جامعة الزهراء (ع) للبنات

كلية الصيدلة

فرع الصيدلانيات والصناعة الدوائية

ملزمة العملي لمادة الصيدلة التكنولوجية المرحلة الثالثة

اعداد المدرس المساعد وسام غازي سند الانباري

الهدف من المقرر

يهدف هذه الكورس بجانبه العملي لتوفير بيئة ملائمة للتطبيق العملي لتحضير الاشكال الصيدلانية المختلفة وتقييمها ومناقشة المشاكل العملية التي تواجه الصيدلاني عند تحضيرها، وكذلك يحفز الطلبة على ابتكار طرق وأساليب جديدة لتطوير الاشكال الصيدلانية.

كذلك يوفر الفرصة للطالبات للتعرف على المواد التي تدخل في الصناعة الدوائية وكيفية التعامل معها وكيف تتم عملية تحول المنتج من المختبر الى مستوى التصنيع المعملي ومتطلبات ذلك.

يعتبر هذا المختبر بيئة ملاءمة لبحث ومناقشة وتجريب كل ما يتعلق بالاشكال الصيدلانية

1st semester

Lab 1

Solutions

In pharmaceutical terms, solutions are "homogeneous liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of miscible solvents"

- Solid in liquid (e.g. NaCl in water)
- Liquid in liquid (e.g. alcohol in water)
- Gas in liquid (e.g. ammonia solution)

Classification

- **According to route of administration:** e.g. oral, ophthalmic, topical, etc.
- **According to their composition:**

1. Syrups: aqueous solutions containing a sugar (even though some syrups may contain some alcohol)
2. Elixirs: sweetened hydro-alcoholic solutions (combinations of water and ethanol)
3. Spirits: solutions of aromatic materials (the solvent is alcoholic)
4. Aromatic waters: solutions of aromatic materials (the solvent is water)

5. Tinctures or fluidextracts: solutions prepared by extracting active constituents from crude drugs (depending on their method of preparation and concentration).
6. Injections: are certain solutions prepared to be sterile and pyrogenic-free intended for parenteral administration.

- **According to the procedure of preparation:**

1. Solutions prepared by "simple solution" method.
2. Solutions prepared by "chemical reaction".
3. Solutions prepared by simple solution with sterilization (e.g. ophthalmic solutions)
4. Solutions prepared by "extraction".

Several Problems Associated with the Preparation of Solutions

- we must know the solubility of the solutes.
- If there are prescriptions that contain substances react to **liberate CO2**, we must wait until there is no liberation of the gas.
- If there are **gum substances**, must be prepared by circulating method in wide mouth container and should avoid using stirrer.
- If there are **fine powder** form, it must be prepared in a mortar and add solvent gradually with mixing.
- If there are substance with **large particle size** (crystals), we must reduce the particle size by using a mortar to increase the solubility of the substance e.g. ferrous sulphate.
- If there are substance **insoluble** in the vehicle, we must add other substance to increase the solubility of the substance e.g. surfactants.
- Applying heat is not suitable for exothermic procedures and for volatile or heat-sensitive materials.
- Some chemical agents in a given solvent require an extended time to dissolve. To increase dissolution rate, a pharmacist may employ one of several techniques, such as applying heat, reducing the particle size of the solute, using a solubilizing agent, and/or subjecting the ingredients to vigorous agitation.

We will focus on oral solutions…

- Solutes other than the medicinal agent (excipients) are usually present in orally administered solutions. These additional agents are frequently included to provide color, flavor, sweetness, or stabilizer.
- We must check the solubility and stability of each solute with regard to the solvent or solvent system. Also, combinations of medicinal or pharmaceutical agents that will result

in chemical and/or physical interactions affecting the therapeutic quality or pharmaceutical stability of the product must be avoided.

- Solubility; check United States Pharmacopeia-National Formulary (USP-NF) as well as other reference books.

General method of preparation of simple solution

1. Weigh solid ingredients and mix them together.
2. Measure ¾ of the final volume of the preparation (mitt.) in a beaker.

i.e. (¾ × final volume)

3. Dissolve the solid ingredients in the beaker with stirring.
4. Filter if necessary.
5. Transfer to graduated cylinder and complete the volume with solvent to the required amount (mitt.).
6. Transfer to suitable container and label it.

If there are liquid ingredient(s):

1. Weigh solid ingredients and mix them together.
2. Measure ¾ of the final volume of the preparation (mitt.).
3. Subtract the volume of liquid ingredient from the ¾ the final volume.

i.e. (¾ × final volume) – liquid ingredients)

4. Dissolve the solid ingredients in the beaker with stirring.
5. Add the liquid ingredients with mixing.
6. Transfer to graduated cylinder and complete the volume with solvent to the required amount (mitt.).
7. Transfer to suitable container and label it.

EXAMPLE 1

NaCl 25 mg

Water q.s. 100 ml

Mitte 200 ml

Calculations:

Enlargement Factor = Mitt./q.s. = 200/100 = 2

⇨ 25 × 2 = 50 mg of NaCl

⇨ 100 × 2 = 200 ml of water

¾ × 200 = 150 ml of water will be used to dissolve NaCl initially.

Procedure:

1. Weigh 50 mg of NaCl.
2. Measure 150 ml of water and place it in a beaker.
3. Dissolve the NaCl in the beaker with stirring.
4. Transfer to graduated cylinder and complete the volume to 200 ml with water.
5. Transfer to suitable container and label it.

EXAMPLE 2

NaCl 25 mg

Coloring agent 10 ml

Water q.s. 100 ml

Mitt. 50 ml

Calculations:

Reducing Factor = mitte/q.s. = 50/100 = ½

⇨ 25 × ½ = 12.5 mg of NaCl

10 × ½ = 5 ml of the colouring agent 100 × ½ = 50 ml of water

(¾ × 50) – 5 = 32.5 ml of water be used to dissolve NaCl initially.

Procedure:

1. Weigh 12.5 mg of NaCl.
2. Measure 32.5 ml of water and place it in a beaker.
3. Dissolve the NaCl in the beaker with stirring.
4. Add 5 ml of the colouring agent and mix.
5. Transfer to graduated cylinder and complete the volume to 50 ml with water.
6. Transfer to suitable container and label it.

