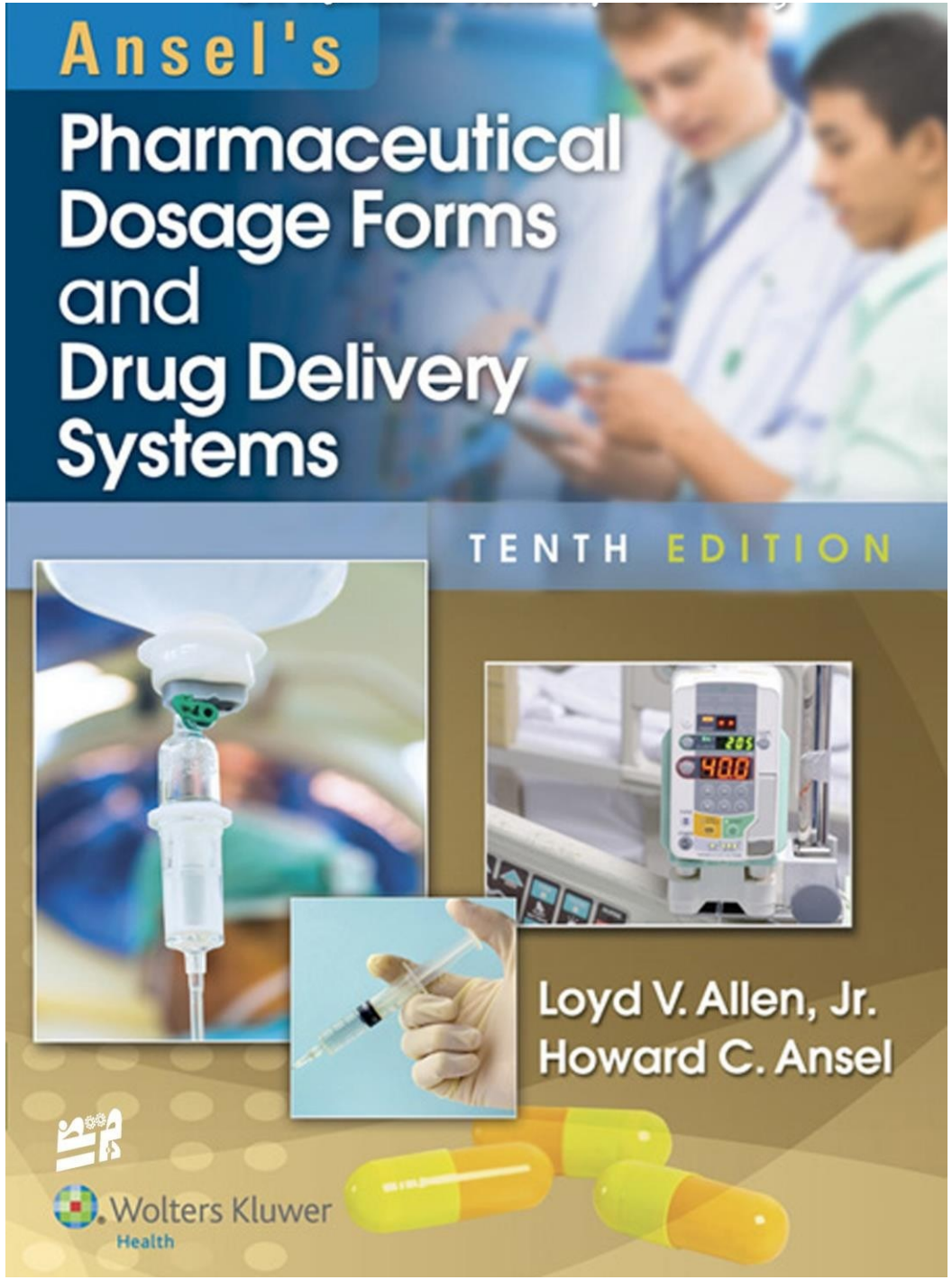
3rd Stage
2nd Semester

Pharmaceutical Technology II

Qutaiba Akram

B.Sc M.Sc in Pharmaceutical Sciences
qutaiba.ak@uoalfarahidi.edu.iq


Ansel's
Pharmaceutical Dosage Forms and Drug Delivery Systems
TENTH EDITION
Loyd V. Allen, Jr.
Howard C. Ansel
Wolters Kluwer
Health

Pharmaceutical Technology II Syllabus

Emulsions

Lotions, liniments

Semisolids (creams, ointments and gels)

Transdermal patches

Suppositories

Powders

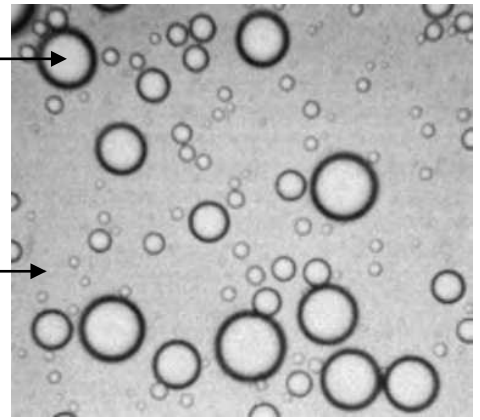
Capsules

Pharmaceutical incompatibilities

Emulsions

An emulsion may be defined as a preparation consisting of two immiscible liquids usually water and oil, one of which is dispersed as small globules in the other.

The formation and stabilisation of an emulsion is made possible by the incorporation of a third substance 'the emulsifying agent'

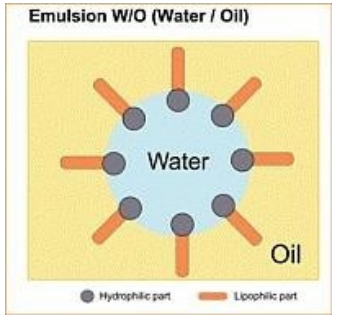


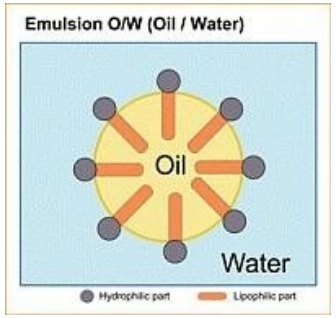
Mineral oil in water emulsion

The dispersed phase is referred to as the internal phase and the dispersion medium as the external or continuous phase.

Two distinct types of emulsions may exist:

1. A product in which oil is dispersed as globules in water (o/w)
2. Water is dispersed as globules in the oil phase (w/o)





Purpose of Emulsions and of Emulsification

- The process of emulsification enables the pharmacist to prepare relatively stable and homogeneous mixtures of two immiscible liquids.

  (i.e. The reason for emulsification centres around the desirability of administering both aqueous and oil soluble substances in the same mixture).

- For orally administered emulsions, the o/w emulsion permits the palatable administration of distasteful oil by dispersing it in a sweetened flavoured aqueous vehicle.

(i.e. masking the disagreeable taste and oily sensation which often accompany the oral administration of a drug. Flavouring agents may be added to the external aqueous phase of the emulsion to increase the palatability.

- It permits the administration of a liquid drug in the form of minute globules rather in bulk.

The reduced particle size of the oil globules may render the oil more digestible and more readily absorbed (more effective in its task) for example, the increased efficacy of mineral oil as a cathartic when in the emulsified form.

Based on the use to which they may be put, emulsions are divided into two groups:

1. Emulsions for internal use (orally or by I.V. injection)
2. Emulsions for external use (skin or mucous membrane)

Orally Administered Emulsions:

Pharmaceutical emulsions which are given orally are of (o/w) type.

Intravenous Injection of Emulsions

Parenterally administered emulsions require special care during manufacture, the choice of the emulsifying agent, the size and the uniformity of the globules are critical in preparations for intravenous use.

The preparation of emulsions for injection involves the formation of a coarse emulsion which is then homogenised, collected and sealed in sterile flasks and autoclaved. Finally the product is tested for sterility and for globule size e.g. (Vitamin A and vitamin K and some sex hormones).

Emulsions for External Application:

Both o/w and w/o emulsions may be applied to the surface of the skin and the mucous membranes. By the process of emulsification it is possible to produce a lotion or a cream that has the proper consistency, spreads well over an affected area and washed easily, does not stain clothing and is attractive to patient.

Emulsions to be applied to the skin may be o/w or w/o depending on the nature of the therapeutic agent, condition of skin and the desirability for an emollient or tissue softening effect.

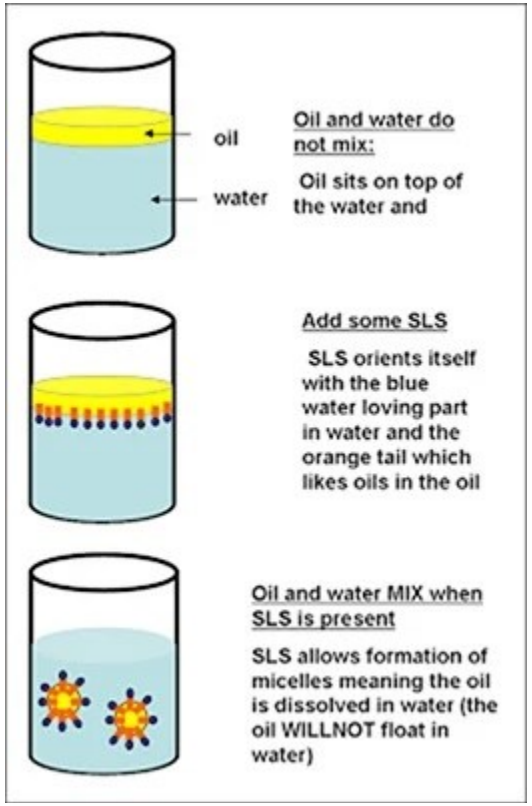
Medicinal agents that irritate the skin are less irritating in the internal phase of an emulsion than in external phase.

Note: A w/o emulsion can be applied more evenly because the skin is covered with a film of sebum and this surface is more readily wetted by oil than by water. In addition, w/o emulsion is also more softening to the skin because it resists drying out and removal by contact with water

Theories of emulsification

1. **Surface tension theory**

The use of emulsifiers lower the interfacial tension of the two immiscible liquid, reducing the repellent force between the liquids and diminishing each liquid's attraction for its own molecules. Thus, the surface active agent facilitates the breaking up of large globules into smaller ones which then have a lesser extent to coalesce.



2. **Oriented-wedge theory**

It assumes monomolecular layer of EA curved around a droplet of the internal phase of the emulsion.

3. **Plastic or interfacial film theory**

It places the EA at the interface between the oil and water, surrounding the droplet of the internal phase as a thin layer of film adsorbed on the surface of the drops. The film prevents contact and coalescing of the dispersed phase.

Note: It is unlikely that a single theory of emulsification can explain the means by which the EAs promote emulsion formation and stability. More than one theory plays a part, for example lowering of the interfacial tension is important in the initial formation of emulsion but the formation of a protective wedge of molecules or film of emulsifier is important for continued stability.

Composition of an Emulsion

❑ The Aqueous Phase

Water is usually used as aqueous phase. In addition, the aqueous phase may contain water soluble drugs, preservatives, colouring and flavouring agents.

Distilled water or deionised water is often used in emulsions, since calcium and magnesium ions of hard water and other electrolytes may have an adverse effect on the stability of some emulsions, particularly those containing soaps as emulsifying agents.

Examples of drugs which are added to the aqueous phase of an emulsion are **potassium iodide**, **ammonium chloride** and **chloral hydrate**.

❑ The Oil Phase

The oil phase of an emulsion consists of fixed or volatile oils, resins, waxes and fats. It may contain oil-soluble drugs such as **phenyl salicylate**, **camphor** and **oil- soluble vitamins**. Sometimes an antioxidant is added to prevent rancidity of the oil and destruction of the drugs for example vitamin E.

❑ The Emulsifying Agent (EA)

In the absence of an emulsifying agent, oil can be dispersed in water to the maximum extent of about 2%. Emulsifying agents are required for the preparation and the stabilisation of the more concentrated emulsions containing about 10-80% of internal phase.

Emulsifying agents are particular type of surfactants that:

1. Reduce the interfacial tension between oil and water, thus aid in the dispersion of one liquid in the other.

2. Envelop the globules in a sheath to prevent coalescence and separation of the dispersed liquid as a distinct layer.

Ideal characteristics of Emulsifying agents

❖ It must be compatible with the other formulative ingredients and must not interfere with the stability or efficacy of the therapeutic agent.

- It should be stable and not deteriorate in the preparation.
- It should be nontoxic with respect to its intended use and the amount to be consumed by the patient.
- It should possess little odour, taste, or colour.
- It should be capable to promote emulsification and maintain the stability of the emulsion for the intended shelf life of the product.

Emulsifying agents can be divided into three groups (**Natural, synthetic and finely divided solids**)

1. Natural Emulsifying Agents

e.g. acacia (Arabic gum), tragacanth, gelatin, starch and pectin.

Acacia generally produces o/w emulsions which are not viscous enough to prevent the rapid rise of the globules with subsequent formation of a cream layer on the surface of the emulsion. Thickening agents such as agar and tragacanth sometimes are added to acacia emulsions to minimise the creaming effect.

Gelatine used as an emulsifying agent. It is a negatively charged colloid at pH values above its iso-electric point and it is a positively charged at pH values below the iso-electric point.

Since the oil globules in an o/w emulsion are negatively charged, gelatine is readily adsorbed on the surface of the particles if the pH is below the iso-electric point.

The iso-electric point of gelatine varies with the origin of the product. Gelatine (Type A) which is obtained from an acid-treated precursor has an iso-electric point between pH (7 and 9) acts best as an emulsifying agent at pH 3.2 at which it is positively charged.

Gelatine from an alkali-treated precursor (Type B) has an iso-electric point between pH (4.7 and 5) and is used at pH 8 at which it is negatively charged.

The disadvantage of gelatine is that the emulsions prepared from it are too fluid and become more fluid upon standing.

2- Synthetic Emulsifying Agents

Synthetic emulsifiers are superior to natural gums and proteins in that they are not susceptible to decomposition by micro-organisms. Furthermore, the ratio of hydrophilic to lipophilic groups in the molecule may be altered to supply a wide range of emulsifying agents.

Only a limited number of synthetic agents are safe for internal use among these are the sorbitan esters (Spans), polyoxyethylene sorbitan esters (Tweens) and glyceryl monostearate.

A- Anionic Emulsifying Agents

This class includes monovalent, polyvalent, organic soaps, sulphates and sulphonates.

Soaps have a disagreeable taste and produce an irritating and laxative action in the intestinal tract, consequently they are not used in orally administered emulsions.

The alkali soaps including sodium, potassium and ammonium salts of lauric, palmitic, stearic and oleic acid are hydrophilic and form o/w emulsion.

The metallic soaps of calcium, magnesium, zinc and aluminium salts of fatty acids are water insoluble and tend to promote w/o emulsions.

Monovalent soaps tend to form o/w emulsions, where as polyvalent soaps form the w/o type.

Organic soaps (amino soaps) such as triethanolamine oleate produce o/w emulsions. They have the advantage over inorganic soaps in that they represent a better balance between hydrophilic and lipophilic groups and the final emulsion is fine-grained and stable.

Sodium lauryl sulphate is an example of sulphonate group used as anionic emulsifying agent.

B- Cationic Emulsifying Agents

Cationic EAs are those in which the action is dependent on the cationic or positively charged group. Benzalkonium chloride is an important member of this class.

Cationic agents have marked bactericidal properties and are used primarily as local anti-infective rather than as emulsifying agents. They must not come in contact with anionic chemicals such as soaps, since the two types are incompatible. The active group of the cationic agent combines with the anion and although precipitation may not be evident immediately when the substances are used in low concentrations, the germicidal action of the cationic agent is destroyed and the emulsifying property of the anionic emulsifier may be impaired.

C- Non-ionic Emulsifying Agents

The entire undissociated molecule of certain chemicals containing hydrophilic and lipophilic groups on proper balance may act as an EA.

Included in this group are glyceryl esters, fatty acid esters of sorbitan and polyethylene glycol esters.

An important group of non-ionic agents are obtained by partial esterifying the anhydrides derived from sorbitol and other sugar alcohols with various fatty acids. Sorbitan laurate, palmitate, stearate and oleate constitute the series of **Spans**.

Spans are lipophilic in nature and therefore they tend to form w/o emulsions.

The polyoxyethylene derivatives of Spans, known as **Tweens** are water soluble or dispersible and favour the formation of o/w emulsions.

3- Finely Divided Solids

Colloidal clays such as bentonite, veegum, magnesium hydroxide, aluminium hydroxide, magnesium oxide and silica gel are some of the insoluble substances that have been used as emulsifying agents.

The finely divided solids form and stabilise emulsions by concentrating at the interface where they produce a coherent film around the globules and prevent coalescence of the internal phase.

Bentonite may be used to form either an o/w or w/o emulsions depending on the order of mixing.

Methods of Emulsification

Emulsions can be prepared by several methods depending on the nature of the emulsion components and the equipment available for use.

1. Dry Gum Method

(Addition of the external phase to the internal phase containing the EA).

It involves mixing the oil and the powdered acacia in a dry Wedgewood or porcelain mortar, triturating the mixture until the powder is distributed uniformly throughout the oil, then adding a measured portion of water all at one time, followed by rapid trituration to form the nucleus or primary emulsion and finally adding water and other ingredients to complete the product.

The primary emulsion formed with 4 parts by volume of fixed oil, 2 parts by volume of water and 1 part by weight of acacia (4 : 2 : 1) method.

2. Wet Gum Method

(Addition of the internal phase to the external phase containing the EA)

This procedure involves the addition of oil to an aqueous solution of the emulsifying agent. The proportion of fixed oil, water and acacia for the preparation of the primary emulsion is the same ratio used in the dry gum method (4 : 2 : 1).

Water is added all at once to acacia in a Wedgewood or porcelain mortar and the mixture is triturated by light rapid movement of the pestle until a smooth mucilage is formed.

The oil is added slowly in small increments with continuous trituration, so that each portion is distributed and emulsified in the mucilage before the next quantity is added.

The primary emulsion is triturated for at least 5 minutes to ensure complete dispersion of the oil and then it is diluted with water to the required volume.

3. Bottle Method

This method can be used for small-scale emulsification of volatile oils and other liquids of low viscosity. The ratio of volatile oil, water and acacia is 2:2:1, the proportion of acacia being greater than that used for fixed oils because of the low viscosity of the oils.

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.

4. In Situ Soap Method

Liniments and lotions may be prepared in a bottle by this method. According to this method, an oil containing sufficient free fatty acid such as linseed or olive oil is placed in a bottle and an equal volume of alkali such as calcium hydroxide solution is added. When the mixture is shaken, the fatty acid of the oil reacts with the alkali to form a calcium soap (EA is calcium oleate) which promotes a w/o emulsion. The soap formed in situ (i.e. at the time of mixing) which is called Nascent soap and the emulsification procedure is called the Nascent soap method and it may be used to prepare either o/w or w/o emulsions.

e.g. Calamine liniment

Calamine	80 g
Zinc Oxide	80 g
Olive Oil	1000 mL
Calcium Hydroxide Solution	1000 mL

Factors influencing Emulsion type

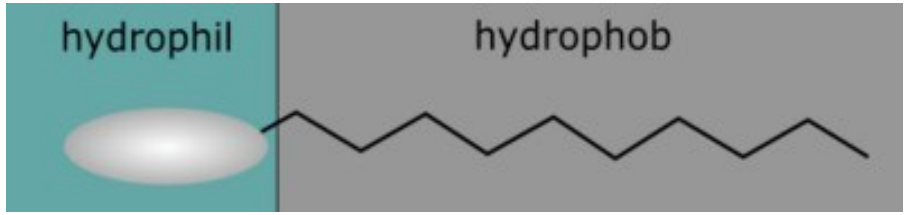
1. The ratio of the two phases.
2. The type of the EA.
3. The order of mixing.

The relative volume of the internal and external phases of an emulsion is important, as the internal phase concentration is increased, there is an increase in the viscosity of the emulsion to certain point, after which the viscosity decreases sharply. At this point, the emulsion has undergone inversion that is it has changed from an o/w emulsion to w/o or vice versa and even it may break. Emulsions may be prepared without inversion with as much as about 75% of the volume of the product being internal phase.

The HLB System

The hydrophilic-lipophilic balance (HLB) of the molecule determines the type of activity which may be expected of the agent. The compound will serve as a wetting agent, a detergent, a solubilising agent, an o/w or w/o emulsifying agent depending on the HLB.

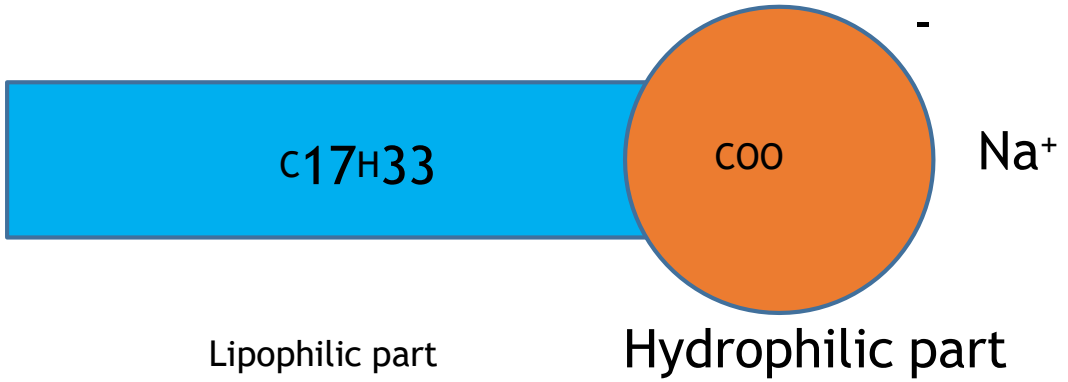
Each EA containsa water-attracting (hydrophilic part) and an oil-attracting (lipophilic part).



If the agent is too hydrophilic it dissolves completely in the aqueous phase and exerts no effect at the interface. If it is too lipophilic it dissolves completely in the oil phase and does not concentrate at the interface.

The molecule of a well-balanced emulsifying agent when dispersed initially in the oil or the aqueous phase, it will migrate to and concentrate predominantly at the interface, where it is oriented with the hydrophilic portion in the water and the lipophilic portion in the oil. An EA which displays these properties is said to have the proper HLB.

If an EA is hydrophilic it will tend to form an o/w emulsion, if it is lipophilic it will favour the formation of a w/o emulsion. Sodium oleate has a good o/w EA characteristics since it possesses a hydrophilic carboxyl group (COO^-) that predominates over the lipophilic hydrocarbon group ($C_{17}H_{33}$).



