

Pharmaceutical Technology II

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College of Pharmacy

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Reference: ANSEL'S Pharmaceutical Dosage Forms and Drug
Delivery Systems

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Disperse Systems

Emulsions

Chapter 14

ANSEL'S Pharmaceutical Dosage Forms and Drug Delivery Systems

Eleventh Edition

Objectives:

After reading this topic, the student will be able to:

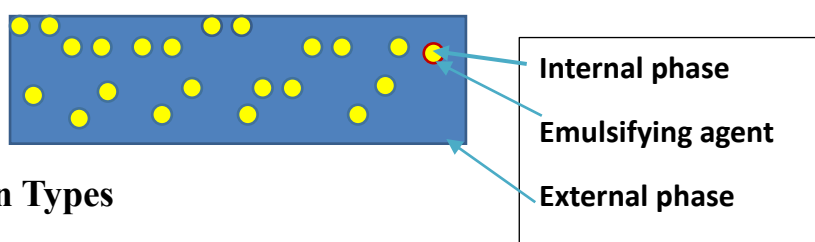
- Define the pharmaceutical emulsions
- Distinguish between the different types of pharmaceutical emulsions based on their physical state
- Differentiate between the different types of pharmaceutical emulsions based on their intended uses.
- Compare and contrast emulsification theories: surface tension, oriented wedge, and Interfacial film.
- Compare and contrast various types of emulsifying agents
- Identify the methods and techniques employed in preparing of stable pharmaceutical emulsions.
- Identify the factors that affect the stability of emulsion, such as temperature and environmental conditions.

Emulsions

Emulsion is a thermodynamically unstable disperse system consisting of two immiscible liquids, one of which is distributed throughout the other in minute globules (droplets).

-In emulsion terminology, the dispersed phase is the internal phase, and the dispersion medium is the external or continuous phase.

Generally, to prepare a stable emulsion, **a third phase, an emulsifying agent**, is necessary.



Emulsion Types

1. Oil-in-Water (o/w) Emulsions:

- In **o/w** emulsions, the internal phase consists of an oleaginous or oily component, dispersed within an aqueous external phase.

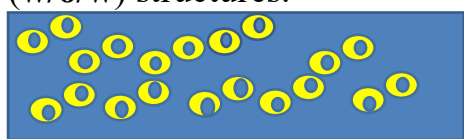
2. Water-in-Oil (w/o) Emulsions:

-In **w/o** emulsions, the internal phase consists of water or an aqueous component, dispersed within an oleaginous external phase.

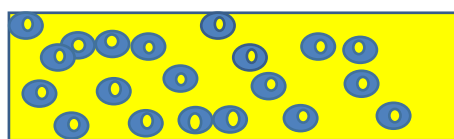
Because the external phase of an emulsion is continuous. An o/w emulsion may be diluted or extended with water or an aqueous preparation and a w/o emulsion, with an oleaginous or oil-miscible liquid.

3. Multiple emulsions:

Multiple emulsions have multiple layers of dispersed and continuous phases, including both oil-in-water-in-oil (**o/w/o**) and water-in-oil-in-water (**w/o/w**) structures.



W/O/W



O/W/O

Macroemulsions vs. Microemulsions

Microemulsions can be formed spontaneously by agitating oil and water phases with carefully selected surfactants.

- The type of microemulsion produced depends on the properties of the oil and surfactants used.
- Microemulsions have significantly smaller droplets compared to macroemulsions, with diameters ranging from 100 Å to 1,000 Å.
- In contrast, macroemulsions have larger droplets, around 5,000 Å in diameter.
- Both o/w (oil-in-water) and w/o (water-in-oil) microemulsions can be formed based on the oil and surfactant properties.

Microemulsions offer advantages in oral drug delivery, providing more rapid and efficient absorption compared to solid dosage forms.

Microemulsions enhance transdermal drug delivery by facilitating increased diffusion into the skin. -The small droplet size of microemulsions promotes efficient absorption through the skin barrier

Macroemulsion	Microemulsion
Size: around 5,000 Å	Size: 100 Å to 1,000 Å
White opaque appearance	Cloudy –Translucent or Transparent
Thermodynamically unstable	Thermodynamically stable
Requires a substantial input energy for production	Forms spontaneously

Determination tests of the emulsion type

1. Miscibility test

o/w emulsion remain stable upon dilution with water, but will not remain homogenous upon addition of oil and vice versa

2. Staining test

Addition of oil soluble stain to the emulsion of unknown type on a glass slide under microscope

- Staining globules and colorless medium= o/w emulsion
- Staining background and colorless globules = w/o emulsion

3. Conductivity test

Water conduct electricity, hence an emulsion in which water forms the continuous phase acts as a conductor. Oil is a non-conductor and emulsion in which forms the external phase act as non-conductor.

Classification of emulsions according to the physical state

Emulsions can be formulated as:

-**Liquid**

-**Semisolids**

According to the route of administration

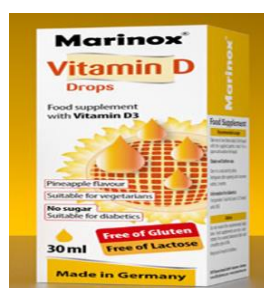
Based on the constituents and the intended application

- **Liquid emulsions may be employed:**

- Orally: o/w for example, castor oil emulsion
- Topically: for example lotion
- Parenterally: (I.V. o/w) (I.M. and S.C. may be w/o)

- **Semisolid emulsions**

- Topically: for examples, lotions, creams and liniments



The choice between o/w and w/o emulsions depends on many factors such as:

- 1- The nature of therapeutic agents,
- 2- Desired effects,
- 3- The intended route of administration

Purpose and Benefits of Emulsions

Improved Drug Administration:

Emulsification allows the pharmacist to create stable mixtures of two immiscible liquids, enabling the administration of a liquid drug in the form of minute globules (introducing of many ingredients in different phases as liquid dosage form).

- **Orally administered emulsions**, are always in the form of o/w emulsions. They can improve the palatability of drug administration by dispersing it in a sweetened, flavored aqueous vehicle (taste masking).

o/w emulsion act as carrier for lipophilic drugs, enabling the oil soluble drug to dissolved in the dispersed phase and potentially enhance oral bioavailability

-**Sterile I.V. o/w emulsions** are used for administration of nutritive oil and oil soluble vitamins to the patients unable to ingest food. Intravenous emulsions must be o/w.

-**Intramuscular and subcutaneous injections** can be formulated as w/o emulsions. In such oily emulsions, the drug's effects are prolonged, as the drug must diffuse from the aqueous dispersed phase through the external oil phase to reach the tissue fluids.

-**Emulsions for topical** use can be either o/w or w/o, depending on the nature of therapeutic agents, the desired effects, and skin conditions.

- An o/w emulsion is more easily removed from the skin with water, making it suitable when easy removal is required. Medicinal agents that irritate the skin generally are less irritating in the internal phase of an emulsified topical preparation than in the external phase.

- w/o emulsions are more softening to the skin, resisting drying and removal by contact with water.

- The diminished particle size of the internal phase in emulsions can enhance **percutaneous absorption** (absorption through the skin), making them a valuable choice for dermatological formulations.

The acceptable emulsion is characterized by the following:

1. The globules of dispersed phase must be remain uniformly distributed throughout the continuous phase
2. The formulation should have a pleasing appearance and texture
3. For oral administration, the flavor must be appropriate
4. For external application, the formulation must be easily spread over the affected area
5. Physically stable (shows no signs of flocculation, creaming, sedimentation and coalescence)
6. Absence of deterioration by microorganisms

Disadvantages of emulsions

1. Pharmaceutical emulsions, being thermodynamically unstable, require careful formulation to prevent the separation of their two phases.
2. Before measuring a dose, it is essential to shake the emulsion thoroughly. Even with efficient shaking, the accuracy of the dose is likely to be lower compared to solutions.
3. Storage conditions may affect the disperse system, potentially causing creaming or cracking

4. There is a possibility of microbial contamination, which can further lead to cracking issues

5. In comparison to solid dosage forms, liquid dosage forms, such as emulsions, tend to be more bulky

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

Theories of Emulsification

There are many theories of emulsification:

1. Surface Tension Theory:

All liquids tend to minimize their surface area by forming spherical shapes, which is the shape with the least surface area.

Surface tension measures this tendency and is a force that resists the formation of smaller droplets when two immiscible liquids come into contact.

- Emulsifying agents, often called surfactants or wetting agents, reduce interfacial tension and diminish the liquids' attraction to their own molecules (reducing the repellent force between the liquids and diminishing each liquid's attraction for its own molecules).

- This theory suggests that emulsifiers lower the interfacial tension between immiscible liquids, thus, the surface-active agents facilitate the breaking up of large globules into smaller ones, which then have a lesser tendency to reunite or coalesce

2. Oriented-Wedge Theory:

- This theory is based on the idea that emulsifying agents form monomolecular layers around the droplets of the internal phase. The theory is based on the assumption that certain emulsifying agents orient themselves about and within a liquid in a manner reflective of their solubility in that particular liquid.

- In a system containing two immiscible liquids, probably the emulsifying agent is preferentially soluble in one of the phases and is embedded more deeply in that phase than the other. Because many molecules of substances

have a hydrophilic or water-loving portion and a hydrophobic or water-hating portion, the molecules position or orient themselves into each phase.

- Emulsifying agents with a greater hydrophilic character tend to promote o/w emulsions, while those with a more hydrophobic character favor w/o emulsions.
- The phase in which the emulsifier is more soluble becomes the continuous phase of the emulsion.

3. Plastic or Interfacial Film Theory:

This theory places emulsifying agents at the interface between the immiscible liquids, forming a thin film adsorbed on the surface of internal phase droplets.

- The film acts as a barrier, preventing contact and coalescence of the dispersed phase.
- The stability of the emulsion depends on the toughness and flexibility of this film.
- The degree of solubility of the emulsifying agent in the two phases determines whether o/w or w/o emulsions are formed.

Preparation of Emulsions

Factors Affecting Emulsion Formation:

The stability and characteristics of an emulsion are influenced by the following factors:

- **Emulsifying agents**

- **pH**

- **The ratio of internal to external phases.**

The success of emulsions depends on the careful selection of emulsifying agents and understanding their properties. The initial step in preparation of an emulsion is selection of the emulsifier.

Criteria for Selecting Emulsifying Agents:

1. Compatibility:

Emulsifying agents must be compatible with other formulation ingredients and should not interfere with the stability or efficacy of the therapeutic agent.

2. Stability:

Emulsifying agents should be stable and not deteriorate during the preparation or storage of the pharmaceutical product.

3. Safety:

Emulsifiers should be nontoxic and safe for consumption by the patient, and they should possess minimal odor, taste, or color.

4. Promotion of Emulsification:

A crucial role of emulsifying agents is to promote emulsification, ensuring that the two immiscible phases are dispersed effectively.

Common Types of Emulsifying Agents

1. Carbohydrate Materials:

- Naturally occurring agents like acacia, tragacanth, agar, chondrus, and pectin are used. These materials form hydrophilic colloids. They typically form o/w emulsions.

- Acacia is often used in extemporaneous emulsions. Tragacanth and agar are commonly employed as thickening agents in acacia-emulsified products.

Microcrystalline cellulose is employed in a number of commercial emulsions as a viscosity regulator.

2. Protein Substances:

- Gelatin, egg yolk, and casein are examples of protein-based emulsifiers that produce o/w emulsions.

- Gelatin, while effective, can lead to emulsions that become more fluid over time.

3. Molecular Weight Alcohols:

- Substances like stearyl alcohol, cetyl alcohol, and glyceryl monostearate are primarily used as thickening agents and stabilizers for o/w emulsions in external applications.

- Cholesterol and cholesterol derivatives may also be employed in externally used emulsions to promote w/o emulsions

4. Wetting Agents:

- These agents can be anionic, cationic, or nonionic and contain both hydrophilic and lipophilic groups. In anionic agents, the lipophilic portion is negatively charged, but in the cationic agent, it is positively charged.

- Anionic and cationic agents tend to neutralize each other and are considered incompatible, while nonionic emulsifiers show no inclination to ionize.

Depending on their individual nature, certain members of these groups form o/w emulsions and others w/o emulsions.

- Anionic emulsifiers** include various monovalent, polyvalent,

- Organic soaps**, such as triethanolamine oleate,

- **Sulfonates**, such as sodium lauryl sulfate.

- **Cationic emulsifier**, such as Benzalkonium chloride (known primarily for its bactericidal properties)

- Nonionic emulsifiers**, such as span and tween

5. Finely Divided Solids:

- Colloidal clays like bentonite, magnesium hydroxide, and aluminum hydroxide can 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. 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.

- The relative volume of internal and external phases is critical for their effectiveness.


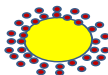

Auxiliary emulsifying agent

- Lipophilic

- High molecular Weight Alcohols Substances like stearyl alcohol, cetyl alcohol, and glyceryl monostearate are primarily used as thickening agents and stabilizers for o/w emulsions in external applications.

- Hydrophilic

Tragacanth and agar are commonly used as thickening agents in acacia – emulsified products

Type	Example	Mechanism	
Mono-molecular	Potassium laureate Tween 80	Coherent flexible film formed by SAA. (Lower interfacial tension) and stabilize the emulsion	
Multi-molecular	Acacia, Gelatin	Strong rigid film formed mostly by hydrocolloids, which produce O/W emulsions. Stability due mainly to strength of interfacial film (forming a coherent multi-molecular film which is strong and prevent the coalescence)	
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 (form a particulate film that prevent the coalescence)	

Hydrophilic-Lipophilic Balance (HLB) System:

Generally, each emulsifying agent has a hydrophilic portion and a lipophilic portion, with one or the other being more or less predominant and influencing in the manner already described the type of emulsion. A method has been devised whereby emulsifying or surface-active agents may be categorized on the basis of their chemical makeup as to their hydrophilic-lipophilic balance, or HLB.

By this method, each agent is assigned an HLB value or number indicating the substance's polarity (the numbers have been assigned up to about 40).

The usual range is between 1 and 20. Each surfactant have an HLB number representing the relative proportions of the lipophilic and hydrophilic parts of the molecule

-Materials that are highly polar or hydrophilic have been assigned higher numbers than materials that are less polar and more lipophilic.

Materials with HLB values of 3 to 6 are highly lipophilic and favor water-in-oil (w/o) emulsions.

- HLB values of about 8 to 18 correspond to emulsifying agents favoring oil-in-water (o/w) emulsions.

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

Required HLB

To ensure emulsion stability, it is necessary to select emulsifying agents having the same or nearly the same HLB value as the oleaginous phase of the intended emulsion. 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."

For example, mineral oil has an assigned HLB value of 4 if a w/o emulsion is desired and a value of 10.5 if an o/w emulsion is to be prepared.

To prepare a stable emulsion, the emulsifying agent should have a required HLB value similar to the one for mineral oil, depending on the type of emulsion desired.