℞

Carminative mixture for infants

Sodium bicarbonate		0.06 g
Aromatic spirit of ammonia		0.06 ml
Compound tr. of cardamom		0.12 ml
Glycerin		0.3 ml
Peppermint water	q.s.	4 ml
ft. mist.		
Mitte		20 ml
sig. fl. ʒi t.i.d. p.c.		

Sodium bicarbonate	Antacid
Aromatic spirit of ammonia	Carminative
Compound tr. of cardamom	Flavoring and coloring agent, carminative
Glycerin	Soothing and sweetening agent
Peppermint water	Solvent, carminative and flavoring agent

Calculations:

Factor = mitte/q.s. = 20/4 = 5

⇨ 0.06 × 5 = 0.3 g of $NaHCO_3$

0.06 × 5 = 0.3 ml of aromatic spirit of ammonia

0.12 × 5 = 0.6 ml of compound tr. of cardamom

0.3 × 5 = 1.5 ml of glycerine

Liquid ingredients = 0.3 + 0.6 + 1.5 = 2.4 ml

(¾ × 20) – 2.4 = 12.6 ml of peppermint water be used to dissolve NaHCO3 initially.

Procedure:

1. Weigh 0.3 g of NaHCO3.
2. Measure 12.6 ml of peppermint water and place it in a beaker.
3. Dissolve the NaHCO3 in the beaker with stirring.
4. Measure 0.3 ml of aromatic spirit of ammonia, 0.6 ml of compound tr. of cardamom and 1.5 ml of glycerine. Add them to the beaker and mix.
5. Transfer to graduated cylinder and complete the volume to 20 ml with peppermint water.
6. Transfer to suitable container and label it.

℞

Aqueous Iodine Oral Solution BP (Lugol's solution) (oral use)

Iodine		50 g
KI		100 g
P.W.	q.s.	1 L
ft. mist.		
Mitte		25 ml

sig. 0.3 ml diluted with milk or water t. i. d.

Procedure:

1. Prepare a concentrated KI solution.
2. Dissolve iodine in KI solution (chemical reaction by complexation)
3. Transfer to graduated cylinder and complete the volume to 25 ml with purified water.
4. Transfer to suitable container and label it (internal use).

Uses:

For use in the pre-operative management of hyperthyroidism.

℞

Alcoholic Iodine Solution BP, Iodine Tincture BP (external use) (antiseptic)

Iodine 25 g

KI 25 g

P.W. 25 ml

Ethanol (90%) q.s. 1000 ml

ft. mist.

mitte 25 ml

sig. externally b. i. d.

Uses:

As an antiseptic for use on minor wounds, cuts and abrasions.

℞

Weak Iodine Solution

Iodine		25 g
KI		15 g
P.W.		25 ml
Ethanol (90%)	q.s.	1000 ml

sig. externally b. i. d.

Procedure:

1. Prepare a concentrated KI solution (25 ml of water + 15 g of KI).
2. Dissolve iodine in KI solution (chemical reaction by complexation)
3. Transfer to graduated cylinder and complete the volume to 1L with ethanol.
4. Transfer to suitable container and label it (external use).

℞

Strong Iodine Solution

Iodine		100 g
KI		60 g
P.W.		100 ml
Ethanol (90%)	q.s.	1000 ml

sig. externally b. i. d.

Lab 2

Solutions for External use

Alcoholic Iodine Solution BP, Iodine Tincture BP (external use) (antiseptic)

Iodine	25 g
KI	25 g
D.W.	25 ml
Ethanol (90%) q.s.	1000 ml

ft. mist.

mitte 25 ml sig. externally b. i. d

.Uses：As an antiseptic for use on minor wounds, cuts and abrasions.

Procedure:

1. Prepare a concentrated KI solution. (KI mixed with D.W)
2. Dissolve iodine in KI solution (chemical reaction by complexation)
3. Transfer to graduated cylinder and complete the volume to 25 ml with ethanol 90%.

Mouthwash

Mouthwashes are aqueous solutions used to rinse the oral cavity. They have refreshing and antiseptic effects.

Sodium Chloride Mouthwash

Sodium chloride	1.5 g
Sodium bicarbonate	1 g
Peppermint water q.s.	100 ml

ft. mist.

mitte 20 ml

sig. dilute with equal volume of warm water before use. Rinse the mouth 3 – 4 times daily as required

Procedure: By simple solution method.

Ear Drops

• Are solutions, suspensions, or emulsions of one or more medicament in a vehicle suitable for installation into the ear (e.g. antibiotics, antiseptics, wax softener, etc.).

• Ear drops may contain preservatives and viscosity enhancers such as glycerin. High viscosity increases contact time and prolongs drug effect. In addition, glycerin acts as a lubricant.

• Commonly used solvents include water, glycerin, dialcohol, propylene glycol, etc.

Sodium Bicarbonate Ear Drops BP

Sodium bicarbonate 5 g

Glycerin 30 ml

P.W. q.s. 100 ml

ft. mist.

mitte 20 ml

Sig. as directed (externally)

Procedure (BP):

1. Dissolve the $NaHCO_3$ in about 60 ml of P.W.

2. Add glycerin and sufficient P.W. to produce 100 ml and mix.

NOTE: It is used as wax softener.

Nasal Drops

• Are aqueous or oily solutions which are designed to be administered the nasal passages in drops or spray forms for their local or systemic effects.

• Nasal drops are usually isotonic with the nasal secretions and have approximately the same pH.

Examples:

O Decongestant: acts as vasoconstrictor (sympathomimetic) to blood vessels in the nasal cavity. e.g. Xylometazoline (Otrivin®).

O Antiseptic (e.g. Nozin®, contains mainly alcohol).

Ephedrine Nasal Drops

Ephedrine HCl		500 mg	(decongestant)
NaCl		500 mg	(isotonicity)
Chlorobutanol		500 mg	(preservative)
D.W.	q.s.	1000 ml	
ft. mist.			
mitt		20 ml	

Sig. 2 drops in each nostril as directed (internally)

Procedure by simple solution method

- Mix ephedrine and NaCl together
- Dissolve the mixture in hot water (60 °C)
- Pure the mixture in graduated cylinder and complete the volume to 20

Lab 3

Syrups

- Syrups are a nearly saturated aqueous solutions of sugar, with or without medicinal or flavoring ingredients.
- They are characterized by a sweet test and relatively high viscosity.
- Medicinally, syrups can be classified into:

o Non-medicated syrups: are used as a vehicle for several preparations.

o Medicated syrups: contain substances (active pharmaceutical ingredients, APIs). They have therapeutic effects such as antihistamine (Allermine®), cough syrup (Sedilar®), etc.

