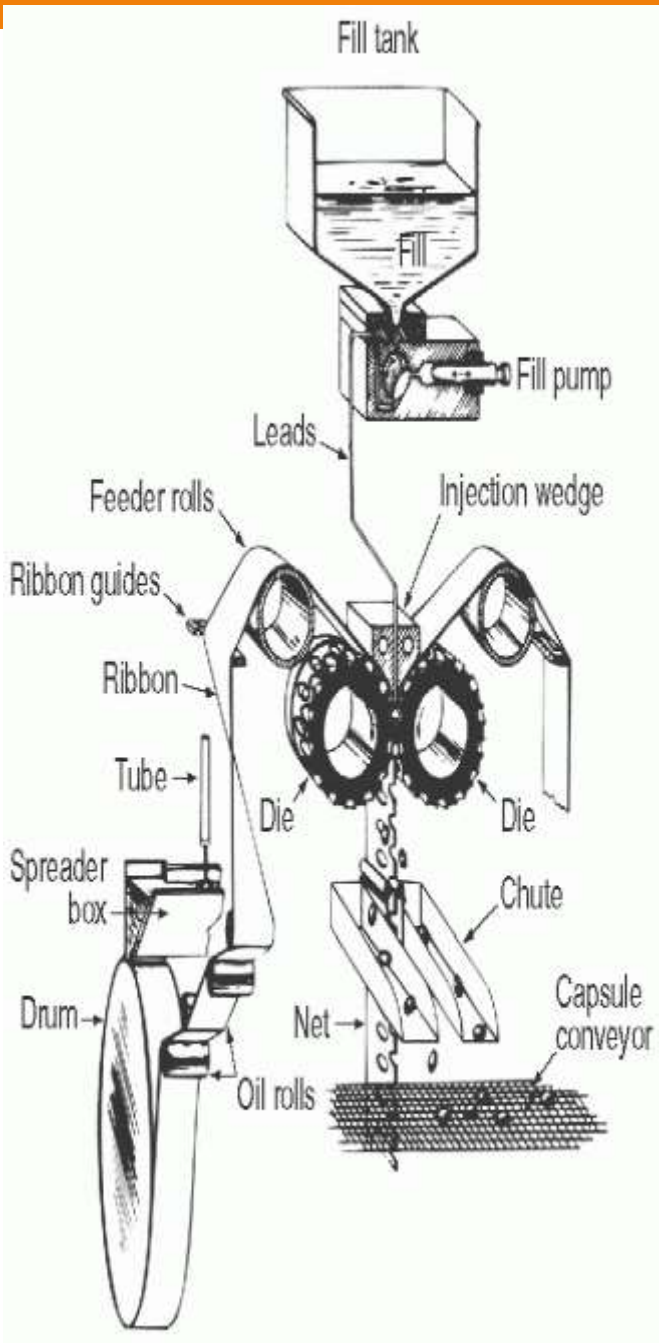
- Soft gelatin capsules may be prepared by the plate process, using a set of molds to form the capsules, or by the more efficient and productive rotary or reciprocating die processes by which they are produced, filled, and sealed in a continuous operation

A - Plate Process

- By the plate process, a warm sheet of plain or colored gelatin is placed on the bottom plate of the mold and the medication-containing liquid is evenly poured on it. Then a second sheet of gelatin is carefully placed on top of the medication and the top plate of the mold is put into place. Pressure is then applied to the mold to form, fill, and seal the capsules simultaneously. The capsules are removed and washed with a solvent harmless to the capsules.

B- Rotatory Die Process

- By this method, liquid gelatin flowing from an overhead tank is formed into two continuous ribbons by the rotary die machine and brought together between twin rotating dies
- At the same time, metered fill material is injected between the ribbons precisely at the moment that the dies form pockets of the gelatin ribbons. These pockets of fill-containing gelatin are sealed by pressure and heat and then severed from the ribbon. Use of ribbons of two different colors results in bicolored capsules.
- The reciprocating die process is similar to the rotary process in that ribbons of gelatin are formed and used to encapsulate the fill, but it differs in the actual encapsulating process. The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film as they progress through the machinery. As the capsules are cut from the ribbons, they fall into refrigerated tanks that prevent the capsules from adhering to one another.



SOFT GELATIN CAPSULES Fill

- Soft gelatin capsules are prepared to contain a variety of liquid, paste, and dry fills. Liquids that may be encapsulated into soft gelatin capsules include the following

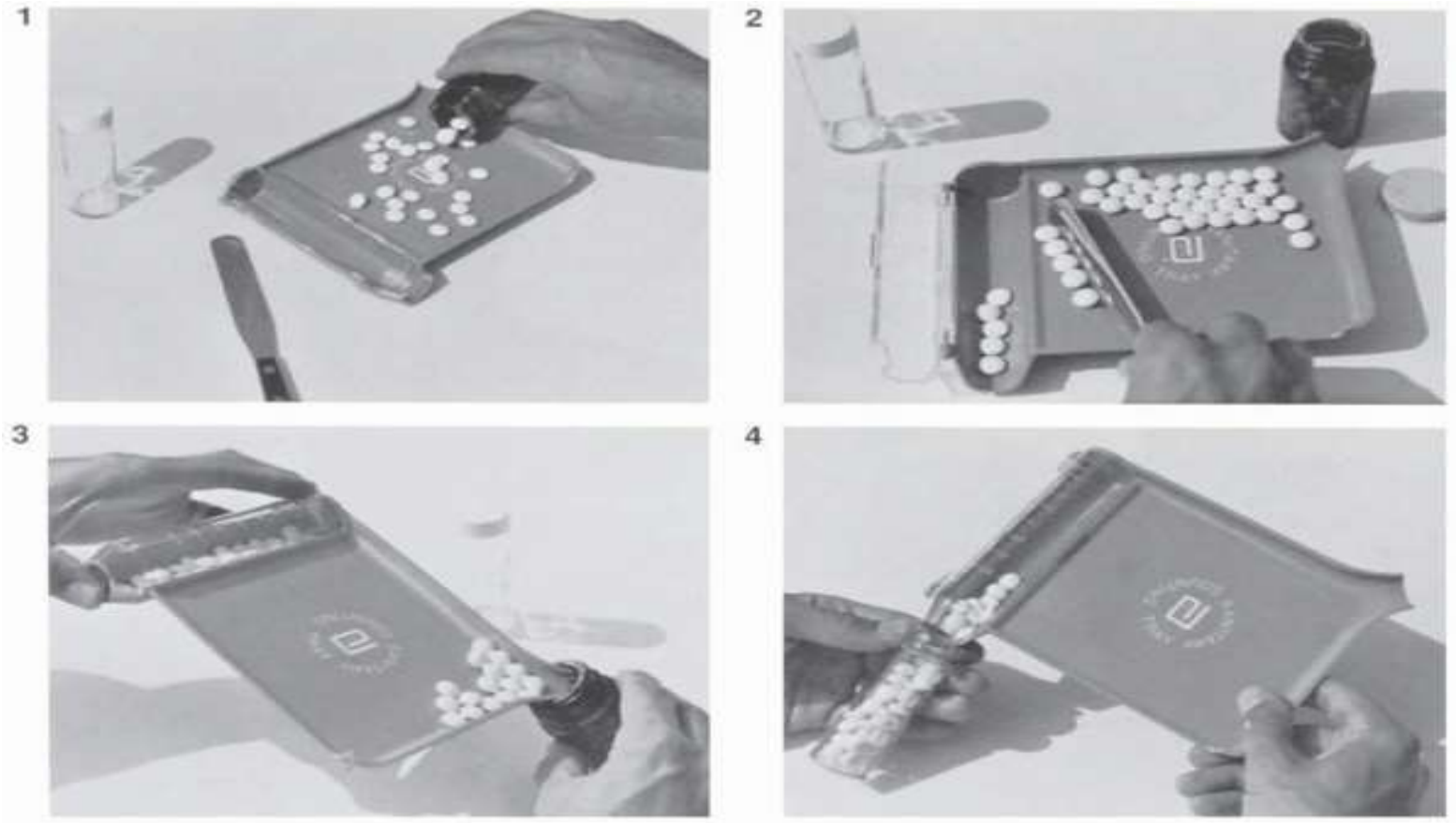
1. Water-immiscible volatile and nonvolatile liquids such as vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols, and organic acids.
2. Water-miscible nonvolatile liquids, such as polyethylene glycols, and nonionic surface active agents, such as polysorbate 80.
3. Water-miscible and relatively nonvolatile compounds such as propylene glycol and isopropyl alcohol, depending on factors such as concentration used and packaging conditions.
4. Solids may be encapsulated into soft gelatin capsules as solutions in a suitable liquid solvent, suspensions, dry powders, granules, pellets, or small tablets.

Disadvantages of soft gel capsules

- 1. Requires special manufacturing equipment
- 2. Stability concerns with highly water soluble compounds, and compounds susceptible to hydrolysis
- 3. Limited choices of excipients/carriers compatible with the gelatin
- Liquids that can easily migrate through the capsule shell are not suitable for soft gelatin capsules.
- These materials include water above 5% and
- low-molecular-weight water-soluble and volatile organic compounds such as alcohols, ketones, acids, amines, and esters.

COUNTING CAPSULES

- In the pharmacy, capsules may be counted manually or by automated equipment. Specially designed trays are used for counting small numbers of solid dosage units.
- In using this tray, the pharmacist pours a supply of capsules or tablets from the bulk source onto the clean tray and, using the spatula, counts and sweeps the dosage units into the trough until the desired number is reached.
- Then the pharmacist closes the trough cover, picks up the tray, returns the uncounted dosage units to the bulk container by means of the lip at the back of the tray, places the prescription container at the opening of the trough, and carefully transfers the capsules or tablets into the container.
- With this method, the dosage units remain untouched by the pharmacist. To prevent batch-to-batch contamination, the tray must be wiped clean after each use because powder, particularly from uncoated tablets, may remain



Steps in counting solid dosage units with the Abbott Sanitary Counting Tray.

1. Transferring units from stock package to tray.
2. Counting and transferring units to trough.
3. Returning excess units to stock container.
4. Placing the counted units in prescription container.

EXAMPLES OF SOME OFFICIAL CAPSULES

OFFICIAL CAPSULE	REPRESENTATIVE COMMERCIAL CAPSULES	STRENGTH	CATEGORY
Amoxicillin	Wymox (Wyeth-Ayerst)	250, 500 mg	Antibacterial
Cephalexin	Keflex (Dista)	250, 333, 500, 750 mg	Antibacterial
Doxycycline Hyclate	Vibramycin (Pfizer)	100 mg	Antibacterial
Erythromycin Estolate	Ilosone (Dista)	250 mg	Antibacterial
Fluoxetine HCl	Prozac (Dista)	10, 20, 40 mg	Antidepressant
Indomethacin	Indocin (Merck)	25, 50 mg	Anti-inflammatory, antipyretic, analgesic

POWDER DOSAGE FORM

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 9th Edition 2011

Chapter 6

Powders and Granules

Powder

- Most active and inactive pharmaceutical ingredients occur in the solid state as amorphous powders or as crystals of various morphologic structures.
- The term “powder” has more than one meaning in pharmacy.

1. It may be used to describe the physical form of a material, that is, a dry substance composed of finely divided particles.
2. Or, it may be used to describe a type of pharmaceutical preparation, that is, a medicated powder intended for internal (i.e., oral powder) or external (i.e., topical powder) use.

Powders and granules

- **Powders** (as a dosage form) are intimate mixtures of dry, finely divided drugs and/or chemicals that may be intended for internal or external use.
- **Granules**, which are prepared agglomerates of powdered materials, may be used per se for the medicinal value of their content, or they may be used for pharmaceutical purposes, as in making tablets

The use of powders

a) Medicated powders for therapeutic effect (limited),
b) The use of powdered substances in the preparation of other dosage forms is extensive. For example, powdered drugs may be blended with powdered fillers and other pharmaceutical ingredients to fabricate

1- solid dosage forms as tablets and capsules;

2-they may be dissolved or suspended in solvents or liquid vehicles to make various liquid dosage forms;

3- or they may be incorporated into semisolid bases in the preparation of medicated ointments and creams.

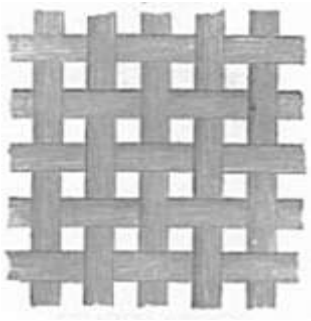
Characterization of powders

- Before their use in the preparation of pharmaceutical products, solid materials first are characterized to determine their chemical and physical features, including

1. morphology,
2. purity,
3. solubility,
4. flowability,
5. stability,
6. particle size,
7. uniformity, and
8. compatibility with any other formulation components

Particle size

- The adjustment and control of a Drug and other materials powder's particle size; enable both the efficient production of a finished dosage form and the optimum therapeutic efficacy.
- United States Pharmacopeia (USP) uses these terms: **very coarse, coarse, moderately coarse, fine, and very fine**, which are related to the proportion of powder that is capable of passing through the openings of standard sieves of varying fineness in a specified period while being shaken, generally in a mechanical sieve shaker
- Sieves can be referred to either by their aperture size or by their mesh size (or sieve number).
- The mesh size is the number of wires per linear inch



USP

United States Pharmacopeia

General Chapters: <811> POWDER FINENESS

Classification of Powders by Fineness

Classification of Powder	d_{50} Sieve Opening (µm)
Very Coarse	> 1000
Coarse	355–1000
Moderately Fine	180–355
Fine	125–180
Very Fine	90–125

d_{50}= smallest sieve opening through which 50% or more of the material passes

OPENING OF STANDARD SIEVES

	SIEVE NUMBER	SIEVE OPENING			SIEVE NUMBER	SIEVE OPENING
Very coarse	2.0	9.50 mm			70.0	212.00 µm
	3.5	5.60 mm			80.0	180.00 µm
Coarse	4.0	4.75 mm	4-12		100.0	150.00 µm
	8.0	2.36 mm	Granules		120.0	125.00 µm
	10.0	2.00 mm			200.0	75.00 µm
Moderately coarse	20.0	850.00 µm	12-20 Tableting	Very fine	230.0	63.00 µm
	30.0	600.00 µm			270.0	53.00 µm
	40.0	425.00 µm			325.0	45.00 µm
Fine	50.0	300.00 µm			400.0	38.00 µm
	60.0	250.00 µm				

Source: USP 31-NF 26.

Terminology of powders

Very coarse (No. 8):	All particles pass through a No. 8 sieve and not more than 20% pass through a No. 60 sieve.
Coarse (No. 20):	All particles pass through a No. 20 sieve and not more than 40% pass through a No. 60 sieve.
Moderately coarse (No. 40):	All particles pass through a No. 40 sieve and not more than 40% pass through a No. 80 sieve.
Fine (No. 60):	All particles pass through a No. 60 sieve and not more than 40% pass through a No. 100 sieve.
Very fine (No. 80):	All particles pass through a No. 80 sieve. There is no limit to greater fineness.

Particle size can influence a variety of important factors

1. Dissolution rate of particles intended to dissolve; drug micronization can increase the rate of drug dissolution and its bioavailability
2. Suspendability of particles intended to remain un-dissolved but uniformly dispersed in a liquid vehicle (e.g., fine dispersions have particles approximately 0.5 to 10 µm)
3. Uniform distribution of a drug substance in a powder mixture or solid dosage form to ensure dose-to-dose content uniformity
4. Penetrability of particles intended to be inhaled for deposition deep in the respiratory tract (e.g., 1 to 5 µm)
5. Lack of grittiness of solid particles in dermal ointments, creams, and ophthalmic preparations (e.g., fine powders may be 50 to 100 µm in size

Micromeritics

- Micromeritics is the science of small particles; a particle is any unit of matter having defined physical dimensions
- Micromeritics is the study of a number of characteristics, including
- particle size and
- size distribution,
- shape,
- angle of repose,
- porosity,
- true volume,
- bulk volume,
- apparent density, and
- bulkiness

A number of methods exist for the determination of particle size

1. **Sieving**, in which particles are passed by mechanical shaking through a series of sieves of known and successively smaller size and the proportion of powder passing through or being withheld on each sieve is determined (range about 40 to 9,500 µm, depending upon sieve sizes)
2. **Microscopy**, in which sample particles are sized through the use of a calibrated grid background or other measuring device (range 0.2 to 100 µm) .
3. **Sedimentation rate**, in which particle size is determined by measuring the terminal settling velocity of particles through a liquid medium in a gravitational or centrifugal environment (range 0.8 to 300 µm) . Sedimentation rate may be calculated from Stokes' law.
4. Light energy diffraction or **light scattering**, in which particle size is determined by the reduction in light reaching the sensor as the particle, dispersed in a liquid or gas, passes through the sensing zone (range 0.2 to 500 µm). Laser scattering utilizes a He-Ne laser, silicon photo diode detectors, and an ultrasonic probe for particle dispersion (range 0.02 to 2,000 µm) .
5. **Laser holography**, in which a pulsed laser is fired through an aerosolized particle spray and is photographed in three dimensions with a holographic camera, allowing the particles to be individually imaged and sized (range 1.4 to 100 µm) .
6. **Cascade impaction**, which is based on the principle that a particle driven by an airstream will hit a surface in its path, provided its inertia is sufficient to overcome the drag force that tends to keep it in the airstream. Particles are separated into various size ranges by successively increasing the velocity of the airstream in which they are carried.