On the other hand, calcium oleate and other polyvalent soaps are predominantly lipophilic and form w/o emulsions.

The hydrophilic-lipophilic balance of surface active agents has been expressed in terms of a numerical scale that extends from 1-50 but the usual range is between 1-20.

An agent with a low HLB is lipophilic, while a surfactant a surfactant having a higher HLB is hydrophilic. For the preparation of a w/o emulsion, the EA should have an HLB value of about (3-6). An o/w emulsion on the other hand is favoured by an EA with HLB value of about (8-18).

ACTIVITY AND HLB VALUE OF SURFACTANTS

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

In practice, Span and Tween usually are mixed to provide an emulsifier combination that has the HLB necessary to produce a stable emulsion of the desired type.

By knowing the required HLB of the oil phase, one may calculate the quantities of any Span and Tween that are necessary to produce the proper balance for a stable emulsion.

Each oil requires an EA of a specific HLB value for the formation of an o/w emulsion and another value for the formation of a w/o product. These are known as the "required HLB" values of the oil.

In the HLB system, in addition to assigning values to the EAs values are also assigned to oils. In using the HLB concept in the preparation of an emulsion, one selects EAs having the same or nearly the same HLB value as the oil phase of the intended emulsion.

For example, mineral oil has an 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. Therefore, to prepare a stable emulsion the EA should have an HLB value similar to the one of mineral oil depending on the type of emulsion required. When needed two or more EAs may be combined to achieve the proper HLB value.

Mixed EAs or a blend of emulsifiers is more efficient to give a stable emulsion than either each agent alone. The mixture contributes one or several actions:

1. It provides the proper hydrophilic-lipophilic nature.
2. It establishes a stable film at the interface.
3. It supplies the desired consistency to the product.

Mixed EAs tend to form interfacial complexes at the surface of the globules, for example the o/w emulsifying action of sodium oleate is improved by combination with cetyl alcohol or cholesterol through the tendency of the molecules to form a complex.

Tragacanth or agar are frequently combined with acacia to thicken the external phase of an o/w emulsion and reduce the rate of creaming. Pectin, alginates and cellulose esters are used as well for this purpose.

HLB VALUES FOR SELECTED EMULSIFIERS

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

Rx

Mineral oil		8 g
E.A. (Span 80 + Tween 80)		2 g
Purified water	q.s.	100 mL

The required HLB for the mineral oil = 10.5, the HLB for Span 80 = 4.3 and the HLB for Tween 80 = 15.

How much Span 80 and Tween 80 are required to produce a stable emulsion?

F_S * HLB s + F_T * HLB_T = Required HLB of the oil

Let the fraction of Span = X

Let the fraction of Tween = 1-X

X*4.3 + (1-X)*15 = 10.5

10.7 X = 4.5

X= 0.42 fraction of Span

Amount of Span = 2 * 0.42 = 0.84 g

1-X = 1- 0.42 = 0.58 fraction of Span

Amount of Tween = 2 * 0.58 = 1.16 g

Let the fraction of Tween = X

Let the fraction of Span = 1-X

(1-X)*4.3 + X*15 = 10.5

10.7 X = 6.2

X= 0.58 fraction of Tween

Amount of Tween = 2 * 0.58 = 1.16 g

1-X = 1- 0.58 = 0.42 fraction of Span

Amount of Span = 2 * 0.42 = 0.84 g

Types of Emulsifying Agents

1. **Carbohydrate materials**, such as acacia, tragacanth, agar and pectin. These materials form hydrophilic colloids when added to water and generally produce o/w emulsions.
2. **Protein substances**, such as gelatine, egg yolk. These substances produce o/w emulsion.
3. **High molecular weight alcohols**, such as stearyl alcohol, cetyl alcohol and glyceryl monostearate. These substances are employed primarily as thickening agents and stabilisers for o/w emulsions used externally. Cholesterol and cholesterol derivatives may also employed in externally used emulsions to promote w/o emulsions.
4. **Wetting agents**, which may be anionic, cationic or non-ionic. The non-ionic surfactants are effective over pH range (3-10), cationic surfactants are effective over pH range (3-7) and anionic surfactants require a pH greater than 8.

5. **Finely divided solids**, such as colloidal clays including bentonite, magnesium hydroxide and aluminium hydroxide. These substances can form either o/w or w/o emulsions depending on the order of mixing.

Examples of oral emulsions

1. Castor oil Emulsion (o/w): This emulsion is utilised as a laxative. Castor oil works directly on the small intestine to promote bowel movement.
2. Simethicone Emulsion (o/w): used as a defoaming agent for the relief of painful symptoms of excess gas in the GIT. Available in drop form for infants.

- Sterile vitamin K Emulsion (o/w) for I.V. administration.

Deterioration and preservation of Emulsions

One of the most important properties of emulsions is the stability of the finished product.

A stable emulsion is characterised by:

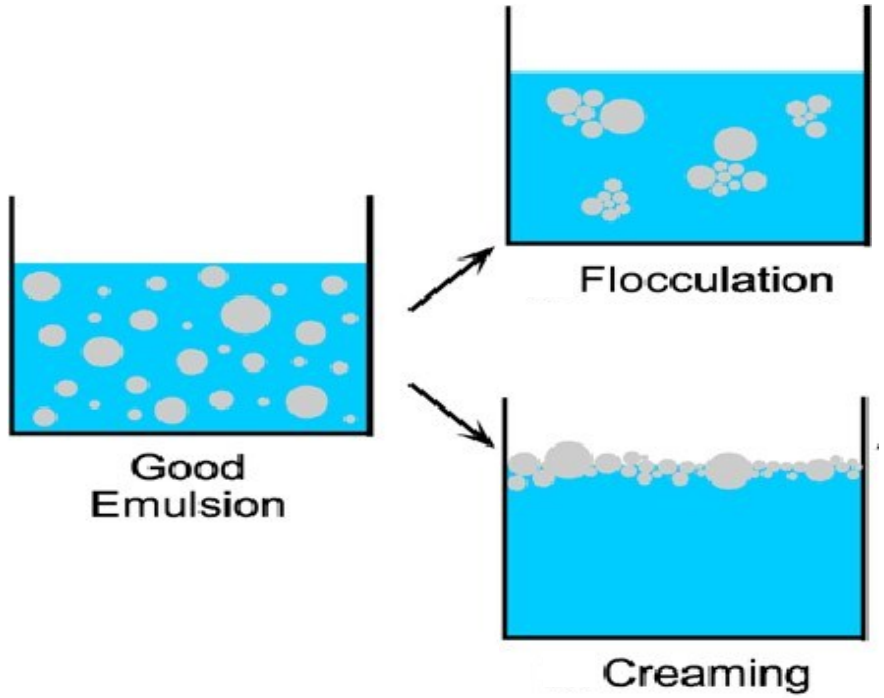
1. The absence of flocculation and creaming.
2. The absence of coalescence of globules and the separation of the internal phase from the emulsion.
3. The absence of deterioration by microorganisms.
4. Maintenance of elegance with respect to general appearance, odour, colour and consistency.

1. Flocculation and creaming

Flocculation is the joining together of globules to form large clumps of floccules, which rise or settle in the emulsion more rapidly than do the individual particles.

The passage of an emulsion through an orifice at a high pressure sometimes results in flocculation.

Creaming is the rising (upward creaming) or settling (downward creaming) of floccules to form a concentrated layer at the surface or at the bottom of the emulsion.



Creaming is regarded as a mark of instability in pharmaceutical emulsions. Creaming results in a lack of uniformity of the product and unless the container is agitated thoroughly before each dose, it may lead to variations in the amount of drug which is administered. Furthermore, the appearance of the emulsion is affected by creaming.

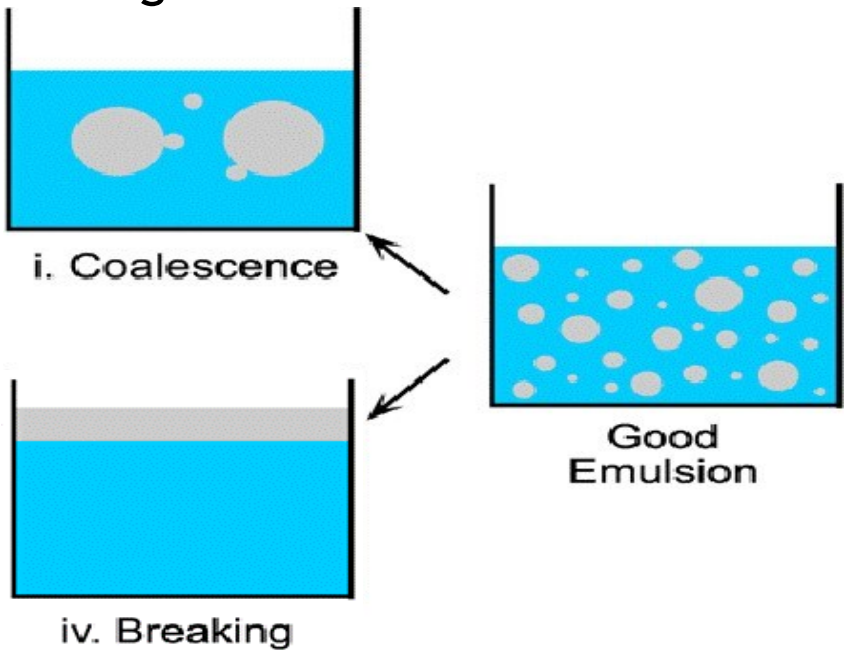
Reducing the particle size by passing the emulsion through a homogeniser decreases the velocity of creaming but homogenisation under high pressure sometimes leads to flocculation and the large clumps which are formed may cream rapidly than individual globules in the unhomogenised emulsion.

2. Coalescence and breaking

Unlike creaming, the coalescence of globules and the subsequent breaking of an emulsion are irreversible processes.

Under the conditions of creaming, the globules are still surrounded by a protective sheath of EA and may redispersed simply by agitating the product.

However, in an emulsion which has broken (i.e.) in which the phases have separated as distinct layers, simple mixing fails to re-establish the stable emulsion.



The emulsion may be reconstituted only by incorporating more emulsifying agent and passing the product through the proper emulsifying machinery.

The globules coalesce slowly or rapidly depending on the strength of the emulsifier film, until the product is completely cracked (broken).

Although many properties such as low interfacial tension and increased viscosity have been suggested as stabilising factors, its generally agreed today that the most significant element in stabilising an emulsion against breaking is the emulsifier film surrounding the dispersed particles.

If the EA is adsorbed and oriented at the interface in a manner such as to form a tough, coherent barrier, the film will withstand the tendency of the globules to coalesce and the emulsion will remain stable for the desired period of time.

3. Deterioration by microorganisms

Moulds, yeasts and bacteria may bring about the decomposition of the emulsifying agents, contaminate the aqueous phase and produce rancidity of the oil phase.

A preservative should be a powerful fungistatic rather than bacteriostatic agent, since it is more likely that fungi (moulds and yeasts) may contaminate emulsions.

The presence of certain drugs such as benzoic and salicylic acid or high concentration of alcoholic solutions may provide adequate protection against microorganisms. However, it is usually desirable to add an agent which will act specifically as a preservative.

Combination of parahydroxybenzoates of methyl ester (0.1-0.2%) and (0.02- 0.05%) of propyl ester are frequently used. This combination is effective against moulds, yeasts and bacteria, as long as the EA and other formulation ingredients do not complex with preservatives to nullify their actions.

4. Miscellaneous physical and chemical changes

Care must be taken to protect emulsions against deterioration by light, extreme temperature, oxidative and hydrolytic rancidity of the oil.

Freezing and thawing result in a coarsening of globules and sometimes breaking of emulsions. High temperatures produce the same effects as well.

Light and rancidity influence the colour and odour of oils and may destroy their vitamin activity.

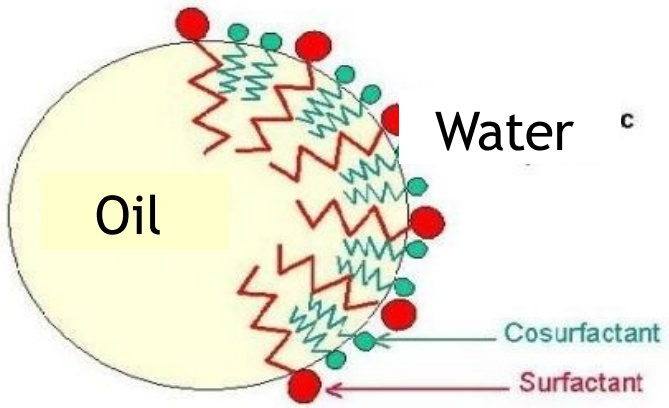
Emulsions should be kept in tight containers and stored at moderate temperature and if they affected by light they should be stored in dark containers.

Microemulsions

Microemulsions are optically transparent, thermodynamically stable, isotropic mixture of a biphasic system (oil and water) stabilised with surfactants and co-surfactants.

Microemulsion

Emulsion



Surfactant forms the interfacial film

Co-surfactant ensures flexibility of the interfacial layer which reduces the interfacial tension to a great extent

The diameter of droplets in a microemulsion may be in the range of 10-100 nm, whereas in a macroemulsion the droplet may be 0.5 μm in diameter.

Property	Emulsions	Microemulsions
Droplet size	0.2-10 μm	<100 nm
Appearance	cloudy	transparent
Preparation	requires energy input	spontaneous formation
Interfacial energy	high	very low

Both o/w or w/o microemulsions may be formed spontaneously by mixing the oil and water phases with carefully selected surfactants and co-surfactants. The type of emulsion produced depends on the proportion of each phase and the properties of the surfactants.

Hydrophilic surfactants in the HLB range of (15-18) can produce transparent o/w microemulsions of many oils including flavouring oils and vitamin oils such as A, D and E.

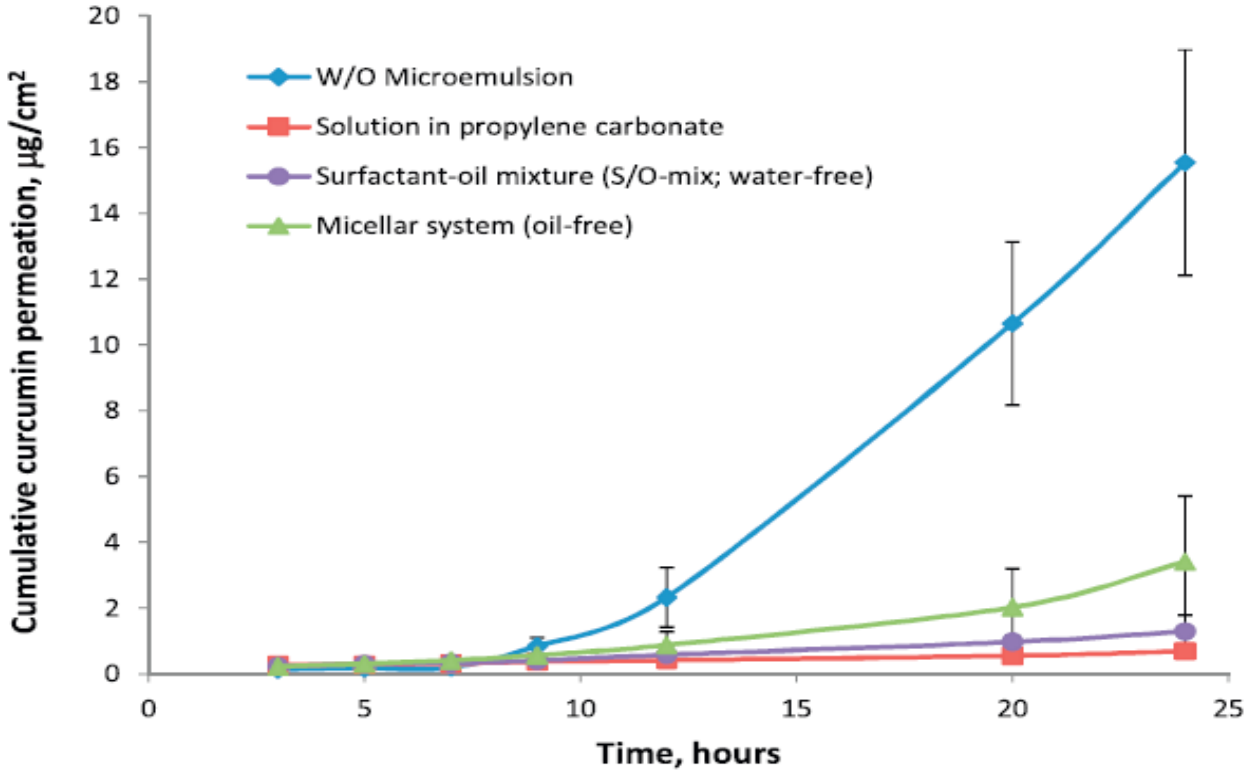
Microemulsions are dispersions of oil, not true solutions. However, because of the appearance of the product, the surfactant mixture is commonly said to solubilise the oil.

Examples of surfactants commonly used in the preparation of microemulsions are Tween 60 and Tween 80. Co-surfactants such as ethanol and propylene glycol.

Advantages of Microemulsions

1. More rapid and efficient oral absorption of drugs.
2. Enhanced transdermal drug delivery through increased drug diffusion through the skin
3. Application of microemulsions in the targeting of cytotoxic drugs to cancer cells.

Several studies have been shown the ability of microemulsions to increase transdermal drug delivery of both hydrophilic and lipophilic drugs in comparison to conventional vehicles. For example, a w/o microemulsion of curcumin has shown significantly higher skin permeation compared to a micellar system, surfactant-oil mixture and a plain solution of curcumin.



Lotions

Lotions are liquid preparations containing material for topical application. Some pharmaceutical lotions belong in the class of true solutions but most of them are suspensions or emulsions.

Medicinal lotions are used as antiseptics in the treatment of skin diseases or as cooling and mild anaesthetic preparation for skin irritation.

Since lotions may contain a suspended matter and are applied topically, they usually carry on their labels the statement “Shake well before use” in addition to “for external use only”.

Properties of good lotions

1. A lotion should pour freely from the bottle.
2. It should Applied evenly over the affected area which dries quickly and provides a protective film on the skin.

3. Lotions should also have an acceptable colour and odour.

4. They must remain physically and chemically stable and free of mould growth during storage.

Note: lotions may be sometimes preferred over semisolid preparations such as ointments and creams due to their non-greasy character and their increased spreadability over large areas of the skin.

Examples:

Benzyl Benzoate Lotion: It is an emulsion of benzyl benzoate in water (o/w) which is stabilised by the EA (triethanolamine oleate). It is used as a non-staining water washable product for the treatment of scabies and lice.

Calamine Lotion: It is a suspension of calamine in calcium hydroxide (used as a vehicle) in the presence of bentonite as the suspending agent. It is used as a mild astringent and protective coating for the treatment of skin irritation and itching such as in chicken pox.

Liniments

Liniments are oily or alcoholic liquids and semisolids for external application, usually applied with friction. This class of pharmaceuticals sometimes is referred to as embrocations because of the method of application.

Liniments can be divided into:

1. Alcoholic solutions
2. Oily solutions
3. Emulsions and suspensions

- **Alcoholic solutions:** alcohol and hydroalcoholic mixtures are used widely as vehicles for liniments, not only because alcohol is a good solvent for many drugs but also because it can penetrate the skin and it is in itself a mild rubefacient, counterirritant and astringent.

  Frequently soaps and oils are added to alcoholic liniments to make them slippery and thus facilitate the rubbing action involved in their application. The official liniments that fall into this class should be clear solutions.

e.g.

- **camphor and soap liniments** (soap liniment or camphorated tincture of soap): prepared by making a solution of camphor, rosemary oil and green soap in hydroalcoholic solvent.

This liniment makes an excellent base for other liniments (i.e. it can be used as a solvent for many substances). The percentage of alcohol present (62-66%) aiding in this respect. The small amount of camphor present gives only a mild rubefacient action.

- **Chloroform liniments:** are made by mixing chloroform with camphor and soap liniment, the addition of chloroform makes these liniments strong, quick acting rubefacient and counterirritants.

- **Oily solutions:** solutions of medicinal agents in fixed or volatile oils are used as liniments. Fixed oils are good solvents for some rubefacient drugs and also they give the necessary lubricant action for the rubbing of a liniment.

Their ability to penetrate the skin is not as great as that of alcoholic liniments, consequently their action is milder.

Cotton seed, olive, almond and other oils such as methyl salicylate and turpentine oil are rubefacient and irritant in themselves. They may be used alone or as solvents for other drugs. Like liniments of class one, they should be free from insoluble materials.

e.g. Camphor liniments (camphorated oil) is 20% solution of camphor in cotton seed oil. Cotton seed oil is preferred for making this liniment because of its lower cost. Camphorated oil is very popular counterirritant for minor sprains and also for chest colds.

- **Emulsions and suspensions:** liniments may contain insoluble materials or they may consist of mixtures of immiscible liquids, when such condition exist it is best that an emulsion be formed to prevent rapid separation of the ingredients and to improve the appearance of the product.

Emulsification of liniments usually is accomplished by the formulation of a soap which acts as the EA.

In addition to the usual label (for external use only), liniments which are emulsions or suspensions should bear the label (shake well) to ensure equal distribution of all constituents.

e.g. Ammonia liniments and calamine liniments

Thank You!

3rd Stage
2nd Semester

Pharmaceutical Technology II

Suppositories

(Part 1)

Ass. Lec. Qutaiba Akram

B.Sc M.Sc in Pharmaceutical Sciences
qutaiba.ak@uoalfarahidi.edu.iq

Suppositories

List of Content

Introduction

- **Suppositories** are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert local or systemic effects.
- **An insert** is a solid dosage form that is inserted into a naturally occurring (nonsurgical) body cavity other than the mouth or rectum, including the vagina and urethra.

Suppository and Insert Shapes

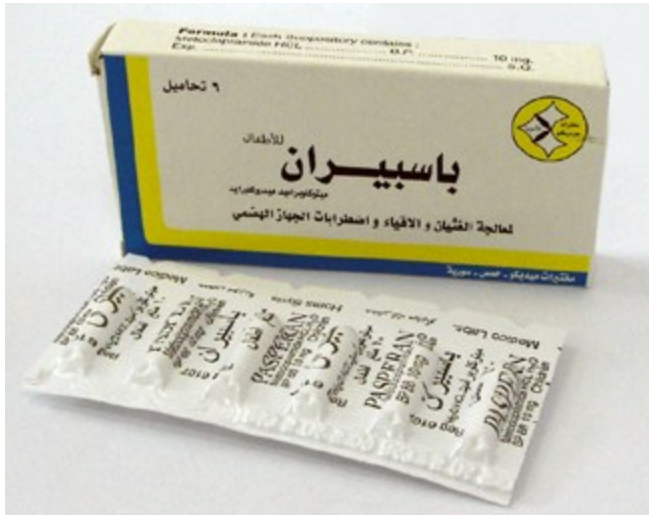
- Suppositories have various shapes and weights; the shape and size of a suppository must be such that:
  - ✓ It can be easily inserted into the intended orifice.
  - ✓ Once inserted, it must be retained for the appropriate period.