- Pharmaceutically, syrups are classified into:

o Sugar-based syrups: which are concentrated solutions of sugar (e.g. sucrose and dextrose).

o Sugar-free syrups: are formulated with artificial sweetening agents and viscosity builders (e.g. saccharin sodium, sorbitol, sodium cyclamate). They are used for patients regulating their diet (e.g. diabetic patients). These syrups are not viscous in nature and therefore, we must add viscosity builder such as glycerine, methyl cellulose (MC), hydroxyethyl cellulose (HEC), etc.

Sugar-based syrups

1. Sucrose-based syrups
2. Dextrose-based syrups

1. Sucrose – based syrups

Sucrose: Is one of the purest commercially available substance and it is the preferred carbohydrate for syrups because:

- Purity.
- Degree of sweetness (100%).
- Lack of color.
- Ease of handling.
- Inertness.
- Availability.

Stability of sucrose-based syrups

Sucrose is subjected to two degenerative pathways in aqueous solution: fermentation and hydrolysis.

1. Fermentation: As a carbohydrate, sucrose in dilute aqueous solution provides a nutrient medium for the growth of molds and yeasts. The consequences of this growth are:

o Turbidity (change in color)

o Change in odor.

o Change in taste.

- The ability of these organisms to grow is reduced as the concentration of sucrose is increased. Therefore, syrups should contain enough sucrose to approach saturation.
- Nearly saturated solutions of sucrose (if stored in good storage conditions) are self-preservatives because they don't contain free water for microorganisms to grow in.
- Few syrups contain 0.1 – 0.2% w/v preservatives such as benzoic acid, sodium benzoate, etc.

2. Hydrolysis: Sucrose is a disaccharide compound. It undergoes hydrolysis to give fructose (levulose) and glucose (dextrose).

- $C_{12}H_{22}O_{11} + H_2O \xrightarrow{H^+, \Delta} C_6H_{12}O_6 + C_6H_{12}O_6$

(Sucrose) (Glucose) (Fructose)

- The reaction takes place in the presence of strong acid and heat.

It is also called "inversion reaction" because the solution of sucrose rotates polarized light to the right while it rotates the polarized light to left after hydrolysis. This is because levulose has greater rotating capacity than dextrose.

• The inverted sugar has specific properties:

o Solutions of inverted sugar are subjected to fermentation at higher degrees than solutions of sucrose.

o After inversion, the solution becomes sweeter because sucrose is rated with a sweetness of 100% while dextrose is rated 74% and levulose with 173%.

o The formed levulose by inversion seems to be responsible for the brown discoloration that develops in some of the colorless syrups. This change in color is called “caramelization” and it occurs in syrups containing strong acids.

• To eliminate this discoloration, dextrose might be used instead of sucrose (i.e. dextrose-based syrups).

Storage of syrups

1. Syrups are stored at room temperature (25 °C) in tightly stoppered and well-filled bottles.

2. Refrigeration inhibits both fermentation and hydrolysis. However, temperatures below 4 °C result in crystallization of sugar, resulting in the formation of large crystals which are difficult to re-dissolve. This lead to lowering the concentration of sucrose below saturation.

Dextrose-based syrups

- Dextrose may be used as a substitute for sucrose in syrups containing strong acids in order to eliminate the discoloration associated with caramelization and the problem related to sucrose hydrolysis.

- The differences between sucrose and dextrose are:

o Dextrose forms a saturated solution in water at 70% w/v which is less viscous than simple syrup.

o Dextrose dissolves more slowly than sucrose.

o Dextrose has less sweetness than sucrose (74%).

o The saturated solution of dextrose readily supports the growth of microorganisms. Consequently, it is more easily fermented (the saturated solution of sucrose is self-preservative).

- Preservatives are usually required for dextrose-based syrups. Glycerin may be used in a concentration of 30 – 45% v/v to act as preservative. In addition, this concentration of glycerin improves the viscosity and gives additional sweetness to the preparation.

Simple Syrup BP (66.7% w/w)

Sucrose	667 g
Purified water (P.W.) q.s.	1000 g

ft. mist.

Mitt. 50 g

Calculations

Factor = mitte/q.s. = 50/1000 = 0.05

 0.05 × 667 = 33.35 g of sucrose will be used.

1000 × 0.05 = 50 g of water will be used.

Procedure

1. Weigh the beaker (empty) and weigh 33.35 g of sucrose in it.

2. Add about 15 g of P.W. and stir to dissolve the sucrose with gentle heating (use water bath).

3. Wight again and complete the weight to 50 g with hot water to avoid crystallization.

4. Allow to cool and transfer the syrup into a dry clean bottle and label it.

Simple Syrup USP (85% w/v)

Sucrose	850 g
P.W. q.s.	1000 ml
ft. mist.	
mitte	50 ml

calculation

1- Mitt/q.s = 50/1000 = 0.05

2- 850 × 0.05 = 42.5 gm

Procedure

1. Weigh the beaker (empty) and weigh 42.5 g of sucrose in it.

2. Add about 15 ml of D.W. and stir to dissolve the sucrose with gentle heating (use water bath).

3. complete the volume to 50 ml with hot water to avoid crystallisation.

4. Allow to cool and transfer the syrup into a dry clean bottle and label it.

Dextrose base syrup

Dextrose	70 gm
D.W q.s	100ml
Mitt	50 ml

Procedure: as previous in sucrose based syrup

Lab 4

Sugar-free syrups (non-nutritive syrups)

Sucrose is the sugar most frequently employed in syrups. However, several formulas have been developed which contain no sugar. These are intended for patients suffering from diabetes mellitus (hyperglycemic).

Some early formulas included glycerin in order to take the advantage of its viscosity and sweetness. However, glycerin as well as propylene glycol are glycogenic substances (i.e. converted to glucose in the body). Therefore, substances to be used as sugar substituents should be non-glycogenic (e.g. methylcellulose or hydroxyethyl cellulose).