Sieving

- The sieving method entails using a set of U.S. standard sieves in the desired size range. A stack of sieves is arranged in order, the powder placed in the top sieve, the stack shaken, the quantity of the powder resting on each sieve weighed

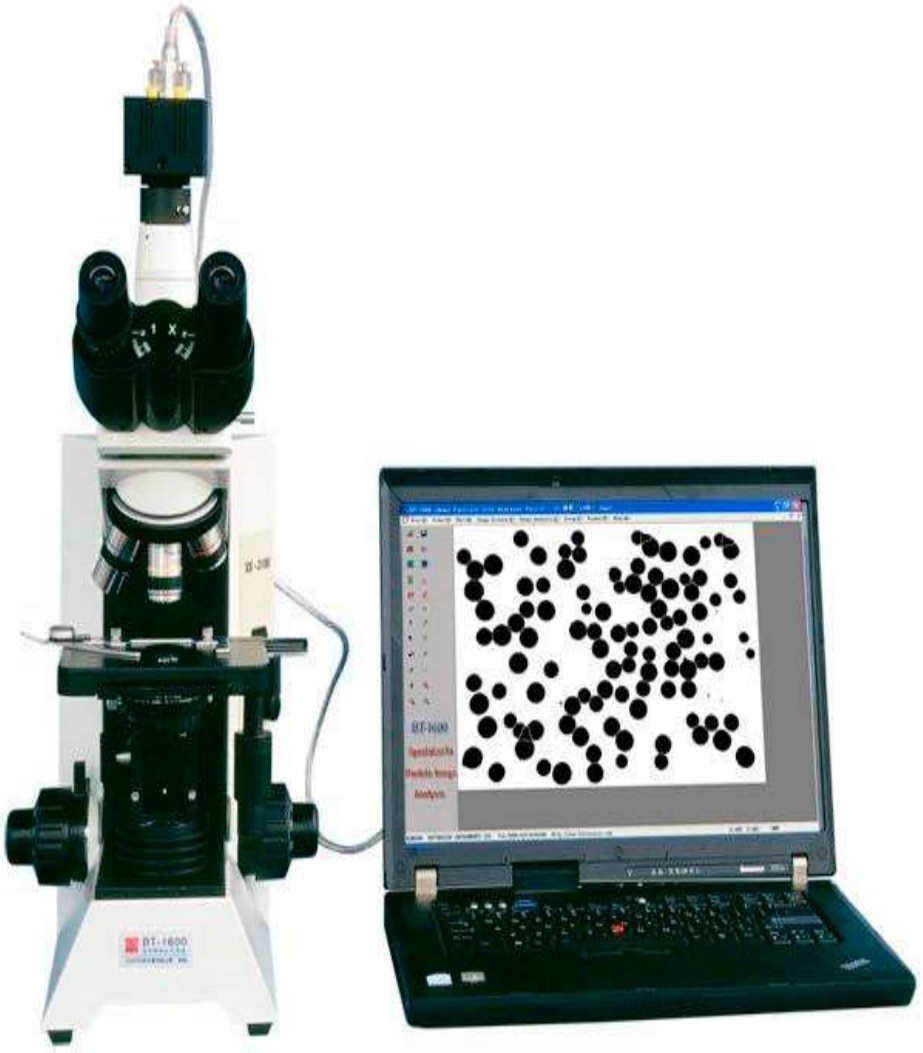
Calculations

SIEVE	ARITHMETIC MEAN OPENING (mm)	WEIGHT RETAINED (g)	% RETAINED	% RETAINED × MEAN OPENING (mm)
20/40	0.630	15.5	14.3	9.009
40/60	0.335	25.8	23.7	7.939
60/80	0.214	48.3	44.4	9.502
80/100	0.163	15.6	14.3	2.330
100/120	0.137	3.5	3.3	0.452
		108.7	100.0	29.232

$$d_{av} = \frac{\Sigma(\%\,\text{retained}) \times (\text{ave.size})}{100} = \frac{29.232}{100} = 0.2923\,\text{mm}$$

Microscopy

- The microscopic method can include not fewer than 200 particles in a single plane using a calibrated ocular on a microscope



Average particle diameter

SIZE OF COUNTED PARTICLES (µm)	MIDDLE VALUE µm "d"	NO. OF PARTICLES PER GROUP "n"	"nd"
40-60	50	15	750
60-80	70	25	1,750
80-100	90	95	8,550
100-120	110	140	15,400
120-140	130	80	10,400
		σn - 355	σnd - 36,850

$$d_{av} = \frac{\Sigma nd}{\Sigma n} = \frac{36,850}{355} = 103.8\,\mu m$$

Sedimentation

- Another method of particle size determination entails sedimentation using the Andreasen pipet, a special cylindrical container from which a sample can be removed from the lower portion at selected intervals. The powder is dispersed in a non-solvent in the pipette and agitated, and 20-mL samples are removed over time. Each 20-mL sample is dried and weighed.

Sedimentation method

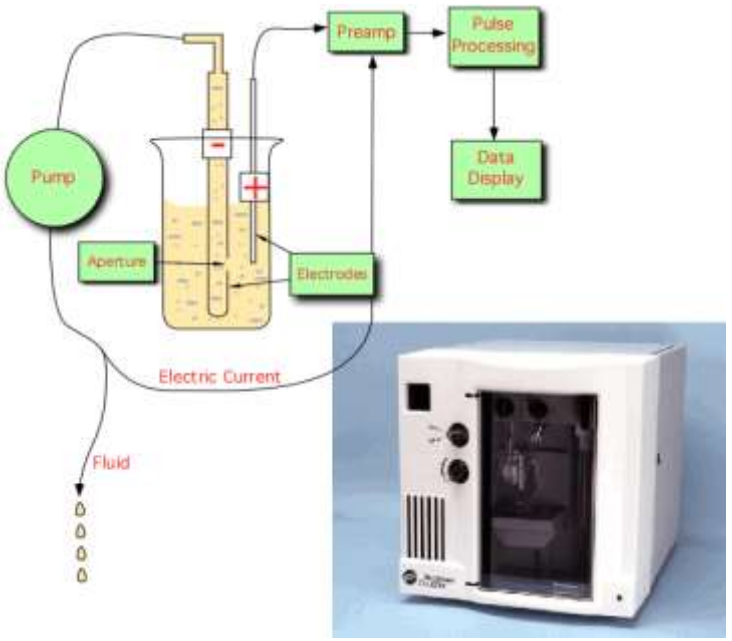
- The particle diameters can be calculated from this equation:

$$d = \frac{18h\eta}{(\rho_i - \rho_e)gt}$$

- d is the diameter of the particles,
- h is the height of the liquid above the sampling tube orifice,
- η is the viscosity of the suspending liquid,
- ρ_i - ρ_e is the density difference between the suspending liquid and the particles,
- g is the gravitational constant, and
- t is the time in seconds.

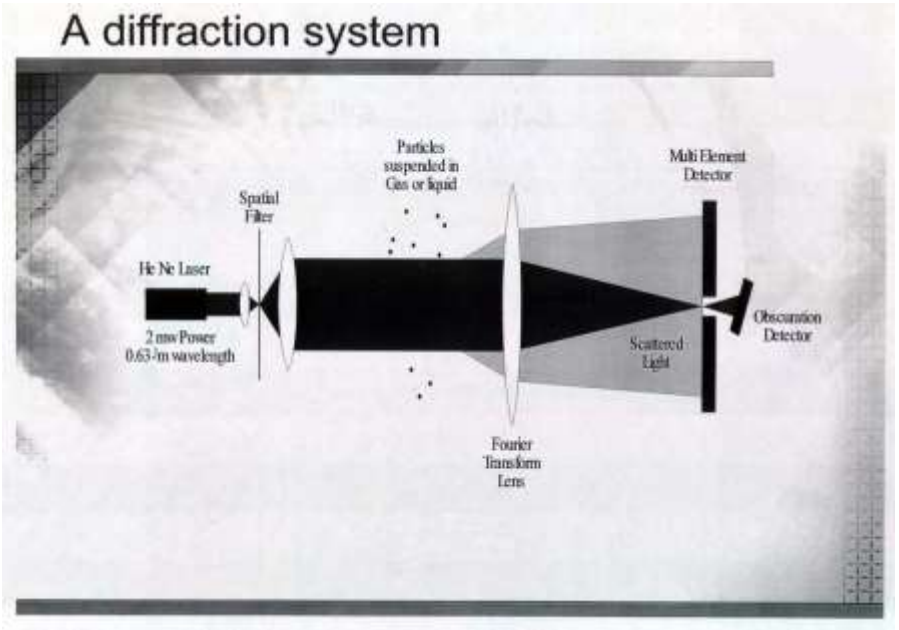
Electrical sensing zone method – Coulter Counter

- Instrument **measures particle volume** which can be expressed as dv : the diameter of a sphere that has the same volume as the particle.
- The number and size of particles suspended in an electrolyte is determined by causing them to pass through an orifice an either side of which is immersed an electrode.
- The changes in electric impedance (resistance) as particles pass through the orifice generate voltage pulses whose amplitude are proportional to the volumes of the particles.
- **Volume** distribution



Laser diffraction

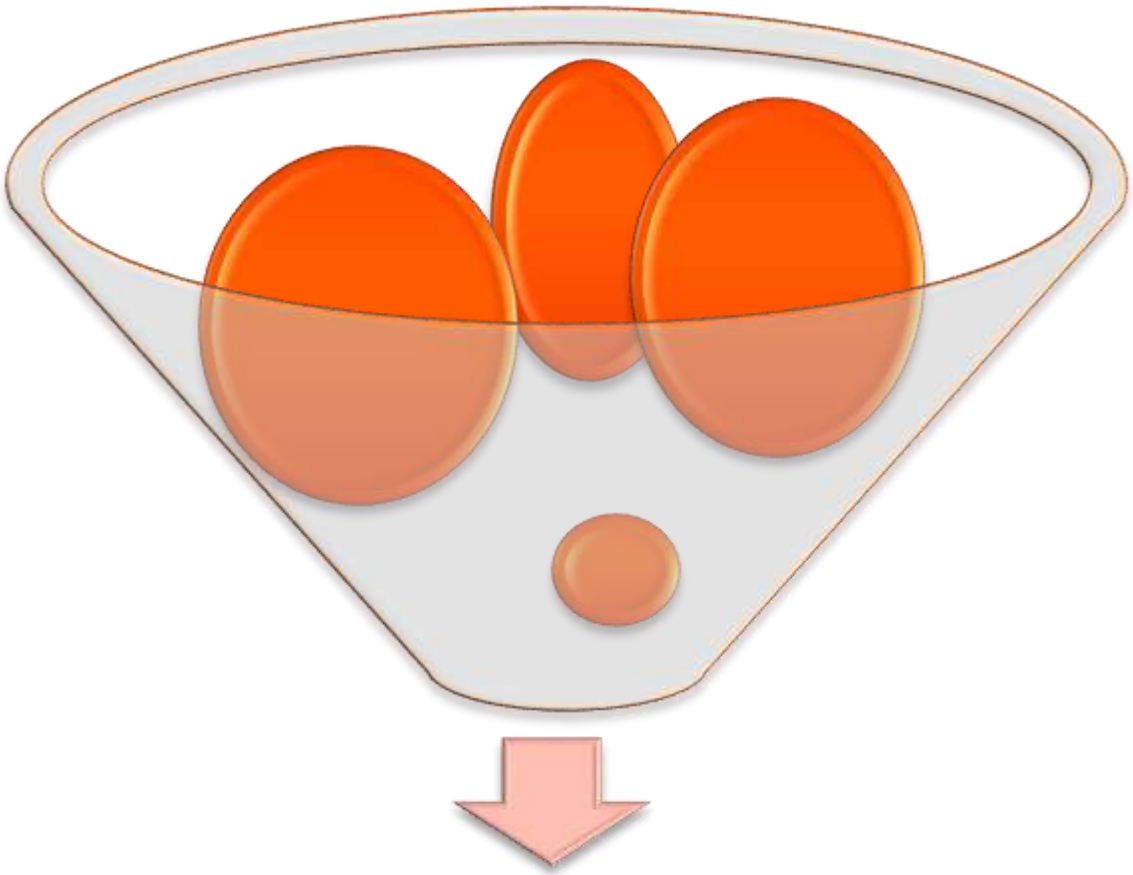
- Particles pass through a laser beam and the light scattered by them is collected over a range of angles in the forward direction.
- The angles of diffraction are, in the simplest case inversely related to the particle size.
- The particles pass through an expanded and collimated laser beam in front of a lens in whose focal plane is positioned a photosensitive detector consisting of a series of concentric rings.
- Distribution of scattered intensity is analysed by computer to yield the particle size distribution.



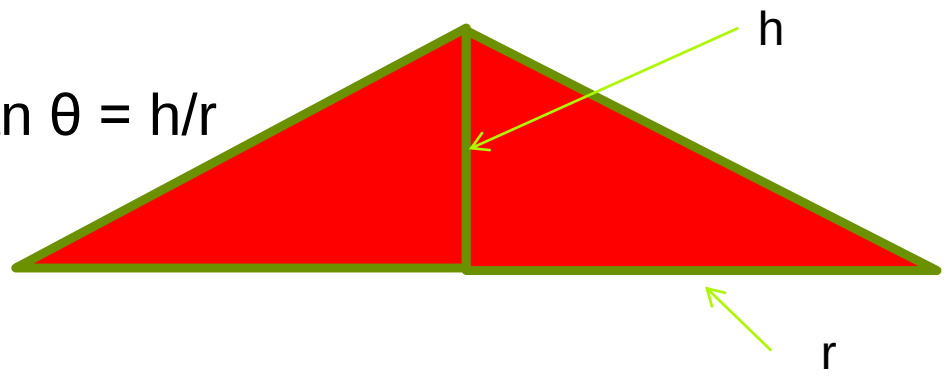
- **Volume** distribution

ANGLE OF REPOSE

- The angle of repose is a relatively simple technique for estimating the flow properties of a powder. It can easily be determined by allowing a powder to flow through a funnel and fall freely onto a surface. The height and diameter of the resulting cone are measured and the angle of repose is calculated from this equation:
- $\tan \theta = h/r$
- where
- h is the height of the powder cone and
- r is the radius of the powder cone.



$\tan \theta = h/r$



Example

- A powder was poured through the funnel and formed a cone 3.3 cm high and 9 cm in diameter. What is the angle of repose?
- $\tan \theta = h/r = 3.3/4.5 = 0.73$
- arc tan 0.73 = 36.25°
- Angle of repose as an indicator of powder flow properties

Angle of repose	Flow
< 20	Excellent
20 – 30	Good
30 – 34	passable
> 40	Very poor

Flowability

- Powders with a low angle of repose flow freely, and powders with a high angle of repose flow poorly
- A number of factors, including shape and size, determine the flow properties of powders. Spherical particles flow better than needles. Very fine particles do not flow as freely as large particles.
- In general, particles in the size range of 250 to 2,000 µm flow freely if the shape is amenable.
- Particles in the size range of 75 to 250 µm may flow freely or cause problems, depending on shape and other factors.
- With most particles smaller than 100 µm, flow is a problem.

Particle Size Reduction

- Size Reduction in particle size, increases the number of particles and the total surface area. The reduction in the particle size of a solid is accompanied by a great increase in the specific surface area of that substance.

- Comminution, reduction of the particle size of a solid substance to a finer state,

1. is used to facilitate crude drug extraction,
2. increase the dissolution rates of a drug,
3. aid in the formulation of pharmaceutically acceptable dosage forms,
4. and enhance the absorption of drugs.

Increase in the number of particles

- If a powder consists of cubes 1 mm on edge and it is reduced to particles 10 µm on edge, what is the number of particles produced?
- 1 mm equals 1,000 µm.
- 1,000/10 µm = 100 pieces produced on each edge; that is, if the cube is sliced into 100 pieces on the x-axis, each 10 µm long, 100 pieces result.
- If this is repeated on the y- and z-axes, the result is 100 × 100 × 100 = 1 million particles produced, each 10 µm on edge, for each original particle 1 mm on edge. This can also be written as $(10^2)^3 = 10^6$.