Hydrophilic-lipophilic balance (HLB) method is used for calculating the relative quantities of SAA (emulgents) that necessary for producing a physically stable emulsion.

Blending Emulsifying Agents and Calculations in the HLB System:

Stability is achieved by selecting emulsifying agents with HLB values similar to the intended emulsion.

Combining two or more emulsifiers may be necessary to achieve the required HLB value.

HLB values are additive, allowing the blending of surfactants to achieve the desired total HLB value.

The HLB of a mixture of surfactants, for example, a mixture consisting of A and B surfactants

Total =1

X=0.58 fraction of A (tween 80) 1-0.58=0.42 fraction of B (span 80)

$0.58 * 5 \text{ g} = 2.9 \text{ g}$ of tween 80 $0.42 * 5 \text{ g} = 2.1 \text{ g}$ of span 80

Example: o/w Emulsion

Liquid petrolatum (Required HLB 10.5) 50 g

Emulsifying agents 5 g

Sorbitan monooleate (HLB 4.3)

Polyoxyethylene 20 sorbitan monooleate (HLB 15.0)

Water, qs 100 g

By simple algebra, it can be shown that 4.5 parts by weight of sorbitan monooleate blended with 6.2 parts by weight of polyoxyethylene 20 sorbitan monooleate will result in a mixed emulsifying agent having the required HLB of 10.5. Because the formula calls for 5 g, the required weights are 2.1 and 2.9 g, respectively. The oil-soluble sorbitan monooleate is dissolved in the oil and heated to 75°; the water-soluble polyoxyethylene 20 sorbitan monooleate is added to the aqueous phase that is heated to 70°. At this point, the oil phase is mixed with the aqueous phase and the whole is stirred continuously until cool.

The formulator is not restricted to these two agents to produce a blend with an HLB of 10.5. There are various proportions required, using other pairs of emulsifying agents,

Agent	HLB
Ethylene glycol distearate	1.5
Sorbitan tristearate (Span 65 ^a)	2.1
Propylene glycol monostearate	3.4
Triton X-15 ^b	3.6
Sorbitan monooleate (Span 80 ^a)	4.3
Sorbitan monostearate (Span 60 ^a)	4.7
Diethylene glycol monolaurate	6.1
Sorbitan monopalmitate (Span 40 ^a)	6.7
Sucrose dioleate	7.1
Acacia	8.0
Amercol L-101 ^c	8.0
Polyoxyethylene lauryl ether (Brij 30 ^a)	9.7
Gelatin	9.8
Triton X-45 ^b	10.4
Methylcellulose	10.5
Polyoxyethylene monostearate (Myrj 45 ^a)	11.1
Triethanolamine oleate	12.0
Tragacanth	13.2
Triton X-100 ^b	13.5
Polyoxyethylene sorbitan monostearate (Tween 60 ^a)	14.9
Polyoxyethylene sorbitan monooleate (Tween 80 ^a)	15.0
Polyoxyethylene sorbitan monolaurate (Tween 20 ^a)	16.7
Pluronic F-68 ^d	17.0
Sodium oleate	18.0
Potassium oleate	20.0
Sodium lauryl sulfate	40.0

Preparation Methods

Various methods are employed for emulsion preparation, ranging from small-scale laboratory techniques to large-scale industrial processes. Each method has its advantages and is chosen based on the nature of components and desired emulsion characteristics

Small-Scale Emulsion Preparation Methods

-Laboratory Equipment:

Small-scale emulsions can be prepared using equipment like:

1. Dry Wedgwood or porcelain mortar and pestle,
2. Mechanical blenders such as milkshake mixers, hand homogenizers, or
3. Simple prescription bottles.



-Laboratory Techniques:

In the small-scale extemporaneous preparation of emulsions, three methods may be used. They are:

- 1. The continental or dry gum method**
- 2. The English or wet gum method**
- 3. The bottle or Forbes bottle method**

-The continental or dry gum method:

The continental or dry gum method involves triturating the emulsifying agent (e.g., acacia) with oil before adding water (**addition of external phase to the internal phase**).

The continental method is also referred to as the **4:2:1 method** because for every **four parts** by volume of **oil**, **two parts of water** and **one part of gum** are added in preparing the initial or primary emulsion. For instance, if 40 mL of oil is to be emulsified, 20 mL of water and 10 g of gum would be employed in the primary emulsion.

In this method, the acacia or other o/w emulsifier is triturated with the oil in a perfectly dry Wedgwood or porcelain mortar until thoroughly mixed. After the oil and gum have been mixed, the **two parts of water** are added **all at once**, and the mixture is triturated immediately, rapidly, and continuously until the primary emulsion is formed. 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.

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.

-English or Wet Gum Method:

The English or wet gum method creates a mucilage of the emulsifying agent with water before slowly incorporating oil (**addition of internal phase to the external phase**).

By this method, the same proportions of oil, water, and gum are used as in the continental or dry gum method, but the order of mixing is different. A mucilage of the gum is prepared by triturating in a mortar granular acacia with twice its weight of water. The oil is then added slowly in portions, and the mixture is triturated to emulsify the oil. After all of the oil has been added, the mixture is thoroughly mixed for several minutes to ensure

uniformity. Then, the other formulative materials are added, and the emulsion is transferred to a graduate and brought to volume with water.

-Bottle or Forbes bottle method:

The bottle or Forbes bottle method is suitable for volatile oils or oleaginous substances of low viscosities, involving shaking the mixture in a capped bottle.

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 formulative agents

Important considerations on emulsion preparation

- ❖ 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
- ❖ 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.
- ❖ If fats waxes or SAA that are solids or semisolid at room temperature are needed, warm the two phases, the aqueous phase temperature is raised 2-3C° above that of oil phase, so that no local crystallization of waxes takes place upon mixing of the two phases
- ❖ 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.

- ❖ Forbes bottle 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

Auxiliary Methods:

An emulsion prepared by either the wet gum or the dry gum method can generally be increased in quality by passing it through a hand homogenizer. In this apparatus, the pumping action of the handle forces the emulsion through a very small orifice that reduces the globules of the internal phase to about 5 μ m and sometimes less. The hand homogenizer is less efficient in reducing the particle size of very thick emulsions.

In Situ Soap Method (Nascent soap method):

The two types of soaps developed by this method are calcium soaps and soft 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.

Large-scale preparation

On a larger scale, mixing tanks equipped with high-speed impellers are used for emulsion formation.

- Colloid mills or large homogenizers may be employed to refine the emulsion further.

Industrial homogenizers have the capacity to handle as much as 100,000 L of product per hour.

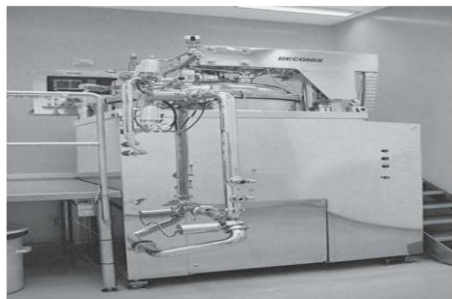


FIGURE 14.5. An industrial mixer for manufacture of disperse systems, including suspensions and emulsions. (Courtesy of Perrigo Company plc.)

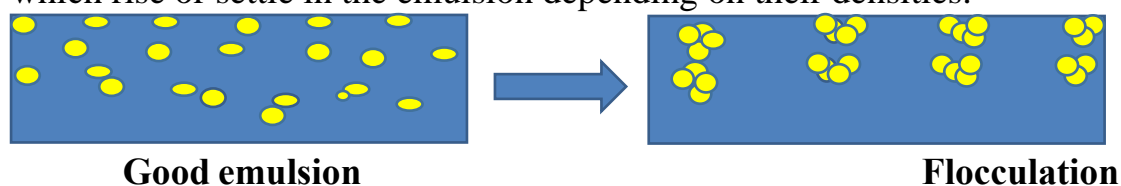
Stability of Emulsions

The instability of emulsions can be categorized as follows:

- 1-. Flocculation
2. Creaming or sedimentation
3. Coalescence or aggregation
4. Cracking or breaking
5. Phase separation

-Flocculation

This process refers to aggregation or joining droplets together (without any change in primary droplet size) to form a large units or clumps (floccules) which rise or settle in the emulsion depending on their densities.



-Creaming

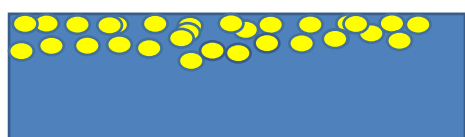
Aggregates of globules of the internal phase have a greater tendency than do individual particles to rise to the top of the emulsion or fall to the bottom. Such a preparation of the globules is termed the creaming of the emulsion, it is a reversible process. Creamed emulsion can be restored to its original state by gentle agitation, if insufficient shaking is employed before each dose, improper dosage of the internal phase substance may result.

According to the Stokes equation the rate of separation of the dispersed phase of an emulsion may be related to such factors:

1. The particle size of the dispersed phase,
2. The difference in density between the phases,
3. The viscosity of the external phase.

-Larger particle size, greater density difference, and lower viscosity increase the rate of creaming.

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

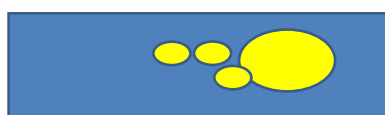


Strategies for enhanced the stability:

1. The globule or particle size should be reduced as fine as is practically possible,
2. The density difference between the internal and external phases should be minimal,
3. The viscosity of the external phase should be reasonably high.

-Coalescence and Breaking (Cracking)

If the droplet contacts another droplet, coalescence will occur to produce a single droplet of greater diameter and, the surface area of the new droplet will be less than the surface areas of the two individual droplets. This process will continue until there is complete phase separation (i.e. two liquid layers occur). Separation of the internal phase from the emulsion is called breaking, and the emulsion is described as being cracked or broken. This is irreversible, because the protective sheath about the globules of the internal phase no longer exists. If an emulsion has cracked it cannot be recovered or redispersed by shaking.



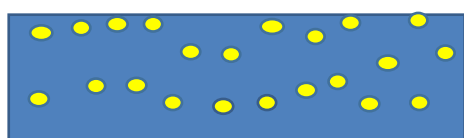
Coalescence



Separation (Breaking)

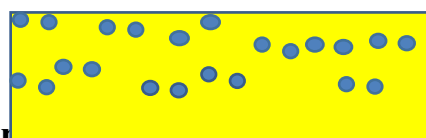
-Phase Inversion

It is the process of an exchange between the disperse phase and the medium. For example, an o/w emulsion may with time or change of conditions invert to a w/o emulsion (occurs when the dispersed phase exceed a theoretical maximum of 74% of the total volume).



o/w emulsion

Inversion



w/o emulsion

Consideration for temperature, light, environmental factors and 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.
- ❖ 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 of emulsion

Many molds, yeasts, and bacteria can decompose the emulsifying agent, disrupting the system. 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.

Therapeutic examples of Oral and Topical Emulsions

• Oral Emulsions

-Mineral Oil Emulsion:

- Mineral oil emulsion, or liquid petrolatum emulsion, is an o/w emulsion prepared from the following materials: Mineral oil, acacia, syrup, vanillin, alcohol, and purified water.

- Preparation by the dry gum method (4:2:1).

- Used as a lubricating cathartic with enhanced palatability compared to plain mineral oil.

- Commercial variations may include additional cathartic agents.

-Castor Oil Emulsion:

- Indications: Laxative for constipation and colon preparation for diagnostic examinations.

- Simethicone Emulsion:

- Indications: Defoaming agent for relief of gastrointestinal gas symptoms.

• Topical Emulsions

-Lotions

Many hand and body lotions for dry skin are o/w emulsions.

A number of topical emulsions, or lotions, are used therapeutically to deliver a drug systemically. An example is Estrasorb, which contains estradiol for menopausal symptom relief.

-Shampoos:

- Shampoos are **solution, emulsion, or suspension** dosage forms used for hair and scalp cleansing.

-Liniments

Liniments are **alcoholic or oleaginous solutions or emulsions** of various medicinal substances intended to be rubbed on the skin

- The vehicle for a liniment should therefore be selected for the type of action desired (**rubefacient, counterirritant, or massage**) and also on the solubility of the desired components in the various solvents.
- All liniments should bear a label indicating that they are suitable only for external use and must never be taken internally.
- Liniments that are **emulsions** or that contain insoluble matter must be shaken thoroughly before use to ensure even distribution of the dispersed phase, and these preparations should be labeled shake well.
- liniments are prepared in the same manner as **solutions, emulsions, or suspensions**

Suppositories and Inserts

Chapter 12

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

Objectives

After reading this topic, the student will be able to :

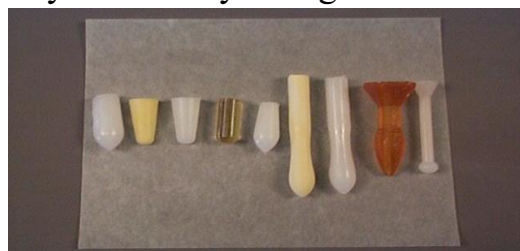
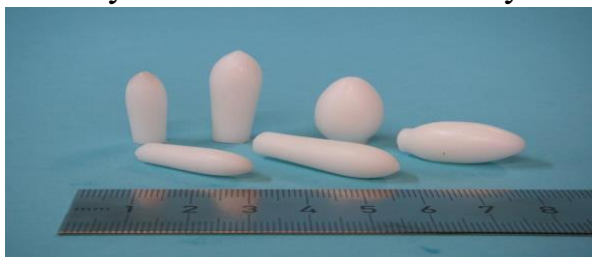
- Compare and contrast various suppository and insert, in terms of physical appearance, size and shape
- Describe the advantages of suppositories and inserts .
- Identify and explain physiologic factors that influence the drug absorption from rectal suppository administration
- Identify and explain the physicochemical factors of the drug and suppository/insert base as these influence absorption
- Compare and contrast the various classes of suppository bases
- Describe the three methods of suppository preparation

Suppositories

Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert local or systemic effects.

Suppositories are commonly used rectally, 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.