General formula for sugar-free syrup

1. Sweetening agent.
2. Viscosity builder.
3. Preservative.
4. Purified water.

1. Sweetening agent:

a. Saccharin sodium: Its sweetening power is approximately 300 – 600 times that of sucrose. It may be used in concentration of 0.04–0.25 %w/v. It has somehow metallic or bitter aftertaste. The aftertaste can be masked by blending saccharin sodium with other sweeteners.

b. Sodium cyclamate: Its sweetening power is approximately 30 times that of sucrose. Used in concentrations around 0.17% w/v. It has less bitter aftertaste than saccharin sodium. In most applications, sodium cyclamate is used in combination with saccharin, often in a ratio of 10:1.

c. Other synthetic sweeteners: such as aspartame which has an approximate sweetening power of 180 – 200 times that of sucrose.

2. Viscosity builder:

a. Natural gums: such as acacia and tragacanth. Their solutions are not colorless and their characteristics tend to change upon aging. Preservatives must be included in the formulations containing these agents since their aqueous solutions support the growth of microorganisms.

b. Methylcellulose and hydroxyethyl cellulose: They are non-glycogenic and produce colorless products.

3. Preservative: such as benzoic acid, sodium benzoate, etc.

Sorbitol-based syrups

- Sorbitol is hexahydric alcohol ($C_6H_{14}O_6$). It can be obtained by hydrogenation of glucose.

- It is used in the concentration of 70 %w/w which does not support the growth of microorganisms. Preservatives should be added in solutions containing less than 60 %w/w of sorbitol.
- Sorbitol has a pleasant, cooling, sweet taste and has approximately 50 – 60% of the sweetness of sucrose. Its viscosity is about half of that of sucrose- based syrups.
- Unlike sucrose, sorbitol doesn't support the formation of dental caries.
- Sorbitol is metabolized and converted to glucose. However, it is not absorbed from GIT quickly. No significant hyperglycemia has been found in

patient taking sorbitol-based syrups and therefore, it can be used as a component of non-nutritive vehicles.

- The ingestion of excessive quantities of sorbitol may have a laxative effective.

Chloral Hydrate Syrup (Official)

Chloral hydrate 0.5 g (sedative)

Simple syrup q.s. 100 ml

ft. mist.

mitte 25 ml

Sig. one tablespoonful o.n.

Procedure:

By simple solution method.

Chloral Hydrate Syrup (Non-official)

Chloral hydrate 0.5 g (sedative)

Sorbitol 25 g

P.W q.s. 100 ml

ft. mist.

mitte 25 ml

Sig. one tablespoonful o.n.

Procedure:

By simple solution method.

Ferrous Sulphate Syrup

Ferrous Sulphate	1 g
Citric acid (hydrous)	0.05 g (to prevent auto-oxidation of Fe+2)
Alcohol	0.1 ml
Peppermint oil	0.02 ml
P.W.	10 ml
Simple syr. q.s.	25 ml

ft. mist.

Procedure

1. Dissolve the ferrous sulphate and citric acid in water.

2. Dissolve peppermint oil in alcohol.

3. Add the aqueous solution to the alcoholic one and complete the volume to 25 ml with simple syrup.

Elixirs

- It may be defined as a clear sweetened solution containing flavoring materials and usually medicinal substance intended for oral use.

- The main ingredients are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, preservatives and sugar (syrup).

Classification of Elixir

1. Non-medicated elixir: are used as flavors and vehicles for drugs substances, ex. Aromatic Elixir USP.

2. Medicated elixir: when drug substance is incorporated into the specified solvent, ex. Dexamethasone, Phenobarbital Elixirs.

Lab 5

Suspensions

- Suspensions are heterogeneous disperse systems consisting of two phases. The continuous or external phase is generally a liquid, and the dispersed or internal phase is made up of particulate matter that is essentially insoluble in, but dispersed throughout, the continuous phase.

- A disperse phase with a mean particle diameter of up to 1 µm is usually termed a colloidal dispersion while the solid in liquid dispersion in which the particles are above colloidal size termed coarse suspension.

- Suspensions can be used orally, parenterally, topically, rectally, ophthalmically , etc.
- Some suspensions are available in ready to use form (e.g. metronidazole (Flagyl®)) and others are available as dry powders intended for suspension in liquid vehicles, most often purified water (e.g. amoxicillin (Amoxil®).
- Almost all suspension systems separate on standing. The aim here is not to prevent this settling, but:

1. To decrease the rate of the settling
2. To permit easy re-suspendability of any settled particulate matter (no caking).

- Caking is defined as the formation of non-re-dispersible sediment within a suspension system.

Features Desired in the Pharmaceutical Suspension

A desirable suspension should:

1. Settle down slowly (remain suspended long enough to withdraw an accurate dose).
2. Readily re dispersed upon gentle shaking of the container.
3. The particle size should remain fairly constant throughout long periods of storage (no caking).
4. Easily pourable from its container (not highly viscous).
5. Suitable odor, color, and taste. Stable and not decompose or support growth of molds.

Why Suspensions?

- Solubility.
- Stability: Certain drugs are chemically unstable in solution but stable when suspended.
- Palatability: The disadvantage of a disagreeable taste of certain drugs in solution form is overcome when the drug is administered as undissolved particles of an oral suspension. For example, erythromycin estolate is a less water-soluble ester form of erythromycin and is used to prepare a palatable liquid dosage form of erythromycin.

Some Advantages of Suspensions

- Sterile suspensions are injected hypo-dermally or intramuscularly to produce prolonged release of medication than would a true solution of the same drug.
- Can improve chemical stability of certain drugs.

Some Disadvantages of Suspensions

- They must be well shaken prior to measuring a dose.
- The accuracy of the dose is likely to be less than with the equivalent solution.
- Conditions of storage may adversely affect the disperse system and in the case of non-diffusible solids clumping may occur, leading to potential dosing inaccuracy.

Storage of Suspensions

- The physical stability of suspensions is adversely affected by variations in temperature. Suspensions should be stored in cool place, neither in refrigerator nor in freezer because the suspended particles may aggregate at low temperatures.
- In addition, suspension should be stored in a wide mouth bottle which has enough space to allow good agitation before use.
- Light protection or tightly closed bottles >>> depend on the ingredients.