Increase in surface area

- What increase in the surface area of the powder is produced by decreasing the particle size from 1 mm to 10 μm?
- The 1-mm cube has six surfaces, each 1 mm on edge. Each face has a surface area of 1 mm^2. Because there are six faces, this is 6 mm^2 surface area per particle.
- Each 10-μm cube has six surfaces, each 10 μm on edge. Each face has a surface area of 10 × 10 = 100 μm^2. Because there are six faces, this is 6 × 100 μm^2, or 600 μm^2 surface area per particle. Since 10^6 particles resulted from comminuting the 1-mm cube, each 10 μm on edge, the surface area now is 600 $\mu m^2 \times 10^6$, or 6×10^8 μm^2.
- To get everything in the same units for ease of comparison, convert the 6×10^8 μm^2 into square millimeters as follows.
- Since there are 1,000 μm/mm, there must be $1{,}000^2$, or 1 million $\mu m^2/mm^2$. This is more appropriately expressed as 10^6 $\mu m^2/mm^2$,

Increase in surface area

$$\frac{6\times10^{8}\,\mu m^{2}}{10^{6}\,\mu m^{2}/mm^{2}}=6\times10^{2}\,mm^{2}$$

- The surface areas have been increased from 6 mm² to 600 mm² by the reduction in particle size of cubes 1 mm on edge to cubes 10 µm on edge, a 100-fold increase in surface area. This can have a significant increase in the rate of dissolution of a drug product.

COMMINUTION OF DRUGS

- On a small scale, the pharmacist reduces the size of chemical substances by grinding with a mortar and pestle. A finer grinding action is accomplished by using a mortar with a rough surface (as a porcelain mortar) than one with a smooth surface (as a glass mortar). Grinding a drug in a mortar to reduce its particle size is termed trituration or comminution.

COMMINUTION (large scale)

Various types of mills and pulverizers may be used to reduce particle size. FitzMill comminuting machine with a product containment system. Through the grinding action of rapidly moving blades in the comminuting chamber, particles are reduced in size and passed through a screen of desired dimension to the collection container. The collection and containment system protects the environment from chemical dust, reduces product loss, and prevents product contamination.

Levigation

- Used in small-scale preparation of ointments and suspensions to reduce the particle size and grittiness of the added powders.
- A mortar and pestle or an ointment tile may be used.
- A paste is formed by combining the powder and a small amount of liquid (the levigating agent) in which the powder is insoluble.
- The paste is then triturated, reducing the particle size. The levigated paste may then be added to the ointment base and the mixture made uniform and smooth by rubbing them together with a spatula on the ointment tile.
- A figure 8 track is commonly used to incorporate the materials. Mineral oil and glycerin are commonly used levigating agents

BLENDING POWDERS

- When two or more powdered substances are to be combined to form a uniform mixture, it is best to reduce the particle size of each powder individually before weighing and blending.
- Depending on the nature of the ingredients, the amount of powder, and the equipment, powders may be blended by

a) spatulation,
b) trituration,
c) sifting, and
d) tumbling.

A- Spatulation

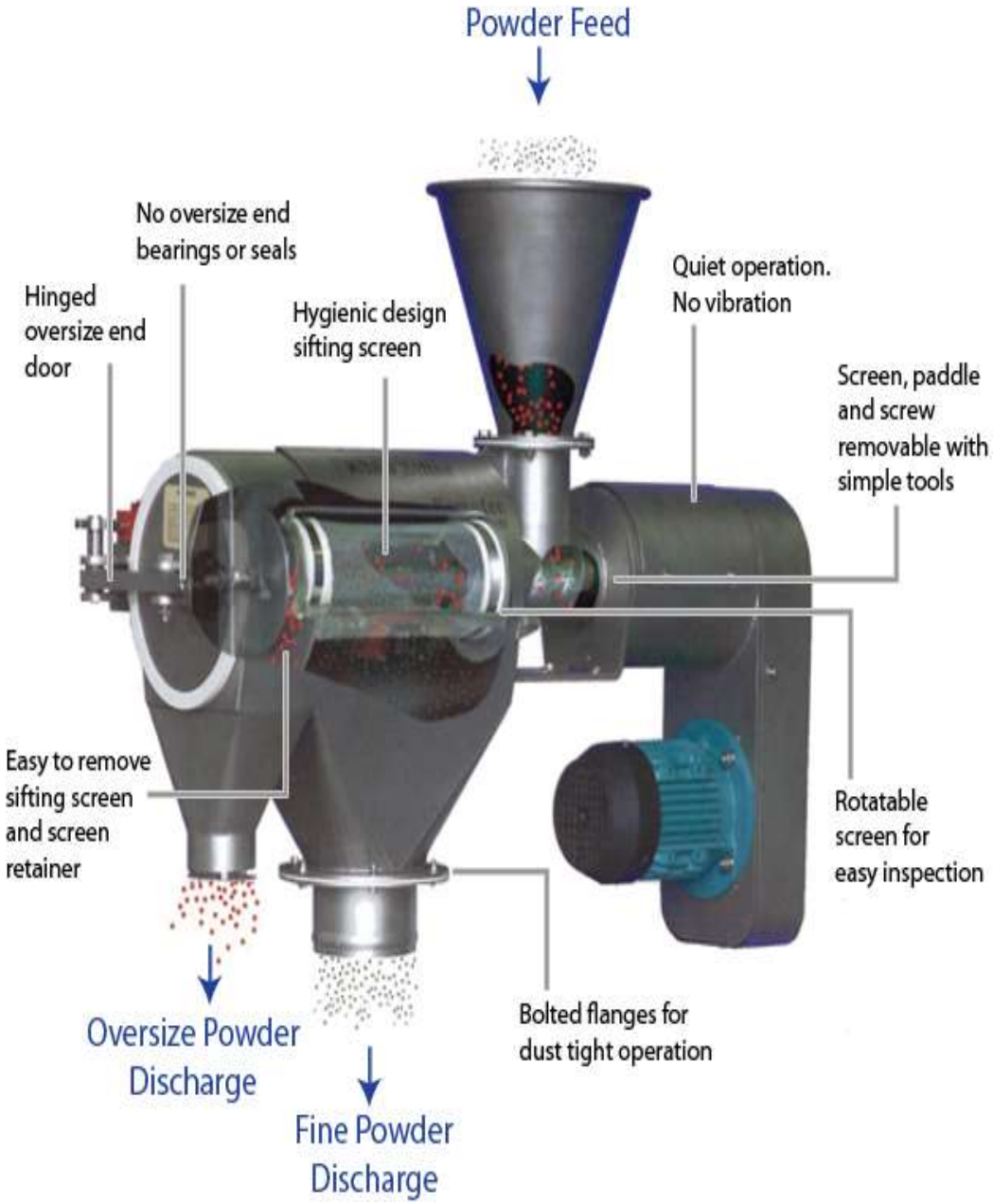
- Spatulation is blending small amounts of powders by movement of a spatula through them on a sheet of paper or an ointment tile.
- It is not suitable for large quantities of powders or for powders containing potent substances, because homogeneous blending is not as certain as other methods.
- Very little compression or compacting of the powder results from spatulation, which is especially suited to mixing solid substances that form eutectic mixtures (or liquefy) when in close and prolonged contact with one another.
- Substances that form eutectic mixtures when combined include phenol, camphor, menthol, thymol, aspirin, phenyl salicylate, and other similar chemicals. To diminish contact, a powder prepared from such substances is commonly mixed in the presence of an inert diluent, such as light magnesium oxide or magnesium carbonate, to separate the troublesome agents physically.

B- Trituration

- Trituration may be employed both to comminute and to mix powders.
- If simple admixture is desired without the special need for comminution, the glass mortar is usually preferred.
- When a small amount of a potent substance is to be mixed with a large amount of diluent, the **geometric dilution** method is used to ensure the uniform distribution of the potent drug. This method is especially indicated when the potent substance and other ingredients are the same color and a visible sign of mixing is lacking. By this method, the potent drug is placed with an approximately equal volume of the diluent in a mortar and is mixed thoroughly by trituration. Then, a second portion of diluent equal in volume to the mixture is added and the trituration repeated. This process is continued by adding an equal volume of diluent to the powder mixture and repeating this until all of the diluent is incorporated. Some pharmacists add an inert colored powder to the diluent before mixing to permit visual inspection of the mixing process.

C-sifting

- Powders may also be mixed by passing them through sifters like those used in the kitchen to sift flour.
- Sifting (sieving) results in a light, fluffy product. This process is not acceptable for the incorporation of potent drugs into a diluent powder.



D-Tumbling

- Another method of mixing powders is tumbling the powder in a rotating chamber.
- Special small-scale and large-scale motorized powder blenders mix powders by tumbling them
- Mixing by this process is thorough but time consuming. Such blenders are widely employed in industry, as are mixers that use motorized blades to blend powders in a large vessel.

Problems associated with particle size reduction

1. **Segregation** is an undesirable separation of the different components of the blend. Segregation may occur sifting or percolation, air entrapment (fluidization), Fine particles tend to sift or percolate through coarse particles and end up at the bottom of the container and actually “lift” the larger particles to the surface. Fine, aerated powders with differences in particle size or density may result in a striation pattern and may occur during powder transfer.
2. Particle entrapment (**Dusting**). Dusting occurs when the finer, lighter particles remain suspended in air longer and do not settle as quickly as the larger or denser particles.

- General guidelines to minimize or prevent segregation include
- (a) minimum number of transfer steps and drop heights,
- (b) control of dust generation,
- (c) control of fluidization of the powder,
- (d) slow fill/transfer rate,
- (e) appropriate venting,
- (f) use of a deflector, vane, or distributor,
- (g) proper hopper design and operating valves (if present).

MEDICATED POWDERS

- Some medicated powders are intended to be used

1- **Internally** Most powders for internal use .

- Some powders are intended to be inhaled for local and systemic effects.
- Other dry powders are commercially packaged for constitution with a liquid solvent or vehicle,

some for administration orally, are taken orally after mixing with water or in the case of infants in their infant formulas

others for use as an injection,

others for use as a vaginal douche,

2-**Externally**.

. Medicated powders for external use are dusted on the affected area from a sifter-type container or applied from a powder aerosol. Powders intended for external use should bear a label marked EXTERNAL USE ONLY or a similar label.

Medicated powders for oral use

1. Medicated powders for oral use may be intended for local effects (e.g., laxatives) or systemic effects (e.g., analgesics)
2. and may be preferred to counterpart tablets and capsules by patients who have difficulty swallowing solid dosage forms.
3. The doses of some drugs are too bulky to be formed into tablets or capsules of convenient size, so they may be administered as powders.
4. For administration, they can be mixed with a liquid or soft food.
5. Powders taken orally for systemic use may be expected to result in faster rates of dissolution and absorption than solid dosage forms, because there is immediate contact with the gastric fluids; however, the actual advantage in terms of therapeutic response may be negligible or only minimal, depending on the drug release characteristics of the counterpart products.

Medicated powders for oral use

6- Some medications, notably antibiotics for children, are intended for oral administration as liquids but are relatively unstable in liquid form. They are provided to the pharmacist by the manufacturer as a dry powder or granule for constitution with a specified quantity of purified water at the time of dispensing. Under labeled conditions of storage, the resultant product remains stable for the prescribed period of use, generally up to 2 weeks.

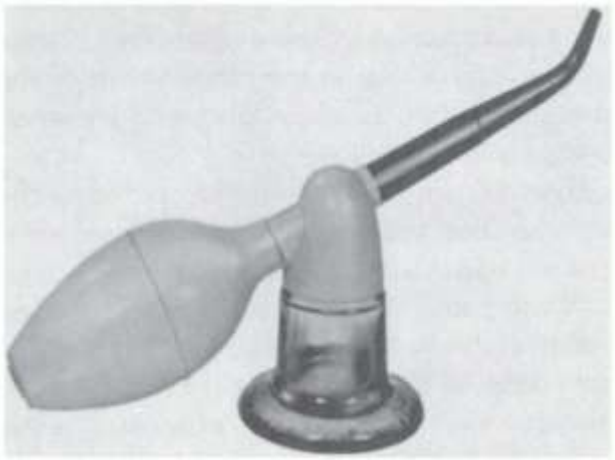
A primary disadvantage of the use of oral powders is the undesirable taste of the drug.

AEROSOL POWDERS

1. Some medicated powders are administered by inhalation with the aid of dry-powder inhalers, which deliver micronized particles of medication in metered quantities
2. Most of these products are used in the treatment of asthma and other bronchial disorders that require distribution of medication deep in the To accomplish this, the particle size of the micronized medication is prepared in the range of 1 to 6 µm in diameter.
3. In addition to the therapeutic agent, these products contain inert propellants and pharmaceutical diluents, such as crystalline alpha-lactose monohydrate, to aid the formulation's flow properties and metering uniformity and to protect the powder from humidity

Powder blowers or insufflators

1. Powder blowers or insufflators may be used to deliver dry powders to various parts of the body, e.g., nose, throat, lung, vagina. Depression of the device's rubber bulb causes turbulence of the powder in the vessel, forcing it out through the orifice in the tip



BULK AND DIVIDED POWDERS

- Medicated powders may be provided to the patient in bulk or may be divided into unit-of-use packages.
- Some powders are packaged by manufacturers, whereas others are prepared and packaged by the pharmacist.

Bulk Powders

- Among the bulk powders available in prepackaged amounts are
- (a) antacids (e.g., sodium bicarbonate) and laxatives (e.g., psyllium [Metamucil]), which the patient takes by mixing with water or another beverages before swallowing;
- (b) douche powders (e.g., Massengill powder), dissolved in warm water by the patient for vaginal use;
- (c) medicated powders for external application to the skin, usually topical anti-infectives (e.g., bacitracin zinc and polymyxin B sulfate) or antifungals (e.g., tolnaftate); and
- (d) brewer's yeast powder containing B-complex vitamins and other nutritional supplements.

In some cases, a small measuring scoop, spoon, or other device is dispensed with the powder for measuring the dose of the drug

Bulk powder

1. Dispensing powder medication in bulk quantities is limited to non-potent substances.
2. Powders containing substances that should be administered in controlled dosage are supplied to the patient in divided amounts in folded papers or packets.
3. Patients should be educated about appropriate handling, storage, measurement, and preparation of bulk powder prescription and nonprescription products in addition to the customary counseling at the time of dispensing or purchase. Generally, these products are stored at room temperature in a clean, dry place. These products should be kept out of the reach of children and animals. Patients should be instructed how to measure the appropriate amount of the powder and be told the type of liquid or vehicle to use to deliver the medication consistent with package and/or physician instructions.

Divided Powders

- After a powder has been properly blended (using the geometric dilution method for potent substances), it may be divided into individual dosing units based on the amount to be taken or used at a single time.
- Each divided portion of powder may be placed on a small piece of paper (Latin chartula; abbrev. chart.; powder paper) that is folded to enclose the medication.

Divided powder

- A number of commercially prepared premeasured products are available in folded papers or packets, including
- headache powders (e.g., Aspegic powders),
- powdered laxatives (e.g., psyllium mucilloid, Fybrogel),
- douche powders (e.g., Massengill powder packets).

Divided powders may be prepared by the pharmacist

- Depending on the potency of the drug substance, the pharmacist decides whether to
- weigh each portion of powder separately before enfolding in a paper or
- to approximate each portion by using the block-and-divide method, used only for non-potent drugs, the pharmacist places the entire amount of the prepared powder on a flat surface such as a porcelain or glass plate, pill tile, or large sheet of paper and, with a large spatula, forms a rectangular or square block of the powder having a uniform depth. Then, using the spatula, the pharmacist cuts into the powder lengthwise and crosswise to delineate the appropriate number of smaller, uniform blocks, each representing a dose or unit of medication. Each of the smaller blocks is separated from the main block with the spatula, transferred to a powder paper, and wrapped.

Powder paper

The powder papers may be of any size convenient to hold the amount of powder required, but the most popular commercially available sizes are 2.75 × 3.75 in., 3 × 4.5 in., 3.75 × 5 in., and 4.5 × 6 in..

The papers may be

(a) simple bond paper;

(b) vegetable parchment, a thin, semi-opaque paper with limited moisture resistance;

(c) glassine, a glazed, transparent paper, also with limited moisture resistance; and

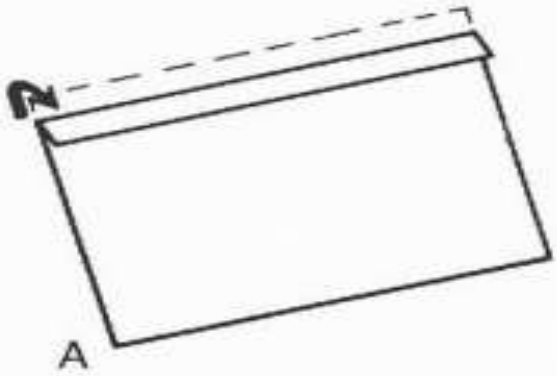
(d) waxed paper, a transparent waterproof paper.