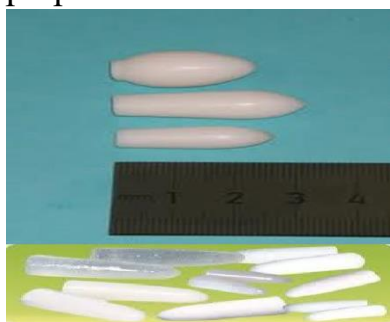
Vaginal suppositories

Vaginal suppositories, also called (in past) **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 .
- 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 anoctal 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 microorganism



Systemic effect of rectal suppositories

- For systemic effects, the mucous membranes of the rectum and vagina permit the absorption of many soluble drugs. However, **vaginal route is not frequently used for systemic purpose.**
-

The advantages of the rectal route (for systemic effects) over oral therapy are:

- (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 (partially) after rectal administration.
- (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

Prochlorperazine for the relief of nausea and vomiting, indomethacin (NSAIDs) and ondansetron for the relief of nausea and vomiting

Some factors affecting on 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
- Its ability to traverse the physiologic barriers to absorption
- 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) Physiological factors
- (b) Physicochemical factors of the drug and the base

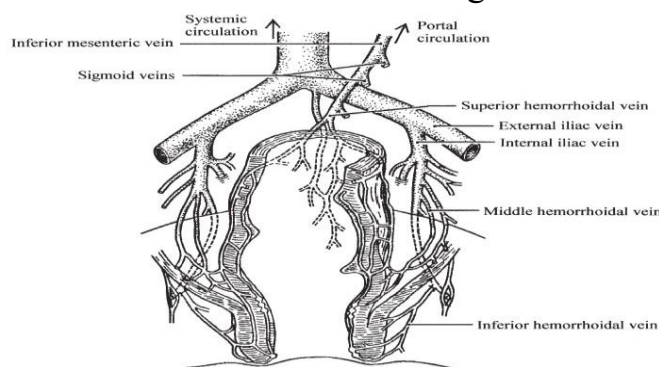


Figure 10. Anatomy of colonic and hemorrhoidal veins.

Physiological 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 evacuation 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 (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.

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
3. Its hydrophilic or hydrophobic character (composition of the base)
4. Rheological properties.

Lipid-Water Solubility of drug

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.

Drug solubility and suppository formulation

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

Amount of drug

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.

Particle Size

For un-dissolved drugs in a suppository (suspension), 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 .

Main types of suppository bases:

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 anorectal 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.

■

TABLE 12.5. Melting Ranges of some Suppository Bases		
Base	Composition	Melting Range (°C)
Cocoa butter	Mixed triglycerides of oleic, palmitic, and stearic acids	34–35
Fattibase	Triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostearate and polyoxyl stearate	35.5–37
Polybase	A homogeneous blend of PEGs and polysorbate 80	60–71
Suppocire OSI	Eutectic mixtures of mono-, di-, and triglycerides derived from natural vegetable oils, each type having slightly different properties	33–35
Wecobee W	Triglycerides derived from coconut oil	31.7–32.8
Witepsol H15	Triglycerides of saturated fatty acids C12–C18 with varied portions of the corresponding partial glycerides	33–35

Fatty or Oleaginous Bases

1. Cocoa butter
 2. Hydrogenated fatty acids of vegetable oils, such as palm kernel oil and cotton seed 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

- Are 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 (naturally occurring comp.)
 - Chemically, the main constituent of cocoa butter is the triglyceride derived from palmitic acid, stearic acid, and oleic acid, primarily of oleo-palmito-stearin and oleo-distearin
- Cocoa butter melts at 30°C to 36°C, it is an ideal suppository base, melting just below body temperature and yet maintain in its solidity at usual room temperature.
- However, because of its triglyceride content, cocoa butter exhibits marked polymorphism, or existence in several crystalline forms

Cocoa Butter polymorphism

- When cocoa butter is 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 (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.
- 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.

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 °C it will form β -polymorph form which is stable form, if melted suddenly and quickly at high temperature then freezing or cooling it will form unstable γ form that melt at 15 °C.
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 .
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),
- **Wecobee bases** (triglycerides derived from coconut oil)
- **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

- A- 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 to maintain their shape and consistency.
- B- Due to hygroscopic nature, they may have a dehydrating effect and irritate the tissues upon insertion. 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.

Polyethylene glycols (PEG)

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. The numeric designations refer to the average molecular weight of each of the polymers.

- 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	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

PEG 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.

- It is possible to prepare suppositories from PEG 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, PEG-based suppositories do not leak from the orifice, as many cocoa butter-based suppositories.
- PEG 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

The miscellaneous group of bases are mixtures of oleaginous and water-soluble or water-miscible materials. These materials may be chemical or physical mixtures.

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.

Preparation of suppositories

Suppositories are prepared by three methods:

- (a) Molding from a melt
 - (b) Compression
 - (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.

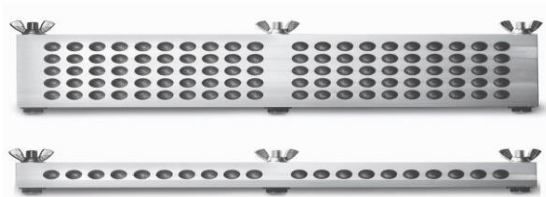
Cocoa butter, glycerinated gelatin, polyethylene glycol, and most other bases are suitable for preparation by molding.

Suppository Molds

Molds in common use today are made from stainless steel, aluminum, brass, or plastic.

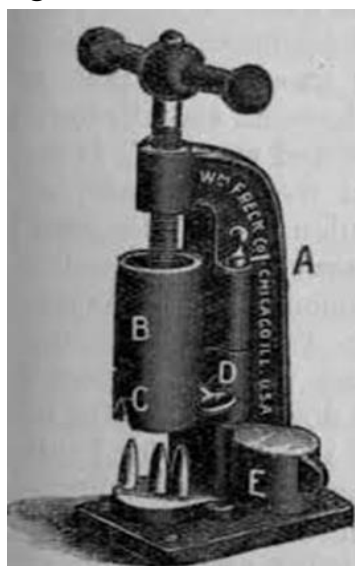
The molds, which separate into sections, generally longitudinally, are opened for cleaning before and after preparation of a batch of suppositories, closed when the melt is poured, and opened again to remove the cold molded suppositories.

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.



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



Preparation by hand rolling and shaping

It is the oldest and simplest method of supp. preparation

- 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 (it requires considerable practice and skill).

Determination of the Amount of Base Required

- Generally, in preparing suppositories, the pharmacist calculates 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.
- In determining the amount of base to be incorporated with the medicaments, the pharmacist must be certain that the required amount of drug is provided in each suppository.
- Because the volume of the mold is known (from 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.
- 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.

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.

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

- The three methods of calculating the quantity of base that the active medication will occupy and the quantities of ingredients required are:
 - (a) Dosage replacement factor
 - (b) Density factor
 - (c) Occupied volume method

Displacement value (D.V)

Displacement value is defined as the quantity of drug that displaces one part of the base (eg. 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 displace high amount of base
 - DV. for liquids equals 1

Calculations using displacement values

Prepare 8 codeine phosphate suppositories (D.V=1.1) using mold of 1g size each suppository containing 60mg of codeine phosphate

- Prepare 10 suppositories to compensate for any loss

$60 \times 10 = 600\text{mg} = 0.6\text{g}$ of codeine phosphate

- Supp. Base $1\text{g} \times 10 = 10\text{g}$ total weight of pure base
- Drug base
- $\frac{1.1 \text{ displace } 1\text{g}}{0.6 \quad ?}$ base displaced $= (1\text{g} \times 0.6) / 1.1 = 0.55 \text{ g}$

- Amount of base needed is $10\text{g} - 0.55 = 9.45 \text{ g}$

Example: Calculate the quantities required to make 8 theobroma oil supp. (2g mold) each containing 400 mg of zinc oxide (DV= 4.7).

1. Calculate the total weight of zinc oxide required. $0.4 \times 10 = 4\text{g}$
2. Calculate what weight of base would be required to prepare 10 unmedicated supp. $2\text{g} \times 10 = 20 \text{ g}$
3. Determine what weight of base would be displaced by the medicament.
Replaced base = wt. of drug/ D.V = $4 / 4.7 = 0.85$

4. Calculate, therefore, the weight of base required to prepare the medicated supps.

$$20 - 0.85 = 19.15 \text{ g wt. of base required}$$

- **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 containing 100 mg aminophylline (Displacement value = 1.3)

$$\text{Drug } 6 \times 100 = 0.6 \text{ g}$$

$$\text{Glycerin gelatin Base } 6 \times 4 \text{ g} \times 1.2 = 28.8 \text{ g}$$

$$\text{Glycerin gelatin Base replaced} = 0.6 / 1.3 = 0.46 \text{ (by theobroma oil base)}$$

$$0.46 \times 1.2 = 0.55 \text{ g base displaced by the base (glycero gelatin)}$$

$$\text{Base required } 28.8 - 0.55 = 28.25 \text{ g of the base required}$$

Vaginal suppositories

The most commonly used base for vaginal suppositories consists of combinations of the various molecular weight polyethylene glycols. To this base is frequently added surfactants and preservative agents, commonly the parabens. Many vaginal suppositories and other types of vaginal dosage forms are buffered to an acid pH usually about 4.5, consistent with the normal vagina. This acidity discourages pathogenic organisms and provides a favorable environment for eventual recolonization by the acid-producing bacilli normally found in the vagina.

Rx

Progesterone, micronized powder	q.s.
Polyethylene glycol 400	60%
Polyethylene glycol 8000	40%

Vaginal inserts

Vaginal tablets are more widely used nowadays than are commercial vaginal supps; but compounded vaginal supps are very widely used. The tablets are easier to manufacture, more stable, and less messy. Vaginal tablets, frequently referred as vaginal inserts, are usually ovoid and are accompanied in their packaging with a plastic inserter, a device for easy

placement of the tablet within the vagina. Vaginal tablets contain the same types of anti-infective and hormonal substances as vaginal supps.

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

Some vaginal inserts are capsules of gelatin containing medication to be released intravaginally.

Packaging and storage

Most commercial supps are individually wrapped in either foil or plastic. Some are packaged in a continuous strip, separated by tearing along perforations or otherwise separated in compartmented boxes to prevent contact and adhesion.

Suppositories containing light-sensitive drugs are individually wrapped in an opaque material such as a metallic foil. Because supps. are adversely affected by heat, it is necessary to maintain them in a cool place.

Cocoa butter supps. must be stored below 30°C and preferably in a refrigerator (2°C to 8°C).

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

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

Semi- solid dosage forms

Chapter 10

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems

Objectives

At the end of this topic, the student will be:

- Differentiate between the various types of semisolid bases on the basis of physical and chemical properties .
- List the criteria for the selection of a semisolid base to treat a topical affliction. Describe the methods to incorporate (an) active ingredient(s) into a semisolid base .
- Explain the difference between an ointment, a cream, and a gel.
- Compare and contrast an ophthalmic ointment base and a topical ointment base for application to the skin.

Semisolid Dosage Forms

Ointments, creams, and gels are semisolid dosage forms intended for topical application.

- They may be applied to the skin ,
- Placed on the surface of the eye ,
- Or used nasally, vaginally and rectally .



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

The unmedicated ones are used for their physical effects as protectants or lubricants.

Topical preparations are used for both local and systemic effects.

A topical drug (API) dosage form would be one that is designed to deliver the drug into the skin in treating skin disorders where the skin is the target organ .

Systemic effects

Skin consists of three anatomical layers, the epidermis, the dermis and a subcutaneous fat layer.

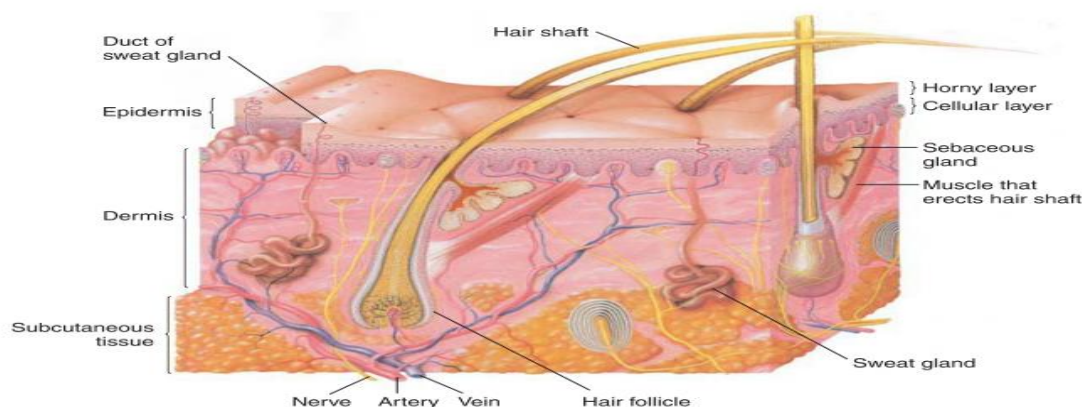
A transdermal product is designed to deliver drugs through the skin (percutaneous absorption) to the general circulation for systemic effects, with the skin not being the target organ.

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 .

- Recently there is an increase in the number of topical ointments, creams, and gels designed to deliver a drug systemically. This is often accomplished by addition of penetration enhancers to the topical vehicle

The rate of drug movement across skin layer depends on:

- The drug concentration in the vehicle ,
- Physicochemical properties of the drug substance such as solubility, partition coefficient, pKa, and molecular weight
- The characteristics of the base or vehicle, hydrophilic– lipophilic character and viscosity
- Conditions of the skin itself “broken, hydrated other features of the skin.



Ointments

Ointments are semisolid preparations intended for external application to the skin or mucous membranes .

Ointments may be medicated or Unmedicated .

Unmedicated ointments are used for the physical effects they provide as **protectants, emollients, or lubricants** .

Ointment bases, as described, may be used for their physical effects or as vehicles for medicated ointments .

Ointment Bases

Ointment bases are generally classified by the United States Pharmacopeia (USP) into four groups :

1. **Oleaginous bases**
2. **Absorption bases**
3. **Water removable bases**
4. **Water soluble bases**

Ideal properties of ointment bases

1. Stable
2. Neutral in reaction
3. Non-greasy
4. Not degreasing in action
5. Nonirritating
6. Non-dehydrating
7. Non-hygroscopic
8. Water-removable
9. Compatible with medications
10. Free from objectionable odor
11. Non-staining
12. Capable of serving as medium for drugs that are water and lipid soluble
13. Efficient on dry, oily or moist skin
14. Composed of readily available components of known chemical composition
15. Easily compounded by the pharmacist
16. Can melt or softened at body temperature

Oleaginous Bases (Hydrocarbon bases)

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
 3. They are effective as occlusive dressings
 4. Can remain on the skin for long periods without drying out ,
- 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

Examples:

- Petrolatum “Vaseline,”
- White petrolatum “White Vaseline”
- Yellow ointment
- White ointment.

Petrolatum, USP, is a purified mixture of semisolid hydrocarbons obtained from petroleum. It has yellow to light amber color. it is also known as yellow petrolatum and petroleum jelly. A commercial product is Vaseline.



White petrolatum, USP, is a purified mixture of semisolid hydrocarbons obtained from petroleum that has been wholly or nearly decolorized. White petrolatum is also known as white petroleum jelly. A commercial product is White Vaseline



Yellow ointment, USP, this ointment has the following formula for the preparation of 1,000 g:

Yellow wax	50 g
Petrolatum	950 g

Yellow wax is the purified wax obtained from the honey comb of the bee

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.