Classification of Suspensions

1. Suspensions containing diffusible solid(s).
2. Suspensions containing non-diffusible solid(s).
3. Suspensions containing precipitate forming liquid.
4. Suspensions containing poorly wettable solid(s).
5. Dispersions of oil in inhalation.
6. Suspensions prepared by chemical reaction.

1. Suspensions containing diffusible solid(s)

- Some insoluble powders are light and easily wettable and therefore readily mixed with water and upon shaking they diffuse evenly through the liquid for long period enough to ensure dosing consistency. Such substances are known as diffusible or dispersible solids (e.g. kaolin, pectin, magnesium carbonate, bismuth carbonate).
- Some substances are soluble at low concentrations only and at high concentration, they form suspensions. These are classified as diffusible solids as well.

Example: Boric acid is soluble at concentration ≤ 4% w/v (forms clear solution). At concentrations > 4% w/v, it is not completely dissolved (suspension).

General method to prepare suspension containing diffusible solid(s)

1. Using mortar and pestle, reduce the particle size of any ingredient having coarse particles to produce fine powders.

2. Mix insoluble powders in mortar by adding the ingredient with the smallest quantity first then diluting it with others in increasing order of bulk using amount approximately equal to the bulk already exists in the mortar. This method is called geometric dilution method.

3. After taking in consideration any liquid ingredients, measure ¾ of the vehicle, then use it as follows:

- ¼ of the vehicle to prepare smooth paste.
- ¼ of the vehicle for dilution to produce a pourable paste.
- ¼ of the vehicle to wash the mortar.

4. The mortar's content must be homogenous before transferring it and should not be thick and rigid nor sticking to the pestle or mortar's edges.

5. Transfer the mixture from the mortar to a measuring cylinder and rinse the mortar with ¼ of the vehicle.

6. Add any liquid ingredients and complete the volume with the vehicle.

7. Label: Shake before use.

Notes:

- Soluble solids such as sodium bicarbonate should be dissolved in the second

¼ of the vehicle (dilution part).

- Volatile substances should be added to suspension before completing the volume to avoid their loss by volatilization (e.g. chloroform, some tinctures, flavoring spirits, etc).
- Liquids with high viscosity such as syrup, glycerin, or propylene glycol are added to the smooth paste before dilution.
- Dyes are added to the smooth paste before dilution to allow penetration and distribution of the color among insoluble particles (e.g. amaranth solution).

Boric acid		10 g	(diffusible solid)
D.W.	qs.	30 ml	(vehicle)
mitte		15 ml	

- Used as antiseptic for minor burns.
- The diluted one can be used for eye wash and as a douche (for vaginosis).

Light magnesium carbonate	650 mg	(diffusible solid)

Sodium bicarbonate

Chloroform water mitte

sig

qs. 975 mg

30 ml

120 ml

15 ml q.i.d. (water soluble solid)

(vehicle)

- Used as antacid and has a laxative effect.

Bismuth carbonate 585 (diffusible solid)

Compound powder of rhubarb 325 mg (diffusible solid)

Compound tincture of cardamom 0.9 ml (volatile liquid) Syrup 1.8 ml (thick liquid)
Peppermint water qs. 30 ml (vehicle)

sig 4 ml o.n.

- Used to form a protective layer for ulcers… etc. The compound powder of rhubarb has a laxative effect.

Light kaolin 650 mg (diffusible solid)

Bismuth carbonate 650 mg (diffusible solid)

Heavy magnesium oxide 650 mg (diffusible solid)

Tincture of belladonna

Peppermint water

Mitte

qs. 4 ml

30 ml

60 ml (volatile liquid)

(vehicle)

- Used as antidiarrheal and belladonna acts as antispasmodic.

Lab 6

Suspensions containing non-diffusible solid(s)

- A solid is regarded non-diffusible when it will not remain evenly distributed in the vehicle long enough to ensure uniformity of the measured dose (e.g. aspirin, calamine, chalk, zinc oxide).

- The simplest way to solve this problem is to increase the viscosity of the vehicle by adding a thickening agent (suspending agent) which will:

1. Decrease the sedimentation rate of particles.

2. Decrease the collisions of particles by each other which can lead to formation of aggregates that settle down rapidly.

- Some suspending agents for general use are:

1. Acacia Gum BP: Not commonly used alone because:

o It supports the growth of microorganisms.

o Not used externally as it can cause shrinkage of skin cells.

o Also not used externally as it can be oxidized to give bad odor.

2. Powdered Tragacanth BP: Used in a concentration of 0.2% w/v.

3. Compound Tragacanth Powder BP: Used in a concentration of 2% w/v. Composed of powdered tragacanth 15%, acacia 20%, sucrose 45% and starch 20%. Also not to be used for suspension applied externally as it contains acacia.

4. Bentonite BP: Used in a concentration of 2-3% w/v.

5. Tragacanth mucilage: Used in a concentration of 25% v/v (¼ of the vehicle is displaced). Composed of tragacanth powder (12.5 g) + alcohol (25 ml) + chloroform water (qs. 1000 ml). It is used for internal and external suspensions.

Methods of preparing suspension containing non-diffusible solid(s)

- Using tragacanth mucilage:

1. Using mortar and pestle, reduce the particle size of any ingredient having coarse particles to produce fine powders.

2. Mix insoluble powders by geometrical dilution method.

3. Triturate the powder mixture above with tragacanth mucilage (25 % v/v, i.e. ¼ the final volume) to produce a smooth paste.

4. After taking in consideration any liquid ingredients, measure ½ the vehicle and add part of it (≅ ¼) for dilution to produce pourable paste (soluble solids are dissolved in this portion).

5. Transfer the content to a measuring cylinder and rinse the mortar with ¼ of the vehicle.

6. Add any liquid ingredients and complete the volume with the vehicle.

7. Label: Shake before use.

- Using Powdered Tragacanth BP or Compound Tragacanth Powder BP:

1. Using mortar and pestle, reduce the particle size of any ingredient having coarse particles to produce fine powders.

2. Mix insoluble powders and suspending agent by geometrical dilution method.

3. After taking in consideration any liquid ingredients, measure ¾ of the vehicle and add

1. part of it (≅ ¼) to the mortar and triturate until smooth paste is formed.