1. Rectal Suppositories

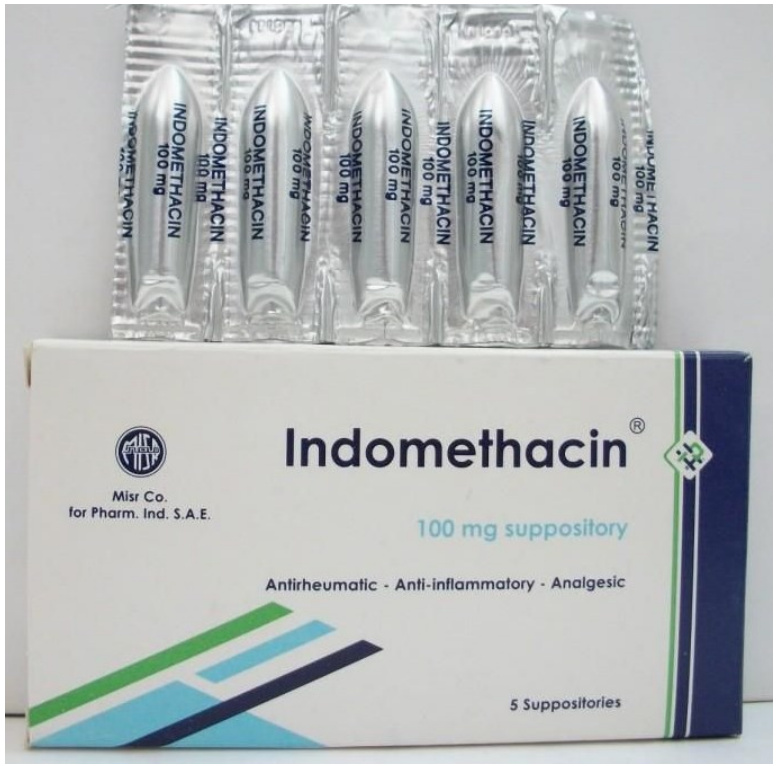
- Rectal suppositories are **inserted with the fingers**, but certain vaginal inserts (and tablets prepared by compression) may be inserted with the aid of an **appliance**.
- Rectal suppositories are usually about **3.2 cm long**, are **cylindrical**, and have one or both ends tapered. Some rectal suppositories 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 **2g** 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**.


adol
suppositories
Paracetamol 125 mg
Pain Reliever
Fever Reducer
10 suppositories
julphar


Diclogesic®
12.5 Children
Diclofenac Sodium
10 Suppositories
دار الدواء
Dar Al Dawa
Manufactured by Dar Al Dawa, Na'ur - Jordan


باسبيران


Meloxicam
5 Suppositories
Antirheumatic
Non-steroidal Anti-inflammatory
Analgesic
AMRIYA PHARM. IND.


INDOMETHACIN
100 mg
Misr Co.
for Pharm. Ind. S.A.E.
Indomethacin®
100 mg suppository
Antirheumatic - Anti-inflammatory - Analgesic
5 Suppositories


Dulcolax®
SUPPOSITORIES
10mg Bisacodyl
contact laxative
For adults/ 成人肛門塞
Untuk dewasa
5 SUPPOSITORIES/
5 个成人肛門塞 /
5 SUPOSITORI
SANOFI
Dulcolax
SUPPOSITORIES
10mg Bisacodyl for adults
Istituto De Angeli S.r.l

2. Vaginal Inserts

- Vaginal inserts, formerly called suppositories or 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 inserts may vary widely.

3. Urethral Inserts

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

List of Content

4. Suppositories Action

4.1 Local Action

- 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**.
- Rectal suppositories intended for local action are most frequently used to relieve **constipation** or **the pain**, **irritation**, **itching**, and **inflammation associated with hemorrhoids** or other anorectal conditions.
- Anti-hemorrhoidal suppositories frequently contain a number of components, including **local anesthetics**, **vasoconstrictors**, **astringents**, **analgesics**, **soothing emollients**, and **protective agents**. 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.

4.1 Local Action

- Vaginal inserts (or suppositories) intended for local effects are employed mainly as **contraceptives**, as **antiseptics** in feminine hygiene, and as specific agents to **combat an invading pathogen**.
- Most commonly, the drugs used are **nonoxynol 9 for contraception**, **trichomonacides to combat vaginitis** caused by Trichomonas vaginalis, **antifungals to treat Candida** (Monilia) albicans, and **anti-infectives/ antibiotics directed at other microorganisms**.
- Urethral suppositories may be antibacterial or a **local anesthetic** preparative for a urethral examination.

4.2 Systemic Action

- For systemic effects, the mucous membranes of the rectum and vagina permit the absorption of many soluble drugs. Although the rectum is used frequently as the site for the systemic absorption of drugs, **the vagina is not as frequently used for this purpose**.
- **Examples of drugs administered rectally in the form of suppositories for their systemic effects include:**

1. **Prochlorperazine** and **chlorpromazine** for the relief of nausea and vomiting and as a tranquilizer.
2. **Paracetamol** for analgesia.
3. **Indomethacin**, a nonsteroidal anti-inflammatory analgesic and antipyretic.

List of Content

5. Advantages & Disadvantages of Rectal Suppositories

5.1 Advantages

1) **First-pass effect**: Avoiding, at least partially, the first-pass effect that may result in higher blood levels for those drugs subject to extensive first-pass metabolism upon oral administration.

2) **Drug stability**: Avoiding the breakdown of certain drugs that are susceptible to gastric degradation.

3) **Large dose drugs**: Ability to administer somewhat larger doses of drugs than using oral administration.

4) **Irritating drugs**: Ability to administer drugs that may have an irritating effect on the oral or gastrointestinal mucosa when administered orally.

5) **Unpleasant tasting or smelling drugs**: Ability to administer unpleasant tasting or smelling drugs whose oral administration is limited.

6) **In children, the rectal route is especially useful**. An ill child may refuse oral medication and may fear injections.

7) In patients experiencing **nausea and vomiting** or when the patient is **unconscious**.

8) The presence of **disease** of the upper **gastrointestinal tract that may interfere with drug absorption.**

9) For some drugs, achievement of a **rapid drug effect systemically**.

5.2 Disadvantages

1) **Lack of flexibility** regarding dosage of commercially available suppositories resulting in underuse and a lack of availability.
2) Suppositories as a dosage form are safe, but they **exhibit variable effectiveness**, depending upon many factors to be discussed later, including the pathology of the anorectal lesions.
3) **Defecation may interrupt the absorption process of the drug**; this may especially occur if the drug is irritating.
4) The absorbing **surface area of the rectum is much smaller** than that of the small intestine.
5) **The fluid content of the rectum is much less** than that of the small intestine, which may affect dissolution rate, etc.
6) There is **the possibility of degradation of some drugs** by the microflora present in the rectum.

List of Content

6. Factors Affecting 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:
    1. The constitution of the patient (Physiological factors).
    2. The physicochemical nature of the drug and its ability to traverse the physiologic barriers to absorption.
    3. The nature of the suppository vehicle and its capacity to release the drug and make it available for absorption.
- Some drugs are absorbed better orally as compared to rectally, and some cases where the oral and rectal doses are comparable. In some cases, the doses are different, for example, **lincomycin, chloral hydrate requires four times the dose rectally as compared to orally ; phenytoin requires about three times the dose rectally as compared to orally**.

6.1 Physiological Factors

6.1.1 Circulation Route

- Unlike drugs absorbed after oral administration, drugs absorbed rectally can bypass the portal circulation during their first pass into the general circulation. **This enables drugs that are 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.

6.1.2 Colonic Content

- When systemic effects are desired from the administration of a medicated suppository, **greater absorption may be expected from a rectum that is void than from one that is distended with fecal matter**.
- A drug will have greater opportunity to make contact with the absorbing surface of the rectum and colon in the absence of fecal matter.
- 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 rectal site.

6.1.3 Lipid-Water Solubility

- **The lipid-water partition coefficient of a drug** is an important consideration in the selection of the suppository base and in anticipating drug release from that base.
- A lipophilic drug that is distributed in a fatty suppository base in low concentration has **less tendency to escape to the surrounding aqueous fluids** than a hydrophilic substance in a fatty base.
- Fatty base (e.g. cocoa butter) melts rapidly at body temperature but because of its immiscibility with rectal fluids, it fails to release fat-soluble drugs readily. Therefore, it is preferable to incorporate the ionized form (salt form) of the drug rather than the unionized (base form) of the drug **to maximize bioavailability**.

- Water-soluble bases, for example, polyethylene glycols that dissolve in the anorectal fluids, release for absorption both water-soluble and oil-soluble drugs.
- Generally, the more drug a base contains, the more drug will be available for potential absorption.

6.1.4 Particle Size

- For undissolved drugs in a suppository, the size of th**e drug particle** will influence its rate of dissolution and its availability for absorption. As indicated many times previously, 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.
- It is preferable to avoid a too fine particle size because of the high increase of the viscosity of the melted excipient that can result from the use of excessively small particles and possible difficulties in flow during production.

6.2 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 induce a bowel movement, eliminating the possibility of complete drug release and absorption.
- Long-acting or slow-release suppositories have also been prepared. Morphine sulfate in slow-release suppositories is prepared in a base that includes a material such as alginic acid, which will prolong the release of the drug over several hours.

List of Content

7. Suppository Bases

- Suppository bases play an important role in the release of the medication they hold and, therefore, in **the availability of the drug**.
- One of the first requisites for a suppository base is that **it should remain solid at room temperature but soften, melt, or dissolve readily at body temperature** so that the drug is fully available soon after insertion.
- Certain bases are more efficient in drug release than others. For instance, **cocoa butter (theobroma oil)** melts quickly at body temperature, but because it is immiscible with body fluids, 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**.

- **Fat-soluble drugs seem to be released more readily from bases of glycerinated gelatin or polyethylene glycol**, both of which dissolve slowly in body fluids.
- 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**.

- **A suppository base should be:**
  1. Physically and chemically stable.
  2. Nonirritating, nontoxic, no sensitizing
  3. Chemically and physiologically inert.
  4. Compatible with a variety of drugs.

5. Stable during storage, and esthetically acceptable.
6. It should contract slightly on cooling to release itself from the mold with requiring mold lubricants.
7. Has wetting and emulsifying properties.
8. Can be manufactured by molding by hand, machine, compression, or extrusion.
9. It should melt or dissolve in rectal fluids and should not bind or otherwise interfere with the release or absorption of drug substances.

List of Content

7.1 Classification of Supp. Bases

1) **Fatty or oleaginous bases**

2) **Water-soluble or water-miscible bases**

3) **Miscellaneous bases**

   (generally combinations of lipophilic and hydrophilic substances)

7.1.1 Fatty or Oleaginous Bases

- Fatty bases are the most frequently employed suppository bases, principally **because cocoa butter is a member of this group of substances**. Among the other fatty or oleaginous materials used in suppository bases are many hydrogenated fatty acids of vegetable oils, such as palm oil and cottonseed oil.
- Also, fat-based compounds containing compounds of glycerin with the **higher–molecular-weight fatty acids, such as palmitic and stearic acids**, may be found in fatty bases. Such compounds, such as **glyceryl monostearate** and **glyceryl monopalmitate**, are examples of this type of agent.
- 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

- Cocoa Butter, NF, is the fat obtained from **the roasted seed of Theobroma cacao**.
- At room temperature, it is a yellowish-white solid having a faint, agreeable chocolate-like odor.
- Chemically, it is a **triglyceride** (combination of **glycerin** and **one or different fatty acids**) primarily of **oleopalmitostearin** and **oleodistearin**.
- Cocoa Butter Because cocoa butter **melts at 30°C to 36°C** (86°F to 97°F), it is an ideal suppository base, melting just below body temperature and yet **maintaining its solidity at usual room temperatures**.
- However, **because of its triglyceride content, cocoa butter exhibits marked polymorphism or existence in several crystalline forms**.

Cocoa Butter

- Cocoa butter must be slowly and evenly melted, preferably over a bath of warm water, **to avoid formation of the unstable crystalline form**.
- Substances such as **phenol** and **chloral hydrate** have a tendency to lower the melting point of cocoa butter.
- If the melting point is low enough that **it is not feasible to prepare a solid suppository using cocoa butter alone as the base**, solidifying agents like cetyl esters wax (about 20%) or beeswax (about 4%) may be melted with the cocoa butter **to compensate for the softening effect of the added substance**.
- Other bases in this category include commercial products such as **Fattibase** , **the Wecobee bases**, and **Witepsol bases**.

List of Content

7.1.2 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 the 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**.
- 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**.

- Also as a result of the hygroscopicity of the glycerin, **the suppository may have a dehydrating effect and irritate the tissues upon insertion**.
- The water present 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.
- For urethral suppositories, the **gelatin constitutes about 60%** of the weight of the formula, the **glycerin about 20%,** and **the medicated portion about 20%.**
- Urethral suppositories of glycerinated gelatin are much more easily inserted than those with a cocoa butter base owing to the brittleness of cocoa butter and its rapid softening at body temperature.

Polyethylene glycols

- Are polymers of **ethylene oxide and water** prepared to various chain lengths, molecular weights, and physical states.
- They are available in a number of **molecular weight ranges**, 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**.
- Polyethylene glycol suppositories do not melt at body temperature but rather dissolve slowly in the body's fluids.

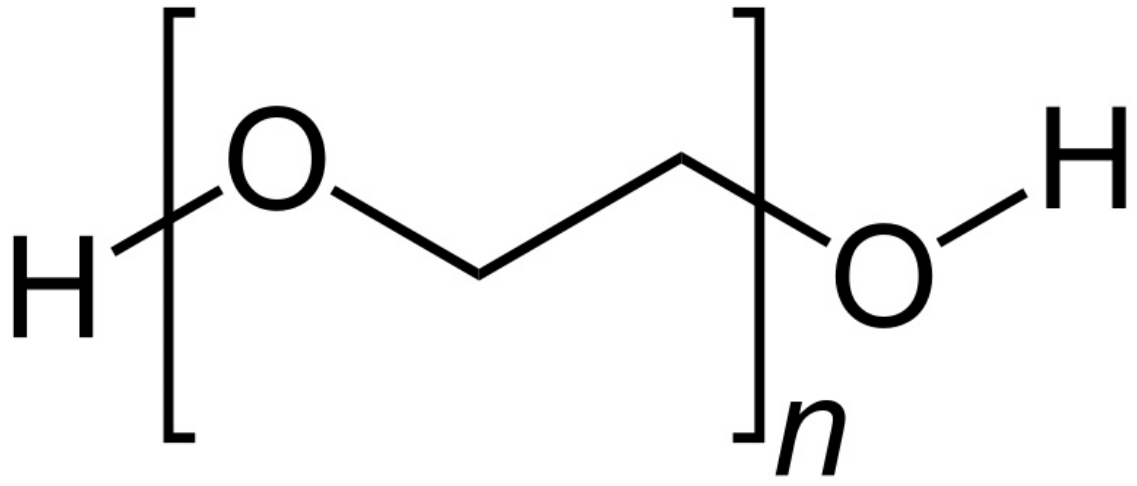
Polyethylene glycols

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

- 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).

Polyethylene glycols

- Because they do not melt at body temperature but mix with mucous secretions upon dissolution, **polyethylene glycol–based suppositories do not leak from the orifice, as do many cocoa butter–based suppositories**.
- Polyethylene glycol suppositories that do not contain at least 20% water should be dipped in water just before use **to avoid irritation of the mucous membranes after insertion**.



List of Content

7.1.3 Miscellaneous Bases

- Are mixtures of **the oleaginous and water-soluble or water-miscible materials**. They are emulsions, generally of w/o type. Mixtures of fatty bases (such as cocoa butter) with emulsifying agents capable of forming w/o emulsions have been prepared. These bases **have the ability to hold water or aqueous solutions**.

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**

Thank You!

3rd Stage
2nd Semester

Pharmaceutical Technology II

Suppositories

(Part 2)

Ass. Lec. Qutaiba Akram

B.Sc M.Sc in Pharmaceutical Sciences
qutaiba.ak@uoalfarahidi.edu.iq

Suppositories

List of Content

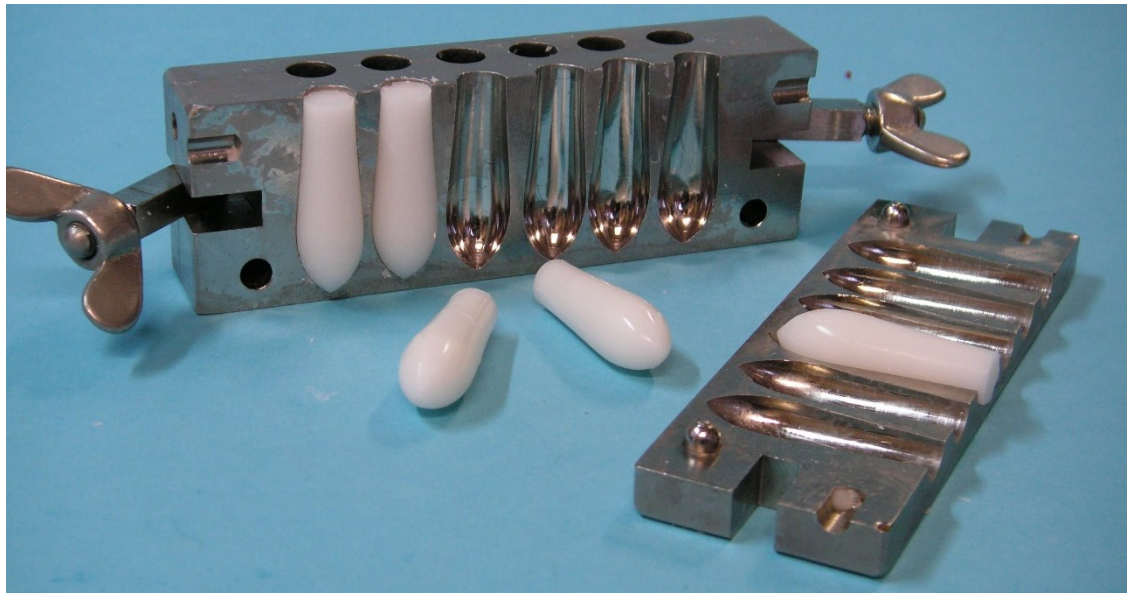
1. Preparation of Suppositories

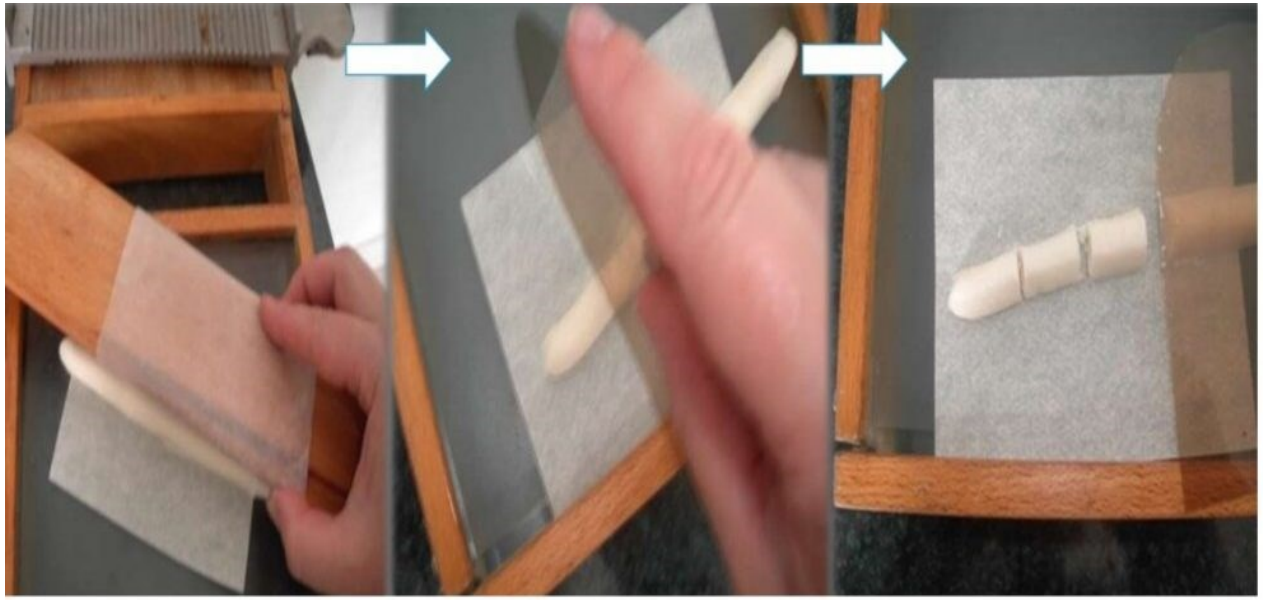
- Suppositories are prepared by two methods:

    1. Molding from a melt.

    2. Hand rolling and shaping.

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





1.1 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.

1.1 Preparation by Molding

1.1.1 Suppository Molds

- Commercially available molds can produce individual or large numbers of suppositories of various shapes and sizes.
- Molds in common use today are made from **stainless steel**, **aluminum**, **brass**, or **plastic**.
- The molds, which separate into sections, generally longitudinally, are opened for cleaning before and after preparation of a batch of suppositories, closed when the melt is poured, and opened again to remove the cold, molded suppositories.
- Care must be taken in cleaning the molds, as any scratches on the molding surfaces will take away from the desired smoothness of the suppositories. Plastic molds are especially prone to scratching.

1.1 Preparation by Molding

1.1.2 Lubrication of the Mold

- Depending on the formulation, suppository molds may require lubrication before the melt is poured **to facilitate clean and easy removal of the molded suppositories**.
- Lubrication is seldom necessary when the base is **cocoa butter** or **polyethylene glycol**, as these materials contract sufficiently on cooling to separate from the inner surfaces and allow easy removal.
- Lubrication is usually **necessary with glycerinated gelatin**. A thin coating of mineral oil applied with the finger to the molding surfaces usually suffices. However, no material that might irritate the mucous membranes should be employed as a mold lubricant.