The selection of the type of paper is based primarily on the nature of the powder. If the powder contains hygroscopic or deliquescent materials, waterproof or waxed paper should be used.

In practice, such powders are double wrapped in waxed paper, and then for aesthetic appeal they are wrapped in bond paper. Glassine and vegetable parchment papers may be used when only a limited barrier against moisture is necessary. Powders containing volatile components should be wrapped in waxed or glassine papers. Powders containing neither volatile components nor ingredients adversely affected by air or moisture are usually wrapped in a white bond paper.

Paper folding

1. Place the paper flat on a hard surface and fold toward you a uniform flap of about 0.5 in. of the long side of the paper. To ensure uniformity of all of the papers, this step should be performed on all the required papers concurrently, using the first folded paper as the guide (A).
2. With the flap of each paper away and on top, place the weighed or divided powder in the center of each paper.
3. Being careful not to disturb the powder excessively, bring the lower edge of the paper upward and tuck it into the crease of the flap (B)
4. Grasp the flap, press it down upon the tucked-in bottom edge of the paper, and fold again with an amount of paper equal to the size of the original flap (0.5 in.) (C).
5. Pick up the paper with the flap on top, being careful not to disturb the position of the powder, and place the partially folded paper over the open powder box (to serve as the container) so that the ends of the paper extend equally beyond the sides (lengthwise) of the open container. Then, press the sides of the box slightly inward and the ends of the paper gently down along the sides of the box to form a crease on each end of the paper. Lift the paper from the box and fold the ends of the paper along each crease sharply so that the powder cannot escape (D).
6. Place the folded paper in the box so that the double-folded flaps are at the top, facing you, and the ends are folded away from you (E).



A

B

C

D

E

Nowadays

- For convenience and uniformity of appearance, pharmacists may use commercially available small cellophane or plastic envelopes to enclose individual doses or units of use rather than folding individual powder papers. These envelopes are usually moisture resistant, and their use results in uniform packaging.
- Today, powder papers are rarely used on an out-patient, community practice basis and their use is confined to institutional and research practice

Examples

- Drugs that are provided in this drug delivery form include polyethylene glycol 3350 (i.e., MOVICOL),
- ColonClean

GRANULES

- Granules are prepared agglomerates of smaller particles of powder. They are irregularly shaped but may be prepared to be spherical. They are usually in the 4- to 12-mesh sieve size range, although granules of various mesh sizes may be prepared depending upon their application.

Advantage of granulation

- 1. Granules **flow better** than powders. The easy flow characteristics are important in supplying drug materials from the hopper or feeding container into the tableting presses. For this reason powder mixtures are usually granulated if they are intended to be compressed into tablets. Granules also eliminate or control dust.
- 2. Granules **increase compressibility**.
- 3. Granules have smaller surface area than a comparable volume of powders. This makes granules **more stable physically and chemically** than the corresponding powders. Granules are less likely to cake or harden upon standing than are powders.
- 4. Granules are **more easily wetted** by a solvent than are certain powders, so that granules are also preferred in making solutions. Example: Principen® (ampicillin) for Oral Suspension (Squibb). Ampicillin is unstable in aqueous solution, so it is usually prepared as granules and reconstituted by a pharmacist with purified water just prior to dispensing. The granules also contain colorants, flavorants, and other pharmaceutical ingredients, so the resulting solution or suspension has all the desired medicinal and pharmaceutical features of a liquid pharmaceutical.
- 5. Granules produce particle-size uniformity, thus **content uniformity**.

Wet method for granule preparation

- wet method is **to moisten the powder** or powder mixture and then pass the resulting paste through a screen of the mesh size to produce the desired size of granules.
- The granules are placed on drying trays and are dried by air or under heat. The granules are periodically moved about on the drying trays to prevent adhesion into a large mass.
- Another type of wet method is **fluid bed processing**, in which particles are placed in a conical piece of equipment and are vigorously dispersed and suspended while a liquid excipient is sprayed on the particles and the product dried, forming granules or pellets of defined particle size

Dry method for granulation

- The dry granulation method may be performed in a couple of ways. By one method, the dry powder is passed through a roll compactor and then through a granulating machine .
- A **roll compactor,** also called a roll press or roller compactor, processes a fine powder into dense sheets or forms by forcing it through two mechanically rotating metal rolls running counter to each other. The surface of the compacting rolls may be smooth or may have pocket indentations or corrugations that allow compaction of different forms and textures. The compacted powder is granulated to uniform particle size in a mechanical granulator. Powder compactors are generally combined in sequence in integrated compactor-granulation systems.
- An alternative dry method, termed **slugging**, is the compression of a powder or powder mixture into large tablets or slugs on a compressing machine under 8,000 to 12,000 lb of pressure, depending on the physical characteristics of the powder. The slugs are generally flat-faced and are about 2.5 cm (1 in.) in diameter . The slugs are granulated into the desired particle size, generally for use in the production of tablets. The dry process often results in the production of fines, that is, powder that has not agglomerated into granules. These fines are separated, collected, and reprocessed

EFFERVESCENT GRANULATED SALTS

- Effervescent salts are granules or coarse to very coarse powders containing a medicinal agent in a dry mixture usually composed of sodium bicarbonate, citric acid, and tartaric acid. When added to water, the acids and the base react to liberate carbon dioxide, resulting in effervescence.
- The resulting carbonated solution masks undesirable taste of any medicinal agent.
- Using granules or coarse particles of the mixed powders rather than small powder particles decreases the rate of solution and prevents violent and uncontrollable effervescence. Sudden and rapid effervescence could overflow the glass and leave little residual carbonation in the solution.
- Using a combination of citric and tartaric acids rather than either acid alone avoids certain difficulties. When tartaric acid is used as the sole acid, the resulting granules readily lose their firmness and crumble. Citric acid alone results in a sticky mixture difficult to granulate.

Effervescence

- A good effervescent blend consists of both **citric acid and tartaric acid (1:2 ratio)**.

$$3NaHCO_3 + C_6H_8O_7\ H_2O \rightarrow 4\ H_2O + 3\ CO_2 + Na_3C_6H_5O_7$$

- (Mwt = 84) Citric acid (Mwt = 210)

$$2\ NaHCO_3 + C_4H_6O_6 \rightarrow 2\ H_2O + 2CO_2 + Na_2C4H_4O_6$$

- Tartaric acid (Mwt = 150)
- The ratio of the effervescent ingredients is **1:2:3.4** for the citric acid: tartaric acid: sodium bicarbonate.
- Effervescent granules are prepared by two general methods: (a) the dry or fusion method and (b) the wet method

Fusion or dry method

- In the fusion method, the one molecule of water present in each molecule of citric acid acts as the binding agent for the powder mixture. Before mixing the powders, the citric acid crystals are powdered and then mixed with the other powders of the same sieve size to ensure uniformity of the mixture.
- The sieves and the mixing equipment should be made of stainless steel or other material resistant to the effect of the acids.
- The mixing of the powders is performed as rapidly as is practical, preferably in an environment of low humidity to avoid absorption of moisture and a premature chemical reaction.
- After mixing, the powder is placed on a suitable dish in an oven at 34°C to 40°C. During the heating process, an acid-resistant spatula is used to turn the powder. The heat releases the water of crystallization from the citric acid, which in turn dissolves a portion of the powder mixture, setting the chemical reaction and consequently releasing some carbon dioxide.

Screening

- This causes the softened mass of powder to become somewhat spongy, and when it has reached the proper consistency (as bread dough), it is removed from the oven and rubbed through a sieve to produce granules of the desired size.
- A No. 4 sieve produces large granules,
- a No. 8 sieve prepares medium size granules, and
- a No. 10 sieve prepares small granules.
- The granules are dried at a temperature not exceeding 54°C and are immediately placed in containers and tightly sealed

Wet Method

- The wet method differs from the fusion method in that the source of binding agent is not the water of crystallization from the citric acid but the water added to alcohol as the moistening agent, forming the pliable mass for granulation.
- In this method, all of the powders may be anhydrous as long as water is added to the moistening liquid. Just enough liquid is added (in portions) to prepare a mass of proper consistency; then the granules are prepared and dried in the same manner as described

Examples

- A number of commercial products containing antibiotic drugs that are unstable in aqueous solution are prepared as small granules for constitution by the pharmacist with purified water just prior to dispensing.
- Examples include
- KLACID granules for oral suspension (clarithromycin, Abbot),
- Augmentin ES-600 (amoxicillin/ clavulanate potassium, GSK
- Uricol granules.
- The granules are prepared to contain not only the medicinal agent but also colorants, flavorants, and other pharmaceutical ingredients.
- The granules are measured and mixed with water or other beverages, sprinkled on food, or eaten plain.
- Granulations of effervescent products may be compressed into tablet form, as Zantac EFFERdose tablets (Glaxo Wellcome). also(Multivitamins) Effervescent granules and tablets are dissolved in water before use.

Pharmaceutical drug interactions and Incompatibilities

Physiochemical approach

Drug Incompatibility (In-vitro)

- Incompatibility occurs when one drug is mixed with other drugs or agents detected by the change in physical, chemical, or therapeutic qualities
- and produces an **unsuitable drug** for administration either because

➢ Modification of the effect of the active drug such as increase in toxicity, or inactivation(affect the safety, efficacy)

➢ Or because of some physical change such as decrease in solubility or stability (affect appearance of a medicine)

DRUG INTERACTIONS (In-vivo)

- The term drug interaction is applied most frequently in **pharmacological or pharmacodynamic** point of view to

1. (**drug–drug interactions**), the actions of one drug are altered by the concurrent use of another
2. (**drug– nutrient–food interactions**) in which the actions of nutrients affect drugs or vice versa
3. (**drug–laboratory test interactions**) a drug causes alterations of laboratory test results
4. (**drug–disease interactions**) a drug causes undesired effects in patients with certain disease states

Related to absorption , distribution, metabolism and excretion

ADME

Types of Incompatibility

- Incompatibility is an **undesirable reaction** that occurs between the
- drug and the solution,
- drug and the container
- and another drug.(Drug –drug interactions)
- Drug -excipient interaction

- The two types of incompatibilities are

➢ Physical Result in decrease in solubility (precipitation),Loss of potency,

➢ Chemical result in Chemical instability , complexation

- It may occur mostly in solution state or even in the solid state

Physical Incompatibility Solubility

- When mixing concentrated hydroalcoholic solution of volatile oils (spirits) or aromatic waters with aqueous preparations
- The spirit or aromatic water must be added gradually to prevent sudden change in solvent
- Addition of high concentration of a strong electrolyte
- to saturated solutions of volatile oils
- to tinctures or fluidextracts of slightly soluble active constituents
- to colloidal dispersion
- to saturated solution of a weak electrolyte
- Also addition of alcohol to syrups and colloidal dispersions may cause ppt..

Solubility decrease of drugs

- Precipitation at the site of injection due
- Solvent dilution or alteration of pH (avoid i.v. route)
- Drugs like phenytoin, digoxin and diazepam are formulated in non aqueous but water miscible solvent (alcohol-water mixture) or micellar system, addition of the formulation to water may result in ppt.. depending on the final concentration of the drug and the solvent
- Diazepam injection may contain propylene glycol /alcohol / sodium benzoate / benzoic acid / benzyl alcohol.
- Upon dilution of the injection both the drug and the co-solvent is diluted , ppt. will depend on the solubility of the drug in the diluted system which mostly depend on the initial concentration of the drug in co-solvent mixture.

Eutectic mixture

- Some Solids of low melting when mixed together the melting point be lower the solids liquefy at room temperature like
- Camphor, menthol, phenol, thymol, and choral hydrate
- Aspirin and phenazone
- The phenomenon has no consequences for some type of dosage forms
- Menthol and thymol inhalation
- Camphor and menthol ointment
- But certain conditions like powders and capsules
- Triturate with adsorbent powder like light kaolin or light magnesium carbonate separately them mix them together

Chemical incompatibility

- This type of incompatibility is generally caused by

1. pH change
2. Chemical interaction
   cationic –anionic interaction
3. Complex formation

1- pH effects

- Salts of weak acids or weak bases will ppt.. when the pH changes but this depends on the

1. Solubility of the un-dissociated weak acid or the weak base (pHp : pH limit of solubility)
2. The pH of the solution
3. The pKa of the acid or the base
4. Buffering capacity

pH effects

- Solanaceous alkaloids.
- Atropine solubility
- 1 g in 400ml
- Belladonna tincture contains 0.3mg alkaloids /1ml
- $\frac{1000mg}{400ml} = \frac{0.3mg}{X}$
- X= 0.12ml
- Highest concentration is 5ml /100ml
- No risk of ppt. in alkaline conditions

- Barbiturates
- Solutions of salts are very alkaline and are incompatible with acids, acidic salts(ammonium bromide), and acidic syrups (lemon syrup)

Concentration of sodium phenobarbitone /10ml	pHp
30	7.5
60	7.9
100	8.3
200	8.6

pH effects (incompatibility)

- I.V admixtures (in-vitro)
- Be careful when mixing injectable drugs solution with specific diluents or pH range weak bases may ppt. according to the pKa at physiological pH.

CALCIUM PHOSPHATE DIBASIC	CALCIUM PHOSPHATE MONOBASIC
$CaHPO_4$ (pKa =7.2)	**Calcium $(H_2PO_4)_2$**
0.03%w/v solubility	1.8%w/v
At pH 7.4 (60%)	Soluble in acidic media < pH 5 (90%)

- Calcium phosphate will ppt. at physiological pH, should use I.V solution of low pH
- Discard I.V. admixture with precipitation immediately,
- Discard any I.V. admixture after 24hr of mixing

pH effects (interaction)

- Gastric pH is between (1-3) in normal subjects
- Administration of antacid, food and weak electrolytes will change the pH of the stomach
- Weakly acidic drug unionized in the stomach are absorbed by passive diffusion
- Increasing the pH of the stomach increasing ionization and reducing absorption (Tetracycline, Nalidixic acid , Nitrofurantoin, Benzyl pencillin , sulfonamides)
- Increasing gastric pH may lead to enhance gastric emptying
- This will be of advantage for acid liable drugs like levodopa

pH and dispersed system

- Outside an optimum pH range dispersion of polysaccharide Carbomer or sod CMC lose viscosity very rapidly
- Below pH 3 alginic acid is ppt.. from dispersions of sodium alginate,
- Strong acids ppt.. CMC from mucilage of sod CMC
- The gelling property of bentonite is greatly reduced in acid media but improved by adding alkaline substances
- When a dispersed (cream) is diluted with another of different pH ppt.. and/or degradation of the active ingredient may occur

2- Cation- anion interactions

- Interaction of ions of opposing types
- Cation –anion interactions result in formulation of a relatively insoluble precipitate, and lack the useful properties of the ions. Interaction is effected by the ionic strength, temperature, and pH.
- The complexes that form may not always be fully active.

Cationic –anionic incompatibly

1. Gentamicin sulphate and heparin sulphate groups interfere with the anticoagulant activity of heparin
2. Cloxacillin sodium and ephedrine HCl
3. The soluble dyes are usually sodium salts of large anions(amaranth, tartrazine) and should not be dispensed with cationic dyes (methylene blue, crystal violet) or with cationic drugs (antihistamine salts, chlorpromazine)
4. Cationic dyes may be ppt.. by soaps and clays
5. Ceftriaxone is incompatible with any I.V. fluid containing Calcium salts, (Ringer, Ringer Lactate)

Cationic –anionic incompatibly

- Detection may not be always apparent,
- For creams made with an anionic EA may

a) Cream or crack if mixed with a cream in which a cationic EA (Cetrimide)
b) Hinder the release of cationic drugs to the body
c) Lower the antimicrobial activity of a cationic drug or preservative. (Neomycin sulphate and sodium lauryl sulphate) the skin must be washed from soap well before application of cationic antibacterial

For suspensions made from anionic suspending agents and cationic preservatives may lead to coagulation and sedimentation due to neutralization of the charge of the dispersed particles

Use unionized suspending agent for ionic drugs

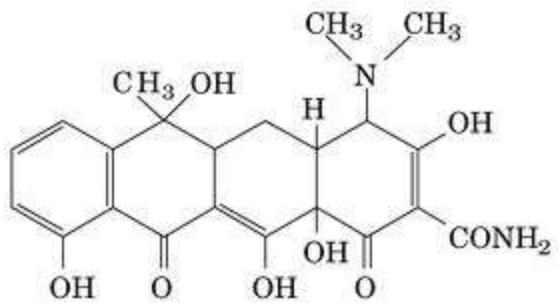
3- Chelation (complexation)

- The term chelation derived from the Greek chele meaning lobster's claw referring to the interaction between a metal atom or ion and another species known as a ligand
- Chelation changes the physical and chemical characteristics of both the metal ion and the ligand
- These complexes are too large to penetrate the cell membrane,

a) activity of the drug may be reduced
b) Act as a reservoir of drug to prolong drug release
c) Reduced irritancy and improve stability (Povidone iodine)

Chelation

- Tetracyclines
- Polyvalent cations such as Fe and Mg , Calcium , Al, and anions such as phosphate interfere with the absorption of tetracycline's
- Tetracycline is responsible teeth discoloration or bone deformation in growing babies



Tetracycline

Incompatibility with the container

- The plastic tubes and connections used in intravenous containers and giving sets can adsorb or absorb a number of drugs, leading to significant lose.
- PVC poly vinyl-chloride insulin, diazepam, Vitamin A
- glyceryl trinitrate, warafarin
- `
- Preservatives such as methyl and propyl parabens adsorbed to the rubber and plastic membranes and closures leading to decreased level of preservative and may loss of preservative activity

Pharmaceutical cosmetics

Hanan Kassab

How does the law define a drug?