White wax	50 g
White Petrolatum	950 g

1. Absorption Bases

These bases are of two types:

- Those that permit the incorporation of solutions resulting in the formation of **w/o emulsion** for example, **Hydrophilic petrolatum**.
- Those that are **w/o emulsions** that permit the incorporation of an additional quantities of aqueous solutions for example, **lanolin**

- They are used as emollients
- They are not easily removed from the skin by water washing, because the external phase is oleaginous
- They do not provide the degree of occlusion afforded by the oleaginous bases

Examples: **Hydrophilic petrolatum, lanolin and modified lanolin.**

Hydrophilic Petrolatum, USP, has the following formula for the preparation of 1,000 g :

Cholesterol	30 g
Stearyl alc.	30 g
White wax	80 g
White petrolatum	860 g

- Commercial products, **Aquaphor** and **Aquabase** variations of hydrophilic petrolatum, have the capacity to absorb up to three times their weight in water and are useful to help incorporate a water-soluble drug, for example, tobramycin sulfate, into an oleaginous ointment base

Lanolin, USP

Lanolin, USP (**anhydrous lanolin**), obtained from the wool of sheep, is a purified waxlike substance that has been cleaned, deodorized, and decolorized. It contains not more than 0.25% water.

2. Water-Removable Bases (Water-washable)

They are oil-in- water emulsions (o/w) resembling creams.

- Because the external phase of the emulsion is aqueous, they are easily washed from skin and are often called water-washable bases .
- They may be diluted with water or aqueous solutions.
- They can absorb serous discharges.

Hydrophilic Ointment, USP, is an example of this type of base.

Hydrophilic Ointment, USP, has the following formula for 1,000 g:

Methylparaben	0.25 g
Propylparaben	0.15 g
Sodium lauryl sulfate	10 g
propylene glycol	120 g
Stearyl alcohol.	250 g
White petrolatum	250 g
Purified water	370 g

Water-Soluble Bases (Greaseless)

- These bases do not contain oleaginous components.
- They are completely water washable.
- Because they soften greatly with the addition of water, large amounts of aqueous solutions are not effectively incorporated into these bases.

Example: Polyethylene Glycol Ointment NF

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

PEG 335 400 g

PEG 4000 600 g

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 or hydrous	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 ointment 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. The release rate of the drug substance from the base.

2. Desirability of topical or systemic action.
3. Desirability of occlusion of the moisture from the skin.
4. Stability of the drug in the ointment base.
5. Effect of drug on the consistency of the base.
6. Water wash ability of the base.
7. Characteristics of the surface to which it is applied.

For example, **an ointment is generally applied to dry, scaly skin; a cream is applied to weeping or oozing surfaces**

Preparation of Ointments

Depending primarily on the nature of the ingredients, ointments are prepared by two general methods.

(a) Incorporation (b) Fusion

Incorporation Method

In this method, the components are mixed until uniform preparation is attained.

On small scale, the pharmacist may mix the components using **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).

- If the components of an ointment react with metal (as does iodine), hard rubber or silicone 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.
- Incorporation of solids. When preparing an ointments 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.

- 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.
- 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. For example, only very small amounts of an aqueous solution may be incorporated into an oleaginous ointment, whereas hydrophilic ointment bases readily accept aqueous solutions.

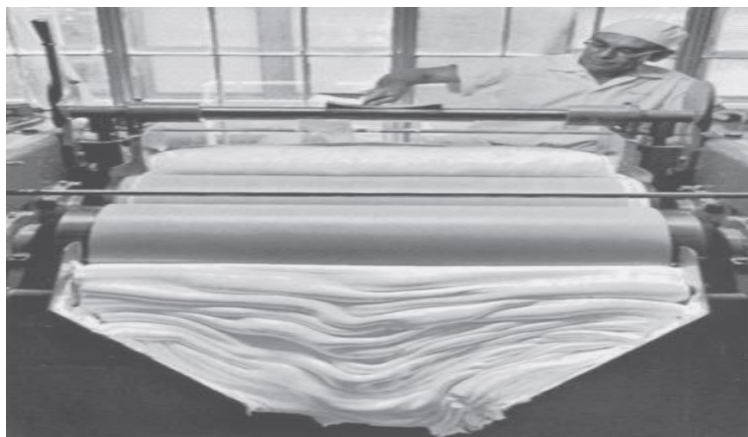
Levigation in ointment preparation

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.

The reduction in particle size of the powder be done by levigating, or mixing the solid material in a vehicle in which it is insoluble to make a smooth dispersion. “wet grinding.”

- The levigating agent like mineral oil or glycerin should be physically and chemically compatible with the drug and the base.
- The levigating agent is used in an equal volume of the solid material.
- A mortar and pestle are used in levigation.
- Levigation allows both the reduction in particle size and the dispersion of the substance in the vehicle.
- 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.

On large scale, 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



Fusion Method

By this method, all or some of the components of an ointment are combined and melted together and cooled with constant stirring until congealed.

Other components like **heat labile substances** and **volatile oils** are added after cooling the mixture to prevent their decomposition and volatilization respectively.

Substances may be added to the congealing mixture as

Solutions

Or insoluble powders levigated with a portion of the base.

On a small scale, fusion may be done by using porcelain dish or glass beaker .

On a large scale, it is carried out in large steam-jacketed kettles.

After congealing, the ointment may be passed through an ointment mill “large scale”, or rubbed with a spatula or in a mortar “small scale” to ensure uniform texture.

- Medicated ointments containing components like beeswax, stearyl alcohol, high molecular weight PEGs are best prepared by fusion method rather than incorporation method.

- By fusion method, the materials with the highest melting points are heated to the lowest required temperature to produce a melt, then the additional substances are added with constant stirring during cooling the melt until the melt is congealed. In this way, not all components are subjected to the highest temperature.

Compendial requirements for ointments

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

- Microbial content
- Minimum fill
- Packaging, storage and labeling .

Microbial Content

- With the exception of ophthalmic preparations, topical applications are not required to be sterile.
- Topical preparations must meet the acceptable standards for microbial contents
- Preparations that contain water tend to support microbial growth to a greater extent than water-free preparations.
- Dermatological products should be examined for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*.
- Other products intended for rectal, vaginal and urethral application should be tested for yeasts and molds .
- Preparations subjected to microbial growth must contain preservatives.

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 limit test is conducted for both raw materials and finished products.

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

Minimum fill

The USP's minimum fill test is used to determine the net weight or volume of the content of the filled containers to ensure proper content compared with the labeled amount.

Packaging, Storage, and Labeling

Ointments and other semisolid preparations are packaged either in **large-mouth ointment jars** or in **metal** or **plastic tubes**.

Topical dermatologic products are packaged either in jars or in tubes, whereas ophthalmic, nasal, vaginal and rectal semisolid products are almost always packaged in tubes.

- Ointment jars are either clear or opaque glass or plastic.
- The jars and tubes should be compatible and stable with the intended product.
- Tubes are superior to jars because they are lighter in weight, relatively inexpensive, conveniently used, compatible with most formulative ingredients, and provide greater protection against external contamination and environmental conditions. They are made of aluminum or plastic sometimes equipped with applicator.



- 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 ointments

Ophthalmic ointments differ from conventional ointments in that they must be sterile.

In selecting an ointment base for an ophthalmic preparation, it must meet several qualities such as

- Must not be irritating to the eye
 - Must permit the diffusion of the medicinal substance throughout the secretions bathing the eye
 - Ointment bases used for ophthalmic should have a softening point close to body temperature, both for comfort and for drug release.
- **Mixtures of mineral oil and white petrolatum** are commonly used as the base in medicated and non-medicated (lubricating) ophthalmic ointments.
- Usually, the 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:

1. The short residence time on the surface of the eye because of rapid removal by tearing and other natural mechanisms.

2. The small surface area of the cornea for drug absorption ,

3.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 and preservation of ophthalmic ointments

In addition to the quality standards for ointments, ophthalmic ointments must meet the USP sterility tests and the test for metal particles in ophthalmic ointment

- Rendering an ophthalmic ointment sterile requires special aseptic techniques and processing.
- Each drug, along with other components, is rendered sterile separately, aseptically weighed, and incorporated in preparing a final product that meets the sterility requirement.

This is done because of difficulty in terminal product sterilization, such as lack of penetration of steam into the ointment base and instability of components owing to high dry heating.

- Antimicrobial preservatives such as **methylparaben and propylparaben combinations, chlorobutanol and benzalkonium chloride** are used as needed.
- The USP test for metal particles is microscopic examination of a heat-melted ophthalmic ointment

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.
- 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.
- Because of the stiffness of pastes, they remain in place after application and are effectively employed to absorb serous secretions.
- Because of their stiffness and impenetrability, pastes are not suited for application to hairy parts of the body.
- Among the few pastes in use today is zinc oxide paste, 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.

Creams

Pharmaceutical creams are semisolid preparations containing one or more medicinal agents dissolved or dispersed in either a water-in-oil (w/o) emulsion or an oil-in-water (o/w) emulsion intended for external use.

Their consistency and rheological properties are based on whether the emulsion is o/w or w/o and on the nature of the solid in the internal phase.

- Creams are used topically, rectally and vaginally.
- Creams are preferred by many patients and physicians because they are easier to spread and remove

Example:

Vanishing creams are oil in water emulsions (o/w) containing large percentage of water, stearic acid and other oleaginous components.

They are named so because water is evaporating leaving a thin layer of the stearic acid and other oleaginous components.

Preparation of creams

Preparation usually involves separating the formula components into two portions: lipid and aqueous. The lipid portion contains all water-insoluble components and the aqueous portion the water-soluble components. Both phases are heated to a temperature above the melting point of the highest melting component. The phases then are mixed, and the mixture is stirred until the mixture has congealed.

- Creams usually require the addition of a preservative(s) unless they are compounded immediately prior to use and intended to be consumed in a relatively short period of time

Gels

Gels (sometimes called jellies) are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jellylike by the addition of a gelling agent ..

Among the gelling agents used are:

1. Synthetic macromolecules, such as carbomer
 2. Cellulose derivatives, such CMC (Carboxymethylcellulose), HPMC (hydroxypropyl methylcellulose)
 3. Natural gums, such as tragacanth
- 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.

- Gels may thicken on standing, forming a thixotropic , and must be shaken before use to liquefy the gel and enable pouring

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

- 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; antimicrobial preservatives, such as methylparaben propyl paraben; and stabilizers, such as edetate disodium .

Examples on gels :

Active Ingredient	Proprietary Product	Gelling Agent	Route and Use
Metronidazole	MetroGel Vaginal	Carbomer 934P	Vaginal: bacterial vaginosis
Clobetasol propionate	Temovate Gel	Carbomer 934P	Dermatologic: antipruritic
Cyanocobalamin	Nascobal	Methylcellulose	Nasal: hematologic
Diclofenac sodium	Voltaren emulgel		Systemic effect (transdermal)

Emulgel

Emulgel is an emerging topical drug formulation which is becoming increasingly popular due to its advantages over the conventional topical preparations. The emulgel is a combination of an emulsion and a gel and thus has a dual release control system .

Its biggest and most favorable advantage has been the ability to incorporate hydrophobic drugs, thus making it emerge as a more popular choice these days. The emulgel is also greaseless, transparent; it can be easily spread and removed, has a long shelf- life, is thixotropic and is also pleasant looking. Voltaren emulgel contain diclofenac diethyl ammonium is an example on emulgel .



Powders and Granules

Chapter 6

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems Eleventh Edition

Objectives:

After reading this topic, the student will be able to:

- Differentiate a powder from a granule.
- Explain how a drug's powder particle size influences the pharmaceutical dosage forms which will be used to administer it.
- Define micrometrics, the angle of repose, levigation, spatulation, and trituration.
- Compare and contrast the various types of medicated powders, e.g., bulk, divided.
- Provide examples of medicated powders used in prescription and nonprescription products.

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.

➤ It may be used to describe the physical form of a material, that is, a dry substance composed of finely divided particles.

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.

A powder is defined as a dosage form composed of a solid or mixture of solids reduced to a finely divided state and intended for internal or external use.

Granules which are used as a dosage form consist of powder particles which have been aggregated to form a larger particle which is usually 2-4 mm diameter.

This is much larger than granules prepared as an intermediate for tablet manufacture.

Powders have qualities that make them an attractive dosage form for certain situations:

- Unlike a standardized capsule or tablet, powders enable a primary care provider to **easily alter the quantity of medication for each dose.**
- Powders can also aid in clinical studies of drug preparations because the dose can be so readily adjusted.
- Doses can **be individually weighed and placed in powder papers,** envelopes, or small vials/bottles
- **Infants and young children who cannot swallow tablets or capsules will accept powders** that can be mixed with a formula or sprinkled in applesauce or some other appropriate food.
- If a drug is too bulky to be prepared as a capsule or tablet, it may be suitable for a powder dosage form.
- **Powders provide a rapid onset of action** because they are readily dispersed, have a large surface area, and usually require only dissolution, not disintegration, before absorption.

The use of powders:

Although the use of *medicated powders* per se in therapeutics is limited, 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:

- Solid dosage forms as tablets and capsules;

- They may be dissolved or suspended in solvents or liquid vehicles to make various liquid dosage forms;
- They may be incorporated into semisolid bases in the preparation of medicated ointments and creams.

Physicochemical Considerations

Particle Characteristics

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

- Morphology,
- Purity,
- Solubility,
- Flowability,
- Stability,
- Particle size,
- Uniformity, and
- 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.

The particles of pharmaceutical powders and granules may range from being extremely coarse, about 10 mm (1 cm) in diameter, to extremely fine, approaching colloidal dimensions of 1 μm or less.

In order to characterize the particle size of a given powder, the *United States Pharmacopeia* (USP) uses these descriptive 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. The **sieve number** denotes the **number** of holes present in the **sieve** within one-inch length of the **sieve** mesh.

OPENING OF STANDARD SIEVES

			SIEVE NUMBER	SIEVE OPENING				SIEVE NUMBER	SIEVE OPENING
Very coarse Coarse Coars e	Mod erately	4-12 Granules	2.0	9.50 mm	Very fine	70.0	212.00 μm		
			3.5	5.60 mm		80.0	180.00 μm		
			4.0	4.75 mm		100.0	150.00 μm		
			8.0	2.36 mm		120.0	125.00 μm		
			10.0	2.00 mm		200.0	75.00 μm		
	Fine	12-20 Tableting	20.0	850.00 μm		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		
			50.0	300.00 μm		400.0	38.00 μm		
			60.0	250.00 μm					
Source: USP 31-NF 26.									