1.1 Preparation by Molding

1.1.3 Calibration of the Mold

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

1.1 Preparation by Molding

1.1.4 Preparing and Pouring the Melt

- Using the least possible heat, the weighed suppository base material is melted, generally over a water bath. **A porcelain casserole**, that is, a dish with a pouring lip and a handle, is perhaps the best utensil, because it later **permits convenient pouring of the melt into the cavities of the mold**.
- Usually, medicinal substances are incorporated into a portion of the melted base by mixing with a spatula. After incorporation, this material is stirred into the remaining base and poured to the mold and allowed to cool to its congealing point.
- Any volatile materials or heat-labile substances should be incorporated at this point with stirring. The melt is poured carefully and continuously into each cavity of the mold.

1.1.4 Preparing and Pouring the Melt

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

1.1.4 Preparing and Pouring the Melt

- In filling each suppository cavity, the pouring must be continuous **to prevent layering**, which may lead to a product easily broken on handling.
- To ensure a completely filled mold upon congealing, the melt is poured excessively over each opening, actually rising above the level of the mold. This use of extra suppository material prevents formation of recessed dips in the ends of the suppositories and justifies preparation of extra melt.
- When solidified, the excess material is evenly scraped off of the top of the mold with a spatula warmed by dipping into a beaker of warm water; this will make a smooth surface on the back of the suppository during trimming.

List of Content

2. Quality Control

- Quality control for manufactured suppositories and inserts includes:

    1) Identification
    2) Assay
    3) Loss on drying
    4) Disintegration
    5) Dissolution
    6) Physical and chemical stability.

3. Packaging and Storage

- Glycerin and glycerinated gelatin suppositories are packaged in tightly closed containers **to prevent a change in moisture content**.
- Suppositories prepared from a cocoa butter base are usually individually wrapped or otherwise separated in compartmented boxes **to prevent contact and adhesion**.
- Suppositories containing light sensitive drugs are individually wrapped in an opaque material such as a metallic foil.
- In fact, most commercial suppositories are individually wrapped in either **foil or plastic material**.

- Because suppositories are adversely affected by heat, **it is necessary to maintain them in a cool place.**
- Cocoa butter suppositories must be stored below 30°C and preferably in a refrigerator (2°C to 8°C).
- Glycerinated gelatin suppositories can be stored at controlled room temperature (20°C to 25°C).
- Suppositories made from a base of polyethylene glycol may be stored at usual room temperatures.
- Suppositories stored in high humidity may absorb moisture and tend to become spongy, whereas suppositories stored in places of extreme dryness may lose moisture and become brittle.

4. Displacement Value (DV)

- The 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 displaces high amount of base.
- **DV. for liquids equals 1**

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

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

List of Content

4.1 Calculations using displacement values

Prepare 6 codeine phosphate suppositories (D.V=1.1) using mold of 1g size each supp. Containing 60mg /supp

- **“prepare 10 supp. to compensate for any loss”**

1. **Calculate the total weight of codeine phosphate required**

   60mg x 10 = 600mg = 0.6g codeine phosphate

2. **Calculate the weight of base required to prepare 10 medicated supp**

   Supp. Base >>> 1g x 10 = 10g total wt. of base

3. **Determine what weight of base would be displaced by the medicament**

Drug	**Base**	
1.1	1g	
0.6	**X**	**X** = (1g x 0.6) / 1.1 = **0.55**

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

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

4.1.1 Practical Examples

Q1/ Calculate the quantities required to make 8 theobroma oil supp. (2g mold) each containing 400 mg of zinc oxide (DV= 4.7)

- **"prepare 10 supp. to compensate for any loss"**

1. **Calculate the total weight of zinc oxide required**

   400mg x 10 = 4000mg = 4g zinc oxide

2. **Calculate the weight of base required to prepare 10 medicated supp**

   Supp. Base >>> 2g x 10 = 20g total wt. of base

3. **Determine what weight of base would be displaced by the medicament**

Drug	**Base**	
4.7	1g	
4	**X**	**X** = (1g x 4) / 4.7 = **0.85**

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

   Amount of base needed is >>> 20g - 0.85 = 19.15g

- **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.

Q2/ Calculate the quantities required to make six glycerol-gelatin supp. (4g mold), each containing 100 mg aminophylline (Displacement value = 1.3)

"prepare 10 supp. to compensate for any loss"

1. **Calculate the total weight of aminophylline required**

   100mg x 10 = 1000mg = 1g aminophylline

2. **Calculate the weight of base required to prepare 10 medicated supp**

   Supp. Base >>> 4g x 10 x **1.2** = 48g total wt. of base

3. **Determine what weight of base would be displaced by the medicament**

Drug	**Base**	
1.3	**1.2g**	
1	**X**	**X** = (1.2g x 1) / 1.3 = **0.92**

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

   Amount of base needed is >>> 48g - 0.92 = 39.08g

Q3/ Prepare 10 supp. non-medicated (only theobroma oil) weight 12g . Then prepare 10 medicated supp. weighted 14g , the weight of drug incorporated = 4.2g , calculate the displacement value ?

14 – 4.2 = 9.8 g (the weight of base required to prepare 10 medicated supp)

12 – 9.8 = 2.2 g (the amount of theobroma oil displace by the drug)

Drug	**Base**	
4.2 g	2.2 g	
X	1	**X** = (1 x 4.2g) / 2.2 = **1.909 (= 1.91 D.V)**

Q4/ Calculate the quantities required to make 10 theobroma oil supp. (1.4g mold) each containing 420 mg of drug (DV= 1.91)

1. **Calculate the total weight of drug required**

   420mg x 10 = 4200mg = 4.2g of drug

2. **Calculate the weight of base required to prepare 10 medicated supp**

   Supp. Base >>> 1.4g x 10 = 14g total wt. of base

3. **Determine what weight of base would be displaced by the medicament**

Drug	**Base**	
1.91	1g	
4.2	**X**	**X** = (1g x 4.2) / 1.91 = **2.198 (= 2.2)**

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

   Amount of base needed is >>> 14g – 2.2 = 11.8g

Q5/ What quantities are required to prepare 8 theobroma oil supp., in a 4g mold, containing 1% w/w lignocaine hydrochloride?

1. **Calculate the weight of base required to prepare 8 medicated supp**

   8 x 4g = 32 g (Base required)

2. **Calculate the total weight of aminophylline required**

   1% w/w of lignocaine means (1% of 32 “Base”)

   1 100

   X 32 **X** = (1 x 32) / 100 = **0.32g (of drug)**

List of Content

Thank You!

3rd Stage
2nd Semester

Pharmaceutical Technology II

Powders & Granules

Ass. Lec. Qutaiba Akram

B.Sc M.Sc in Pharmaceutical Sciences
qutaiba.ak@uoalfarahidi.edu.iq

Powders & Granules

List of Content

POWDERS

GRANULES

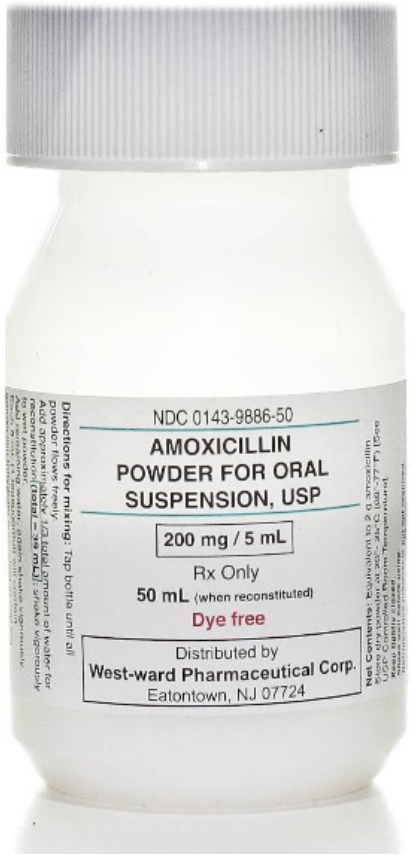
Powders

Overview

- Most active and inactive pharmaceutical ingredients occur in the solid state as **amorphous** powders or as **crystals** of various morphologic structures.
- The term **"powder"** has more than one meaning in pharmacy.
  1. It may be used to describe the physical form of a material, that is, a dry substance composed of finely divided particles.
  2. Or, it may be used to describe a type of pharmaceutical preparation, that is, a medicated powder intended for internal (i.e., **oral powder**) or external (i.e., **topical powder**) use.

Overview

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



Overview

The use of powders:

a) Medicated powders for therapeutic effect (limited)

b) The use of powdered substances in the preparation of other dosage forms is extensive. For example, powdered drugs may be blended with powdered fillers and other pharmaceutical ingredients to fabricate:

1. Solid dosage forms as tablets and capsules.
2. They may be dissolved or suspended in solvents or liquid vehicles to make various liquid dosage forms.
3. They may be incorporated into semisolid bases in the preparation of medicated ointments and creams.

1. Characterization of Powders

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

1. Morphology
2. Purity
3. Solubility
4. Flowability
5. Stability
6. Particle size
7. Uniformity
8. Compatibility with any other formulation components

2. Particle Size

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


2 mm
2,00X50

Classification of Powders by Fineness

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

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

Sieve No.	Opening (mm)	Sieve No.	Opening (mm)
4	4.75	35	0.500
5	4.00	40	0.425
6	3.35	45	0.355
7	2.80	50	0.300
8	2.36	60	0.250
10	2.00	70	0.212
12	1.70	80	0.180
14	1.40	100	0.150
16	1.18	120	0.125
18	1.00	140	0.106
20	0.85	200	0.075
25	0.71	270	0.053
30	0.60	400	0.038

Table 1: U.S. Sieve Size

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

- **Particle size can influence a variety of important factors:**

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

List of Content

POWDERS

GRANULES

2.1 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:

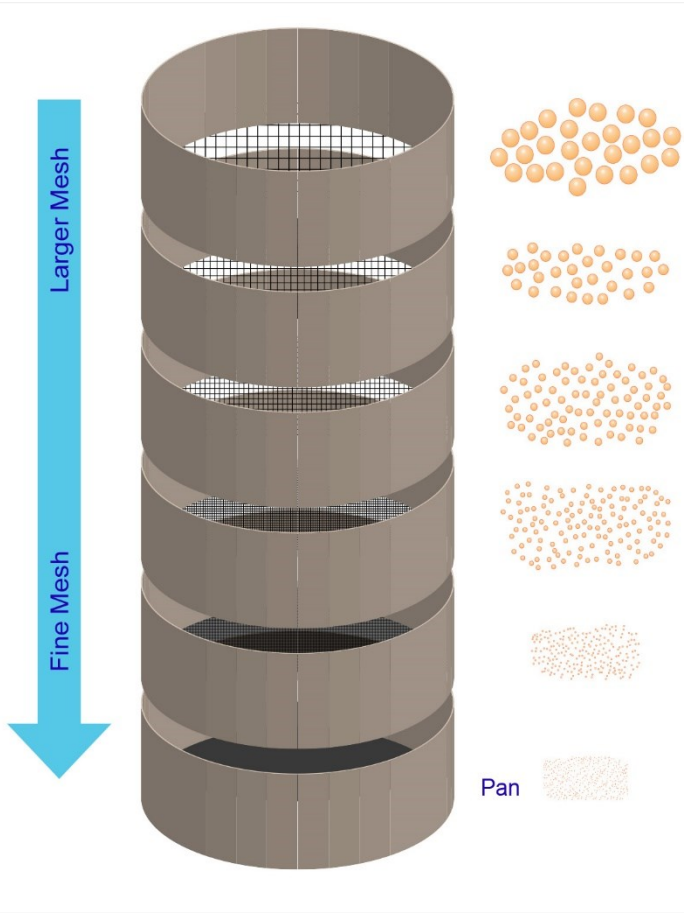
1. Particle size
2. Size distribution
3. Shape
4. Angle of repose
5. Porosity
6. True volume
7. Bulk volume
8. Apparent density
9. Bulkiness

2.2 Methods for the determination of particle size

- **A number of methods exist for the determination of particle size:**

2.2.1 Sieving

In which particles are passed by mechanical shaking through a series of sieves of known and successively smaller size and the proportion of powder passing through or being withheld on each sieve is determined (range about 40 to 9,500 µm, depending upon sieve sizes).

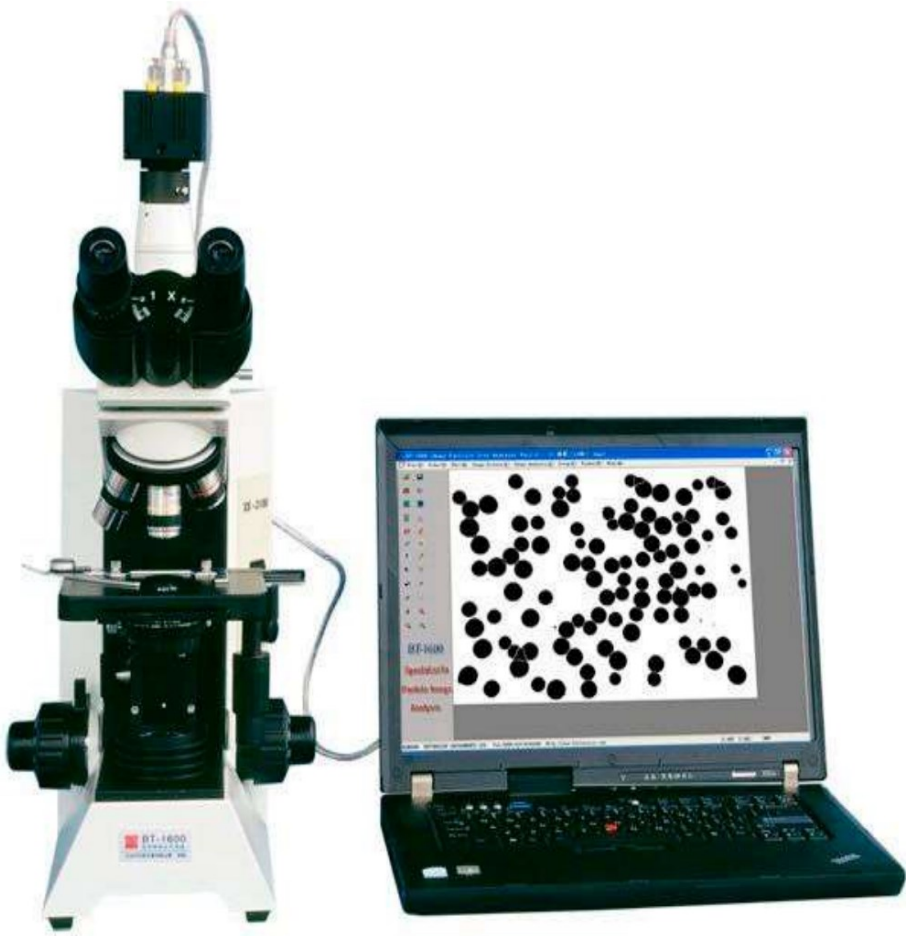


2.2 Methods for the determination of particle size

2.2.2 Microscopy

in which sample particles are sized through the use of a calibrated grid background or other measuring device (range 0.2 to 100 µm) .

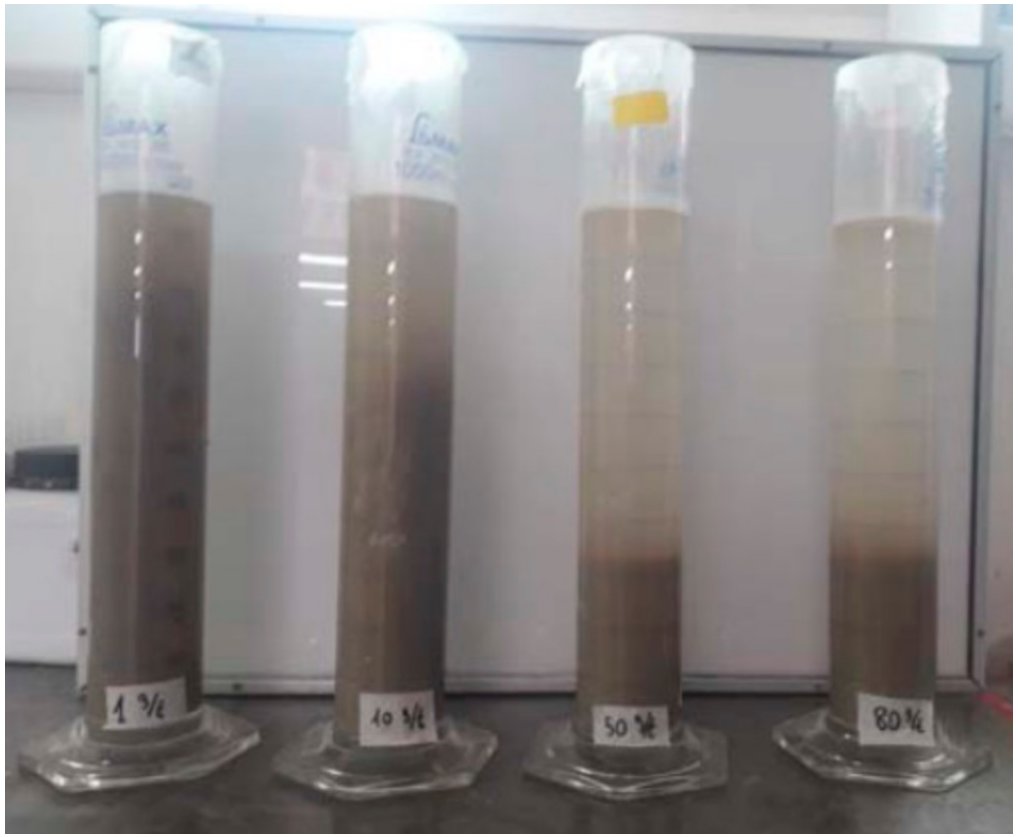
The microscopic method can include not fewer than 200 particles in a single plane using a calibrated ocular on a microscope.



2.2 Methods for the determination of particle size

2.2.3 Sedimentation rate

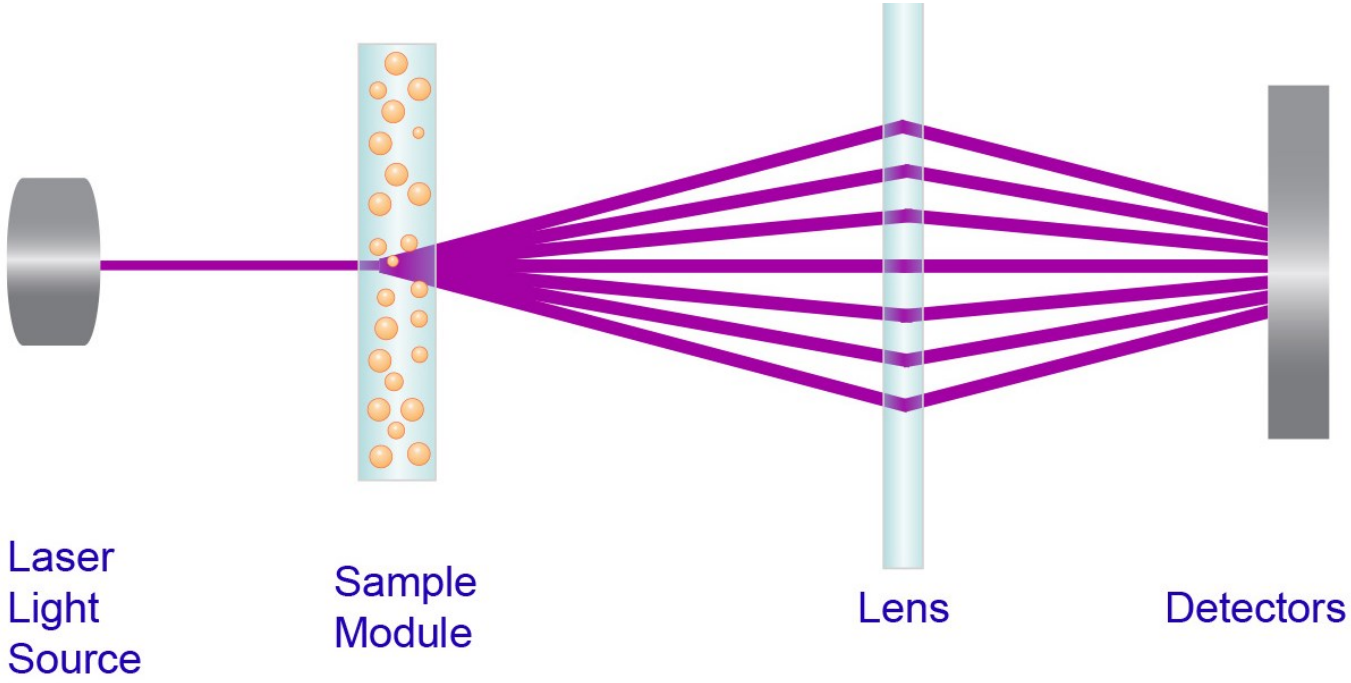
In which particle size is determined by measuring the terminal settling velocity of particles through a liquid medium in a gravitational or centrifugal environment (range 0.8 to 300 µm) . Sedimentation rate may be calculated from Stokes' law.



2.2 Methods for the determination of particle size

2.2.4 Light Energy Diffraction (or light scattering)

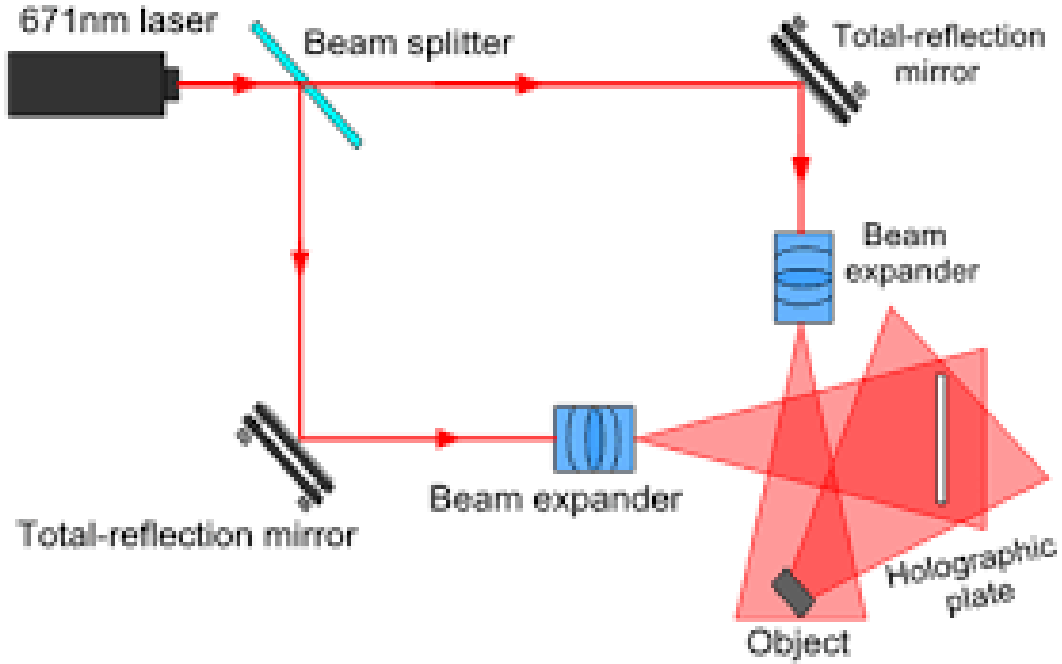
In which particle size is determined by the reduction in light reaching the sensor as the particle, dispersed in a liquid or gas, passes through the sensing zone (range 0.2 to 500 µm).