- The Federal Food, Drug, and Cosmetic Act FD&C Act defines drugs, in part, by their intended use, as
- "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals"
- [FD&C Act, sec. 201(g)(1)]

How does the law define a cosmetic?

- The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines cosmetics by their intended use, as "**articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance**" [FD&C Act, sec. 201(i)].

To prohibit the movement in interstate commerce of adulterated and misbranded food, drugs, devices, and cosmetics, and for other purposes.

FFDCA, "FD&C Act

Cosmetics

- Among the products included in this definition are
- skin moisturizers, and other skin products
- perfumes,
- lipsticks,
- fingernail polishes,
- eye and facial makeup preparations,
- cleansing shampoos,
- permanent waves,
- hair colors,
- and deodorants,
- as well as any substance intended for use as a component of a cosmetic product.

Cosmetic

- Chewing gum
- Cleansing shampoo
- Soaps
- Perfumes (V.O)
- Massage oil
- Lipstick
- Hair lotions or oils
- Skin moisturizer

Drug

- Nicorette chewing gum
- Antidandruff shampoo
- Antibacterial soaps,
- Aromatherapy
- Oils to relieve muscle pain
- Moisturizing lipstick
- Products which restore hair growth,
- Products which reduce cellulite, treat varicose veins, increase or decrease the production of melanin (pigment) in the skin, or regenerate cells.

How can a product be both a cosmetic and a drug?

- Some products meet the definitions of both cosmetics and drugs. This may happen when a product has two intended uses.
- For example, a shampoo is a cosmetic because its intended use is to cleanse the hair. An antidandruff treatment is a drug because its intended use is to treat dandruff. Consequently, an antidandruff shampoo is both a cosmetic and a drug.
- Among other cosmetic/drug combinations are toothpastes that contain fluoride,
- deodorants that are also antiperspirants,
- and moisturizers and makeup marketed with sun-protection claims.
- Such products must comply with the requirements for both cosmetics and drugs.

What about "cosmeceuticals"?

- The FD&C Act does not recognize any such category as "cosmeceuticals." A product can be a drug, a cosmetic, or a combination of both, but the term "cosmeceutical" has no meaning under the law

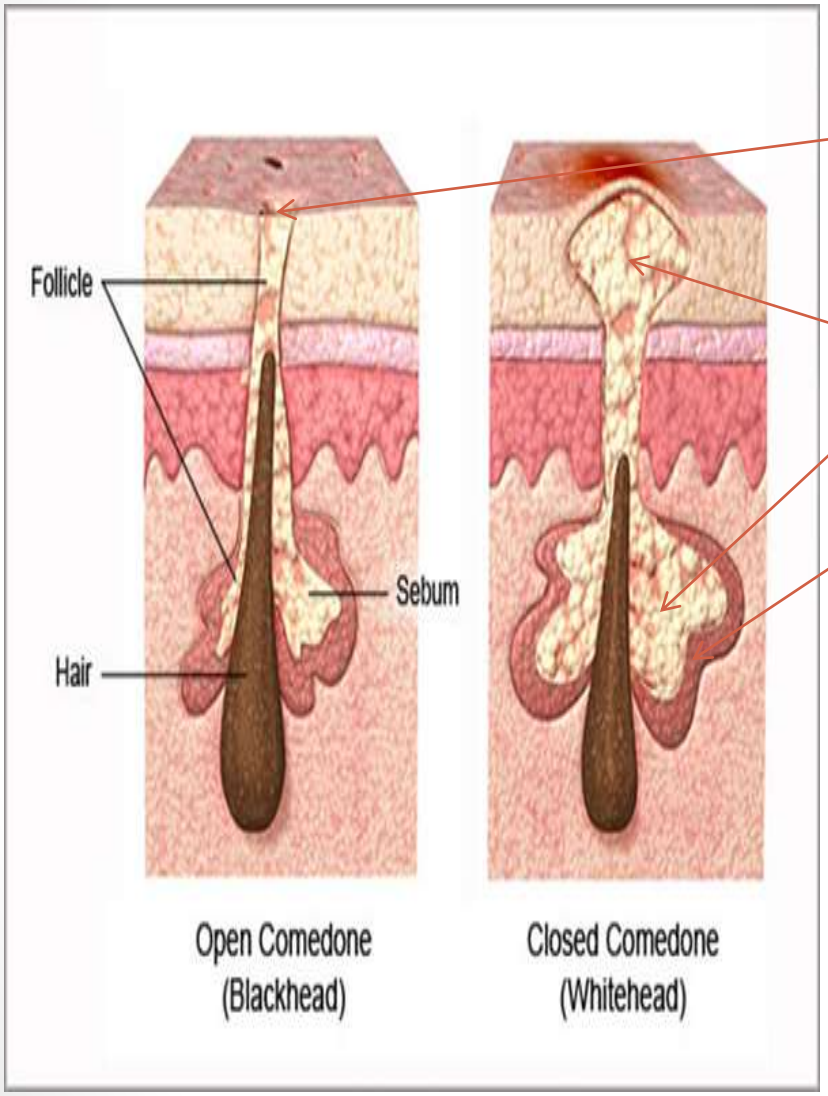
OTC

- OTC Over-the-counter drugs are defined as drugs that are safe and effective for use by the general public without a prescription.
- FDA has published **monographs**, or rules, for a number of OTC (nonprescription)drug categories. OTC are generally recognized as safe and effective (GRAS/E)
- Some of the drug categories covered by OTC are
  - acne medications
  - treatments for dandruff, seborrheic dermatitis, and psoriasis
  - sunscreens

Acne

- Acne vulgaris is a common, usually self-limiting, multifactorial disease involving inflammation of the sebaceous follicles of the face and upper trunk.
- Acne vulgaris is the medical name for common acne -- the presence of blackheads, whiteheads, and other types of pimples on the skin.
- The four primary factors involved in the formation of acne lesions are
- increased sebum production,
- sloughing of keratinocytes,
- bacterial growth,
- and inflammation.
- Increased androgen activity at puberty triggers growth of sebaceous glands and enhanced sebum production. Sebum consists of glycerides, wax esters, squalene, and cholesterol. Glyceride is converted to free fatty acids and glycerol by lipases, which are products of ***Propionibacterium acnes***. Free fatty acids may irritate the follicular wall and cause increased cell turnover and inflammation.

Acne - Medications



- Unplugging skin pores and stopping them from getting plugged with oil (tretinoin, which is sold as Retin-A).
- Killing bacteria (antibiotics).
- Reducing the amount of skin oil (isotretinoin).
- Reducing the effects of hormones in producing acne (certain oral contraceptive pills for women).
- Or you may take medicines suchas clindamycin/benzoyl peroxide, a gel that contains two topical medicines

Benzoyl peroxide

- Benzoyl peroxide is available in prescription and over-the-counter medications, in **cream, gel, and wash form.**
- Benzoyl peroxide is the **most effective acne treatmen**t ingredient in the OTC market. It is an anti-bacterial agent.
- When benzoyl peroxide touches the skin, it breaks down into benzoic acid and oxygen,
- Benzoyl peroxide is the only known substance which can bring oxygen under the skin surface. Since bacteria cannot survive in the presence of oxygen, when used in an adequate dosage, benzoyl peroxide eradicates 99.9% of these bacteria almost immediately.
- It also exerts a mild drying and peeling effect, which is thought to help prevent breakouts.
- Benzoyl peroxide also helps lessen inflammation.2.5% benzoyl peroxide is just as effective as higher concentrations with less side effects.

Salicylic Acid

- Salicylic acid is another major comedolytic , it is able to exfoliate in the oily milieu of the pore.
- Salicylic acid can be applied to the skin in a variety of different formulations It can be applied as a solution in an alcohol-detergent vehicle or in the form of an impregnated pad .
- It can be formulated as a 2% salicylic acid scrub, with clinical data demonstrating a reduction in open comedones
- Also, 10% and 20% salicylic acid peels are used to promote comedolysis.

Sulfur

- Sulfur is a known bacteriostatic and antifungal agent,
- Sulfur is thought to interact with cysteine in the stratum corneum causing a reduction in sulfur to hydrogen sulfide,
- Hydrogen sulfide in turn degrades keratin, which has a comedolytic effect beneficial in curing acne.
- Sulfur is available in concentrations of 3–8% in OTC acne formulations.
- It has a characteristic foul odor and unusual yellow color.
- It stains clothing and is typically formulated as a thick paste.

Cosmetic acne therapies (not monographed)

❖ **Hydroxy Acids**

- Glycolic acid is the smallest alpha hydroxy acid **AHA** appearing as a colorless, odorless, hygroscopic crystalline solid. Used as a desquamating agents (remove the comedonal plugs)

❖ **Triclosan**

- Triclosan decreases the *P. acnes* count on the skin surface, used in soap as part of an acne treatment regimen.
- **Tea Tree Oil (TTO)** obtained from the Australian tree
- *Melaleuca alternifolia* **,** contains several anti microbial substances such as terpinen-4-ol, alpha-terpineol, and alpha-pinene, the oil has an antiseptic, antifungal, and antibacterial effect

Skin care in acne patients (NONPHARMACOLOGIC THERAPY)

Beyond the acne treatments discussed earlier, skin care products and cosmetics can aid in acne therapy or contribute to disease worsening.

- Surface skin cleansing with soap and water has a relatively small effect on acne because it has minimal impact within follicles
- Skin scrubbing or excessive face washing does not necessarily open or cleanse pores and may lead to skin irritation.
- Use of gentle, nondrying cleansing agents is important to avoid skin irritation and dryness during some acne therapies.

Acne Skin care products as

- cleansers,
- astringents, and exfoliants,
- facial scrubs,
- textured cloths ,
- mechanized skin care devices,
- and face masks.

Cleansers

- A variety of cleansers are useful in removing sebum and normalizing the acne biofilm.

- **Soaps** are some of the major cleansers used in acne treatment. These include true soaps that are composed of long chain fatty acid alkali salts, with a pH of 9–10. They may contain triclosan,
- Synthetic detergents, known as **syndets**. (milder detergent) These cleansers contain less than 10% soap with a more neutral pH adjusted to 5.5–7.0, called cleansing or dermatological bars

- **Facial scrubs** are mechanical exfoliants, as opposed to the glycolic acid chemical exfoliants, employing small granules in a cleansing base to enhance corneocyte desquamation. The scrubbing granules may be polyethylene beads, aluminum oxide, ground fruit pits, or sodium tetraborate decahydrate granules aiding in the removal desquamating stratum corneum from the face

Astringents

- Astringents are liquids applied to the face following cleansing and are used widely in cosmetic acne treatments, astringents were developed to remove alkaline soap scum from the face following cleansing with lye-based soaps and high-mineral content well water.
- They are known by many terms: **toners**, clarifying lotions, controlling lotions, protections lotions, skin fresheners, toning lotions, T-zone tonics, etc.
- Oily skin astringents contain a high concentration of alcohols, water, and fragrance functioning to remove any sebum left behind after cleansing, to produce a clean feel, and possibly apply some treatment product to the face. For example, **2% salicylic acid** or **witch hazel** may be added for a keratolytic and drying effect on the facial skin of acne patients. Clays, starches, or synthetic polymers may be added to absorb sebum and minimize the appearance of facial oil.

Exfoliants (removes the dead layers of skin on top)

- Exfoliants are similar to astringents, but these are solutions, lotions, or creams applied to the face after cleansing and after the application of an exfoliant designed to hasten stratum corneum exfoliation and assist in comedolysis in the acne patient.
- Their exfoliant effect is based on the use of alpha, poly, or beta hydroxy acids, thus inducing chemical exfoliation. The goal is to loosen the retained comedonal plug chemically from the lining of the pore. **Glycolic acid** exfoliants based on alpha hydroxy acids may be useful in patients with acne and photoaged skin to improve appearance; however,
- the **salicylic beta hydroxy acid** exfoliants are more effective. This is due to their inherent oil solubility that allows them to exfoliate in the oily milieu of the pore.
- Polyhydroxy acid exfoliants based on **gluconolactone** are also marketed with the main claim of reduced irritation. Their large molecular weight impedes skin penetration and reduces irritation.

Dandruff

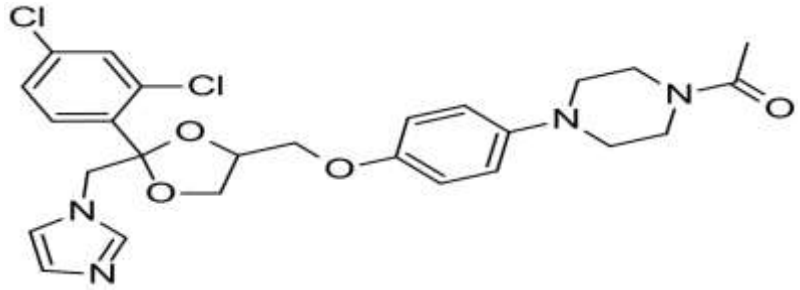
- **Dandruff** is the shedding of dead skin cells from the scalp
- It often causes itching. It has been well established that keratinocytes play a key role in the expression and generation of immunological reactions during dandruff formation.
- The severity of dandruff may fluctuate with season as it often worsens in winter.
- Dandruff scale is a cluster of corneocytes, which have retained a large degree of cohesion with one another and detach as such from the surface of the stratum corneum.

Causes of dandruff

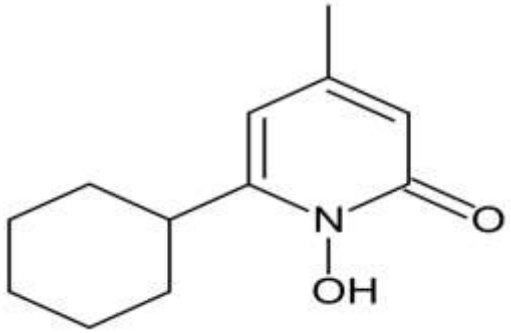
- Dandruff has been shown to possibly be the result of three factors:

1. Skin oil commonly referred to as sebum or sebaceous secretions For people with dandruff, the new cells are produced at a faster rate than they die, resulting in more skin being shed, making dandruff more noticeable.
2. The metabolic by-products of skin micro-organisms (most specifically the scalp specific fungus Malassezia yeasts) that metabolizes triglycerides present in sebum by the expression of lipase, resulting in a lipid byproduct oleic acid (OA). During dandruff, the levels of *Malassezia* increase by 1.5 to 2 times its normal level. Penetration by OA of the top layer of the epidermis, the stratum corneum, results in an inflammatory response in susceptible persons which disturbs homeostasis and results in erratic cleavage of stratum corneum cells
3. Individual susceptibility and allergy sensitivity

Antifungals



- **Ketoconazole** as a shampoo 2% Ketoconazole is a broad spectrum, antimycotic agent that is active against both Candida and M. furfur. It prevents growth of several types of fungi by preventing production of the membranes that surround fungal cells. Of all the imidazoles, ketoconazole has become the leading contender among treatment options because of its effectiveness in treating seborrheic dermatitis as well.
- **Ciclopirox** is widely used as an anti-dandruff agent in most preparations, It is most useful against Tinea versicolor



SELSUN ® (selenium)

- Selenium SULFIDE LOTION, USP
- this reduces the production of natural oils your scalp glands produce and appears to have a cytostatic effect on cells of the epidermis and follicular epithelium, reducing corneocyte production
- A liquid antiseborrheic, antifungal preparation for topical application. In the United States,
- a 1% strength is available over-the-counter, and a 2.5% strength is also available with a prescription.
- At the 2.5% strength, selenium disulfide is also used on the body to treat tinea versicolor, a type of fungal skin infection caused by a different species of *Malassezia*.
- A new concentration of 0.6% of micronized Selenium disulfide is available

Zinc pyrithione

It has fungistatic (an ingredient which slows down the production of yeasts) and <u>bacteriostatic effect</u>

It is thought that zinc pyrithione (ZPT) heals the scalp by normalizing epithelial keratinization, sebum production, or both. Some studies have also shown a significant reduction in the numbers of yeast organisms after the application of zinc pyrithione.
Therefore, normalization of the stratum corneum ultrastructure by zinc pyrithione is thought to be secondary to the correction of the pathology in the living epidermal layers.