- 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 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 undissolved but uniformly dispersed in a liquid vehicle (e.g., fine dispersions have particles ~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

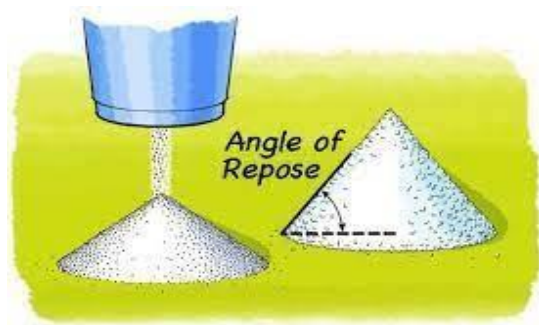
Micromeritics is the science of small particles; a particle is any unit of matter having defined physical dimensions. Micromeritics is the study of a number of characteristics, including:

- a. particle size and
- b. size distribution,
- c. shape,
- d. angle of repose,
- e. porosity,
- f. true volume,
- g. bulk volume,
- h. apparent density, and
- i. bulkiness

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:



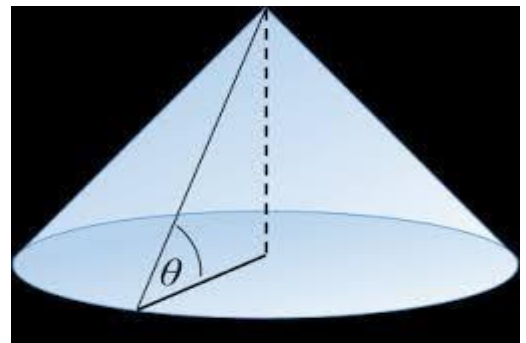
$$\tan \theta = h/r$$

Where **h** is the height of the powder cone and **r** is the radius of the powder cone.

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?

$$\tan \theta = h/r = 3.3/4.5 = 0.73$$

$$\arctan 0.73 = 36.25^\circ$$



Powders with a low angle of repose flow freely, and powders with a high angle of repose flow poorly.

Angle of repose as an indication of powder flow properties	
Angle of repose (degrees)	Types of flow
< 20	Excellent
20 – 30	Good
30 – 34	passable
> 40	Very poor

Flowability:

A number of factors determine the flow properties of powders, including:

- Shape : Spherical particles flow better than needles.
- Size : Very fine particles do not flow as freely as large particles.

In general, particles in the size range of 250 to 2,000 μ m flow freely if the shape is amenable.

Particles in the size range of 75 to 250 μ m may flow freely or cause problems, depending on shape and other factors.

With most particles smaller than 100 μ m, flow is a problem.

Particle Size Reduction

Comminution, reduction of the particle size of a solid substance to a finer state, is used to facilitate:

- Crude drug extraction,

- Increase the dissolution rates of a drug,
- Aid in the formulation of pharmaceutically acceptable dosage forms, and
- Enhance the absorption of drugs.

The reduction in the particle size of a solid is accompanied by a great increase in the specific surface area of that substance.

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***.

- On a large scale, various types of mills and pulverizers may be used to reduce particle size.

Manual methods include

1. Trituration It is the principle method of comminution in pharmacy.

It is the process of reduction of particle size by rubbing in mortar and pestle.

The size reduction is the result of both pressure and attrition as the pestle is firmly pressed down and given a circular motion over the inner surface of the mortar. Care must be taken to scraping the side down with spatula frequently

2. Levigation is commonly 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.
- Mineral oil and glycerin are commonly used levigating agents.

3. Pulverization by intervention: This method includes reduction of particle size with the aid of a second agent, which can readily remove from the pulverized product.

This method is usually used to reduce the particle size of camphor which is otherwise difficult to triturate. When a few drops of alcohol or other volatile solvent are added, camphor is readily triturated and the pulverized camphor is readily recovered as soon as the solvent evaporates.

On a large scale, various types of mills and pulverizers may be used to reduce particle size.

Fitz Mill 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 have the following advantages:

- Protects the environment from chemical dust,
- Reduces product loss, and
- Prevents product contamination.

Special processes of particle size reduction

These processes may be used to prepare powders for dosage forms include freeze-drying and spray drying.

Freeze Drying :(Drying by sublimation, lyophilization): It refers to the removal of water by sublimation from frozen products at low temperatures.

Freeze drying is usually carried out in temperature range of -10 to -40°C . It is used to dry biological products such as blood serum, plasma, certain antibiotics such as penicillin, and other substances that are heat-labile and cannot be dried by the usual application of heat.

Spray drying: Is a process for converting solution or suspensions into dry, free-flowing powders in a single drying step. The solution or suspension is atomized or sprayed into an enclosed chamber into which heated air is also introduced. The atomization process produces very fine, generally spherical droplets with large surface areas that dry almost instantaneously.

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

- Spatulation,
- Trituration,
- Sifting, and
- Tumbling

➤ 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.

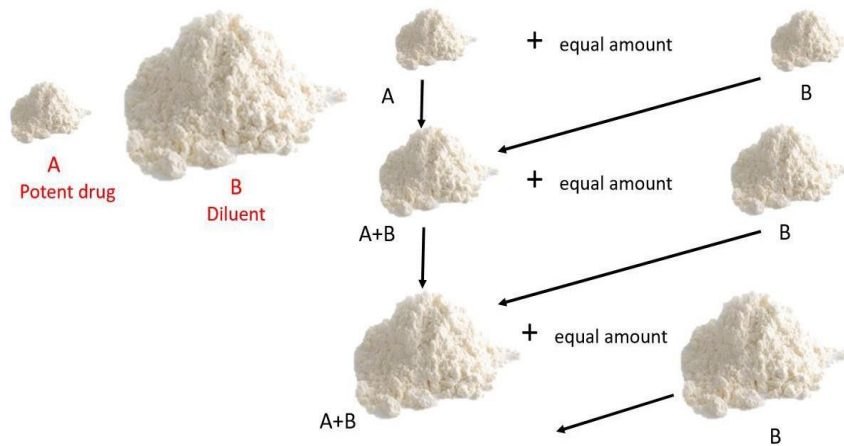
- Substances that form eutectic mixtures when combined include phenol, camphor, menthol, thymol, aspirin, phenyl salicylate, and other similar chemicals. To diminish contact, a powder prepared from such substances is commonly mixed in the presence of an inert diluent, such as light magnesium oxide or magnesium carbonate, to separate the troublesome agents physically.



➤ **Trituration**

- Trituration may be employed both to triturate and to mix powders. If simple mixing is desired without 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 is used to ensure the uniform distribution of the potent drug.

Geometric dilution



The process is repeated until all of the diluent B is incorporated.

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. (to ensure uniform distribution)

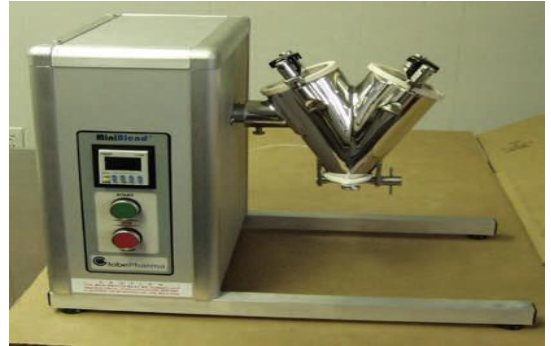
➤ **Sifting (sieving)**



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

➤ **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

- **Segregation:** is an undesirable separation of the different components of the powder mixture (blend) due to differences in density and size.
- **Segregation may occur by:**
- Sifting or percolation

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.

- Air entrapment (fluidization),

Fine, aerated powders with differences in particle size or density may result in a striation pattern and may occur during powder transfer.

- 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; and
- (g) Proper hopper design and operating valves (if present).

Medicated Powders

- Some medicated powders are intended to be used **internally** and others, **externally**.

A. Internal powders

- Most powders for internal use are taken **orally** after mixing with water or in the case of infants in their infant formulas. 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**, others for use as an **injection**, and still others for use as a **vaginal douche**.

1) Medicated powders for oral use

- Medicated powders for oral use may be intended for **local effects** (e.g., laxatives) or **systemic effects** (e.g., analgesics)
- and may be preferred to counterpart tablets and capsules by patients who have **difficulty swallowing solid dosage forms**.

- 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. For administration, they can be mixed with a liquid or softfood.
- 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.
- A **primary disadvantage** of the use of oral powders is the undesirable taste of the drug.
- 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
- Oral powders are formulations composed of solid, loose, dry particles of varying degrees of fine particle size. They contain one or more active substances with or without excipients and if necessary, approved colouring matter and flavouring.
- They are generally administered with water or another suitable

liquid, or they may also be swallowed directly.

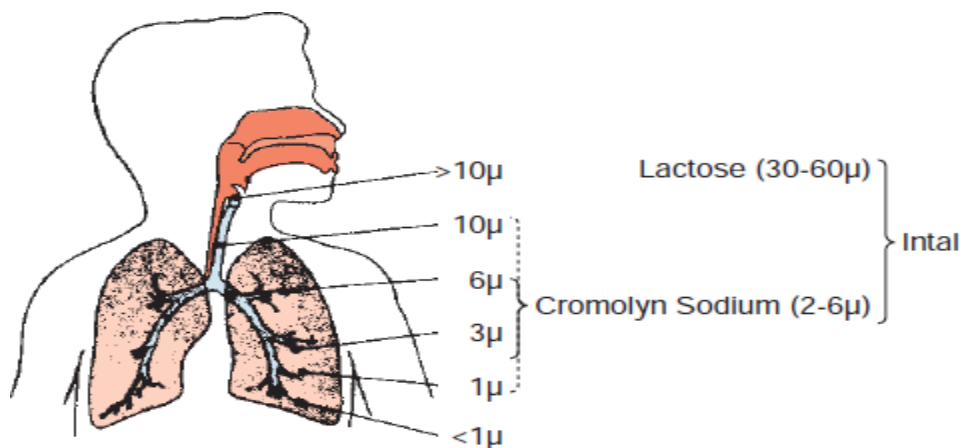
- All powders and granules should be stored in a dry place **to prevent deterioration due to ingress of moisture. Even if hydrolytic decomposition of susceptible ingredients does not occur, the particles will adhere and cake, producing an inelegant, often unusable product.**

2) Aerosol powders

Some medicated powders are administered by inhalation with the aid of dry powder inhalers (DPIs), which deliver micronized particles of medication in metered quantities.

A DPI is a device used to administer an inhalation powder in a finely divided state suitable for oral inhalation by the patient. An inhalation powder is one used with a device that aerosolizes and delivers an accurately metered amount.

Most of these products are used in the treatment of asthma and other bronchial disorders that require distribution of medication deep in the lungs. To accomplish this, the particle size of the micronized medication is prepared in the range of 1 to 6 μm in diameter.



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**.

They administered in a metered-valve container that apply a specific dose (Each dose is delivered through the mouthpiece upon activation of the aerosol unit's valve) or can use a powder blowers or insufflators

3) Nasal powder

They are medicated powders intended for inhalation into the nasal cavity by means of a suitable device. Some potent drugs are presented in this way because they are rapidly absorbed when administered as a fine powder via the nose.

- Delivery devices have been developed:
- To enhance convenience.
- To ensure that a uniform dose is delivered on each occasion.
- Sufficient drug for one dose may be presented in a hard gelatin capsule diluted with an inert, soluble diluent such as lactose. The capsule is placed in the body of the nasal delivery device and is broken when the device is assembled. The drug is inhaled, via the nose, by the patient as a fine powder.

B. External powders

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.

Powders for cutaneous application are presented as single-dose powders or multidose powders. They should be free from grittiness. Powders specifically intended for use on large open wounds or on severely injured skin must be sterile.

- Dusting powders contain ingredients used for therapeutic, prophylactic or lubricant purposes and are intended for external use.

Dispensing of Powders

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.

A. Bulk Powders

Among the bulk powders available in pre-packaged amounts are:

- (a) Antacids (e.g., sodium bicarbonate) and laxatives (e.g., psyllium (Metamucil)), which the patient takes by mixing with water or other beverage 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-infective (e.g., bacitracin zinc and polymyxin B sulfate) or antifungal (e.g., tolnaftate)

(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.

Dispensing powder medication in bulk quantities is limited to non-potent substances.

➤ 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.

➤ Patients should be instructed how to measure the appropriate amount of the powder and be told the type and volume of liquid or vehicle to use to deliver the medication consistent with package and/or physician instructions.

B. Divided powder

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. 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

Weighing method: weigh each portion of powder separately before enfolding in a paper (for potent drugs) (The smallest amount of powders in a packet is 130mg).

block-and-divide method: 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.

- 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, compounded powder papers are rarely used on an outpatient, community practice basis. Their use is usually limited to institutional and research practice

Granules Dosage Forms

One disadvantage of bulk powders is that, because of particle size differences, the ingredients may segregate, either on storage in the final container or in the hoppers of packaging machines. If this happens the product will be non-uniform and the patient will not receive the same dose of the ingredients on each occasion. This can be prevented by granulating the mixed powders.

Granules are aggregates of a group of particles to form larger particles sufficiently robust to withstand handling.

They are irregular or spherical in shape.

They are usually in the 4-12-mesh 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

(which tend to float on the surface), 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**.

Examples of granules

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 EFFER dose tablets (Glaxo Wellcome). Also (Multivitamins) effervescent granules and tablets are dissolved in water before use.

Preparation of granules

Granules are prepared by wet methods and dry methods.

Wet method:

- 1) Moisten the powder or powder mixture with a fluid (with or without a binder).
- 2) Pass the resulting paste through a screen of the mesh size to produce the desired size of granules.
- 3) The resultant 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.
- 4) Screening stage.

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:

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.

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:

An effervescent dosage form, frequently tablets or granules, contains ingredients that, when in contact with water, rapidly release carbon dioxide. The dosage form is dissolved or dispersed in water to initiate the effervescence prior to ingestion.

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).
- 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.

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.

Chapter 7 Capsules

ANSEL'S Pharmaceutical Dosage Forms and Drug Delivery Systems Eleventh Edition

Objectives:

After reading this topic, the student will be able to:

- Differentiate between hard and soft gelatin capsule.
- Advantages and disadvantages of each type of capsule
- The excipients used for both type of capsules
- The compendial requirement of capsules
- The appropriate method for compounding and packaging and storage of capsules

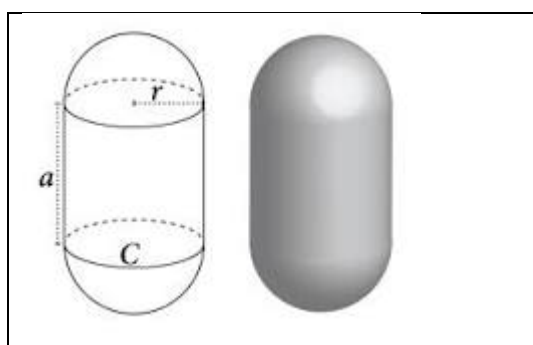


Capsules

Capsules are solid dosage form 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.

A capsule (from Latin capsula, "small box or chest"), or stadium of revolution, is a basic three-dimensional geometric shape consisting of a cylinder with hemispherical ends. Another name for this shape is spherocylinder.



Advantages of Capsule dosage form

1. Elegant and conveniently carried, readily identified.
2. Easily swallowed, there is no need for spoons or other measuring devices,
3. Are tasteless and odourless when swallowed (mask the bitter taste and bad odour of medicinal agents)
4. Available for many medications in a variety of dosage strengths, providing flexibility to the prescriber and accurate individualized dosage for the patient.
5. They are packaged and shipped by manufacturers at lower cost and with less breakage than liquid dosage forms.
6. They are also more stable and have a longer shelf life than their liquid counterparts.