4. Dissolve any soluble solid ingredients in the other ¼ and add it to the mortar for diluting it to a pourable paste.

5. Transfer the content to a measuring cylinder and rinse the mortar with ¼ of the vehicle.

6. Add any liquid ingredients and complete the volume with the vehicle.

Phenacetin (non-diffusible)	500 mg	
Caffeine	50 mg	
Glycerin (thick liquid)	6 ml	
P.W. qs.	100 ml	(vehicle)

mitte 20ml

Phenacetin is analgesic and antipyretic. Caffeine is CNS stimulant.

Aspirin	500 mg	(non-diffusible solid)
Syrup of orange	1 ml	(thick liquid)
Concentrated chloroform water	0.25 ml	(volatile liquid)
Peppermint water qs.	20 ml	(vehicle)

- Aspirin is analgesic, antipyretic and anti-inflammatory.

Lab 7

Suspensions containing poorly wettable solid(s)

- Some substances as Sulphur and hydrocortisone are insoluble in water and poorly wetted by it. Upon preparing simple aqueous dispersions, it is difficult to disperse clumps and the foam produced upon shaking will not rapidly subside because it is stabilized by a film of a non-wettable solid at the liquid- air interface.
- The interfacial energy between the solid and liquid must be reduced. This could be achieved by adding a suitable wetting agent which is adsorbed at the solid-liquid interface to increase the affinity of solid particles to the surrounding medium and reduce the antiparticle forces.
- Examples on wetting agents: Alcohol, glycerin and propylene glycol.

℞

Compound Sulphur lotion

Precipitated Sulphur		40 g	(poorly wettable solid)
Alcohol (95%)		60 ml	(wetting agent)
Glycerol		20 ml	(wetting agent)
Tween 80		1 % v/v	(wetting agent – saponin)
Calcium hydroxide solution		1000 ml	(vehicle)
mitte	qs.	25 ml	
Sig. External use.			

- Used for scabies.

Procedure:

1. Mix wetting agent together in a mortar then add the Sulphur with continuous trituration.
2. Gradually dilute using CaOH.
3. Transfer to a measuring cylinder and complete the volume with lime water.
4. Transfer to suitable bottle and label.

Suspensions of oil in inhalation

Suspensions are useful formulations for inhalations. The volatile components are adsorbed on a diffusible solid to ensure uniform dispersion throughout the liquid. When hot water is added the oils vaporize.

Menthol and eucalyptus inhalation

Eucalyptus oil	10 ml (volatile oil)
Menthol	3 g (volatile solid)
Light magnesium carbonate	5 g (suspending agent)
P.W. qs.	100 ml (vehicle)

Ft. aqueous inhalation

Mitte 25 ml

Special procedure:

1. Grind the menthol to a fine powder in a mortar and add the eucalyptus oil, which will dissolve the menthol.

2. Gradually add the light magnesium carbonate to the mortar and mix well.

3. Add the water gradually to produce a pourable suspension.

4. Transfer the mixture to measuring cylinder and rinse the mortar, then

complete the volume.

2nd semester

Lab 1

Emulsions

Emulsions: may be defined as two immiscible liquids, one of which is finely subdivided and uniformly dispersed as droplets throughout the other.

The system is stabilized by the presence of an emulsifying agent.

- The dispersed liquid or internal phase usually consists of globules of diameter down to 0.1 μm which are distributed within the external (continuous) phase.
- Emulsifying agents have the ability to stabilize the emulsion by one or more mechanism.

Types of emulsions

Pharmaceutical emulsions usually consist of mixtures of an aqueous phase with various oils and/or waxes. Accordingly, two types of emulsions may be formed:

1. Oil in water emulsion (O/W): The oil droplets are dispersed throughout the aqueous phase.

2. Water in oil emulsion (W/O): The water is dispersed throughout the oil phase.

The type of emulsion is determined by three factors:

1. The ratio of the two immiscible phases.

2. The type of emulsifying agent used.

3. The order of mixing of the two immiscible phases.

Identification of emulsion type

1. Miscibility test: An emulsion will mix with a liquid that is miscible with its external phase. Therefore, O/W emulsion is miscible with water while W/O emulsion is miscible with oils.

2. Conductivity measurement: Systems with aqueous external phases will readily conduct electricity, whilst systems with oily external phases will not.

3. Staining test: Water-soluble and oil-soluble dyes are used. They will mix and stain the external phase of the emulsion.

Why emulsions?

1. To enhance the palatability of oils and oil-soluble drugs.

2. To increase the solubility. i.e. when we have two liquids that are immiscible, we cannot form solution so we prepare emulsion.

3. Emulsion can increase the absorption of oils and oil-soluble drugs through intestinal walls.

4. TPN (total parenteral nutrition) is feeding a person intravenously, bypassing the usual process of eating and digestion. The person receives nutritional formula that contain nutrients such as glucose, amino acids, lipids and added vitamins and dietary minerals usually in a form of emulsion.

Uses of emulsions

1. Emulsions for internal use: Oral emulsions are stabilized O/W dispersions that may contain one or more active ingredients.

2. Emulsions for intravenous administration must also be of the O/W type. However, intramuscular injections can also be formulated as W/O products.

3. Emulsions for external use: Semisolid emulsions are termed creams and more fluid preparations are either lotions or liniments (liniments are intended for massage). Both W/O and O/W are available for external use.

Preparation of emulsions

- Emulsions can be prepared on a small scale using mortar and pestle. Electrical mixers (homogenizers) can also be used.
- All equipment used must be clean and dry.
- All water-soluble and oil-soluble components of the emulsion are separately dissolved in the appropriate phase.
- A suitable emulsifying agent must be chosen. Acacia gum is usually used when making O/W emulsions for oral use.
- A primary emulsion should be prepared first, which is thick and stable emulsion.

Calculating quantities for primary emulsion

	Oil	Water	Acacia
Fixed	4	2	1
Mineral	3	2	1
Volatile	2	2	1

- These numbers refer to parts by volume (ml) for the water and oils and weight of acacia gum (g).
- If more than one oil is to be incorporated, the quantity of acacia for each one is calculated separately and the sum of the quantities is used.
- Amount of acacia = ¼ × amount of fixed oil.
- Amount of acacia = ½ × amount of volatile oil.
- Water is always double the amount of acacia (water = acacia × 2).