2.2 Methods for the determination of particle size

2.2.5 Laser Holography

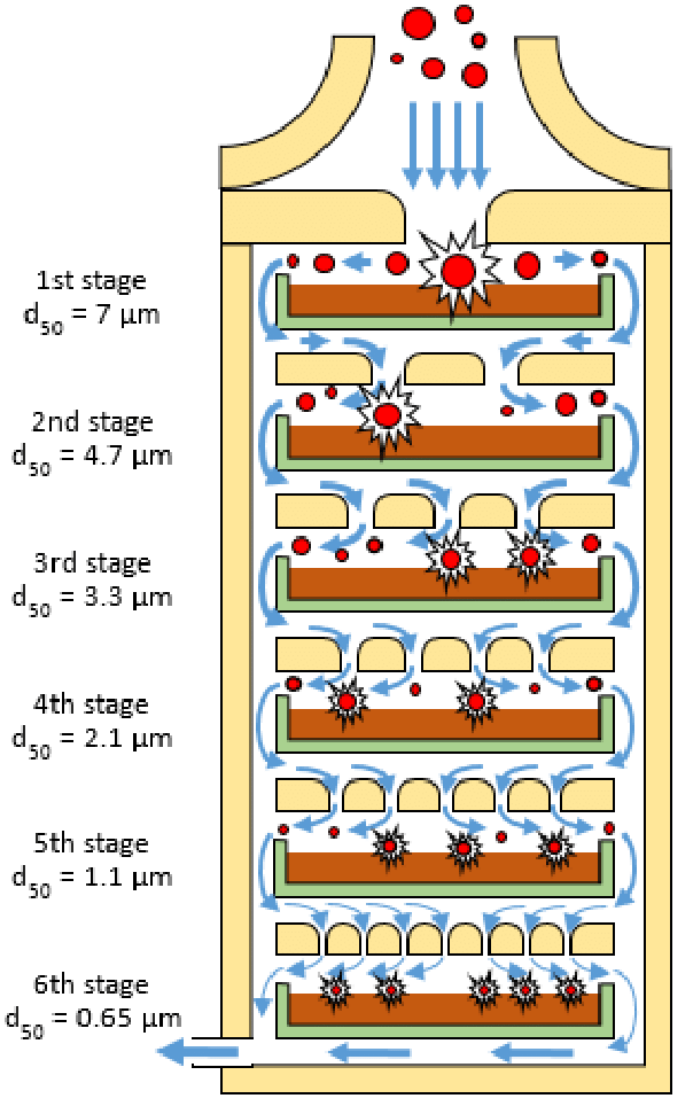
In which a pulsed laser is fired through an aerosolized particle spray and is photographed in three dimensions with a holographic camera, allowing the particles to be individually imaged and sized (range 1.4 to 100 µm) .



2.2 Methods for the determination of particle size

2.2.6 Cascade impaction

Which is based on the principle that a particle driven by an airstream will hit a surface in its path, provided its inertia is sufficient to overcome the drag force that tends to keep it in the airstream. Particles are separated into various size ranges by successively increasing the velocity of the airstream in which they are carried.



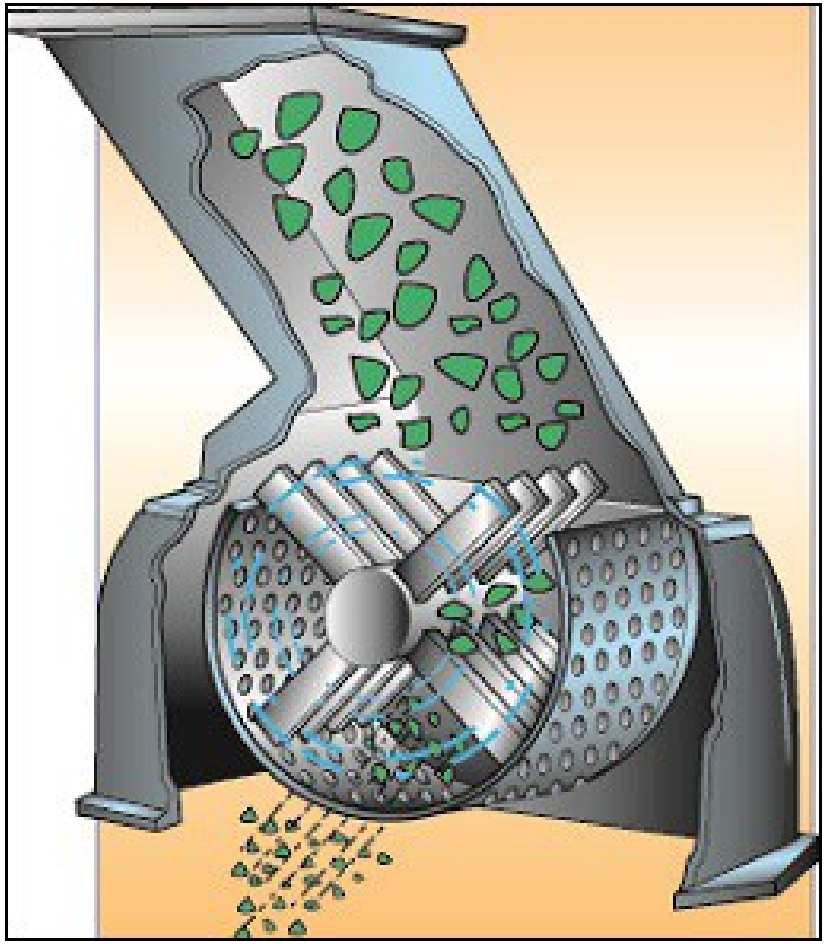
2.3 Particle Size Reduction

- Size reduction in particle size, increases the number of particles and the total surface area.
- The reduction in the particle size of a solid is accompanied by a great increase in the specific surface area of that substance.
- **Comminution** “reduction of the particle size of a solid substance to a finer state” is used to:

1. Facilitate crude drug extraction.
2. Increase the dissolution rates of a drug.
3. Aid in the formulation of pharmaceutically acceptable dosage forms.
4. Enhance the absorption 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**.

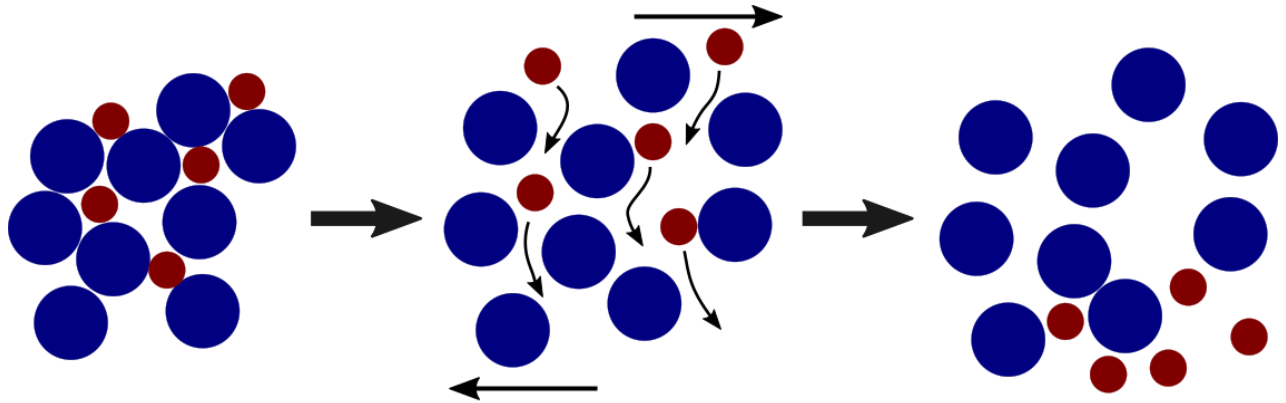
- **On a large scale**, various types of **mills** and **pulverizers** may be used.
- **FitzMill** comminuting machine with a product containment system. Through the grinding action of rapidly moving blades in the comminuting chamber, particles are reduced in size and passed through a screen of desired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



Problems associated with particle size reduction

1) **Segregation** is an undesirable separation of the different components of the blend. Segregation may occur sifting or percolation, air entrapment (fluidization), Fine particles tend to sift or percolate through coarse particles and end up at the bottom of the container and actually “lift” the larger particles to the surface. Fine, aerated powders with differences in particle size or density may result in a striation pattern and may occur during powder transfer.

2) **Particle entrapment (Dusting)**. Dusting occurs when the finer, lighter particles remain suspended in air longer and do not settle as quickly as the larger or denser particles.



List of Content

POWDERS

GRANULES

3. Flowability

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

4. Blending of 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:

1) **Spatulation**
2) **Trituration**
3) **Sifting**
4) **Tumbling**

4. Blending of Powders

4.1 Spatulation

- Spatulation is blending small amounts of powders by movement of a spatula through them on a sheet of paper or an ointment tile.

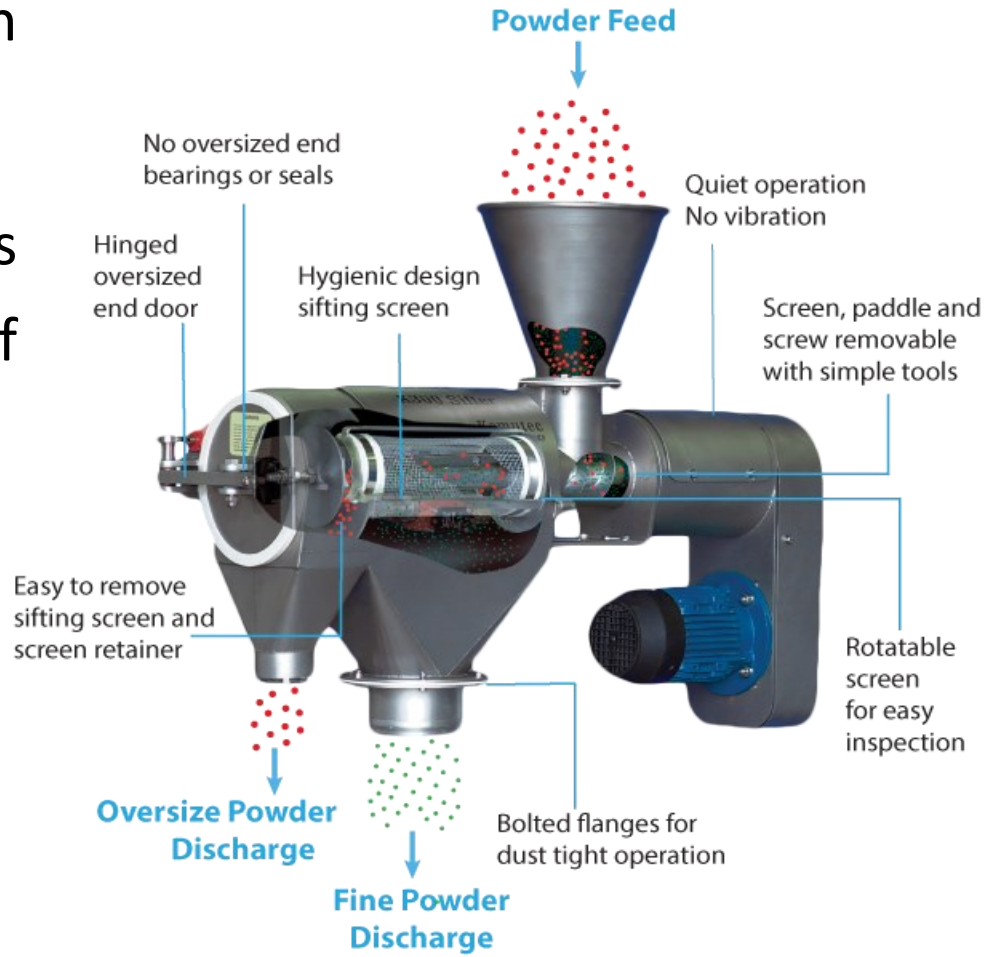
- It is not suitable for large quantities of powders or for powders containing potent substances, because homogeneous blending is not as certain as other methods.

4.2 Trituration

- Trituration may be employed both to comminute and to mix powders. If simple admixture is desired without the special need for comminution, the glass mortar is usually preferred.
- When a small amount of a potent substance is to be mixed with a large amount of diluent, **the geometric dilution method** is used to ensure the uniform distribution of the potent drug. This method is especially indicated when the potent substance and other ingredients are the same color and a visible sign of mixing is lacking.

4.3 Sifting

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



4.4 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.

List of Content

POWDERS

GRANULES

5. Medicated Powder

Some medicated powders are intended to be used:

1. **Internally:** Most powders for internal use. Some powders are intended to be inhaled for local and systemic effects. Other dry powders are commercially packaged for constitution with a liquid solvent or vehicle, some for administration orally, are taken orally after mixing with water or in the case of infants in their infant formulas others for use as an injection, others for use as a vaginal douche.

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

5. Medicated Powder

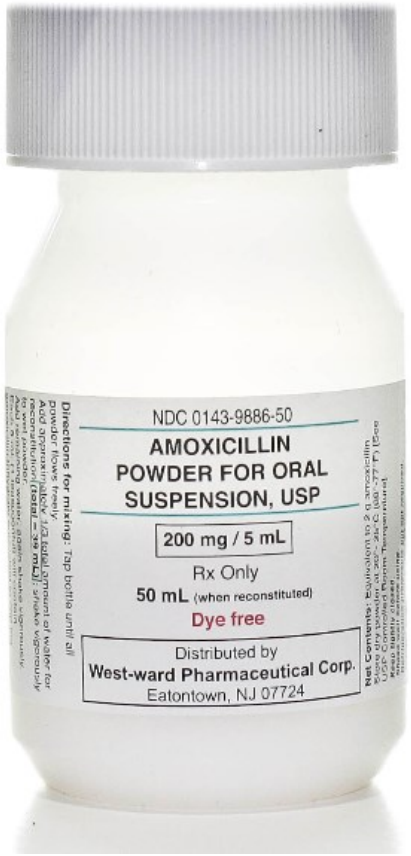
5.1 Medicated powders for oral use

- May be intended for local effects (e.g., laxatives) or systemic effects (e.g., analgesics).
- 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 soft food.
- 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.
- A primary disadvantage of the use of oral powders is the undesirable taste of the drug.

5.1 Medicated powders for oral use

5.1 Medicated powders for oral use

- 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.



5. Medicated Powder

5.2 Aerosol Powders

- Some medicated powders are administered **by inhalation** with the aid of dry-powder inhalers, which deliver micronized particles of medication in metered quantities.
- Most of these products are used in the treatment of asthma and other bronchial disorders that require distribution of medication deep. 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.

5.2 Aerosol Powders

5. Medicated Powder

5.3 Powder blowers or insufflators

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

6. Bulk and Divided Powders

6.1 Bulk Powders

- Among the bulk powders available in prepackaged amounts are:

a) **Antacids** (e.g., sodium bicarbonate), which the patient takes by mixing with water or another beverages before swallowing.

b) **Douche powders** (e.g., sodium bicarbonate), dissolved in warm water by the patient for vaginal use.

c) **Medicated powders for external application to the skin**, usually topical anti-infectives (e.g., bacitracin zinc and polymyxin B sulfate) or **antifungals** (e.g., Clotrimazole).

d) **Multivitamins** 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.

6. Bulk and Divided Powders

6.2 Divided Powders

- After a powder has been properly blended, 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 that is folded to enclose the medication.
- A number of commercially prepared premeasured products are available in folded papers or packets, including:

1. Headache powders (e.g., Aspegic powders)
2. Powdered laxatives (e.g., psyllium mucilloid, Fybrogel)
3. Douche powders (e.g., Massengill powder packets).

6. Bulk and Divided Powders

6.2 Divided Powders

- Several kinds of papers may be used: **(1) Simple bond paper** ; **(2) Vegetable parchment**, a thin, semiopaque paper with limited moisture resistance. **(3) Glassine,** a glazed, transparent paper, also with limited moisture resistance; **(4) 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**.
- Powders containing **volatile components** should be wrapped in **waxed or glassine papers**.
- Powders containing **neither volatile components nor ingredients** adversely affected by air or moisture are usually wrapped in a **white bond paper**.

List of Content

POWDERS

GRANULES

Granules

Overview

- Granules are defined as **“a dosage form composed of dry aggregates of powder particles that may contain one or more APIs, with or without other ingredients”**.
- They may be swallowed as such, dispersed in food, or dissolved in water.
- Granules are frequently compacted into tablets or filled into capsules, with or without additional ingredients.
- Granules are prepared agglomerates of smaller particles of powder. They are irregularly shaped but may be prepared to be spherical. They are usually in the 4- to 12- mesh sieve size range, although granules of various mesh sizes may be prepared depending upon their application.

1. Advantages of Granules

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.

1. Advantages of Granules

4) Granules are **more easily wetted by a solvent** than are certain powders,

   So that granules are also preferred in making solutions. Example: Principen® (ampicillin) for Oral Suspension. 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.

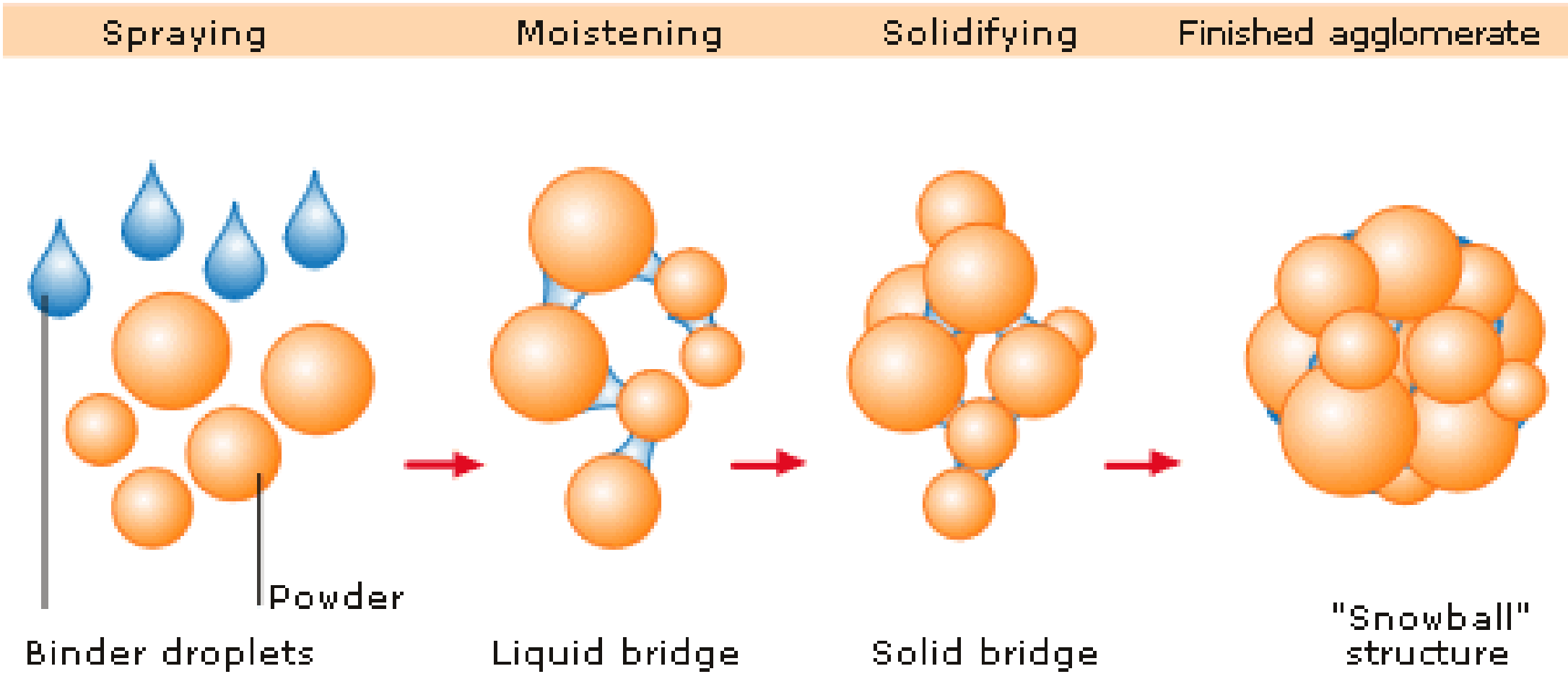
5) Granules **produce particle-size uniformity, thus content uniformity**.

2. Preparation of Granules

2.1 Wet Granulation Method

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

2.1 Wet Granulation Method



2. Preparation of Granules

2.2 Dry Granulation 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.
- A roll compactor, also called a roll press or roller compactor, processes a fine powder into dense sheets or forms by forcing it through two mechanically rotating metal rolls running counter to each other. The surface of the compacting rolls may be smooth or may have pocket indentations or corrugations that allow compaction of different forms and textures. The compacted powder is granulated to uniform particle size in a mechanical granulator. Powder compactors are generally combined in sequence in integrated compactor-granulation systems.

2.2 Dry Granulation Method

- 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.

List of Content

POWDERS

GRANULES

3. Effervescent Granulated Salts

- Effervescent salts are granules or coarse to very coarse powders containing a medicinal agent in a dry mixture usually composed of **sodium bicarbonate, citric acid,** and **tartaric acid**. When added to water, the acids and the base react to liberate carbon dioxide, resulting in effervescence.
- The resulting carbonated solution masks undesirable taste of any medicinal agent.
- Using granules or coarse particles of the mixed powders rather than small powder particles decreases the rate of solution and prevents violent and uncontrollable effervescence.
- Sudden and rapid effervescence could overflow the glass and leave little residual carbonation in the solution.


٦ أكياس
فوارليمون
ملح فوار
لعلاج الإنتفاخ وعسر الهضم
والحموضة
صنع في مصر
فاركو
للأدوية
الإسكندرية


إينو
ENO
Fruit Salt Antacid
LEMON FLAVOUR
Fast Effective Relief from
Acid Indigestion
Heartburn
150gm

3. Effervescent Granulated Salts

- 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.
- Effervescent granules are prepared by two general methods:

  a) **Dry or fusion method**

  b) **Wet method.**

3.1 Dry or Fusion 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.

3.1 Dry or Fusion Method

- 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.