Hard Gelatin Capsule

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.

Composition of Hard gelatin capsule

- 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

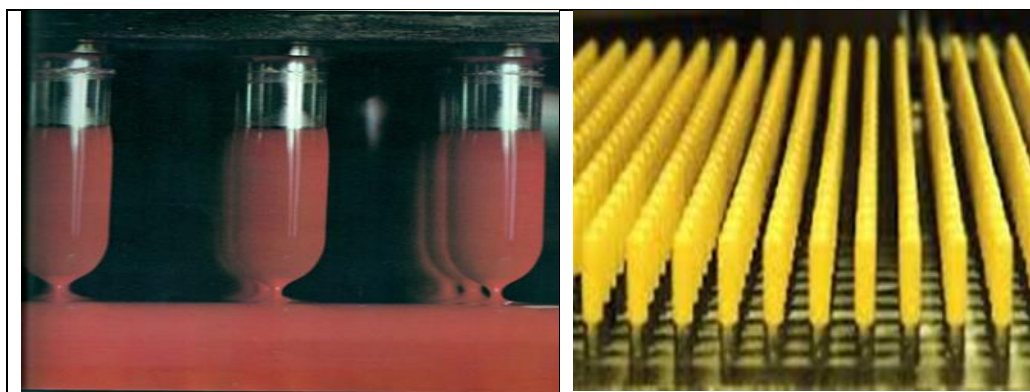
- Because moisture may be absorbed by gelatin capsules and may affect hygroscopic agents within, many capsules are packaged along with a small packet of a desiccant material to protect against the absorption of atmospheric moisture.
- The desiccant materials most often used are dried silica gel, clay, 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 manufacture consideration.

- 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

1. Conventional Hard Gelatin Capsule

Hard gelatin capsule is cylindrical with hemispherical ends. A manufacturer also may prepare distinctive-looking capsules by altering the usual rounded shape of the capsule-making pegs. 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).

Conventional Hard Gelatin Capsule	Tapered capsule body	Tapered both the cap and body

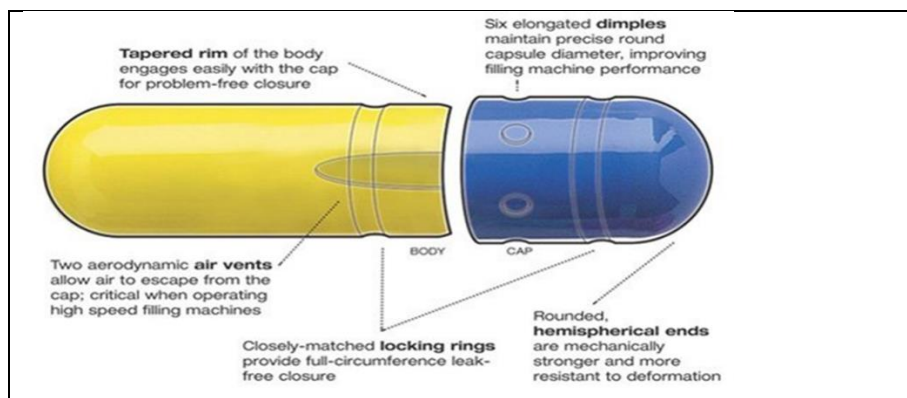
During the closing process, the capsule body is inserted into the cap. With the high-capacity filling rates of the modern capsule filling machines (more than 180,000 capsules per hour), splitting (telescoping) and/or denting of

the capsule shell occur with the slightest contact between the two rims when they are joined.

To ensure reliable closing of the filled capsules, capsule shells with locking grooves (or indentations) have been prepared such as snap fit and coni snap fit capsules.

2. Snap-fit. Snap-Fit® has the concentric locking rings of the body and cap which prevent reopening after filling.

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.

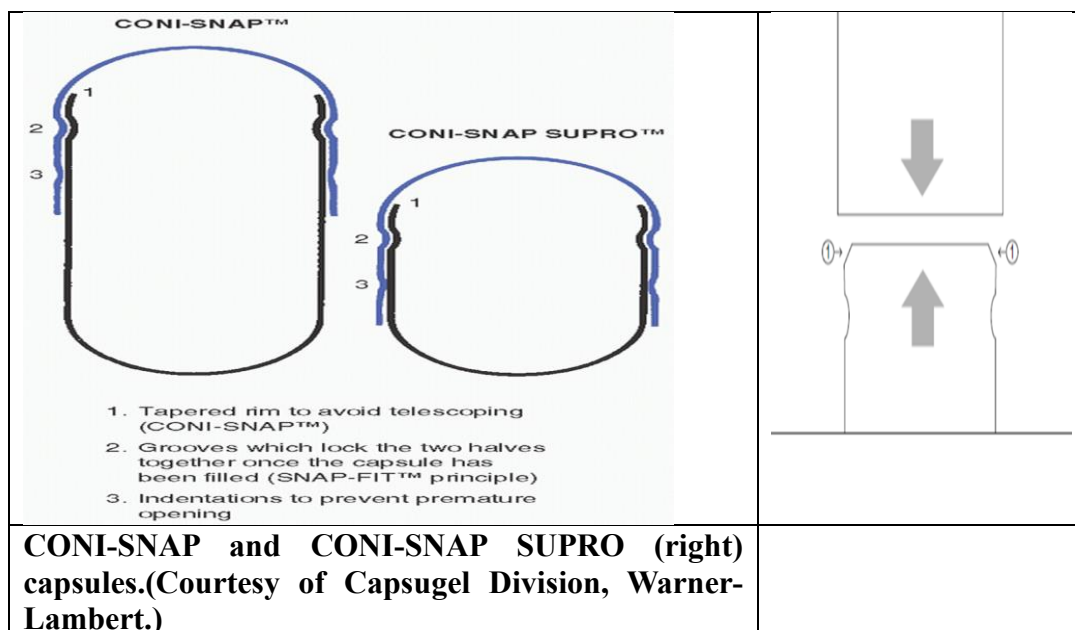


3. Coni -snap and Coni – snap Supro hard gelation

The **Coni-Snap® capsule**, which is the improved form of Snap-Fit®, has the rim of the capsule body which is slightly tapered. These capsules have a rounded hemispherical end which are stronger and more resistant to deformation, 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. This type of capsule 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.

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.

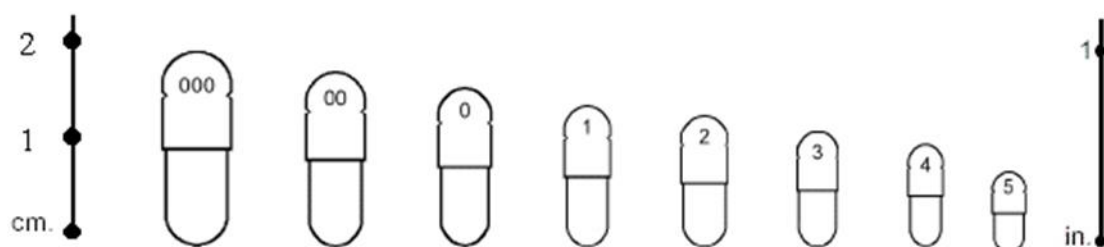


Capsule sizes

- 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									
Drug substance (mg) ^a	Capsule size	000	00	0	1	2	3	4	5
	Volume (mL)	1.40	0.95	0.68	0.5	0.37	0.3	0.21	0.13
	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 and 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 = $0.45\text{g} / 0.8\text{g/mL} = 0.56\text{mL}$
- 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

Developing the Capsule Formulation

In developing a capsule formulation, the goal is to prepare a capsule with;

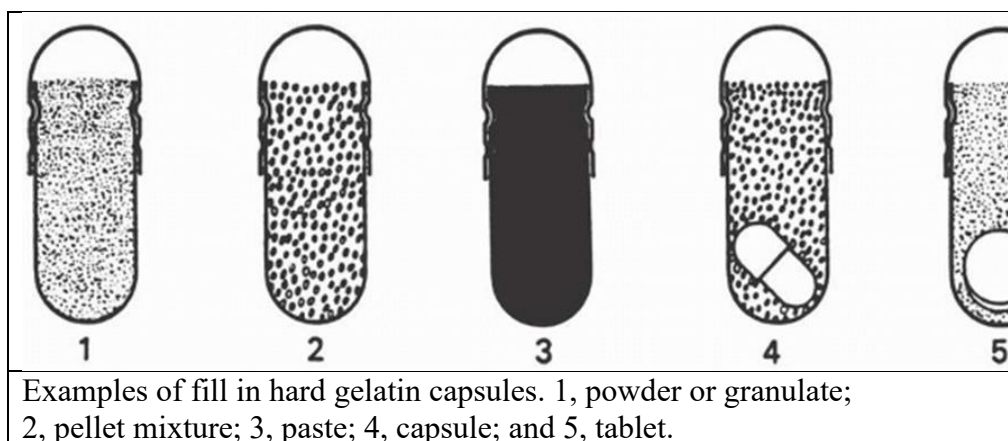
1. Accurate dosage,
 2. Good bioavailability,
 3. Ease of filling and production,
 4. Stability, and
 5. Elegance.
- In dry formulations, the active and inactive components must be blended thoroughly to ensure a **uniform powder mix** for the fill.
 - Care in blending is especially important for **low-dose 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.
 - 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.
 - 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.

Excipients	Example	Function
Diluent or Filler	Lactose, Microcrystalline cellulose, Starch	Provide bulk to powder lend to produce the proper capsule fill volume often provide cohesion to the powders
Disintegrants	Pregelatinized starch, Croscarmellose, Sodium starch glycolate.	Assist the breakup and distribution of the capsule's contents in the stomach.
Lubricant or Glidant	Fumed silicon dioxide, Magnesium stearate, Calcium stearate, Stearic acid, or Talc (about 0.25% to 1%)	Enhances flow properties
Wetting agent	Sodium lauryl sulphate	Improve dissolution

- When **magnesium stearate** is used as the lubricant, the waterproofing characteristics of this water-insoluble material can retard penetration by the gastrointestinal fluids and delay drug dissolution and absorption. A surface-active agent, such as **sodium lauryl sulphate**, is used to facilitate wetting by the gastrointestinal fluids to overcome the problem.

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.



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.

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.

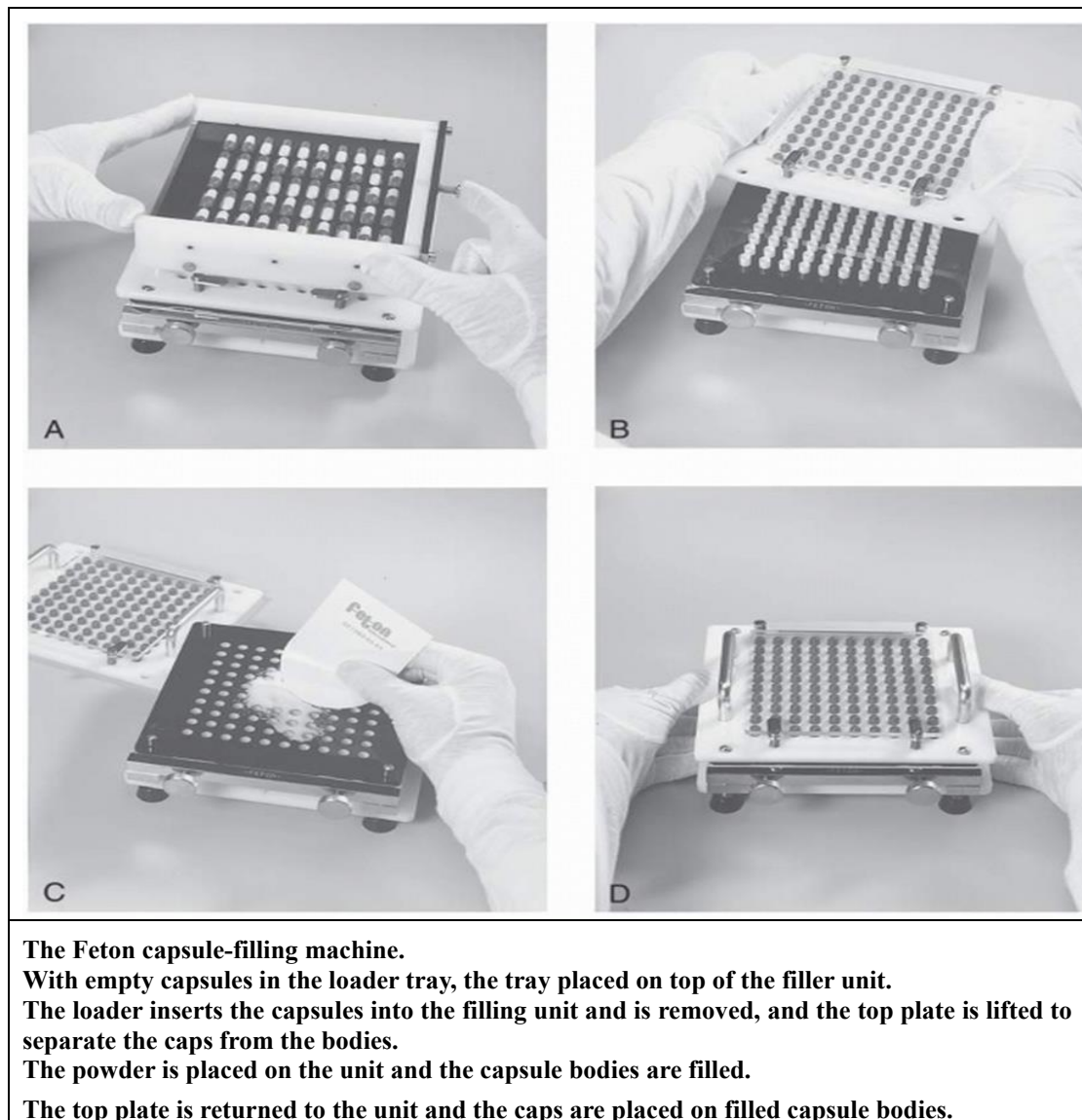
The powder to be encapsulated is placed on a sheet of clean paper or on a glass or porcelain plate. Using the spatula, the powder mix is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body.

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.

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 weighing protects 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.



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.

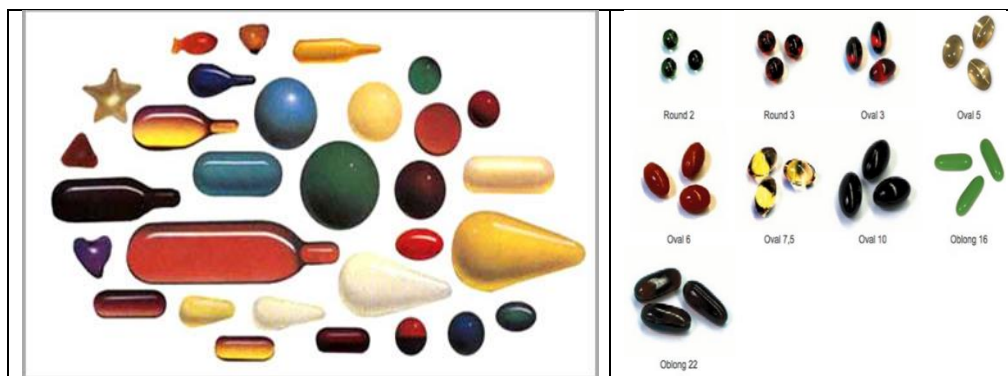
Cleaning and Polishing Capsules

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.