1. Example 1: If the volume of a fixed oil is 8 ml then we will need 4 ml of water and 2 g of acacia to prepare the primary emulsion.
2. Example 2: If the volume of a volatile oil is 60 ml then we will need 60 ml of water and 30 g of acacia to prepare the primary emulsion.

Methods of preparing emulsions

1. Continental or dry gum method

a) Triturate the oil with acacia powder in a dry mortar.

b) Measure water for the primary emulsion and immediately add all of it to the mortar with vigorous trituration in one direction until the mixture becomes thicker and the primary emulsion is formed. The primary emulsion is characterized by crackling (or clicking) sound. Generally, about 3 minutes of mixing is required to produce a primary emulsion.

c) Calculate the remaining vehicle: Final volume – (liquid ingredients).

d) Divide the remaining vehicle into 3 parts:

1st part for dilution of the primary emulsion.

2nd part for washing the mortar and pestle.

3rd part for completing the emulsion to its final volume.

Notes:

- Precipitate forming liquids (e.g. tincture of tolu) are added gradually to the center of the primary emulsion with continuous trituration.
- Soluble solid substances such as preservatives, stabilizers, colorants and flavoring agents are usually dissolved in the dilution and/or washing parts of the emulsion.
- Liquid ingredients that are soluble in or miscible with the external phase are mixed into the primary emulsion.
- Any substances that might interfere with the stability of the emulsion or the emulsifying agent are added as near last as is practical. For instance, alcohol has a precipitating action on gums such as acacia; thus, no alcohol or solution containing alcohol should be added directly to the primary emulsion, because the total alcoholic concentration of the mixture would be greater at that point than after other diluents were added.

2. English or wet gum method

a) Here, the order of mixing is different: Water is added to acacia with quick trituration to form mucilage.

b) Oil is measured with a dry measuring cylinder and added to the mucilage in small portions (gradually). Continuous trituration in one direction is required after each addition until a thick primary emulsion is obtained.

c) Other steps are the same as continental method.

How we choose a suitable method????

1. If we have one or more volatile oil, use a dry gum method.

2. If we have one or more fixed oil, use a wet gum method.

3. If we have a mixture of volatile and fixed oil, use a dry gum method.

3. Bottle or Forbes bottle method

- The bottle method is useful for the preparation of emulsions from volatile oils or oleaginous substances of low viscosities.
- Powdered acacia is placed in a dry bottle, two parts of oil are added, and the mixture is thoroughly shaken in the capped container.
- A volume of water approximately equal to that of the oil is then added in portions and the mixture thoroughly shaken after each addition.

- When all of the water has been added, the primary emulsion thus formed may be diluted to the proper volume with water or an aqueous solution of other formulated agents.
- This method is not suited for viscous oils because they cannot be thoroughly agitated in the bottle when mixed with the emulsifying agent.

4. Auxiliary methods

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

The hand homogenizer is less efficient in reducing the particle size of very thick emulsions, and it should not be employed for emulsions containing a high proportion of solid matter because of possible damage to the valve.

5. In-situ soap method

Calcium soaps are w/o emulsions that contain certain vegetable oils, such as oleic acid, in combination with limewater (synonym: Calcium Hydroxide Solution, USP). They are prepared simply by mixing equal volumes of the oil and limewater. The emulsifying agent in this instance is the calcium salt of the free fatty acid formed from the combination of the two entities. In the case of olive oil, the free fatty acid is oleic acid, and the resultant emulsifying agent is calcium oleate.

A difficulty that sometimes arises when preparing this self-emulsifying product is that the amount of free fatty acids in the oil may be insufficient on a 1:1 basis with calcium hydroxide.

Typically, to make up for this deficiency, a little excess of the olive oil, or even a small amount of oleic acid, is needed to ensure a nice, homogeneous emulsion. Otherwise, tiny droplets of water form on the surface of the preparation.

Because the oil phase is the external phase, this formulation is ideal where occlusion and skin softening are desired, such as for itchy, dry skin or sunburned skin.

Rx

Oil of turpentine	8 ml	(volatile oil)
P.W.	qs. 30 ml	

Calculations

1. Volatile oil to the acacia = ½ the oil = 4 g

2. Water = 2 × acacia = 8 ml

3. 8 ml of water and 4 g of acacia will be used to form the primary emulsion.

4. Approximate volume of the remaining vehicle (water) = 30 – (8 + 8) = 14 ml.

5. 14 ÷ 3 = 4.66 ml

4.66 ml for dilution, 4.66 ml for washing the mortar and pestle, and 4.66 ml for completing the emulsion to its final volume.

Procedure

1. Triturate 8 ml of turpentine oil with 4 g of acacia powder in a dry mortar.

2. Measure 8 ml of water and add all of it at once to the mortar with immediate vigorous trituration in one direction until the mixture becomes thicker and the primary emulsion is formed.

3. Add 4.66 ml of water gradually to the mortar with mixing to dilute the primary emulsion.

7. Transfer to a measuring cylinder and wash the mortar with 4.66 ml of water. Add this part to the cylinder.

8. Complete the volume to 30 ml with the last 4.66 ml of water.

9. Transfer to a suitable container and label.

This emulsion is O/W and used as rubefacient and muscle relaxant (topically), while orally used for lung problems.

Rx

Castor oil	8 ml	(fixed oil)
P.W. qs.	30 ml	(vehicle)

Calculations

1. Fixed oil to acacia = ¼ the oil = 2 g

2. Water = 2 × acacia = 4 ml

3. 4 ml of water and 2 g of acacia will be used to form the primary emulsion.

4. Approximate volume of the remaining vehicle (water) = 30 – (8 + 4) = 18 ml.

5. 18 ÷ 3 = 6 ml

6 ml for dilution, 6 ml for washing the mortar and pestle, and 6 ml for completing the emulsion to its final volume.

Procedure

1. Weigh 2 g of acacia and place it in the mortar.

2. Measure 4 ml of water and add it to the mortar with trituration to form mucilage.

3. Measure 8 ml of castor oil and add it gradually (part by part) to the mucilage in the mortar with continuous trituration in one direction until the mixture becomes thicker and the primary emulsion is formed.