3.1 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 alcohol used as the moistening agent, forming the pliable mass for granulation.
- 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 previously described.

List of Content

POWDERS

GRANULES

Thank You!

3rd Stage
2nd Semester

Pharmaceutical Technology II

Capsules

Ass. Lec. Qutaiba Akram

B.Sc M.Sc in Pharmaceutical Sciences
qutaiba.ak@uoalfarahidi.edu.iq

Capsules

Overview

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

Overview

- **Hard and soft gelatin capsules differ in both their:**

1) Mechanical properties

Hard gelatin capsules are less flexible, whereas soft gelatin capsules are more flexible.

2) Capsule design

Hard gelatin capsules are composed of two pieces, termed **the caps** and **the body**, and soft gelatin capsules are composed of a one piece capsule shell.

3) Capsule Fill

A wide range of formulation types may be included within the interior of the capsule. For example, powders, tablets, semisolids and nonaqueous liquids/gels may be filled into hard capsules, with powders being the most common formulation option. Soft gelatin capsules are usually filled with non-aqueous liquids containing the therapeutic agent either dispersed or dissolved within this carrier.

Overview

Advantages of Capsules

1) **Elegant and Attractive** (colored) and readily identified.
2) **Conveniently Carried** (resist mechanical stress).
3) **Easily swallowed** (There is no need for spoons or other measuring devices, shell is inert and easily digested in the GIT).
4) **Tasteless and Odorless** when swallowed (cover the taste and odor of unpleasant drugs).
5) **Available for many medications in a variety of dosage strengths**, providing flexibility to the prescriber and accurate individualized dosage for the patient.
6) **They are packaged and shipped by manufacturers at lower cost and with less breakage**.
7) They are also **more stable and have a longer shelf life** than their liquid counterparts. (can be made as light resistant).

Overview

Disadvantages of Capsules

1) The requirement for specialized manufacturing equipment.

2) Potential stability problems associated with capsules containing liquid fills.

3) Problems regarding the homogeneity of fill weight and content may be associated with capsule formulations.

1. Hard Gelatin Capsule

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

1.1 Gelatin

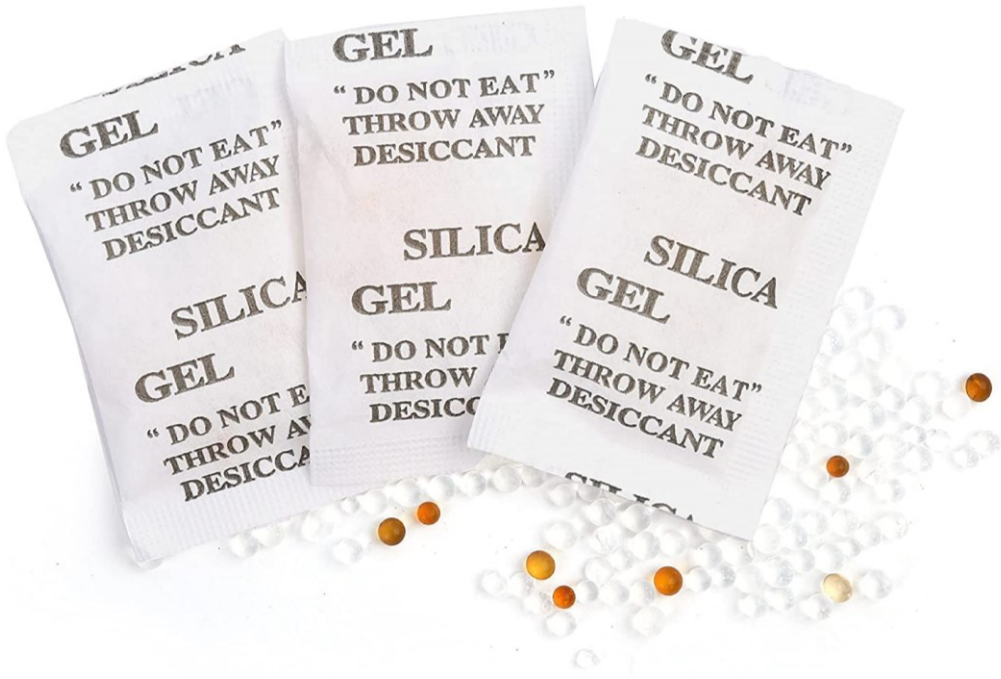
- Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals.
- It is available in the form of a fine powder, a coarse powder, shreds, flakes, or sheets.
- Normally, hard gelatin capsules contain **13% to 16%** of moisture.
- Type A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

1.1.1 Storage Conditions of Gelatin

- Gelatin is stable in air when dry but is subject to **microbial decomposition** when it becomes moist.
- Gelatin if stored in an environment of high humidity, additional moisture is absorbed by the capsules, and they may become **distorted and lose their rigid shape**.
- In an environment of extreme dryness, some of the moisture normally present in the gelatin capsules is lost, and the capsules may become **brittle and crumble when handled**. Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excessive humidity or dryness.

1.1.1 Storage Conditions of 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**.



1.1.2 Gelatin After Administration

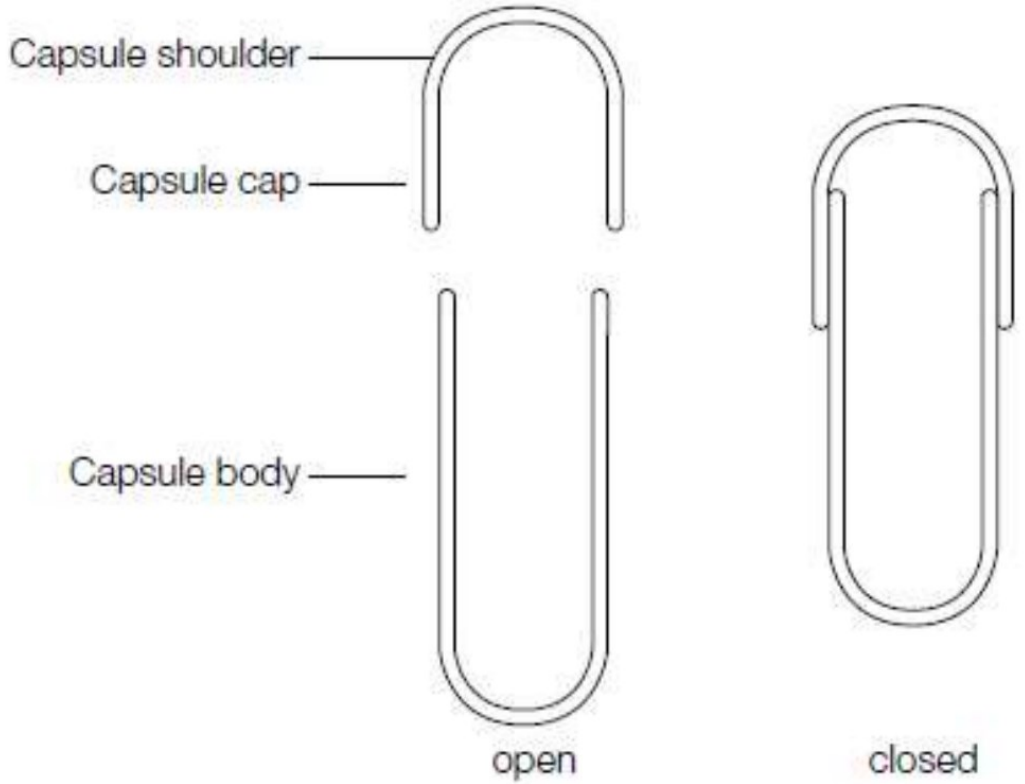
- Although gelatin is insoluble, it does soften in cold water through the absorption of water up to 10 times its weight of water.
- Some patients prefer to swallow a capsule wetted with water or saliva because a wetted capsule slides down the throat more readily than a dry capsule.
- Gelatin is soluble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

Overview ✓

1. Hard Gelatin Capsule ✓
   - 1.1 Gelatin ✓
     - 1.1.1 Storage Conditions of Gelatin ✓
     - 1.1.2 Gelatin After Administration ✓
   - 1.2 The Manufacture of Hard Gelatin Capsule Shells
     - 1.2.1 Capsule Shapes and Designs
     - 1.2.2 Capsule Sizes
   - 1.3 Preparation of Filled Hard Gelatin Capsules
     - 1.3.1 Developing and preparing the formulation and selecting the capsule size
     - 1.3.2 Filling the capsule shells
     - 1.3.3 Capsule sealing (optional)
     - 1.3.4 Cleaning and polishing the filled capsules
2. Soft Gelatin Capsules
   - 2.1 Preparation of Soft Gelatin Capsules
     - 2.1.1 Plate Process
     - 2.1.2 Rotatory Process
   - 2.2 Uses of Soft Gelatin Capsules
3. Compendial Requirements for Capsules
4. Counting Capsules
5. Examples of Some Official Capsules

1.2 The Manufacture of Hard Gelatin Capsule Shells

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



1.2 The Manufacture of Hard Gelatin Capsule Shells

1. Dipping and Spinning

The shells are produced industrially by the mechanical dipping of pins or pegs of the desired shape and diameter into a temperature-controlled reservoir of melted gelatin mixture.

The pegs, made of manganese bronze, are affixed to plates, each capable of holding up to about 500 pegs. Each plate is mechanically lowered to the gelatin bath, the pegs submerged to the desired depth and maintained for the desired period to achieve the proper length and thickness of coating.

2. Drying

Then the plate and the pegs are slowly lifted from the bath and the gelatin is dried by a gentle flow of temperature- and humidity controlled air.

1.2 The Manufacture of Hard Gelatin Capsule Shells

3. Trimming and Stripping

When dried, each capsule part is trimmed mechanically to the proper length and removed from the pegs.

4. Joining

Then the capsule bodies and caps are joined together.

5. 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.


Preliminary Inspection
Gelatin Melting
Blending
Dipping &Removing
Cutting
Cutting
Printing
Testing
Inspection
Packaging

1.2 The Manufacture of Hard Gelatin Capsule Shells

- 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.

1.2 The Manufacture of Hard Gelatin Capsule Shells

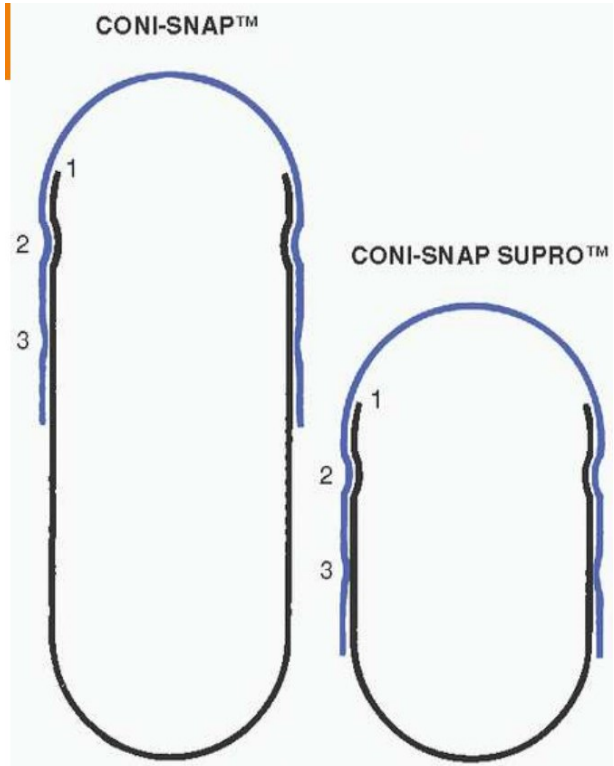
1.2.1 Capsule Shapes and Designs

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

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

2. **Snap-fit**

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



1. Tapered rim to avoid telescoping (CONI-SNAP™)
2. Grooves which lock the two halves together once the capsule has been filled (SNAP-FIT™ principle)
3. Indentations to prevent premature opening

1.2.2 Capsule Sizes

- Empty gelatin capsules are manufactured in various lengths, diameters, and capacities.
- The size selected for use is determined by:
    1) The amount of fill material to be encapsulated.
    2) 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.

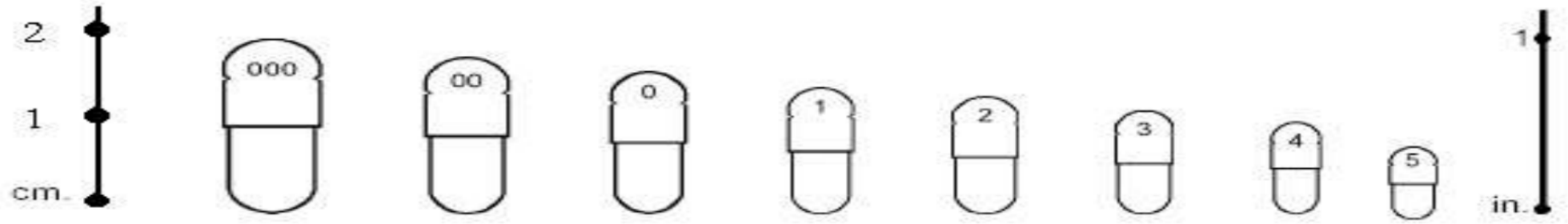
1.2.2 Capsule Sizes

- For human use, empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available.
- Larger capsules are available for veterinary use.
- For prescriptions requiring extemporaneous compounding, hard gelatin capsules permit a wide number of options for the physician.
- The pharmacist may compound capsules of a single medicinal agent or combination of agents at the precise dosage prescribed for the individual patient.

APPROXIMATE CAPACITY OF EMPTY GELATIN CAPSULES

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

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



1.2.2 Capsule Sizes

Selecting the Capsule Size

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

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

1.2.2 Capsule Sizes

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 / 0.8 =0.56mL

So; the size 0 capsule is appropriate

- Overview ✓
- 1. Hard Gelatin Capsule ✓
  - 1.1 Gelatin ✓
    - 1.1.1 Storage Conditions of Gelatin ✓
    - 1.1.2 Gelatin After Administration ✓
  - 1.2 The Manufacture of Hard Gelatin Capsule Shells ✓
    - 1.2.1 Capsule Shapes and Designs ✓
    - 1.2.2 Capsule Sizes ✓
  - 1.3 Preparation of Filled Hard Gelatin Capsules
    - 1.3.1 Developing and preparing the formulation and selecting the capsule size
    - 1.3.2 Filling the capsule shells
    - 1.3.3 Capsule sealing (optional)
    - 1.3.4 Cleaning and polishing the filled capsules
- 2. Soft Gelatin Capsules
  - 2.1 Preparation of Soft Gelatin Capsules
    - 2.1.1 Plate Process
    - 2.1.2 Rotatory Process
  - 2.2 Uses of Soft Gelatin Capsules
- 3. Compendial Requirements for Capsules
- 4. Counting Capsules
- 5. Examples of Some Official Capsules

1.3 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:

1.3.1 Developing and preparing the formulation and selecting the capsule size

1.3.2 Filling the capsule shells

1.3.3 Capsule sealing (optional)

1.3.4 Cleaning and polishing the filled capsules

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

- 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.
- Pre-formulation 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.

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

Particle Size of Capsule Fill :

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

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

Formulation Ingredients :

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

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

Lubricants :

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

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

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.

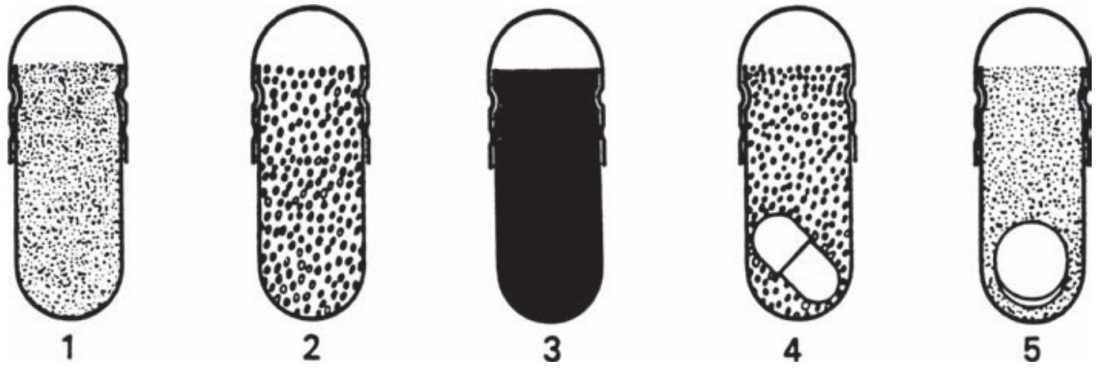


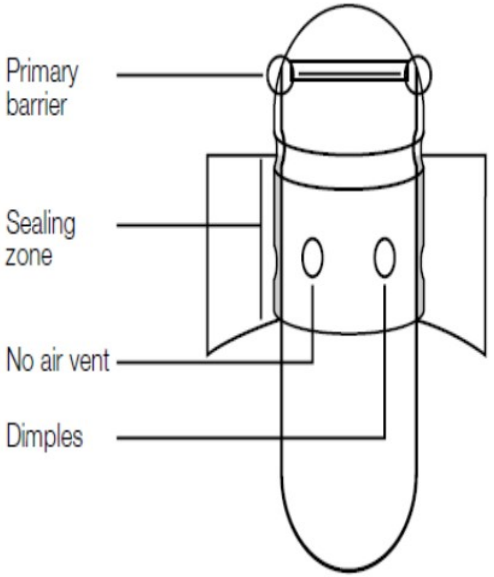
FIGURE 7.8 Examples of fill in hard gelatin capsules. 1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet. (Courtesy of Capsugel Division, Warner-Lambert.)

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

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.

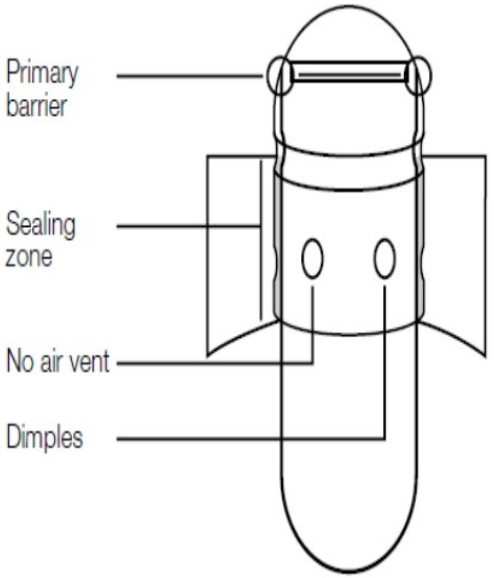


1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

Liquid Fill :

- 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.



1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

Extemporaneous compounding of prescriptions :

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

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

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.
  2. Avoids contaminating the stock container with drug powder.

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.1 Developing and preparing the formulation and selecting the capsule size

Filling Hard Capsule Shells :

- 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.

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.2 Filling the capsule shells

- 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.

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.2 Filling the capsule shells

- When **potent drugs** are being used, each capsule should be weighed after filling to ensure accuracy. Such weighings protect against uneven filling of capsules and premature exhaustion or underuse of the powder. After the body of a capsule has been filled and the cap placed on the body, the body may be squeezed or tapped gently to distribute some powder to the cap end to give the capsule a full appearance.
- Granular material that does not lend itself to the punch method of filling capsules may be poured into each capsule from the powder paper on which it is weighed.

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.2 Filling the capsule shells

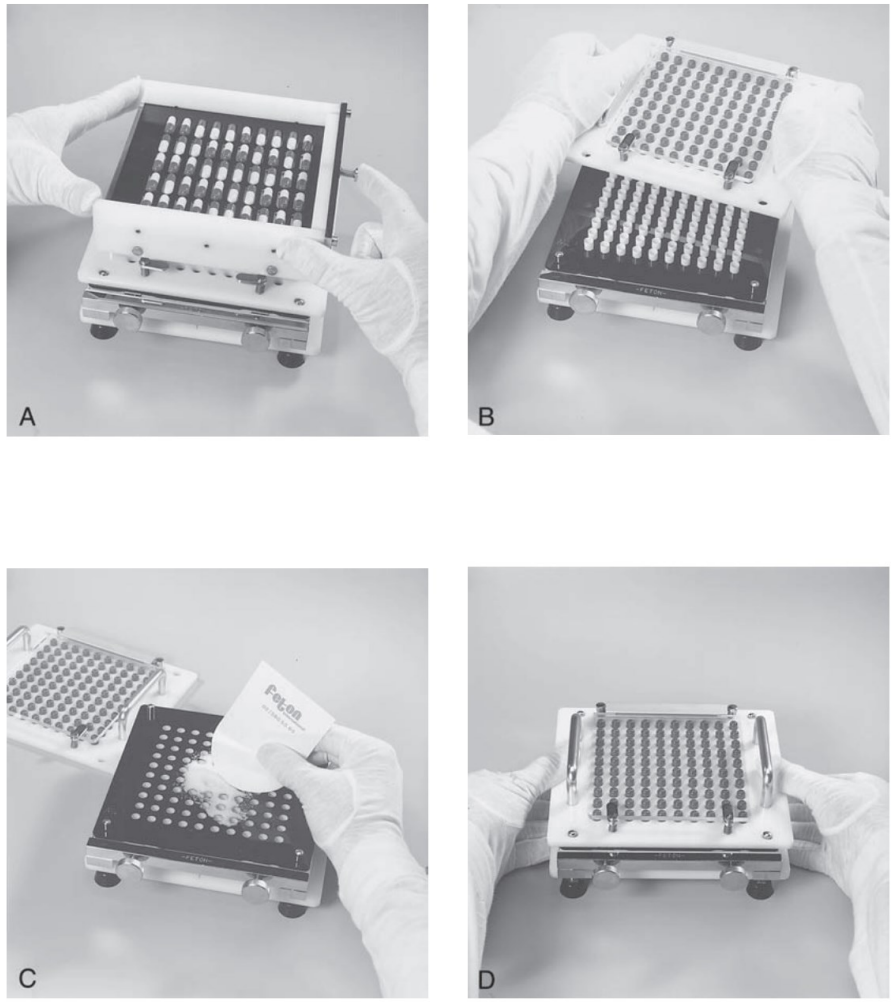
- **The Feton capsule-filling machine:**

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

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

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

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



1.3 Preparation of Filled Hard Gelatin Capsules

1.3.3 Capsule sealing

1. Some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. One manufacturer makes distinctive-looking capsules by sealing them with a colored band of gelatin (Kapseals, Parke-Davis). If removed, the band cannot be restored without expert resealing with gelatin.

2. Capsules may also be sealed through a heat welding process that fuses the capsule cap to the body through the double wall thickness at their juncture . The process results in a distinctive ring around the capsule where heat welded.

3. Still another process uses a liquid wetting agent that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40°C-45°C).