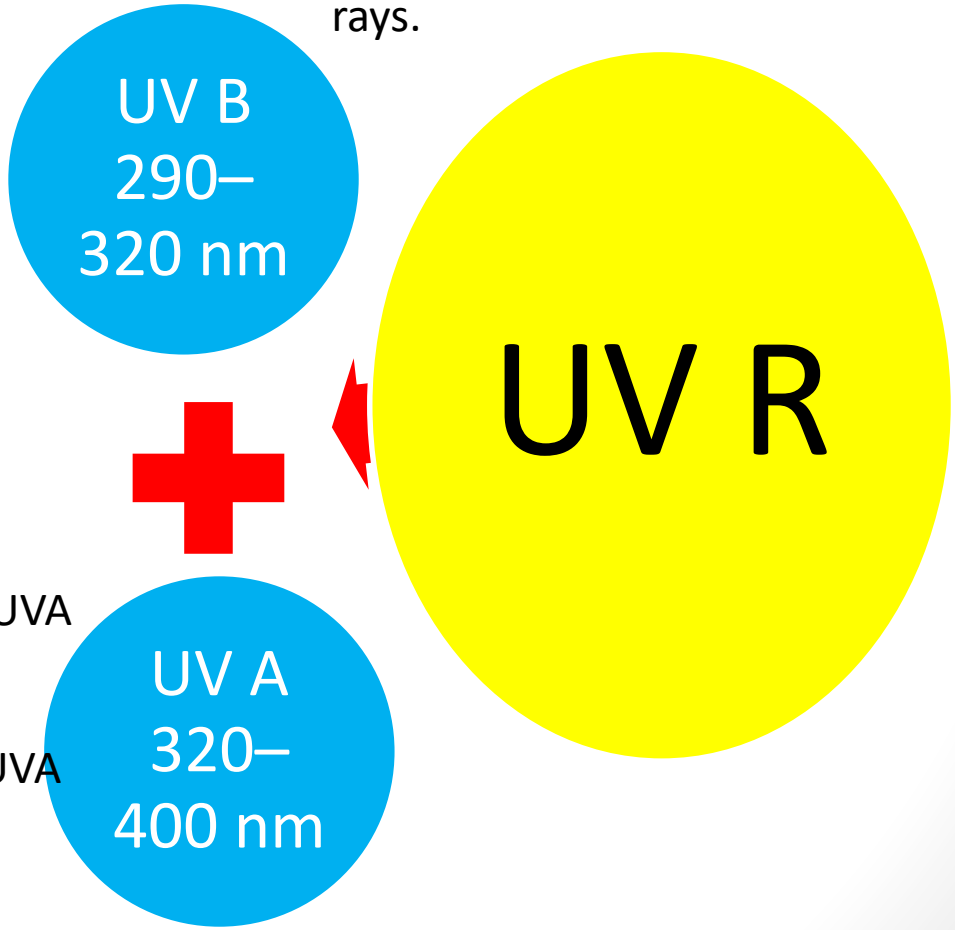
Sun radiation

The solar radiation, also known as the electromagnetic spectrum, comprises about 5% ultraviolet rays, 35% visible light, and 60% infrared rays.

Radiation wavelengths of less than 320 nm are absorbed by the stratum corneum and epidermis,

while wavelengths greater than 320 nm enter the dermis.

Penetration into the dermis can be enhanced by wetting the stratum corneum and altering the refractive index.



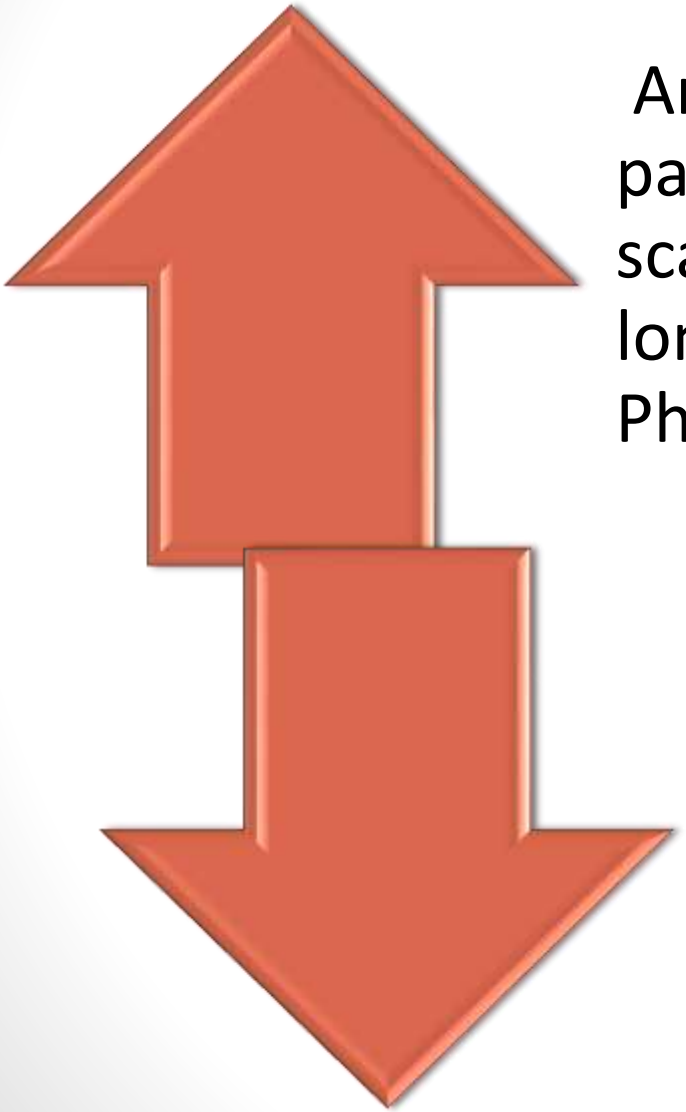
UVA II near UVA (320–340 nm)

UV A1 far UVA (340-400nm)

Effect of sun radiation (photo-aging)

- The target of UVA and UVB damage is DNA, cell membrane lipids, structural proteins, and enzymes. These breakdown products incite an inflammatory response designed to initiate skin repair, but may result in further skin damage.

Types of sunscreens



Physical Inorganic

Are usually ground particulates that reflect or scatter UV radiation, stay a long time on the skin
Photo-stable

Chemical Organic

undergo a chemical transformation, known as resonance delocalization, to absorb UV radiation and transform it to heat

Sunscreen filters

- U VA absorbers: 320 to 360 nm (benzophenones, avobenzone, and anthranilates)
- U VB absorbers: 290 to 320 nm [para-amino benzoic acid (PABA) derivatives, salicylates, and cinnamates]
- U VB/UVA blocks: reflect or scatter UVA and UVB (titanium dioxide and zinc oxide)

UV Filters, Sunscreens

- Protection against the effects of UVR in the skin is achieved by specially designed molecules **(i.e., UV filters)**
- incorporated in suitable formulations **(sunscreens)** such as creams or lotions, oils, gels, sticks, etc.

The sun protection factor (SPF)

(SPF) =

the dose of UVR required to produce 1 minimal erythema dose (MED) on protected skin after application of 2 mg/cm² of product

UVR to produce 1 MED on unprotected skin.

Mathematically, the SPF (or the UPF) is calculated from measured data as

$$SPF = \frac{\delta A(\gamma)E(\gamma)d\gamma}{\delta A(\gamma)E(\gamma)/MPF(\gamma)d\gamma}$$

- where $E(\gamma)$ is the solar irradiance spectrum, $A(\gamma)$ the erythemal action spectrum, and $MPF(\gamma)$ the monochromatic protection factor, all functions of the wavelength . The MPF is roughly the inverse of the transmittance at a given wavelength

FDA UV Filters Final Monograph Ingredients

Drug name	Concentration (%)	Absorbance
Aminobenzoic acid	Up to 15	UVB
Avobenzone	2–3	UVAI
Cinoxate	Up to 3	UVB
Dioxybenzone	Up to 3	UVB, UVAII
Ensulizole	Up to 4	UVB
Homosalate	Up to 15	UVB
Meradimate	Up to 5	UVAII
Octocrylene	Up to 10	UVB
Octinoxate	Up to 7.5	UVB
Octisalate	Up to 5	UVB
Oxybenzone	Up to 6	UVB, UVAII
Padimate O	Up to 8	UVB
Sulisobenzone	Up to 10	UVB, UVAII
Titanium dioxide	2 to 25	Physical
Trolamine salicylate	Up to 12	UVB
Zinc oxide	2 to 20	Physical

CAPSULES

Chapter 7

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 9th Edition

Capsules

- Capsules are solid dosage forms in which medicinal agents and/or inert substances are enclosed in a small shell of gelatin. Gelatin capsule shells may be hard or soft, depending on their composition.

Advantages of capsules

Elegant and Conveniently carried, readily identified, and easily taken.

Easily swallowed .There is no need for spoons or other measuring devices,

Are **Tasteless** and **Odorless** when swallowed

Available for many medications in a **variety of dosage** strengths, providing flexibility to the prescriber and **accurate** individualized dosage for the patient.

They are packaged and shipped by manufacturers at **lower cost** and with less breakage

They are also **more stable** and have a longer shelf life than their liquid counterparts.

HARD GELATIN CAPSULES

- Hard gelatin capsule shells are used in most commercial medicated capsules.
- They are also commonly employed in clinical drug trials to compare the effects of an investigational drug with those of another drug product or placebo.
- The community pharmacist also uses hard gelatin capsules in the extemporaneous compounding of prescriptions.

Hard Gelatin

- The empty capsule shells are made of gelatin, sugar, and water. As such, they can be clear, colorless, and essentially tasteless.
- They may be colored with various FD&C and D&C dyes and made opaque by adding agents such as titanium dioxide.
- Most commercially available medicated capsules contain combinations of colorants and opaquants to make them distinctive, many with caps and bodies of different colors

Gelatin

- Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals.
- It is available in the form of a fine powder, a coarse powder, shreds, flakes, or sheets.
- Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist. Normally, hard gelatin capsules contain 13% to 16% of moisture.
- However, if stored in an environment of high humidity, additional moisture is absorbed by the capsules, and they may become distorted and lose their rigid shape. In an environment of extreme dryness, some of the moisture normally present in the gelatin capsules is lost, and the capsules may become brittle and crumble when handled.
- Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excessive humidity or dryness.

Effect of moisture on gelatin

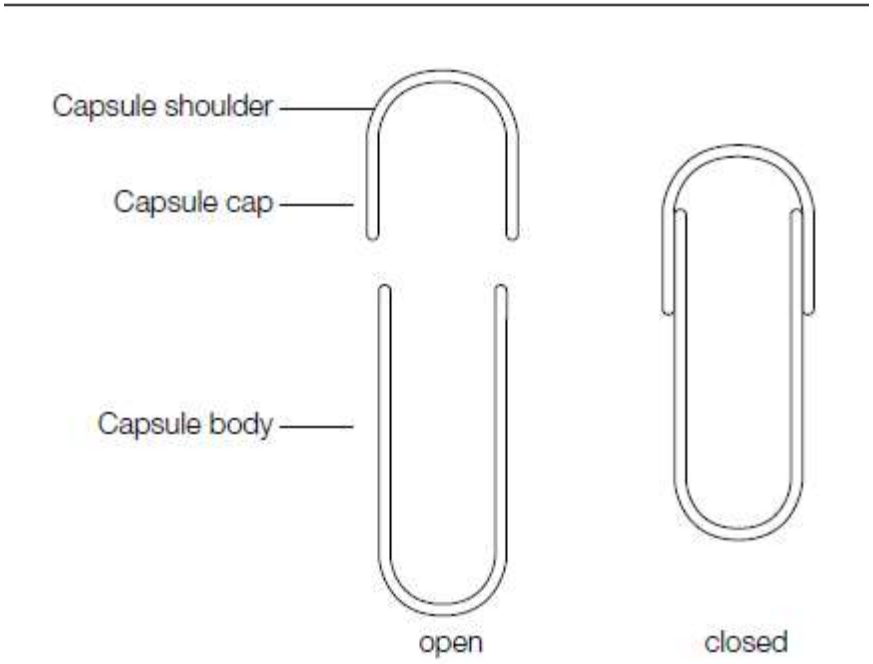
- Because moisture may be absorbed by gelatin capsules and may affect hygroscopic agents within, many capsules are packaged along with a small packet of a desiccant material to protect against the absorption of atmospheric moisture.
- The desiccant materials most often used are dried silica gel, clay, and activated charcoal.
- Prolonged exposure to high humidity can affect in vitro capsule dissolution. Such changes have been observed in capsules containing tetracycline, chloramphenicol, and nitrofurantoin. Because such changes could forewarn of possible changes in bioavailability, capsules subjected to such stress conditions must be evaluated case by case.

Gelatin administration

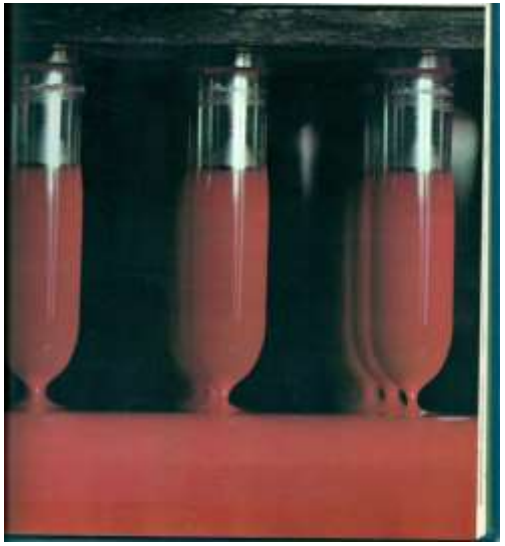
- Although gelatin is insoluble, it does soften in cold water through the absorption of water up to 10 times its weight of water.
- Some patients prefer to swallow a capsule wetted with water or saliva because a wetted capsule slides down the throat more readily than a dry capsule.
- Gelatin is soluble in hot water and in warm gastric fluid; a gelatin capsule rapidly dissolves and exposes its contents.
- Gelatin, being a protein, is digested by proteolytic enzymes and absorbed.

THE MANUFACTURE OF HARD GELATIN CAPSULE SHELLS

- Hard gelatin capsule shells are manufactured in two sections, the capsule body and a shorter cap.
- The two parts overlap when joined, with the cap fitting snugly over the open end of the capsule body.



- The shells are produced industrially by the mechanical dipping of pins or pegs of the desired shape and diameter into a temperature-controlled reservoir of melted gelatin mixture.
- The pegs, made of manganese bronze, are affixed to plates, each capable of holding up to about 500 pegs. Each plate is mechanically lowered to the gelatin bath, the pegs submerged to the desired depth and maintained for the desired period to achieve the proper length and thickness of coating.
- Then the plate and the pegs are slowly lifted from the bath and the gelatin is dried by a gentle flow of temperature- and humidity-controlled air.
- When dried, each capsule part is trimmed mechanically to the proper length and removed from the pegs, and the capsule bodies and caps are joined together.



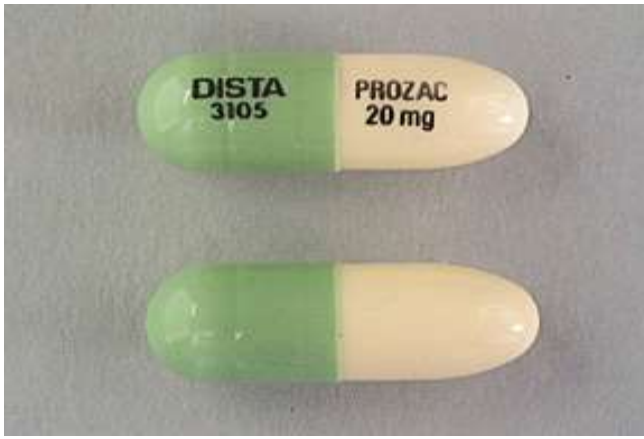
Hard gelatin capsules

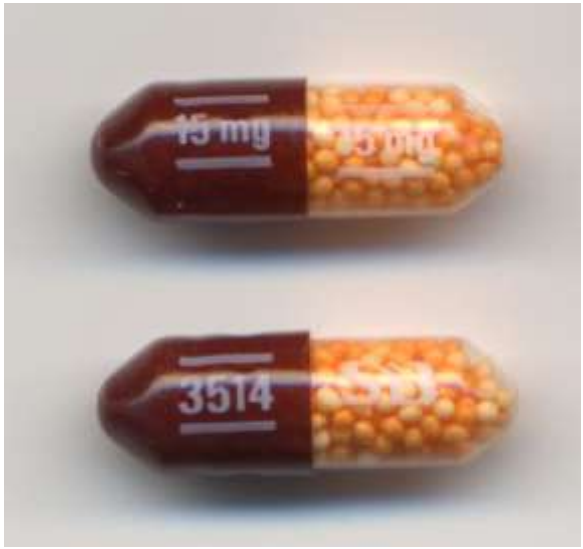
- It is important that the thickness of the gelatin walls be strictly controlled so that the capsule's body and cap fit snugly to prevent disengagement.
- The pegs on which the caps are formed are slightly larger in diameter than the pegs on which the bodies are formed, allowing the telescoping of the caps over the bodies.
- In capsule shell production, there is a continuous dipping, drying, removing, and joining of capsules as the peg-containing plates rotate in and out of the gelatin bath.