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



Uses 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

Enteric coated capsules

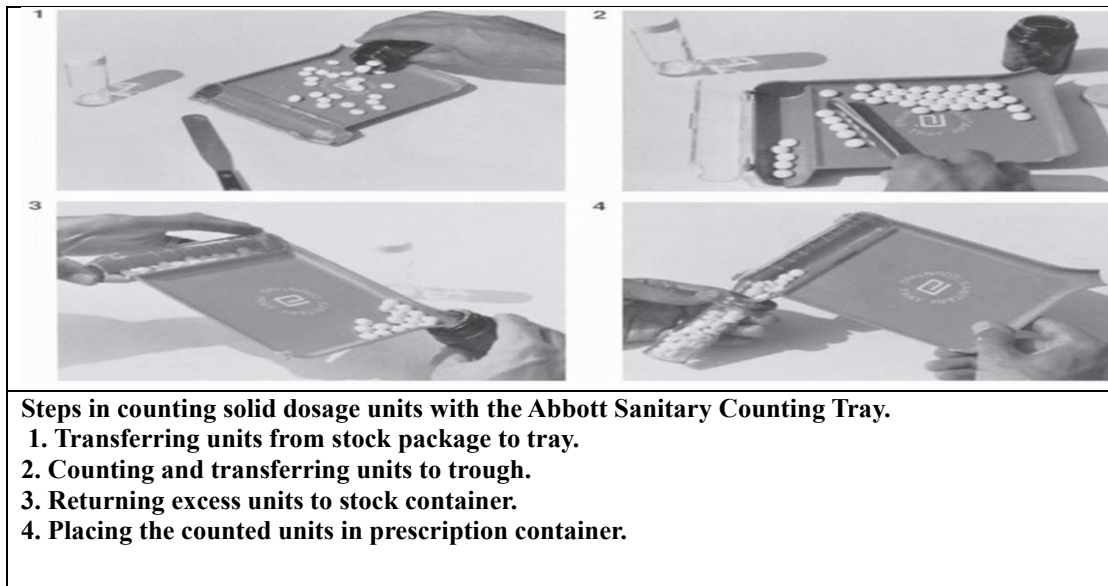
Capsules that have been coated or otherwise treated to resist dissolution in gastric fluids but release their contents in the intestine are said to be enteric.

Enteric coating is a useful strategy for oral delivery for:

- Maintaining the stability of medications that are unstable in acidic conditions of the stomach such as erythromycin, pancreatin, and proton pump inhibitors such as omeprazole
- Such delayed release of medication may be desired if the drug is inactivated in gastric fluids or if the drug is irritating to the gastric mucosa. Minimizing the side effects (e.g. nausea and gastric irritation and bleeding) that can occur with drugs non-steroidal inflammatory drugs , garlic and fish oil (omega 3) which cause nausea
- Delayed action: the drug is given at night and permit effective blood levels of the medication prior to waking.
- Facilitate colonic drug delivery, a high local concentration of the drug may be especially desirable in the intestine, as in the case of anthelmintics.

Typical of materials used for enteric coating are shellac, cellulose acetate phthalate, and fatty waxy materials such as bees wax, carnauba wax and stearic acid. But these materials have a high potential to be hydrolysed when exposed to elevated temperature and humidity, thus replaced with poly vinyl acetate phthalate, hydroxy propyl methyl cellulose phthalate

The recent method of enteric coating involves polymers with poly-acidic groups that are unionized in the acidic media, and dissolve in water above the pKa of the acidic groups around pH 6 such as Eudragit L (poly methacrylic acid : methyl methacrylate 1:1) applied in non-aqueous solvent



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

Examples of some capsules

Official capsule	Type of capsules	Strength (mg)	Category
Amoxicillin	Hard gelatin cap	250, 500	Antibiotic
Erythromycin Estolate	Enteric coated hard gelatin capsule	250 mg	Antibiotic
Fluoxetine HCl Prozac® Pfizer	Tapered capsule body hard gelatin capsule	10, 20, 40	Antidepressant
Indomethacin	Enteric coated hard gelatin capsule	25, 50	Anti-inflammatory, analgesic
Pancreatin Creon® Abbot	Enteric coated micropellets capsules	150, 300	Digestive enzymes
Omeprazole	Enteric coated hard	20, 40	Proton pump inhibitor
Omega 3	Soft gelatin capsule	1000	Nutrient
Vitamin D3	Soft gelatin capsule	1000, 2000, 5000, 10000 IU	Nutrient

Aerosols and Foams

Chapter 14

ANSEL'S Pharmaceutical Dosage Forms and Drug Delivery Systems Eleventh Edition

Objectives:

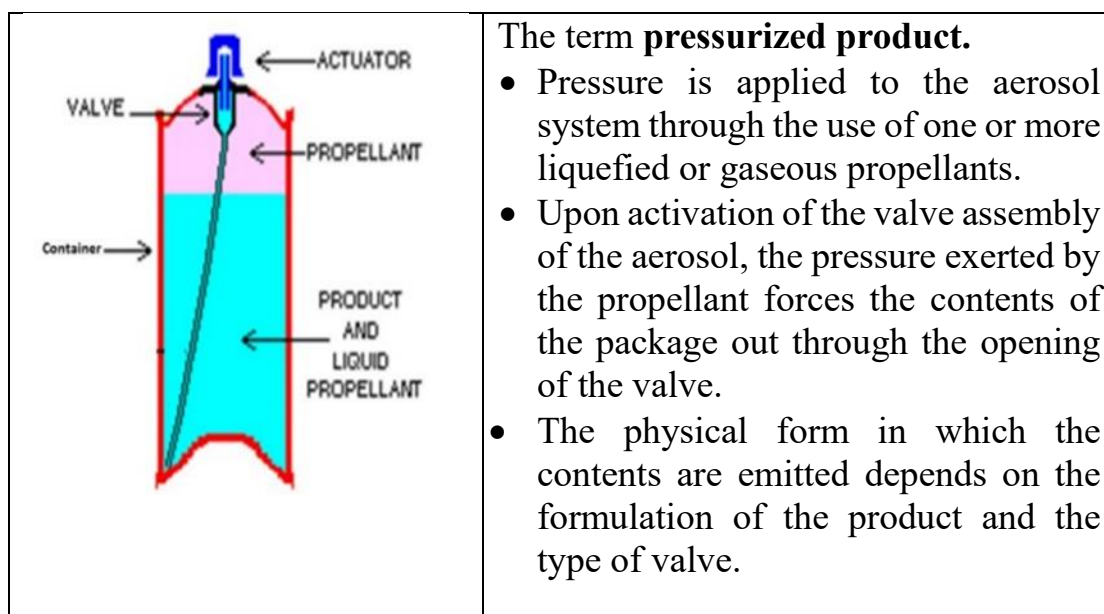
After reading this topic, the student will be able to:

- Define aerosols
- Types and applications of aerosols
- Main advantage of aerosols
- Define foams
- Types and applications of foams
- Main advantage of foams
- Differentiate between aerosols and foams

Pharmaceutical Aerosols

Pharmaceutical aerosols are **pressurized systems** that, **upon valve actuation**, emit a fine dispersion (either **continuous or metered**) of liquid and/ or solid materials containing one or more active ingredients in a gaseous medium.

Pharmaceutical aerosols are similar to other dosage forms because they require the same types of considerations with respect to formulation, product stability, and therapeutic efficacy. However, pharmaceutical aerosols unlike other dosage forms differ in their dependence upon the function of the container, its valve assembly, and an added component the propellant-for the physical delivery of the medication in proper form.



Aerosol products may be designed to expel their contents as a fine mist; a coarse, wet, or dry spray; a steady stream; or a stable or a fast-breaking foam. The physical form selected for a given aerosol is based on intended use.

There are two types of aerosols.

1. *Space sprays*

Aerosols used to provide an **airborne** mist.

For example, **inhalation therapy**, as in the treatment of asthma or emphysema, must present particles in the form of a fine liquid mist or as finely divided solid particles. Particles less than 6 μm will reach the respiratory bronchioles, and those less than 2 μm will reach the alveolar ducts and alveoli, also, room disinfectant's, room deodorizers fall in this list

The particle size of the released product is generally quite small, usually below 50 μm , and must be carefully controlled so that the dispersed droplets or particles remain airborne for a long time.

The valve opening is small, so the particle released are of small size.

The formulation is either solution or suspension.

2. *Surface sprays or surface coatings.*

Aerosols intended to carry the active ingredient to a surface of the body (**dermatologic aerosols**). Included in this group many cosmetic preparations like personal deodorant sprays,

By contrast, the particle size for a dermatologic spray intended for deposition on the skin is coarser and generally less critical to the therapeutic efficacy of the product. Some dermatologic aerosols present the medication in the form of a powder. a wet spray, a stream of liquid (usually a local anaesthetic), or an ointment-like product.

Property	Space Sprays	Surface Sprays
Product Concentrate (%)	2 – 20	20 – 75
Propellant (%)	70 – 98	25 – 80
Pressure (psig at 20°C)	30 – 40	25 – 55
Particles (μm)	<1 – 50	50 – 200

Types of Aerosols According to The Route of Administration

1. Inhalation aerosols, commonly known as metered-dose inhalers (MDIs), are intended to produce fine particles or droplets for inhalation through the mouth and deposition in the pulmonary tree. The design of the delivery system is intended to release measured quantities and of the appropriate quality of the active substance with each actuation.
2. Nasal aerosols, commonly known as nasal MDIs, produce fine particles or droplets for delivery through the nasal vestibule and deposition in the nasal cavity. Each actuation of the valve releases measured mass and appropriate quality of the active substance.
3. Oral (buccal and sublingual aerosols are intended to produce fine particles or droplets for deposition on the surface of the tongue. The design of the delivery system releases one dose with each actuation.
4. Topical aerosols produce fine particles or droplets for application to the skin. Topical aerosol drug products may be designed, as needed. to

deliver a metered amount of formulation upon actuation of the designed valve or continuous release of formulation during depressed status of the valve.

			
Inhaler	Inhaler	Nasal aerosol	Nasal aerosol
			
Topical spray	Sublingual aerosol	Vaginal spray	Rectal spray

Advantages of Aerosols

The main advantages of aerosols are:

1. The use of 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. The rapid evaporation of the propellant also provide cooling and refreshing effect
2. The drug is withdrawn from the container without contamination or expose of the remaining material. If the product is sterile, sterility can be maintained throughout the product's shelf life.
3. Protect the medicinal agent from environment oxygen and light because the container is opaque

4. The formulation and the valve control may affect the physical form and particle size of the emitted product therefore the efficacy of the aerosol especially in MDI
5. Application is a clean process (no need for wash after application)

The Aerosol principle

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, in addition to solvents and surfactant and antioxidants to prepare a stable and efficient product.
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.
 - A. Provide the driving force to expel the product from the container
 - B. Responsible for developing proper pressure inside the container

Types of propellant

Type I - Propellant A Liquefied gas

a- Oral and Inhalation (fluorinated HC) $\text{Cl}_3\text{F C}$, $\text{Cl}_2\text{F}_2\text{C}$

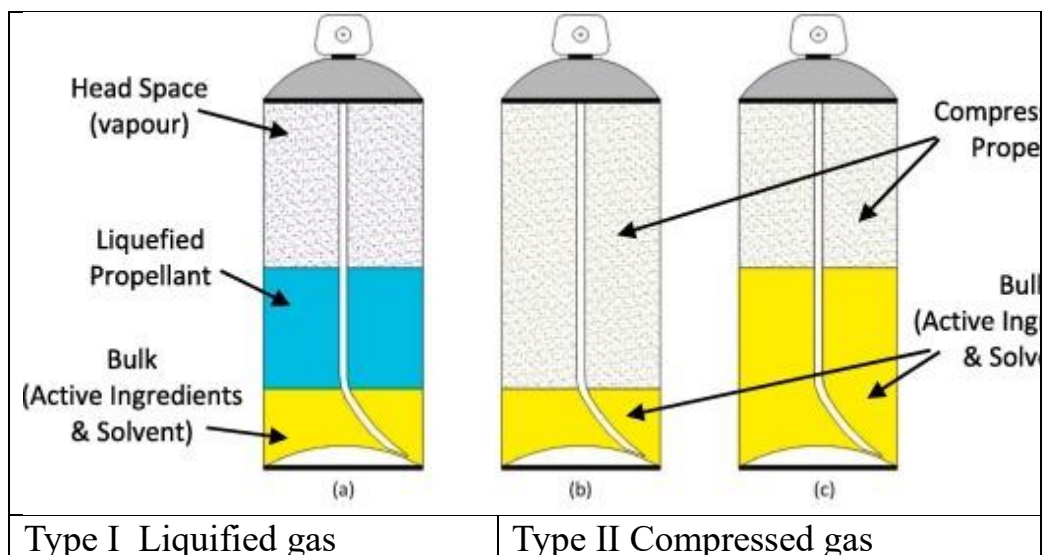
b- Topical Pharmaceutical Aerosol (HC) propane, butane

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.

They are immiscible with water and have a density less than 1.

When the propellant is in the external phase, foams are not created but sprays or wet streams result.

The propellant exist as liquids under pressure, but also as gas in the head space. As the valve is opened some of the liquid propellant turn to gas to keep the head space full of gas. The pressure in the container remains essentially constant.



Type II Propellant B Compressed gas N_2 , CO_2

Compressed gas propellant occupy the head space above the liquid in the container. When the aerosol valve is opened the gas pushes the liquid out of the container

The amount of gas in the headspace remains the same but it has more space and as a result the pressure will drop during the life of the product

Spray performance is maintained by careful choice of the aerosol valve and actuator.

Aerosol container and valve assembly

The effective of a pharmaceutical aerosol depends on achieving the proper combination of formulation, container, and valve assembly.