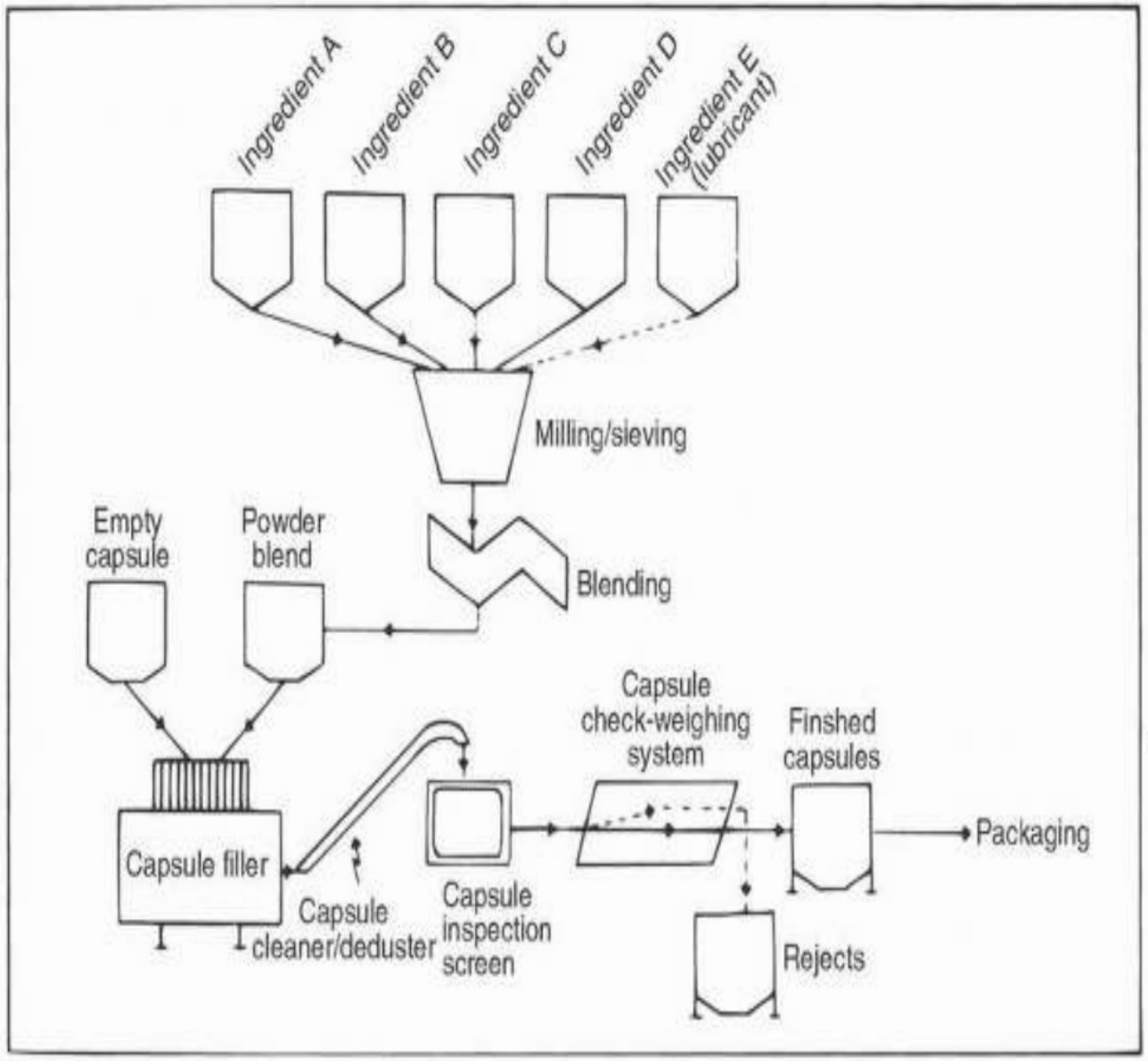
- Industrial capsule sealing machines are capable of producing 60,000 to 150,000 gelatin-banded, heat welded, or thermally coupled capsules per hour.

1.3 Preparation of Filled Hard Gelatin Capsules

1.3.4 Cleaning and polishing the filled capsules

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

1.3 Preparation of Filled Hard Gelatin Capsules



Overview ✓

1. Hard Gelatin Capsule ✓
   - 1.1 Gelatin ✓
     - 1.1.1 Storage Conditions of Gelatin ✓
     - 1.1.2 Gelatin After Administration ✓
   - 1.2 The Manufacture of Hard Gelatin Capsule Shells ✓
     - 1.2.1 Capsule Shapes and Designs ✓
     - 1.2.2 Capsule Sizes ✓
   - 1.3 Preparation of Filled Hard Gelatin Capsules ✓
     - 1.3.1 Developing and preparing the formulation and selecting the capsule size ✓
     - 1.3.2 Filling the capsule shells ✓
     - 1.3.3 Capsule sealing (optional) ✓
     - 1.3.4 Cleaning and polishing the filled capsules ✓
2. Soft Gelatin Capsules
   - 2.1 Preparation of Soft Gelatin Capsules
     - 2.1.1 Plate Process
     - 2.1.2 Rotatory Process
   - 2.2 Uses of Soft Gelatin Capsules
3. Compendial Requirements for Capsules
4. Counting Capsules
5. Examples of Some Official Capsules

2. 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.

2. Soft Gelatin Capsules

2.1 Preparation of Soft Gelatin Capsules

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

2.1 Preparation of Soft Gelatin Capsules

2.1.1 Plate Process

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

2.1 Preparation of Soft Gelatin Capsules

2.1.2 Rotatory Process

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

2.2 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.

2.2 Uses of Soft Gelatin Capsules

- 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.

Overview ✓

1. Hard Gelatin Capsule ✓
   - 1.1 Gelatin ✓
     - 1.1.1 Storage Conditions of Gelatin ✓
     - 1.1.2 Gelatin After Administration ✓
   - 1.2 The Manufacture of Hard Gelatin Capsule Shells ✓
     - 1.2.1 Capsule Shapes and Designs ✓
     - 1.2.2 Capsule Sizes ✓
   - 1.3 Preparation of Filled Hard Gelatin Capsules ✓
     - 1.3.1 Developing and preparing the formulation and selecting the capsule size ✓
     - 1.3.2 Filling the capsule shells ✓
     - 1.3.3 Capsule sealing (optional) ✓
     - 1.3.4 Cleaning and polishing the filled capsules ✓
2. Soft Gelatin Capsules ✓
   - 2.1 Preparation of Soft Gelatin Capsules ✓
     - 2.1.1 Plate Process ✓
     - 2.1.2 Rotatory Process ✓
   - 2.2 Uses of Soft Gelatin Capsules ✓
3. Compendial Requirements for Capsules
4. Counting Capsules
5. Examples of Some Official Capsules

3. 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.

4. 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.

4. Counting Capsules

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

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

5. Examples of Some Official Capsules

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

- Overview ✓
- 1. Hard Gelatin Capsule ✓
  - 1.1 Gelatin ✓
    - 1.1.1 Storage Conditions of Gelatin ✓
    - 1.1.2 Gelatin After Administration ✓
  - 1.2 The Manufacture of Hard Gelatin Capsule Shells ✓
    - 1.2.1 Capsule Shapes and Designs ✓
    - 1.2.2 Capsule Sizes ✓
  - 1.3 Preparation of Filled Hard Gelatin Capsules ✓
    - 1.3.1 Developing and preparing the formulation and selecting the capsule size ✓
    - 1.3.2 Filling the capsule shells ✓
    - 1.3.3 Capsule sealing (optional) ✓
    - 1.3.4 Cleaning and polishing the filled capsules ✓
- 2. Soft Gelatin Capsules ✓
  - 2.1 Preparation of Soft Gelatin Capsules ✓
    - 2.1.1 Plate Process ✓
    - 2.1.2 Rotatory Process ✓
  - 2.2 Uses of Soft Gelatin Capsules ✓
- 3. Compendial Requirements for Capsules ✓
- 4. Counting Capsules ✓
- 5. Examples of Some Official Capsules ✓

Thank You!

3rd Stage
2nd Semester

Pharmaceutical Technology II

Semisolids

Ass. Lec. Qutaiba Akram

B.Sc M.Sc in Pharmaceutical Sciences
qutaiba.ak@uoalfarahidi.edu.iq

Overview

1. Ointments
    - 1.1 Ointment Bases
        - 1.1.1 Hydrocarbon Bases
        - 1.1.2 Absorption Bases
        - 1.1.3 Water-Removable Bases
        - 1.1.4 Water-Soluble Bases
    - 1.2 Selection of appropriate base
    - 1.3 Preparation of Ointments
        - 1.3.1 Incorporation
            - 1.3.1.1 Incorporation of solids
            - 1.3.1.2 Incorporation of Liquids
        - 1.3.2 Fusion
2. Creams
    - 2.1 Preparation of Creams
3. Gels
4. Official requirements for semisolids
    - 4.1 Microbial content
    - 4.2 Minimum Fill
    - 4.3 Packaging and Storage
5. Skin Structure and Function
    - 5.1 Drug transport and permeation through the skin
    - 5.2 Factors Affecting Skin Penetration
6. Ophthalmic Ointments
7. Pastes, Plasters and Glycerogelatins
8. Transdermal Drug Delivery Systems (TDDS)
    - 8.1 Transdermal delivery patches
    - 8.2 Design of transdermal patches
    - 8.3 General clinical consideration in the use of TDDS
    - 8.4 Examples of TDDS

Semisolids

Overview

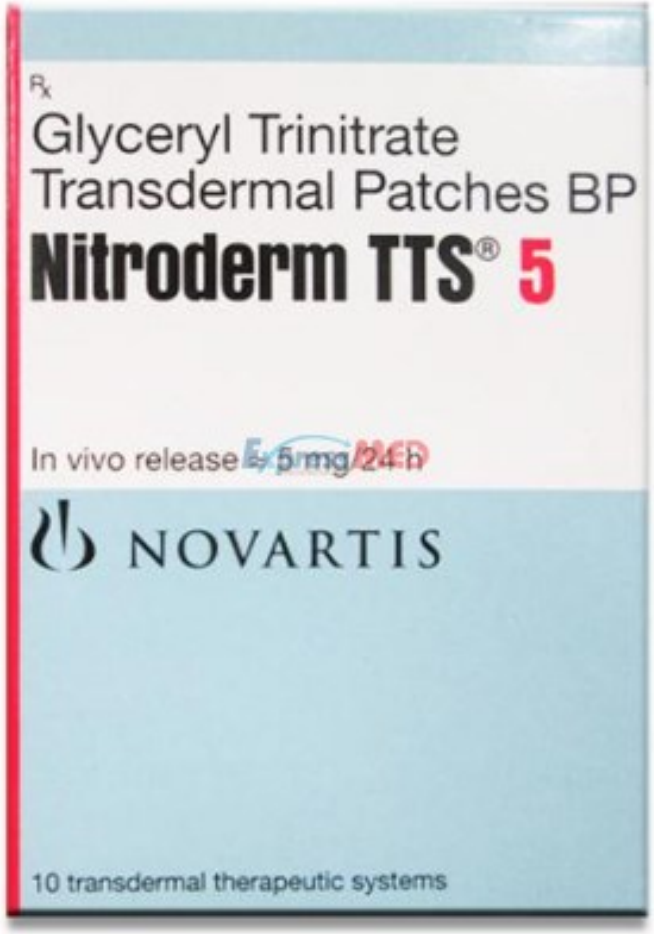
- Ointments, creams and gels are semisolid dosage forms intended for topical application. They may be applied to **the skin**, placed onto the surface of **the eye** or used **nasally**, **vaginally** or **rectally**.
- The majority of these preparations are used for the effects of the therapeutic agents they contain. Those which are non-medicated are used for their physical effects as protectants or lubricants.

Overview

- Topical preparations are used for the localized effects produced at the site of their application, although some unintended systemic drug absorption may occur, it is usually in sub-therapeutic quantities. However, systemic drug absorption can be an important consideration in certain instances, as when 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.

Overview

- **Transdermal drug delivery systems** are designed for the systemic absorption of drug substances in therapeutic quantities.
- A topical product is designed to deliver drug into the skin to treat dermal disorders with the skin as the target organ.
- A transdermal drug delivery system 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.



1. Ointments

- Ointments are semisolid preparations intended for external application to the skin or mucous membranes. Ointments may be medicated or non-medicated, non-medicated ointments are used for the physical effects that they provide as **protectants**, **emollients** or **lubricants**.

1.1 Ointment Bases

- Ointment bases may be used for their physical effects or as vehicles in the preparation of medicated ointments.
- **Ointment bases are classified into FOUR general groups**:

1. **Hydrocarbon bases (oleaginous bases)**
2. **Absorption bases**
3. **Water-removable bases**
4. **Water-soluble bases**

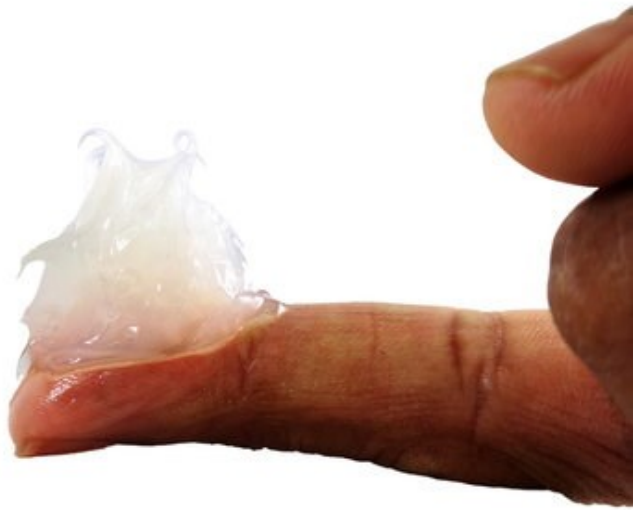
1.1.1 Hydrocarbon Bases

- Hydrocarbon bases are also termed **oleaginous bases**, on application to the skin they have an emollient effect, protect against the escape of moisture, effective as occlusive dressing and can remain on the skin for prolonged periods of time without drying out and because of their immiscibility with water are difficult to wash off.
- Water and aqueous preparations may be incorporated into them but only in small amounts and with some difficulty.
- **Petrolatum**, **white petrolatum**, **white ointment** and **yellow ointment** are examples of hydrocarbon ointment bases. When powdered substances are to be incorporated into hydrocarbon bases, liquid petrolatum (mineral oil) may be used as levigating agent.

1.1.1 Hydrocarbon Bases

Petrolatum, USP:

- Petrolatum, USP is a purified mixture of semisolid hydrocarbons obtained from petroleum. It is an oily mass, varying in color from **yellowish to light amber**. It melts at temperature between (38-60 °C) and may be used alone or in combination with other agents as an ointment base. Petrolatum is also known as '**Yellow Petrolatum**' and '**Petroleum Jelly**'. A commercial product is '**Vaseline**'



1.1.1 Hydrocarbon Bases

Yellow ointment, USP:

- This ointment has the following formula for the preparation of 1000 g:

Yellow wax	50 g
Petrolatum	950 g

- Yellow wax is the purified wax obtained from the honey comb of the bee. The ointment is prepared by melting the yellow wax on a water bath, adding the petrolatum until the mixture is uniform, then cooling with stirring until congealed.

1.1.1 Hydrocarbon Bases

White ointment, USP:

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

1.1.2 Absorption Bases

- Absorption bases are of two types:

1. Those that permit the incorporation of aqueous solutions resulting in the formation of w/o emulsions e.g. Hydrophilic petrolatum.
2. Those that are w/o emulsions (emulsion bases) permit the incorporation of additional quantities of aqueous solutions. e.g. Lanolin

- These bases may be used as emollients although they don't provide the degree of occlusion afforded by the hydrocarbon bases. Absorption bases are not easily removed from the skin, **since the external phase of the emulsion is oleaginous**.
- Absorption bases are useful as pharmaceutical adjuncts to incorporate small volumes of aqueous solutions into hydrocarbon bases. This is accomplished by incorporating the aqueous solution into the absorption base and then incorporating this mixture into the hydrocarbon base.

1.1.2 Absorption Bases

Hydrophilic Petrolatum, USP:

- Hydrophilic petrolatum, USP has the following formula for the preparation of 1000 g:

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

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

1.1.2 Absorption Bases

Lanolin, USP:

Lanolin, USP obtained from the wool of sheep. It is a purified wax like substance that has been cleaned, deodorized and decolorized. It contains not more than 0.25% water. Additional water may be incorporated into lanolin by mixing.

1.1.3 Water-Removable Bases

- Water-removable bases are o/w emulsions resembling creams in appearance and because the external phase of the emulsion is aqueous, they are easily washed from the skin and are often called ‘water-washable bases’. They may be diluted with water or aqueous solutions. They have the ability to absorb serous discharge.
- Hydrophilic ointment USP, is an example of this type of base.

Hydrophilic ointment, USP:

Hydrophilic ointment has the following formula for the preparation of about 1000 g:

Methyl paraben	0.25 g
Propyl paraben	0.15 g
Sodium lauryl sulfate	10 g
Propylene glycol	120 g
Stearyl alcohol	250 g
White petrolatum	250 g
Purified water	370 g

1.1.3 Water-Removable Bases

- In preparing this ointment, the stearyl alcohol and white petrolatum are melted together at about 75 °C.
- The other agents are dissolved in the purified water and then added with stirring until the mixture congeals.
- **Sodium lauryl sulphate (SLS)** is the emulsifying agent.
- **Stearyl alcohol and white petrolatum** comprising the oleaginous phase of the emulsion and the other ingredients form the aqueous phase.
- **Methyl paraben and propyl paraben** are antimicrobial preservatives.

1.1.4 Water-Soluble Bases

- Water-soluble bases don't contain oleaginous components, they are completely water-washable and often referred to as 'greaseless'.
- Since they soften greatly with the addition of water, large amounts of aqueous solutions are not effectively incorporated into these bases.
- Polyethylene glycol ointment, NF is an example of water-soluble base.

Polyethylene Glycol ointment, NF:

- Polyethylene glycol (PEG) is a polymer of ethylene oxide and water represented by the formula $H(OCH_2CH_2)_nOH$ in which (n) represents the average number of oxyethylene groups. The numerical designations associated with PEG refer to the average molecular weight of the polymer.

1.1.4 Water-Soluble Bases

- PEG having average molecular weights below 600 are clear, colourless liquids and those with molecular weights above 1000 are wax-like materials and those with molecular weights in between are semisolids. The greater the molecular weight, the greater the viscosity.
- The general formula for the preparation of 1000 g of PEG ointment is:

  Polyethylene Glycol 3350 400 g

  Polyethylene Glycol 400 600 g

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

1.2 Selection of appropriate base

- The selection of the base to be used in the formula of an ointment depends on a number of factors:

1. Desired release rate of the drug substance from the ointment base.
2. Desirability of occlusion of moisture from the skin.
3. Stability of the drug in the ointment base.
4. Effect of the drug on the consistency of the ointment base.
5. The desire for a base that is easily removed by washing with water.
6. Characteristics of the skin surface to which it is applied

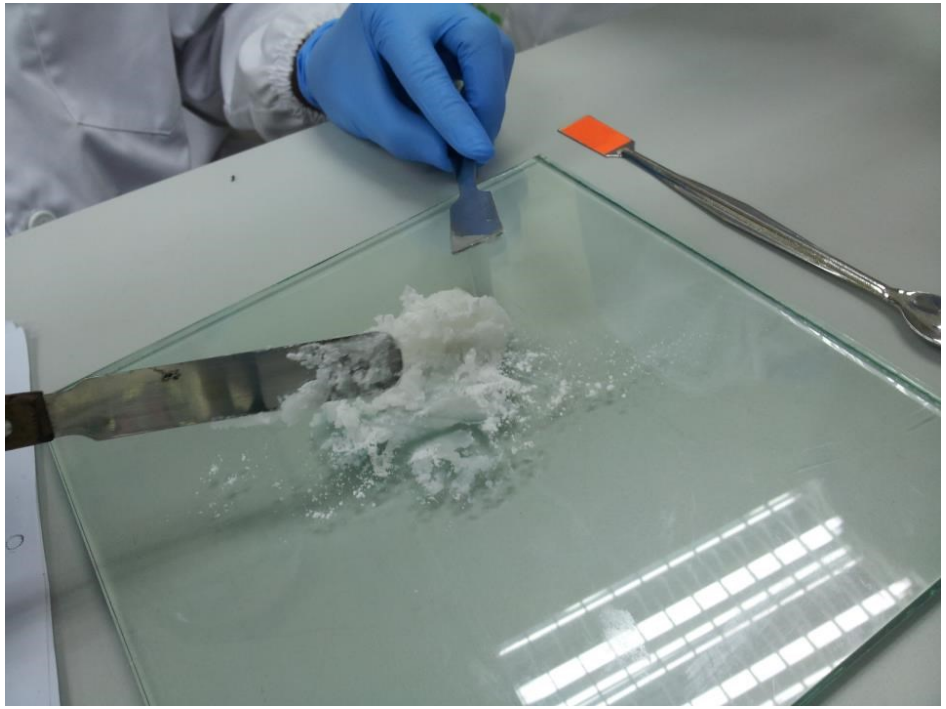
1.3 Preparation of Ointments

- Ointments are prepared by two general methods:

1) **Incorporation**

2) **Fusion**

- The method used depends primarily on the nature of the ingredients



1.3.1 Incorporation

- By the incorporation method, the components are mixed until a uniform preparation is attained, on a small scale the pharmacist may mix the components using a mortar and pestle or a spatula and slab (a glass or porcelain plate).

1.3.1.1 Incorporation of solids

When preparing an ointment by spatulation, the pharmacist works the ointment with a stainless steel spatula having a long, broad blade. If the components of an ointment are reactive with the metal of the spatula (e.g. as in the case of phenol), hard rubber spatula may be used.

The ointment base is placed on one side and the powdered components previously reduced to fine powders on the other side. A small portion of the powder is mixed with a portion of the base until uniform mixture is obtained. The process is continued until all portions of the powder and the base are combined and thoroughly and uniformly blended.

1.3.1 Incorporation

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

1.3.1 Incorporation

• 1.3.1.2 Incorporation of Liquids

- Liquid substances or solutions of drugs are added to an ointment according to 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.
- When it is necessary to add an aqueous preparation to a hydrophobic base, the solution first may be incorporated into a minimum amount of a hydrophilic base and then that mixture added to the hydrophobic base. However, all bases even if hydrophilic have their limit to retain liquids beyond which they become too soft or semiliquid. Alcoholic solutions of small volume may be added well to oleaginous vehicles or emulsion bases.
- On large scale, roller mills force ointments through stainless steel rollers to produce ointments that are uniform in composition and smooth in texture.