Capsule shapes

- A manufacturer also may prepare distinctive-looking capsules by altering the usual rounded shape of the capsule-making pegs.

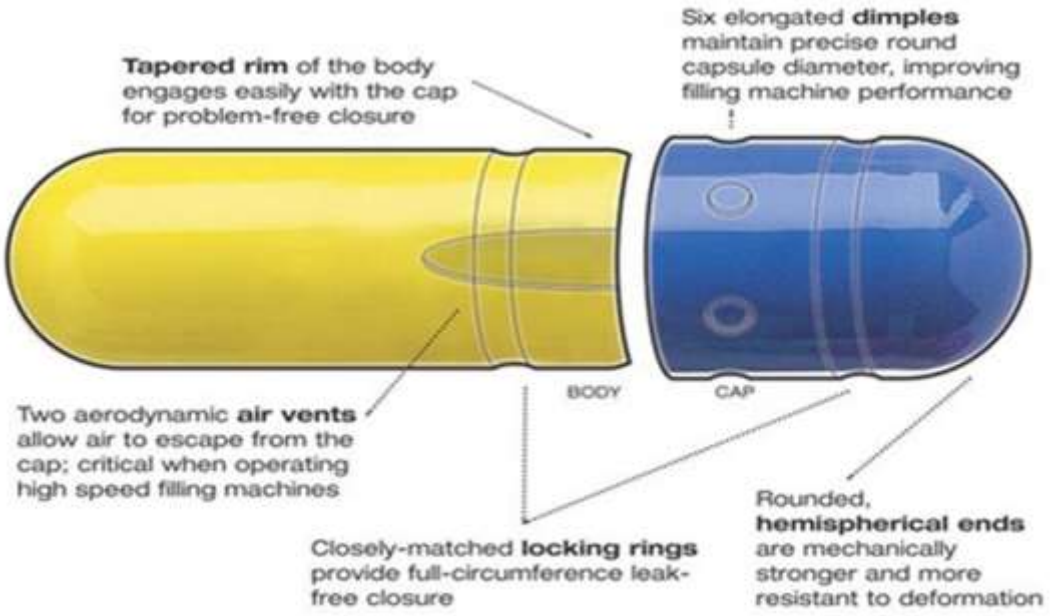
1. By tapering the end of the body-producing peg while leaving the cap-making peg rounded, one manufacturer prepares capsules differentiated from those of other manufacturers (Pulvules, Eli Lilly).
2. Another manufacturer uses capsules with the ends of both the bodies and caps highly tapered (Spansule Capsules, SmithKline Beecham).





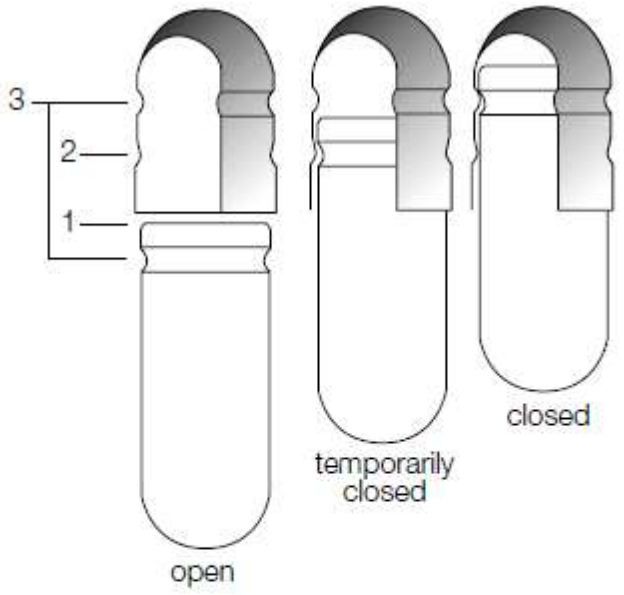
Capsule design

1. Snap-fit . The original Snap-fit construction enables the two halves of the capsule shells to be positively joined through locking grooves in the shell walls. The two grooves fit into each other and thus ensure reliable closing of the filled capsule.



Snap fit

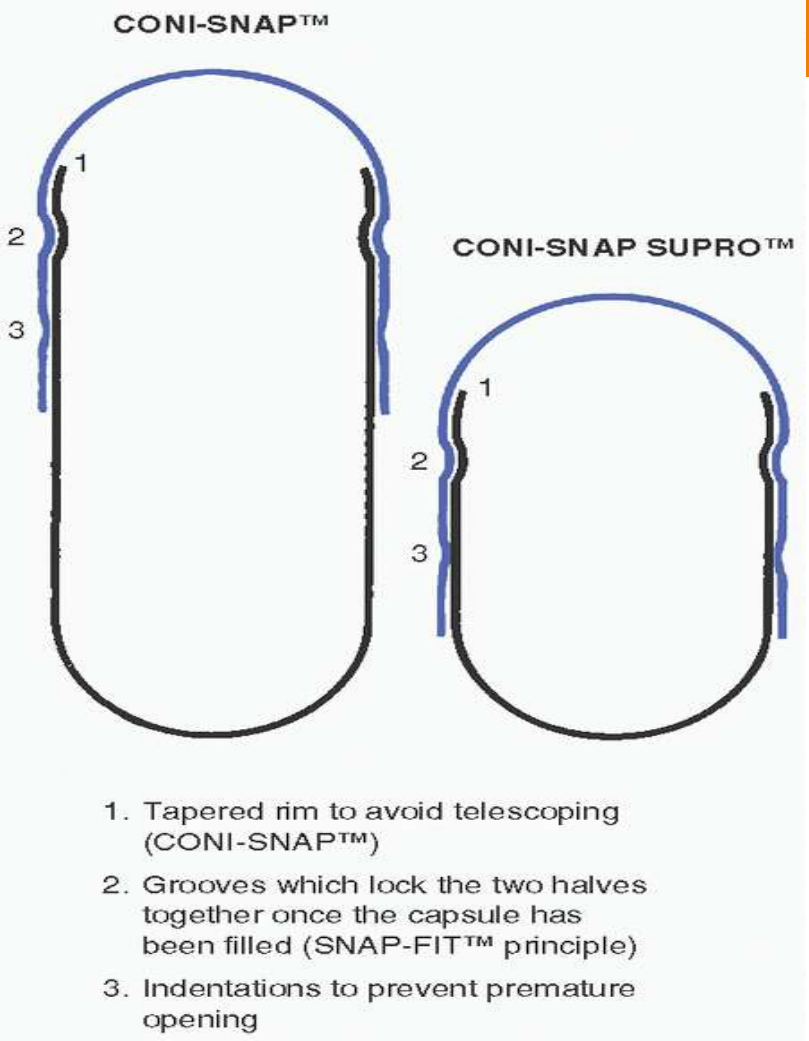
- During the closing process, the capsule body is inserted into the cap. With the high-capacity filling rates of the modern capsule filling machines (more than 180,000 capsules per hour), splitting (telescoping) and/or denting of the capsule shell occur with the slightest contact between the two rims

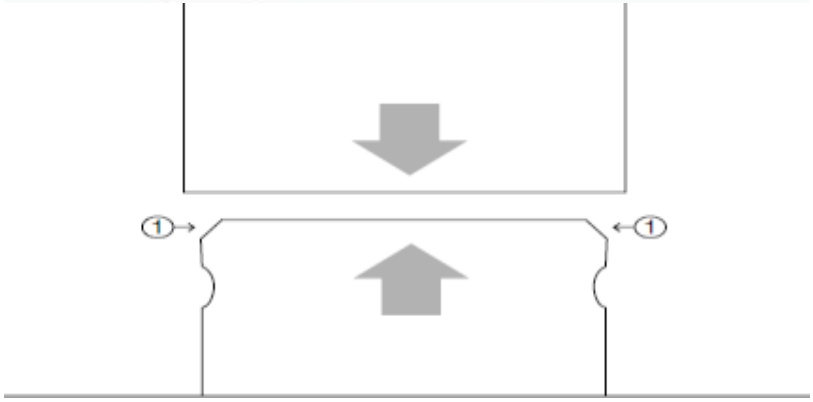


1. The tapered rim prevents splitting and denting of the capsule
2. The notches prevent premature opening of the capsule
3. The rim closes the filled capsule safely (SNAP-FIT™ principle)

Coni-snap, and Coni-snap Supro hard gelatin

- Line drawings of the CONI-SNAP and CONI-SNAP SUPRO (right) capsules. The latter is designed to be smaller and to have the lower portion of the capsule shell concealed except for the rounded end. This makes separation of the two parts more difficult and contributes to capsule integrity. (Courtesy of Capsugel Division, Warner-Lambert.)





Splitting (telescoping) and/or denting of the capsule shell

- Occurs with the slightest contact between the two rims when they are joined.
- This problem, which exists primarily with straight-walled capsule shells, led to the development of the Coni-snap capsule, in which the rim of the capsule body is not straight but tapered slightly
- This reduces the risk of the capsule rims touching on joining and essentially eliminates the problem of splitting during large-scale filling operations.
- In the Coni-snap Supro capsules, the upper capsule part extends so far over the lower part that only the rounded edge of the latter is visible.
- Opening of such a filled capsule is difficult because the lower surface offers less gripping surface to pull the two halves apart. This increases the security of the contents and the integrity of the capsule.
- After filling, some manufacturers render their capsules tamper evident through various sealing techniques.

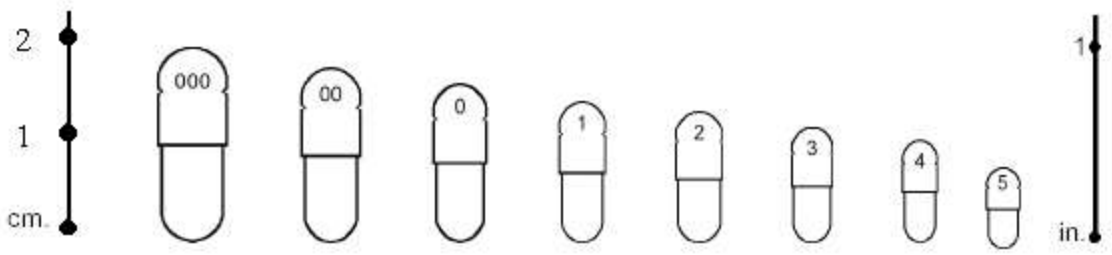
CAPSULE SIZES

- Empty gelatin capsules are manufactured in various lengths, diameters, and capacities.
- The size selected for use is determined by the amount of fill material to be encapsulated. The density and compressibility of the fill will largely determine to what extent it may be packed into a capsule shell
- For estimation, a comparison may be made with powders of well known features and an initial judgment made as to the approximate capsule size needed to hold a specific amount of material.
- However, the final determination may be largely the result of trial and error.
- For human use, empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available
- Larger capsules are available for veterinary use.
- For prescriptions requiring extemporaneous compounding, hard gelatin capsules permit a wide number of options for the physician.
- The pharmacist may compound capsules of a single medicinal agent or combination of agents at the precise dosage prescribed for the individual patient

APPROXIMATE CAPACITY OF EMPTY GELATIN CAPSULES

	Capsule size							
Volume (mL)	**000 1.40**	**00 0.95**	**0 0.68**	**1 0.50**	**2 0.37**	**3 0.30**	**4 0.21**	**5 0.13**
Drug substance (mg)[a]								
Quinine sulfate	650	390	325	227	195	130	97	65
Sodium bicarbonate	1430	975	715	510	390	325	260	130
Aspirin	1040	650	520	325	260	195	162	97

[a] Amount may vary with the degree of pressure used in filling the capsules



PREPARATION OF FILLED HARD GELATIN CAPSULES

- The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps.

1. Developing and preparing the formulation and selecting the capsule size
2. Filling the capsule shells
3. Capsule sealing (optional)
4. Cleaning and polishing the filled capsules

DEVELOPING THE CAPSULE FORMULATION

- In dry formulations, the active and inactive components must be blended thoroughly to ensure a **uniform powder mix** for the fill.
- Care in blending is especially important for **low-dose drugs**, since lack of homogeneity in blending may result in significant therapeutic consequences.
- Preformulation studies are performed to determine whether all of the formulation's bulk powders may be effectively blended together as such or require **reduction of particle size** or any other processing to achieve homogeneity.
- A **diluent or filler** may be added to the formulation to produce the proper capsule fill volume. Lactose, microcrystalline cellulose, and starch are commonly used for this purpose. In addition to providing bulk, these materials often provide cohesion to the powders, which is beneficial in the transfer of the powder blend into capsule shells.
- **Disintegrants** are frequently included in a capsule formulation to assist the breakup and distribution of the capsule's contents in the stomach. Among the disintegrants used are pregelatinized starch, croscarmellose, and sodium starch glycolate

THE CAPSULE SIZE

- To achieve uniform drug distribution, it is advantageous if the density and particle size of the drug and nondrug components are similar.
- This is particularly important when a drug of low dosage is blended with other drugs or nondrug fill .
- When necessary, particle size may be reduced by milling to produce particles ranging from about 50 to 1,000 µm.
- Milled powders may be blended effectively for uniform distribution throughout a powder mix when the drug's dosage is 10 mg or greater.
- For drugs of lower dose or when smaller particles are required, micronization is employed. Depending on the materials and equipment used, micronization produces particles ranging from about 1 to 20 µm.

Selecting the capsule size

- To determine the capsule size to be used
- Capsule fill weight =tapped density of formulation X capsule volume

- Example
- Formulation of capsule has a fill weight of 450mg and tapped density of 0.8g/ml
- Volume occupied =0.45g/0.8g/ml=0.56ml
- So the size 0 capsule is appropriate (0.54ml)

Large Scale Production

- The powder mix or granules must be free-flowing to allow steady passage of the capsule fill from the hopper through the encapsulating equipment and into the capsule shells.
- The addition of a lubricant or glidant such as fumed silicon dioxide, magnesium stearate, calcium stearate, stearic acid, or talc (about 0.25% to 1%) to the powder mix enhances flow properties

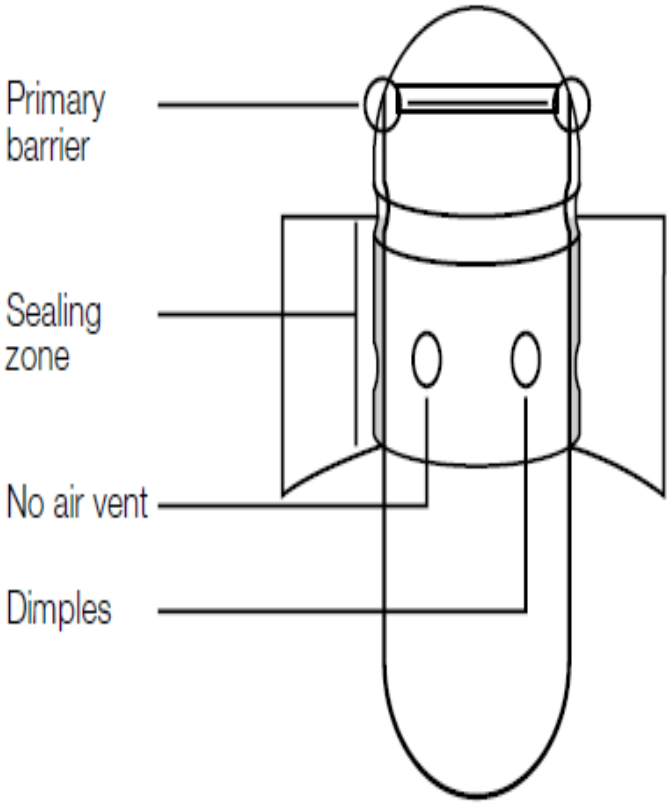
Encapsulation of different ingredients

1. Inserting tablets or small capsules into capsules is sometimes useful in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules This may be done to **separate chemically incompatible** agents or to add premeasured amounts of **potent** drug substances. Rather than weighing a potent drug, a pharmacist may choose to insert a prefabricated tablet of the desired strength in each capsule. Other less potent agents and diluents may then be weighed and added.
2. On an industrial scale, coated pellets designed for modified-release drug delivery are also commonly placed in capsule shells.