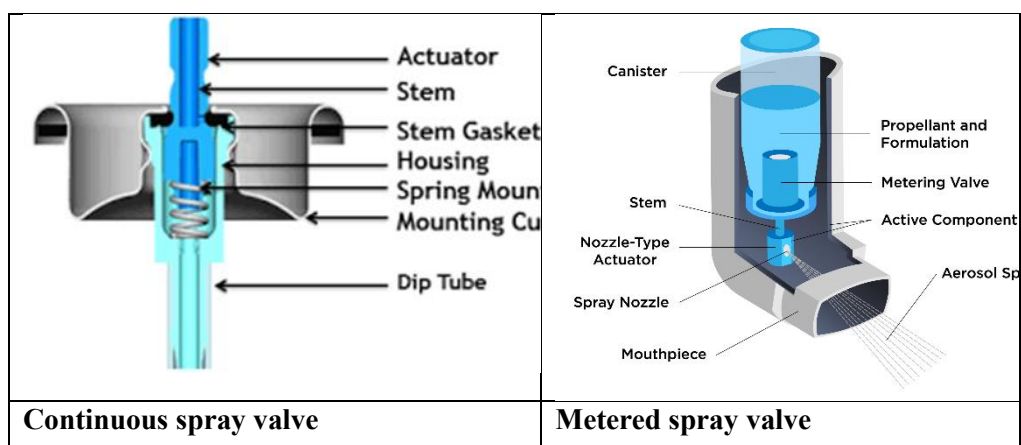
A. Containers are made of a) glass b) metals tin plated steel, aluminium, stainless steel and c) plastic

Selection depends formula compatibility, ability to sustain the required pressure, and cost.

B. Valve assembly allows expulsion of the contents in the desired form at the desired rate and for metered valves the proper amount, **they are two types**

Continuous used in topical applications

Metered used for inhalation of potent medication



Pump spray

Pump spray means a packaging system in which the product ingredients within the container are **not under pressure** and in which the product is expelled only while a pumping action is applied to a button, trigger or other actuator **manually** on the pump to deliver the product in the form of a spray.

Use of special actuator according to the site of administration



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 foams are generally o/w emulsions resembling light creams. They are water miscible and non-greasy.

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.

Advantages of foams

Probably the most convincing argument for the use of foams

- 1) Foam formulations are generally easier to apply, are less dense, and spread more easily than other topical dosage forms,
- 2) Used **without the use of fingertips** especially for places hard to reach (vagina, rectal) or that cause irritation when applied (for burn dressing)
- 3) Patient and consumer acceptance because it is easy to use.
- 4) Foams may be formulated in various ways to provide emollient or drying functions to the skin, depending on the formulation constituents.

Product concentrate

In addition to the formula components, the main constituents that differentiate foams are surfactants such as:

1. Anionic surfactants: Fatty acids saponified with triethanolamine,
2. Nonionic surfactants: such as the Polyoxyethylene fatty esters, Polyoxyethylene sorbitan esters (Tweens) , alkyl phenoxy ethanol, and alkanolamide.

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

Types of Foams

1) Foam Type 1 Breaking Foam

- 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.

2) Foam Type 2 Stable Foam

Depending on the components, the emitted product can be a stable foam (shaving cream type)

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.

Breaking Foam	
	
Stable Foams	
	
Contain estrogenic substances and contraceptive agents	Rectal foams use inserters, to relieve inflammatory anorectal disorders

Site of application of foams

A. Topical Foams

B. Vaginal Foams

The foams are used intravaginally in the same manner as for creams, using a special type of applicator

The aerosol package contains an inserter that is filled with foam and the contents placed in the vagina through activation of the plunger.




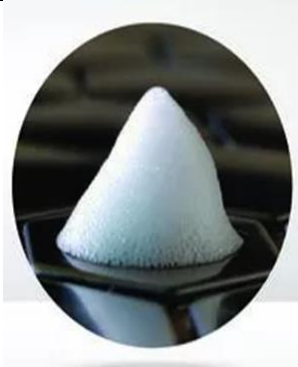
C. Rectal Foams are usually stable foams.

Packaging of foams

Foam valves have only one orifice that leads to a single expansion chamber. The expansion chamber also serves as the delivery nozzle or applicator. The chamber is the appropriate volume to allow the product concentrate to expand into a ball of foam. Foam valves are used for viscous product concentrates such as creams and ointments because of the large orifice and chamber. Foam valves also are used to dispense rectal and vaginal foams. If the size of the orifice and expansion chamber are appropriately reduced, a product concentrate that would produce a foam will be emitted as a solid stream. In this case, the ball of foam begins to develop where the stream impinges on a surface.

Types of packaging

- Aerosol Foam pressurised containers which contain propellant which aid in expulsion of the product concentrate
- Foam Pump without the use of propellant but special type of valve and actuator

Foam Aerosol		Foam Pump	
			
Propellant: 6-10 %			
Pressure (psig at 20°C) 35 – 55			
Emulsion : give rich thick texture, used for damaged sensitive skin condition (stable foam)		Microemulsion, Light texture , quick absorption without residue (Breaking foam) Covientent for hairy skin	
Used for psoriasis, atopic skin		Used for acne, inflammation	

Physicochemical drug interactions and incompatibilities

Physiochemical Principles of Pharmacy

Alexander T Florence, David Attwood

4th Edition Chapter 10 (2006)

5th Edition Chapter 11(2011)

Objectives:

This topic discusses the drug interactions from a physicochemical rather than a pharmacological or pharmacodynamic viewpoint.

Sometimes the interaction is beneficial and sometimes not. In reading this topic, you should appreciate that there are several causes of interactions and incompatibilities, which include:

- pH effects – changes in pH which may lead to precipitation of the drug
- Change of solvent characteristics on dilution, which may also cause precipitation
- Cation – anion interactions in which complexes are formed
- Salting-out and salting-in – the influence of salts in decreasing or increasing solubility, respectively
- Chelation – in which a chelator molecule binds with a metal ion to form a complex
- Ion-exchange interactions – in which ionised drugs interact with opposites charged resins
- Adsorption to excipients and containers – causing loss of drug
- Interactions with plastics – another source of loss of material

Drug Incompatibility

Drug–drug or drug–excipient interactions can take place before administration of a drug.

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 (affect appearance of a medicine) or the precipitation of the drug from solution, may lead loss of potency or instability.

Types of Incompatibility

Incompatibility is an undesirable reaction that occurs between the

- Drug and the solution, solvent
- Drug and the container
- Another drug. (Drug –drug interactions)
- Drug -excipient interaction

With the decline in traditional forms of extemporaneous dispensing, this aspect of pharmaceutical incompatibility may seem to have decreased somewhat in importance, but other forms of extemporaneous preparation occur today.

One example is the addition of drugs to intravenous fluids, a practice which should be carried out with pharmaceutical oversight to avoid incompatibilities and instabilities, particularly with new drugs and formulations and during clinical trials.

- The two types of incompatibilities are:
 - Physical Result in decrease in solubility (precipitation), Loss of potency,
 - Chemical Result in Chemical instability, complexation. They can occur even in the solid state under some circumstances.

Physical Incompatibility

Solubility

Precipitation of drugs in vitro

Example 1. 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.

Example 2 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

Example 3 Addition of high concentration of alcohol to syrups or to colloidal dispersions may cause precipitation (examples: mixing of elixirs with syrups, addition of topical clindamycin solution to isotretinoin gel, etc.)

Precipitation of drugs in vivo

Pain on injection may be the result of precipitation of a drug at the site of injection brought about by either solvent dilution or by alteration in pH.

- Precipitation of drugs from formulations used intravenously can lead to thromboembolism.
- If the rate of infusion is sufficiently slow, precipitated drug may redissolve and so this problem is avoided.

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 precipitate 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.

When a drug dissolved in a cosolvent system is diluted with water, both drug and cosolvent are diluted. The solubility of a drug in a cosolvent system generally increases with the percentage of cosolvent present.

On dilution, the soluble drug concentration falls with a fall in the percentage of cosolvent. When the drug concentration is high, the system may become **supersaturated** on dilution, causing precipitation.

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
- Some dosage forms are unaffected by this phenomenon such as:
- Menthol and thymol inhalation
 - Camphor and menthol ointment

- For certain conditions like powders and capsules, it is advised to triturate with an adsorbent powder such as light kaolin or light magnesium carbonate separately before combining them.

Note

Some drugs designed to be administered by the intravenous route cannot safely be mixed with all available intravenous fluids. If the solubility of a drug in a particular infusion fluid is low, crystallisation may occur (sometimes very slowly) when the drug and fluid are mixed. Microcrystals may be formed which are not immediately visible. When infused, these have potentially serious effects.

Chemical incompatibility

Chemical instability may give rise to the formation of inactive or toxic products.

This type of chemical incompatibility is generally caused by:

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

Effect of pH

In vitro 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 (pH_p : pH limit of solubility)
2. The pH of the solution
3. The pK_a of the acid or the base
4. Buffering capacity

Coadministration of drugs with fluids other than water

The solubility of an ionisable drug is strongly influenced by the pH of the solution because of the effect of pH on the ionisation of the drug.

Undissociated drugs cannot interact with water molecules to the same extent as ionised drugs, which are readily hydrated and therefore more soluble. A change of pH can therefore sometimes lead to precipitation of ionised drugs.

A. Solanaceous alkaloids.

- Atropine solubility is 1 g in 400mL. Belladonna tincture contains 0.3mg alkaloids /1mL so the maximum volume of water required to dissolve 0.3mg of alkaloids is $\frac{1000mg}{400ml} = \frac{0.3mg}{X}$ X= 0.12ml
- Therefore, there is no risk of ppt. in alkaline conditions when given with soda drink

B. Barbiturates

Solutions of barbiturates salts are very alkaline and have limit pH solubility and are incompatible with acids, acidic salts such as (ammonium bromide), and acidic syrups (lemon syrup) it will precipitate when given simultaneously.

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

pH and dispersed system

At low pH (lower than the pKa) dispersions of anionic polymer such as Carbomer or sodium CMC lose viscosity very rapidly

Below pH 3 alginic acid will precipitate from dispersions of sodium alginate,

Strong acids will precipitate CMC from mucilage of sodium 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 precipitation and/or degradation of the active ingredient may occur

Mixing drugs in I.V. fluids

Although infusion times are generally not greater than 2 h, chemical changes following a change in pH may occur rapidly. pH changes often follow from the addition of a drug substance or solution to an infusion fluid. An increase or decrease in pH may then produce physical or chemical changes in the system.

The pH of commercial available NaCl I.V. fluid is ~5.4 and of 5% dextrose water is~ 4.5

For example, as little as 500 mg of ampicillin sodium may raise the pH of 500 cm³ of some fluids to over 8, and carbenicillin or benzylpenicillin may raise the pH of 5% dextrose or dextrose saline to 5.6 or even higher. Both drugs are, however, stable in these conditions.

Chemical instability may give rise to the formation of inactive or toxic products. This increase or decrease in pH may then produce physical or chemical changes in the system. The titratable acidity or alkalinity of a system may be more important than pH itself in determining compatibility and stability.

The solubility of calcium and phosphate in total parenteral nutrition (TPN) solutions independent on the pH of the solution. TPN solutions are, of course, clinically acceptable only when precipitation can be guaranteed not to occur.

Dibasic Calcium Phosphate	Monobasic Calcium Phosphate
CaHPO_4 (pKa =7.2)	$\text{Ca}(\text{H}_2\text{PO}_4)_2$
Solubility 0.03%w/v at pH 7.4 (60%)	Solubility 1.8%w/v in acidic media < pH 5 (90%)

At low pH the monobasic form predominates, while at higher pH values (physiological pH) the dibasic form becomes available to bind with calcium and precipitates tend to form.

- Calcium phosphate I.V. solution is of low pH
- Discard I.V. admixture with precipitation immediately,
- Discard any I.V. admixture after 24hr of mixing

***In vivo* pH effects**

Gastric pH is 1-3 in normal subjects, this pH has a marked influence on the absorption and thus on the activity of drugs. Ingestion of antacids, food, and weak electrolytes will all change the pH of the stomach. Weakly acidic drugs, being unionised in the stomach, will be absorbed from the stomach by passive diffusion. One might expect, therefore, that concomitant antacid therapy would delay or partially prevent absorption of certain acidic drugs. The main mechanism would be an increase in pH of the stomach, increasing ionisation of the drug and reducing absorption.

Drugs whose absorption may be affected by antacid administration	
Drug whose activity would be reduced	Drug whose activity would be potentiated
Tetracyclines Nalidixic acid Nitrofurantoin Benzylpenicillin Sulphonamides	Chloroquine Theophylline Mecamylamine Amphetamine Levodopa

- Levodopa is metabolised within the gastrointestinal tract and more rapidly degraded in the stomach than in the intestine, so the rate at which the drug is emptied from the stomach can affect its availability.
- The use of cimetidine, ranitidine, nizatidine, famotidine and other H₂ antagonists' drugs inhibit gastric acid secretion, so increase in absorption of acid-labile drugs is predictable.
- The aqueous solubility of tetracycline at pH 1-3 is a hundred-fold greater than at pH 5-6. Co administration with sodium bicarbonate will decrease the solubility of tetracycline.

- Increasing the pH of the stomach increasing ionization of acidic drugs (Tetracycline, Nalidixic acid, Nitrofurantoin, Benzyl penicillin, sulphonamides) thus reducing absorption

Cation- anion interactions

The interaction between a large organic anion and an organic cation may result in the formation of a relatively insoluble precipitate.

- Gentamicin sulphate and heparin sulphate groups interfere with the anticoagulant activity of heparin
- Cloxacillin sodium and ephedrine HCl
- 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)
- Cationic dyes may be ppt. by soaps and clays
- Ceftriaxone is incompatible with any I.V. fluid containing Calcium salts, (Ringer, Ringer Lactate)

Chelation

The term chelation is 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, activity of the drug may be reduced

Act as a reservoir of drug to prolong drug release

Reduced irritancy and improve stability (Povidone iodine)

- 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 for teeth discoloration or bone deformation in growing babies
- Chelation of ciprofloxacin and other quinolones by aluminium hydroxide and calcium carbonate reduces bioavailability
- Desferrioxamine (as the mesylate) is used as a drug to sequester iron in iron poisoning or chronic iron overload
- penicillamine is similarly used to aid the elimination of copper in Wilson disease.

Adsorption

Adsorbents generally are nonspecific (such as charcoal, cholestyramine, bentonite, kaolin, pectin,) so will adsorb nutrients, drugs and enzymes when given orally. If the drug remains adsorbed until the preparation reaches the general area of the absorption site, the concentration of the drug presented to the absorbing surfaces will be much reduced.

- A delayed absorption of lincomycin was observed when administered with kaolin and pectinic acid (Kaopectate)
- Talc, a commonly used tablet lubricant, has been reported to adsorb cyanocobalamin and consequently to interfere with intestinal absorption of this vitamin.

Adsorption of 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 losses in some cases. Those drugs which show a significant loss when exposed to plastic, in particular poly(vinyl chloride) (PVC), include insulin, glyceryl trinitrate, diazepam, chlormethiazole, vitamin A acetate, isosorbide dinitrate and a miscellaneous group of drugs such as warfarin phenothiazines, hydralazine hydrochloride and thiopental sodium.

Preservatives such as the methyl and propyl parabens present in formulations can be sorbed into rubber and plastic membranes and closures, thus leading to decreased levels of preservative and, in the extreme, loss of preservative activity.