1.3.2 Fusion

- By the fusion method, all or some of the components of an ointment are combined by being melted together and cooled with constant stirring until congealed. Components not melted are added to the congealing mixture as it is being cooled and stirred.
- Naturally, heat-labile substances and any volatile components are added last when the temperature of the mixture is low enough not to cause decomposition or volatilization of the components.
- Substances may be added to the congealing mixture as solutions or as insoluble powders levigated with a portion of the base. On a small scale, the fusion process may be conducted in a porcelain dish or glass container.
- Medicated ointments and ointment bases containing components as bees wax, paraffin, stearyl alcohol and high molecular weight PEG which do not lend themselves well to mixture by incorporation are prepared by fusion.

1.3.2 Fusion

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

2. Creams

- Pharmaceutical creams are semisolid preparations containing one or more medicinal agents dissolved in either an o/w or w/o emulsion.
- Creams have a relatively soft, spreadable consistency. An example of an **o/w** cream is hydrophilic ointment and an example of a **w/o** cream is cold cream.
- When the term “cream” is used without further qualification, a water-washable formulation is generally inferred.

2. Creams

- Vanishing creams are o/w emulsions containing large percentage of water and stearic acid. After application of the cream, the water evaporates leaving behind a thin residue film of stearic acid or other oleaginous components.

2. Creams

- Many patients and physicians prefer creams to ointments because they are easier to spread and remove than ointments. Pharmaceutical manufacturers frequently manufacture topical preparations of a drug in both ointment and cream bases to satisfy the preference of the patient and physician.

2.1 Preparation of Creams

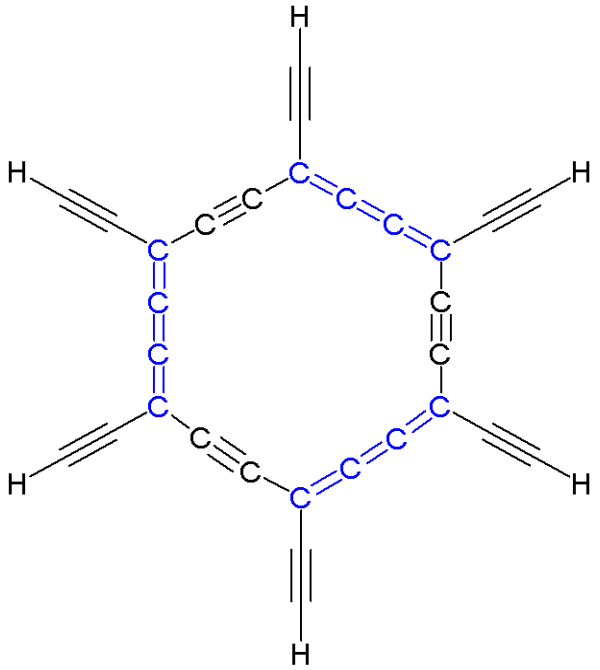
- Creams may be formulated from a variety of oils (both mineral and vegetable) and from fatty alcohols, fatty acids and fatty esters. Emulsifying agents include non-ionic surfactants and soaps.
- Preparation involves separating the formula components into two portions: lipid and aqueous. The lipid portion 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 reaching ambient temperature or the mixture has congealed.
- Mixing is continued during the cooling process to promote uniformity. High shear homogenizers may be employed to reduce particle or droplet size and improve the physical stability of the resultant dosage form.

3. Gels

- Gels are usually clear, transparent non-greasy semisolids containing solubilized active substances in an aqueous liquid vehicle rendered jelly-like by the addition of a gelling agent.
- Among the gelling agents used are synthetic macromolecules such as **carbomer**, cellulose derivatives as **carboxymethyl cellulose** or **hydroxypropyl cellulose** and natural gums as **tragacanth**.

3. Gels

- Carbomers are high molecular weight water-soluble polymers of acrylic acid cross-linked with allyl ethers of sucrose and depending on their polymeric composition different viscosities result, for example carbomer 910, 934 and 940. They are used as gelling agents at concentrations of 0.5-2% in water. Carbomer 940 yields the highest viscosity (40,000 – 60,000 centipoises) as a 0.5% aqueous dispersion.



3. Gels

- Gels may be used as lubricants or medicated gels administered by various routes including the **skin**, the **eye**, the **nose**, the **vagina** and the **rectum**.
- 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 methyl and propyl parabens and stabilizers such as edetate disodium.
- Gels are easy to apply and the evaporation of the water produces a pleasant cooling effect and it is easily removed by washing when treatment is complete. Gels may thicken on standing, forming a **thixotrope** and must be shaken before use to liquefy the gel and enable pouring.
- Single-phase gels are gels in which the macromolecules are uniformly distributed throughout a liquid with no apparent boundaries between the dispersed macromolecules and the liquid. A gel mass consisting of floccules of small distinct particles is termed a two-phase system often referred to as a **magma**.

4. Official requirements for semisolids

- Ointments and other semisolid dosage forms must meet the USP tests for **microbial content**, **minimum fill**, **packaging**, **storage** and **labelling**. **Ophthalmic ointments must meet tests for sterility and metal particle content.**

4.1 Microbial content

- With the exception of ophthalmic preparations, topical applications are not required to be sterile, they must however meet acceptable standards for microbial content and preparations which are prone to microbial growth must be preserved with antimicrobial preservatives. e.g. **methyl and propyl parabens** and **quaternary ammonium salts**.
- For example, Betamethasone valerate ointment USP, must meet the requirements of the tests for the absence of staphylococcus aureus and Pseudomonas aeruginosa.

4. Official requirements for semisolids

- These microbes are of special importance in dermatological preparations because of their capacity to infect the skin. Semisolids intended for rectal and vaginal use should be tested for the presence of yeasts and molds.
- Preparations that contain water tend to support microbial growth to a greater extent than preparations which are water-free.

4.2 Minimum Fill

- The USP minimum fill test involves the determination of the net weight or volume of the contents of the filled containers to assure proper contents compared with the labelled amount.

4. Official requirements for semisolids

4.3 Packaging and Storage

- Ointments and other semisolid preparations are packaged in **metal** or **plastic** tubes. The tubes are first tested for compatibility and stability for the intended product.
- Tubes used to package topical products are light in weight, relatively inexpensive, convenient for use by the patient, compatible with most formulative components and provide greater protection against external contamination and environmental conditions than jars.
- **Ointment tubes are made of aluminum or plastic**. Tubes of aluminum generally are coated with **epoxy resin** to eliminate any interactions between the contents and the tube.
- Plastic tubes are made of high or low density polyethylene (HDPE or LDPE) or blend of them, polypropylene (PP) and plastic-foil paper laminates. **Laminates provide an excellent moisture barrier due to foil content, high durability and product compatibility**.

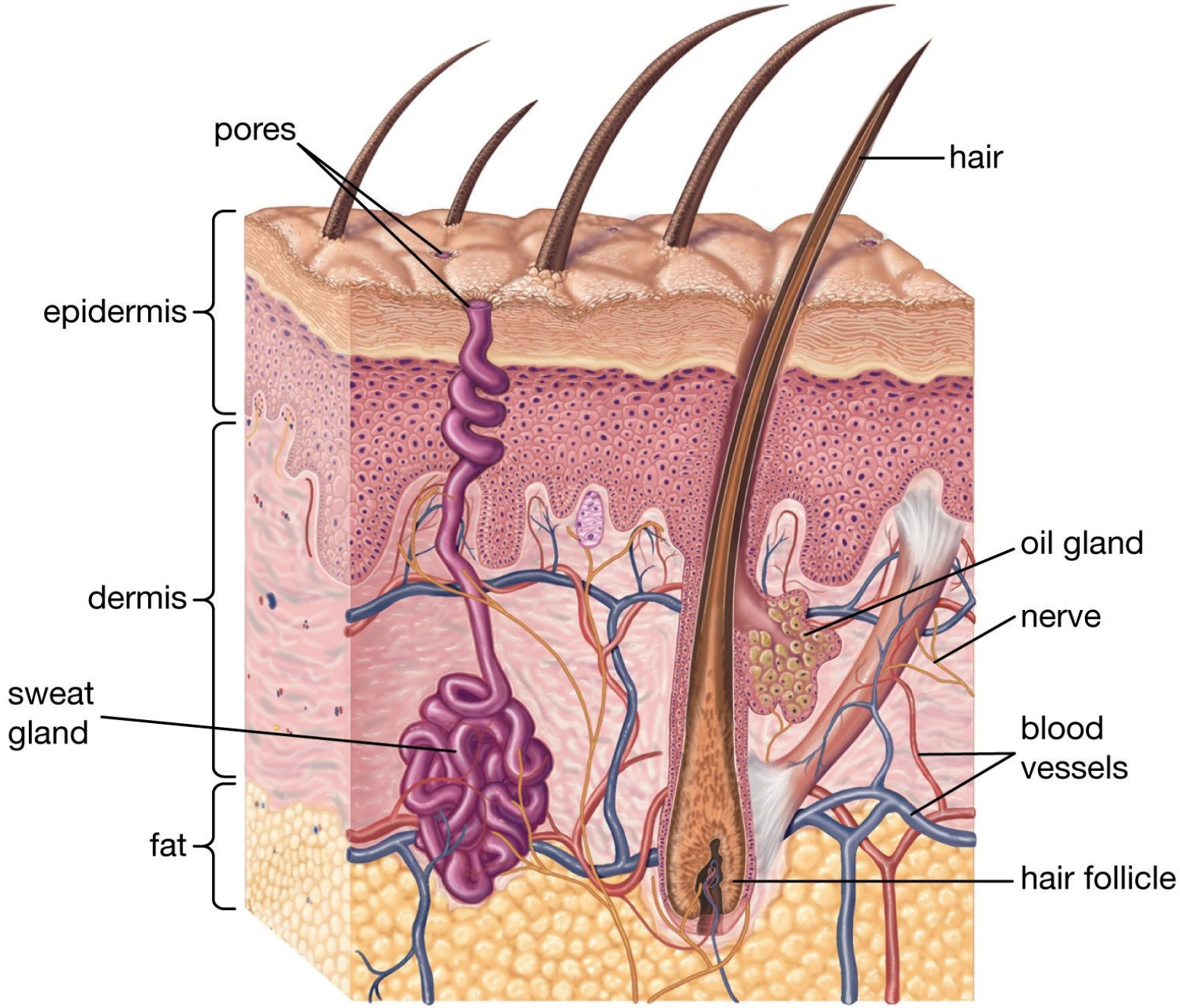
4. Official requirements for semisolids

- These qualities and flexibility make plastic and plastic laminate tubes preferred over metal tubes for the packaging of pharmaceuticals.
- Topical dermatological preparations most frequently are packaged in 5, 15 and 30 g tubes.
- Ophthalmic ointments are packaged in small aluminum or collapsible plastic tubes holding 3.5 g. The tubes are sterilized before being filled.
- Semisolids must be stored in well-closed containers to protect against contamination and in a cool place to protect against product separation due to heat. When required, light-sensitive preparations are packaged in light-resistant containers.

5. Skin Structure and Function

- Human skin is a highly complex multi-layered structure and it represents the largest organ of the body, comprising around 10% of the body mass.
- The main function of the skin is to act as a barrier between the body and the outside environment. This barrier prevents the entry of chemicals, microorganisms, UV radiation and the loss of water and body fluids. In addition, the skin plays a role in the regulation of body temperature and it also acts as a sensory organ.
- **Skin layers:**

1. **The Epidermis**
2. **The Dermis**
3. **The Subcutaneous Fatty layer**



5. Skin Structure and Function

5.1 Drug transport and permeation through the skin

- When a drug is applied topically, the drug diffuses out of its vehicle onto the surface of the skin.
- The drug molecules have three routes to traverse the intact stratum corneum depending on their physicochemical properties, these being:

✓ Intracellular (across corneocytes)

✓ Intercellular (across lipids) considered the major route of penetration

✓ Appendageal (via skin appendages)

5.1 Drug transport and permeation through the skin

- The intracellular pathway provides a polar route for the diffusion of hydrophilic molecules. However, the corneocytes are bound to a lipid envelope that connects to the lipid bilayers which need to be crossed.
- The intercellular route represents the major pathway for drug molecules to cross the stratum corneum, since the intercellular transport occurs through the lipid domains and also the intracellular transport needs the lipid bilayers between the corneocytes to be crossed.
- The appendages (hair follicles, sebaceous and sweat glands ducts) provide pores that overcome the stratum corneum barrier. This route represents a shunt route or shortcut through which the drug molecules can move across the stratum corneum.

5.1 Drug transport and permeation through the skin

- For a permeant with an intermediate partition coefficient (log *P* 1-3), the intercellular route probably predominates.
- For more hydrophilic molecules (log $P < 1$) , the intracellular route increasingly predominates.
- The transport of a highly hydrophilic and charged permeant is predominantly through the appendageal route.

5.2 Factors Affecting Skin Penetration

- **The rate and extent of a drug that penetrate the skin depends on:**

1. Physicochemical properties of the drug (molecular weight, partition coefficient “lipid solubility” and aqueous solubility).
2. Type of vehicle used and concentration of the drug in a vehicle.
3. Skin condition

6. Ophthalmic Ointments

- The major route by which drugs enter the eye is by **simple diffusion via the cornea**.
- The cornea is a lipophilic epithelial layer and lipophilic drugs are more capable of penetration than hydrophilic compounds.
- In general, ocular drug penetration is limited **due to the short residence time that the ophthalmic preparations have on the surface of the eye** because of their rapid removal by tearing, the small surface area of the cornea available for drug absorption and the cornea's natural resistance to drug penetration.
- Compared with ophthalmic solutions, ophthalmic ointments and gels provide extended residence time on the surface of the eye. Therefore, increasing the duration of their effects and bioavailability for absorption into ocular tissue.

6. Ophthalmic Ointments

- 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.
- The ointment base selected for an ophthalmic ointment must be:
  1. Non-irritating to the eye.
  2. Permit the diffusion of the medicinal substance into the eye.
  3. Have a softening point close to body temperature both for patient comfort and for drug release.
- Mixture of white petrolatum and liquid petrolatum (mineral oil) are utilized as the base in medicated and non-medicated ophthalmic ointments. A gel-base of polyethylene glycol and mineral oil is also used.
- Medicinal agents are added to an ointment base either as a solution or as a finely micronized powder. The ointment made uniform by fine milling.

6. Ophthalmic Ointments

- Ophthalmic ointments must meet the USP sterility test and the test of metal particles.
- Rendering an ophthalmic ointments sterile requires special techniques and processing. The terminal sterilization of a finished ointment by standard methods may have some limitations.
- Steam sterilization or ethylene oxide methods are ineffective because neither is capable of penetrating the ointment base.
- Although dry heat can penetrate the ointment base, the high heat required may affect the stability of the drug substance and can separate the ointment base from other components.

6. Ophthalmic Ointments

- Because of these difficulties, terminal sterilization is not undertaken, rather strict methods of aseptic processing are employed as each drug and non-drug component is sterilized and then aseptically weighed and incorporated in a final product, also preservative can be added.
- Among the antimicrobial preservatives used are combination of methylparaben 0.05% and propylparaben 0.01%, chlorobutanol and benzalkonium chloride.
- The USP test for metal particles involves the microscopic examination of a heat-melted ophthalmic ointment. The detected metal particles are counted and measured.
- The requirement met if the total number of particles 50 µm or larger from 10 tubes does not exceed 50.

7. Pastes, Plasters and Glycerogelatins

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 they 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. 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 the paste, they remain in place after application and they are effectively employed to absorb serous secretions. In addition, because of their stiffness and impermeability, pastes are not suitable for application to hairy parts of the body.

7. Pastes, Plasters and Glycerogelatins

- e.g. zinc oxide paste, prepared by mixing 25% each of zinc oxide and starch with white petrolatum. The product is very firm and is able to protect the skin and absorb secretions than is zinc oxide ointment.

Plasters:

- Are solid or semisolid adhesive masses spread on a backing of paper or plastic, the adhesive material is a rubber base or a synthetic resin.
- Plasters are applied to the skin to provide prolonged contact at the site. Unmedicated plasters provide protection or mechanical support at the site of application.

7. Pastes, Plasters and Glycerogelatins

- Medicated plasters provide effects at the site of application. e.g. salicylic acid plaster used on the toes for the removal of corns. The horny layers of skin are removed by the keratolytic action of salicylic acid. The concentration of salicylic acid used ranges from 10-40%.

Glycerogelatins:

- Are plastic masses containing gelatin 15%, glycerin 40%, water 35% and an added medicinal substances 10% such as zinc oxide.
- They are prepared by first softening the gelatin in water for 10 minutes, then heating on a steam bath until gelatin is dissolved, followed by the addition of the medicinal substance mixed with glycerin and allowing the mixture to cool with stirring until congealed.

7. Pastes, Plasters and Glycerogelatins

- Glycerogelatins are applied to the skin for the long term. They are melted before application, cooled to slightly above body temperature and applied to the affected area with a fine brush.
- Following application, the glycerogelatin hardens and is usually covered with a bandage and is allowed to remain in place for weeks.
- e.g. zinc glycerogelatin used in the treatment of varicose ulcer, it was also known as zinc gelatin boot because of its ability to form a pressure bandage.

8. Transdermal Drug Delivery Systems (TDDS)

- TDDS facilitate the passage of therapeutic quantities of drug substances through the skin into the general circulation for their systemic effects, with the skin not being the target organ.

Advantages of TDDS:

1. They can avoid gastrointestinal drug absorption problems caused by GIT pH, enzymes and drug interaction with food, drink or with other orally administered drugs.
2. They avoid the first-pass effect responsible for metabolism and deactivation of drug by liver enzymes.
3. They can substitute for oral administration of drugs when that route is unsuitable as in cases of vomiting and or diarrhoea.

8. Transdermal Drug Delivery Systems (TDDS)

4. They provide extended therapy with a single application, thereby improving patient compliance over other dosage forms requiring more frequent dose administration.
5. TDDS are non-invasive, avoiding the inconvenience of parenteral therapy.
6. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
7. Ease of rapid identification of the medication in emergencies e.g. unconscious or comatose patient due to the identifying-markings on the TDDS.

Disadvantages of TDDS:

1. Not all drugs are suitable candidates for TDDS due to the natural limit of drug entry imposed by the skin impermeability.
2. Some patients may develop contact dermatitis at the application site, requiring the discontinuation of therapy.

8. Transdermal Drug Delivery Systems (TDDS)

- There are certain parameters that can be used to predict the feasibility of an active drug ingredient for transdermal administration. These include:

  1. Log *P*, ideally the log partition coefficient of the drug should be in the range of 1-3.
  2. Molecular weight (MW), ideally the molecular weight of the drug should be less than 500 Dalton.
  3. Aqueous solubility, ideally the aqueous solubility of the drug should be equal or greater than 1 mg/mL.
  4. Melting point of the permeant should be less than 200 °C.
  5. The effective daily dose of the drug should be in the range of 10-40 mg/day

8.1 Transdermal delivery patches

- Are designed to deliver a constant and controlled dosage over extended periods of time for systemic therapy.
- Due to the barrier properties of the skin, relatively few drug molecules have the appropriate physicochemical and therapeutic properties for sustained transdermal delivery. However some successful products have reached the market such as scopolamine, nicotine, estradiol, fentanyl, testosterone and glyceryl trinitrate transdermal patches.

8.2 Design of transdermal patches

- Numerous patch design exist. The simplest systems contain the drug in an adhesive, with more complexity introduced in matrix type patches and reservoir systems.

1. Drug-in-adhesive patches are the simplest and most common patch design and are widely used to deliver nicotine and glyceryl trinitrate.

   These patches are formed by dissolving or dispersing drug within an adhesive which is then coated onto a backing layer before a release liner is applied. Drug-in-adhesive patches tend to be thinner and more flexible than other systems, but drug loading constraints can reduce the period of delivery. For example, nicotine patches are designed for less than one day use.

8.2 Design of transdermal patches

2. Drugs can be included in a separate matrix which can be formulated to increase the drug content in the system, allowing longer term delivery.

   The drug containing matrix or reservoir is often a polymeric mixture, for example polyvinylpyrrolidone and polyvinylacetate, potentially with the addition of a plasticizer such as glycerol. Hydrogels may also be used as the matrix.

   Drug released from the matrix will partition into and diffuse through the adhesive layer.

8.2 Design of transdermal patches

3. More complex rate limiting membrane systems typically contain the drug in a reservoir but with release controlled through a semi-permeable membrane.

   The reservoir may be liquid or more often a gel and can be designed to contain higher drug loadings than a simple drug-in-adhesive system for prolonged delivery.

8.3 General clinical consideration in the use of TDDS

1. Percutaneous absorption may vary according to the site of application, there is a preferred application site stated in the literature of each product.

   The patient should be advised of the importance of using the recommended site and rotating locations within that site in the application of replacement patches.

   Rotating locations is important to allow the skin beneath a patch to regain its normal permeability characteristics after being occluded and also prevent the possibility of skin irritation. Skin sites may be re-used after a week.

2. TDDS should be applied to clean and dry skin areas that are relatively free of hair and not oily or irritated, inflamed broken area.

8.3 General clinical consideration in the use of TDDS

3. TDDS should not be physically altered by cutting (as in attempt to reduce the dose) since this would destroy the integrity of the system.

4. The protective removable release liner should be removed to expose the adhesive layer while being careful not to touch the adhesive surface which may contains drug to the finger tips. The patch should be pressed firmly against the skin site with the hand for 10 seconds to assure uniform contact and adhesion.

5. TDDS should be worn for the full period of time stated in the product's instructions and care should be taken not to touch the eyes or the mouth during handling of the system.

8.4 Examples of TDDS

1. **Transdermal Scopolamine**: used to prevent travel-related motion sickness, nausea and vomiting. The TDDS contains 1.5mg of scopolamine and is designed to deliver the drug at constant rate to the systemic circulation over 3 days. The patch is worn in a hairless area behind the ear.

2. **Transdermal Nitroglycerin**: designed to provide controlled release of nitroglycerin for the treatment of angina. Each patch delivers nitroglycerin over 24 hrs (Daily application) to the chest, shoulder and upper arm.

   Nitroglycerin is rapidly metabolised by the liver when taken orally and therefore this effect can be prevented by the transdermal route. Nitroglycerin patch is available in two strengths 5mg and 10mg.

8.4 Examples of TDDS

3. **Transdermal Nicotine**: are used in smoking cessation programs.

   They have been shown to be an effective aid in quitting the smoking habit when used according to product-recommended strategies.

   They provide sustained blood levels of nicotine as nicotine replacement therapy. The available patches contain from 7-22mg of nicotine for daily application for 6-12 weeks applied to the arm

Thank You!