Examples of fill in hard gelatin capsules.
1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet

Liquid fill

- Gelatin capsules are unsuitable for aqueous liquids because water softens gelatin and distorts the capsules, resulting in leakage of the contents.
- However, some liquids, such as fixed or volatile oils, that do not interfere with the stability of the gelatin shells may be placed in locking gelatin capsules (or the capsules may be sealed with a solution of gelatin thinly coating the interface of the cap and body) to ensure retention of the liquid.
- Rather than placing a liquid as such in a capsule, the liquid may be mixed with an inert powder to make a wet mass or paste, which may then be placed in capsules in the usual manner.
- Eutectic mixtures of drugs, or mixtures of agents that have a propensity to liquefy when admixed, may be mixed with a diluent or absorbent such as magnesium carbonate, kaolin, or light magnesium oxide to separate the interacting agents and to absorb any liquefied material that may form.



Features of the LICAPS™.

Extemporaneous compounding of prescriptions

1. Calculate for the preparation of one or two more capsules than required to fill the prescription, to compensate a slight loss of powder
2. Selection of the capsule size, If the dose of the drug is inadequate to fill the volume of the capsule body, a diluent is added. A properly filled capsule should have its body filled with the drug mixture, not the cap. The cap is intended to fit snugly over the body to retain the contents.

FILLING HARD CAPSULE SHELLS

- When filling a small number of capsules in the pharmacy, the pharmacist may use the **punch method**.
- The pharmacist takes the precise number of empty capsules to be filled from the stock container. By counting the capsules as the initial step rather than taking a capsule from stock as each one is filled,

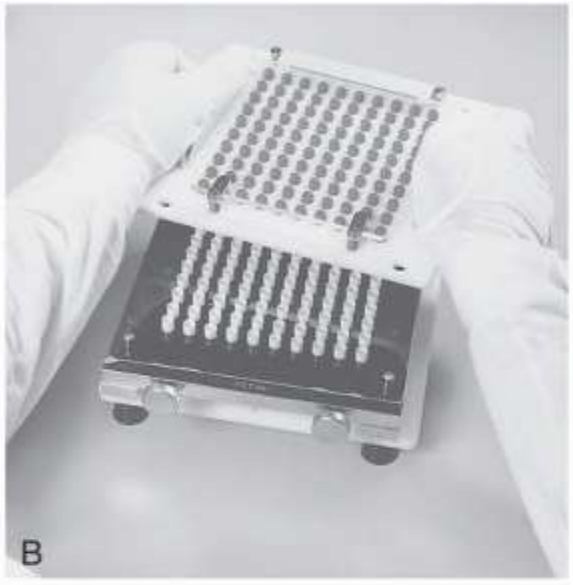
1. the pharmacist guards against filling the wrong number of capsules and
2. avoids contaminating the stock container with drug powder.

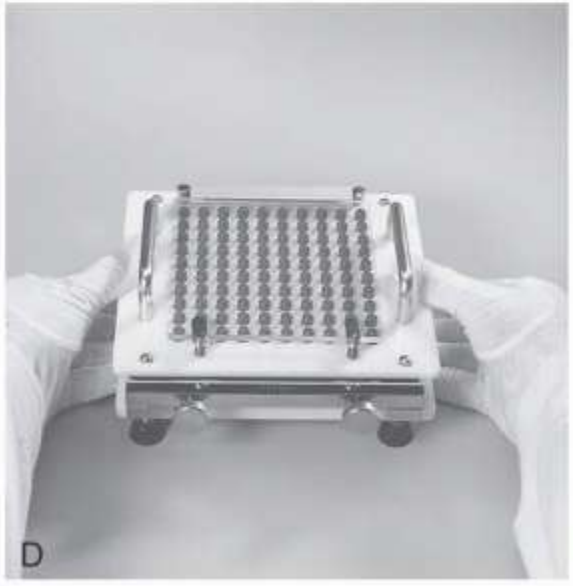
The powder to be encapsulated is placed on a sheet of clean paper or on a glass or porcelain plate. Using the spatula, the powder mix is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body.

Then an empty capsule body is held between the thumb and forefinger and punched vertically into the powder cake repeatedly until filled. Some pharmacists wear surgical gloves or latex finger cots to avoid handling the capsules with bare fingers. Because the amount of powder packed into a capsule depends on the degree of compression, the pharmacist should punch each capsule in the same manner and weigh the product after capping

Filling of capsules

- . When **non-potent** materials are placed in capsules, the first filled capsule should be weighed (using an empty capsule of the same size on the opposite balance pan to counter the weight of the shell) to determine the capsule size to use and the degree of compaction to be used. After this determination, the other capsules should be prepared and weighed periodically to check the uniformity of the process.
- When **potent drugs** are being used, each capsule should be weighed after filling to ensure accuracy. Such weighings protect against uneven filling of capsules and premature exhaustion or underuse of the powder. After the body of a capsule has been filled and the cap placed on the body, the body may be squeezed or tapped gently to distribute some powder to the cap end to give the capsule a full appearance.
- Granular material that does not lend itself to the punch method of filling capsules may be poured into each capsule from the powder paper on which it is weighed.





The Feton capsule-filling machine.

A. With empty capsules in the loader tray, the tray placed on top of the filler unit.

B. The loader inserts the capsules into the filling unit and is removed, and the top plate is lifted to separate the caps from the bodies.

C. The powder is placed on the unit and the capsule bodies are filled.

D. The top plate is returned to the unit and the caps are placed on filled capsule bodies.

(Courtesy of Chemical and Pharmaceutical Industry Company.)

CAPSULE SEALING

- Some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. One manufacturer makes distinctive-looking capsules by sealing them with a colored band of gelatin (Kapseals, Parke-Davis).
- If removed, the band cannot be restored without expert resealing with gelatin. Capsules may also be sealed through a heat-welding process that fuses the capsule cap to the body through the double wall thickness at their juncture . The process results in a distinctive ring around the capsule where heat welded. Still another process uses a liquid wetting agent that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40°C-45°C) . Industrial capsule sealing machines are capable of producing 60,000 to 150,000 gelatin-banded, heat-welded, or thermally coupled capsules per hour

Capsule identification

- Capsules and tablets also may be imprinted with the names or monograms of the manufacturer, the assigned national drug code number, and other markings making the product identifiable and distinguishable from other products.

CLEANING AND POLISHING CAPSULES

- Small amounts of powder may adhere to the outside of capsules after filling. The powder may be bitter or otherwise unpalatable and should be removed before packaging or dispensing. On a small scale, capsules may be cleaned individually or in small numbers by rubbing them with a clean gauze or cloth.
- On a large scale, many capsule-filling machines are affixed with a cleaning vacuum that removes any extraneous material from the capsules as they exit the equipment, using the Accela-Cota apparatus

Large scale processing

SOFT GELATIN CAPSULES

- Soft gelatin capsules are made of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added.
- Soft gelatin capsules, which contain more moisture than hard capsules, may have a preservative, such as methylparaben and/or propylparaben, to retard microbial growth.
- Soft gelatin capsules may be oblong, oval, or round.
- They may be single colored or two-toned and may be imprinted with identifying markings. As with hard gelatin capsules, they may be prepared with opaquants to reduce transparency and render characteristic features to the capsule shell.
- Soft gelatin capsules are used to encapsulate and hermetically seal liquids, suspensions, pasty materials, dry powders, and even preformed tablets. Soft gelatin capsules are pharmaceutically elegant and are easily swallowed

PREPARATION OF SOFT GELATIN CAPSULES

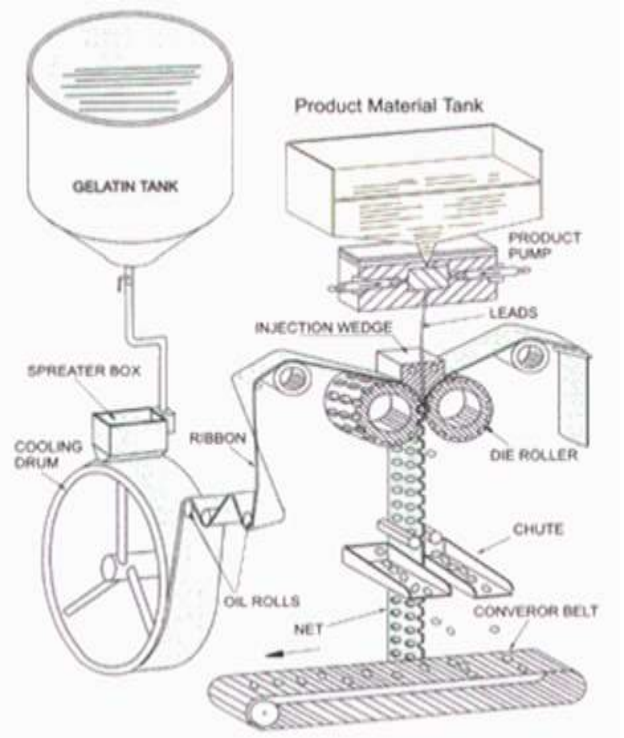
- Soft gelatin capsules may be prepared by the plate process, using a set of molds to form the capsules, or by the more efficient and productive rotary or reciprocating die processes by which they are produced, filled, and sealed in a continuous operation

A - Plate Process

- By the plate process, a warm sheet of plain or colored gelatin is placed on the bottom plate of the mold and the medication-containing liquid is evenly poured on it. Then a second sheet of gelatin is carefully placed on top of the medication and the top plate of the mold is put into place. Pressure is then applied to the mold to form, fill, and seal the capsules simultaneously. The capsules are removed and washed with a solvent harmless to the capsules.

B- Rotatory Die Process

- By this method, liquid gelatin flowing from an overhead tank is formed into two continuous ribbons by the rotary die machine and brought together between twin rotating dies
- At the same time, metered fill material is injected between the ribbons precisely at the moment that the dies form pockets of the gelatin ribbons. These pockets of fill-containing gelatin are sealed by pressure and heat and then severed from the ribbon. Use of ribbons of two different colors results in bicolored capsules.
- The reciprocating die process is similar to the rotary process in that ribbons of gelatin are formed and used to encapsulate the fill, but it differs in the actual encapsulating process. The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film as they progress through the machinery. As the capsules are cut from the ribbons, they fall into refrigerated tanks that prevent the capsules from adhering to one another.



USE OF SOFT GELATIN CAPSULES

- Soft gelatin capsules are prepared to contain a variety of liquid, paste, and dry fills. Liquids that may be encapsulated into soft gelatin capsules include the following

1. Water-immiscible volatile and nonvolatile liquids such as vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols, and organic acids.
2. Water-miscible nonvolatile liquids, such as polyethylene glycols, and nonionic surface active agents, such as polysorbate 80.
3. Water-miscible and relatively nonvolatile compounds such as propylene glycol and isopropyl alcohol, depending on factors such as concentration used and packaging conditions.
4. Solids may be encapsulated into soft gelatin capsules as solutions in a suitable liquid solvent, suspensions, dry powders, granules, pellets, or small tablets.

Soft gelatin capsule contents contraindication

- Liquids that can easily migrate through the capsule shell are not suitable for soft gelatin capsules.
- These materials include water above 5% and
- low-molecular-weight water-soluble and
- volatile organic compounds such as alcohols, ketones, acids, amines, and esters.

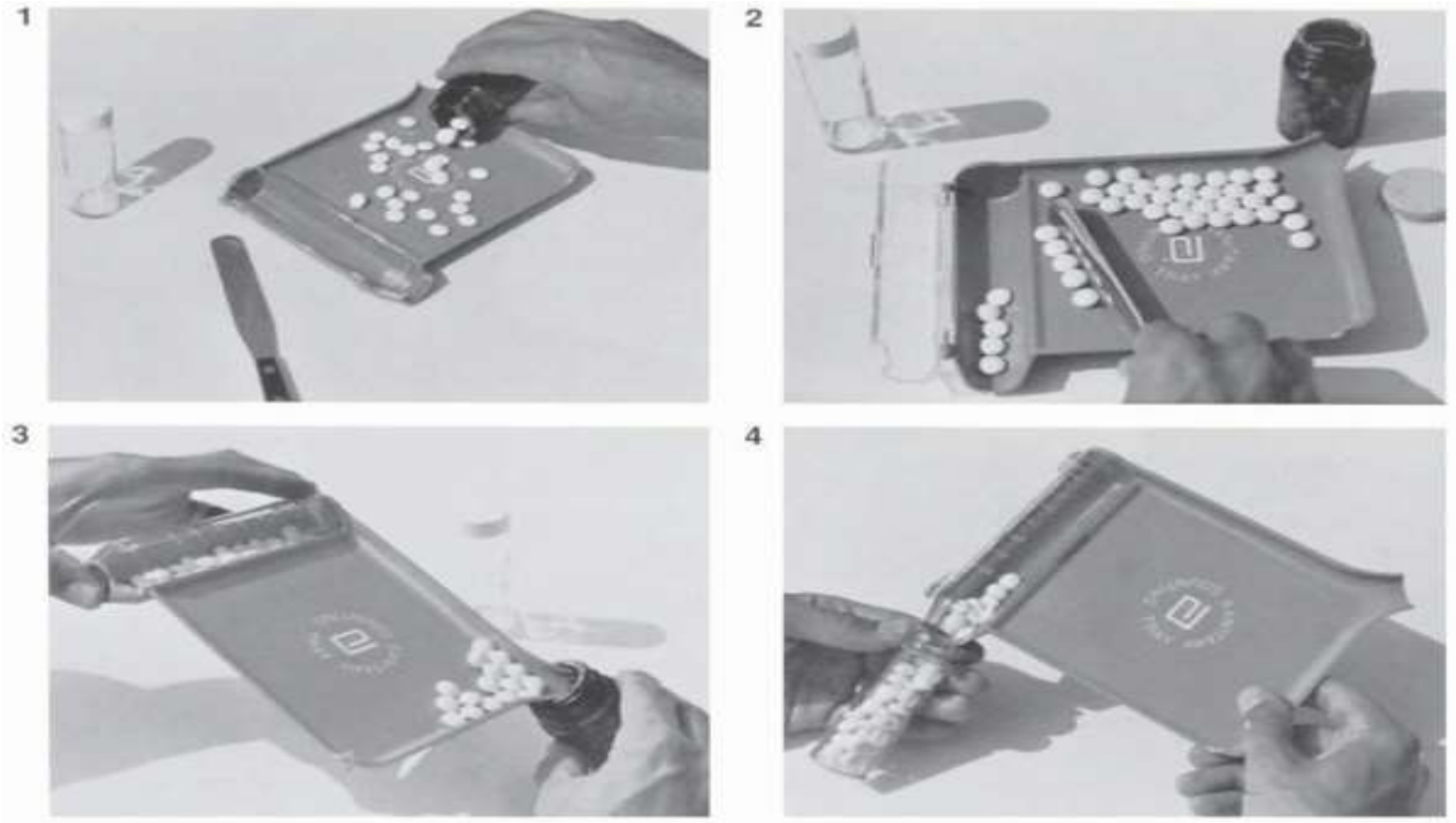
COMPENDIAL REQUIREMENTS FOR CAPSULES ADDED SUBSTANCES

- Substances added to official preparations, including capsules, to enhance their stability, usefulness, or elegance or to facilitate their manufacture may be used only if they

1. Are harmless in the quantities used
2. Do not exceed the minimum amounts required to provide their intended effect
3. Do not impair the product's bioavailability, therapeutic efficacy, or safety
4. Do not interfere with requisite compendial assays and tests

COUNTING CAPSULES

- In the pharmacy, capsules may be counted manually or by automated equipment. Specially designed trays are used for counting small numbers of solid dosage units.
- In using this tray, the pharmacist pours a supply of capsules or tablets from the bulk source onto the clean tray and, using the spatula, counts and sweeps the dosage units into the trough until the desired number is reached.
- Then the pharmacist closes the trough cover, picks up the tray, returns the uncounted dosage units to the bulk container by means of the lip at the back of the tray, places the prescription container at the opening of the trough, and carefully transfers the capsules or tablets into the container.
- With this method, the dosage units remain untouched by the pharmacist. To prevent batch-to-batch contamination, the tray must be wiped clean after each use because powder, particularly from uncoated tablets, may remain



Steps in counting solid dosage units with the Abbott Sanitary Counting Tray.

1. Transferring units from stock package to tray.
2. Counting and transferring units to trough.
3. Returning excess units to stock container.
4. Placing the counted units in prescription container.

EXAMPLES OF SOME OFFICIAL CAPSULES

OFFICIAL CAPSULE	REPRESENTATIVE COMMERCIAL CAPSULES	STRENGTH	CATEGORY
Amoxicillin	Wymox (Wyeth-Ayerst)	250, 500 mg	Antibacterial
Cephalexin	Keflex (Dista)	250, 333, 500, 750 mg	Antibacterial
Doxycycline Hyclate	Vibramycin (Pfizer)	100 mg	Antibacterial
Erythromycin Estolate	Ilosone (Dista)	250 mg	Antibacterial
Fluoxetine HCl	Prozac (Dista)	10, 20, 40 mg	Antidepressant
Indomethacin	Indocin (Merck)	25, 50 mg	Anti-inflammatory, antipyretic, analgesic