4. Dilute the primary emulsion with 6 ml of water with continuous trituration.

5. Transfer to a measuring cylinder and wash the mortar with 6 ml of water. Add this part to the cylinder.

6. Complete the volume to 30 ml with the last 6 ml of water.

7. Transfer to a suitable container and label.

This emulsion is O/W and used as laxative (purgative).

Rx

Olive oil	8ml	(fixed oil)
Ferric ammonium citrate	0.65 g	(electrolyte)
P.W. qs.	30 ml	(vehicle)

Ferric ammonium citrate is dissolved in the washing part. Ferric ammonium citrate is an electrolyte having charges opposite to that of acacia and therefore should be added after dilution (in the washing part).

Rx

Castor oil	8 ml	(fixed oil)
Bismuth carbonate	0.65 g	(water-insoluble solid-polyvalent)
P.W. qs.	30 ml	(vehicle)

- Bismuth carbonate is water insoluble diffusible solid and added after the formation of the primary emulsion before dilution.
- Castor oil is purgative agent and bismuth carbonate is a protective used for GIT ulcers.

Lab 2

Suppositories

Suppositories are solid, single-dose preparations intended for insertion into the body cavities such as rectal, vaginal, or urethral cavity for local or systemic action.

Suppository is a drug delivery system where the drug is incorporated into an inert vehicle (base).

They contain 1 or more active substances dispersed or dissolved in a suitable bases that may be soluble or dispersible in water or may melt at body temperature.

Excipients such as diluents, adsorbents, surface-active agents, lubricants, antimicrobial preservatives and coloring agents may be added if necessary.

Why suppositories?

1. The patient is not able to make use of the oral route.
2. Problem with gastrointestinal tract (nausea, postoperative, etc.).
3. The patient is unconscious or having seizures.
4. Very young, the very old or the mentally disturbed patients.
5. The drug itself is not well suited for oral administration.
6. The drug causes serious gastrointestinal adverse effects.
7. The drug is unstable at the pH present in the gastrointestinal tract.
8. The drug is susceptible to enzymatic degradation in the gastrointestinal tract.
9. The drug undergoes extensive first-pass through the liver following its absorption.
10. When localized treatment is required such as in case of hemorrhoids and infections.

Ideal properties of suppository base

1. 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.

2. It should be non-irritating, physically and chemically stable, and pharmacologically inert.

3. Compatible with any added medicament.

4. Should be stable if heated above its melting point.

5. Easily molded and not adhere to the mold.

6. The melting range should be small enough to give rapid solidification after preparation, thus preventing agglomeration or sedimentation of suspended, especially high-density, drug particles.

7. During solidification, a suppository should exhibit enough volume contraction to permit removal from the mold or plastic former.

8. Should be of suitable viscosity upon melting. Very high viscosity will have low followability and very low viscosity will allow the drug to separate easily before solidification takes place.

Types of suppository bases

1. Fatty or oleaginous bases.

2. Water-soluble or water-miscible bases.

Preparation of suppositories

Suppositories are formulated in different shapes (e.g. bullet, torpedo, etc.) and sizes (usually 1 – 4 g). The suppository consists of a vehicle (base) in which the drug is incorporated and in some cases additives are co-formulated.

Suppositories are prepared by two methods:

1. Molding from a melt, also known as fusion method (hot process). 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.

2. Hand rolling and shaping or compression (cold process). The drug is incorporated with the un-melted base and the resulting mass shaped either by hand or by compressed in a metallic mold.

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

Mold Calibration

The mold is generally made of metal in two halves which are clamped together with a screw. The capacity of the mold is confirmed by filling the mold with the chosen base. The total weight of the perfect products is taken and a mean weight calculated. This value is the calibration value of the mold for that particular base.

Displacement values (DV)

The volume of a suppository from a particular mold is uniform but its weight will vary because the densities of the medicaments usually differ from the density of the base.

Displacement value is a number that represents parts by weight of the drug that displaces one part by weight of the base.

For example: displacement value of aspirin when incorporated into cocoa butter is 1.3. This means that each 1.3 g of aspirin will displace 1 g of cocoa butter.

Rx

Bismuth subgallate	300 mg	(DV = 2.7)
Cocoa butter	qs.	

Mitt. 6 supp. using 1 g mold.

Calculations

1. We usually make our calculations for mitt. + 2 suppositories to avoid unintentional loss of the base 6 + 2 = 8. So we make our calculations for 8 suppositories not 6.

2. Weight of the drug in 8 suppositories = 8 × 300 = 2400 mg = 2.4 g.

3. DV is 2.7 which means that each 2.7 g of bismuth subgallate will displace 1 g of cocoa butter. Here we have 2.4 g of bismuth subgallate:

Bismuth subgallate	Base
2.7 g	displaces 1 g
2.4 g	displaces X

X = 1* 2.4 /2.7 = 0.89 g. This means that our 2.4 g of bismuth subgallate will displace 0.89 g of cocoa butter.

4. Total weight of 8 suppositories = 8 × 1 = 8 g.

5. Actual total amount of cocoa butter that will be used: 8 – 0.89 = 7.21 g.

6. If we want to know the weight of each suppository:

weight of drug in each suppository + weight of base in each suppository.

Weight of base in each suppository = 7.21/8 = 0.9 g.

Weight of each suppository = 300 mg + 0.9 g = 1.2 g.

to calculate the DV of a drug:

A batch of un medicated suppositories is prepared and the products weighed.

A batch of suppositories containing a known concentration of the required drug is prepared and the products are weighted.

Weight of 6 un medicated suppositories = 6 g

Weight of 6 suppositories containing 40% drug = 8.8 g

Weight of the base in this = 60% = (60/100) x 8.8 = 5.28 g

Weight of drug in suppositories = 40% = (40/100) x 8.8 = 3.52 g

Weight of the base displaced by drug = 6 – 5.28 = 0.72 g

If 0.72 g of base is displaced by 3.52 g of base, then 1 g of base will be displaced by 3.52/ 0.72 = 4.88 g

Therefore, displacement value of drug = 4.9

Practical experiment (water soluble base prepared by hot processes)

Rx

Gelatin	2.8 gm
Glycerol	14 gm
Purified water q.s	20 gm

Mitt. 4 capsules

Procedure

1- Weight 2.8 of gelatin in a small beaker

2- Add hot p.w 6 ml to the gelatin

3- Put the mixture on the hot plate magnetic stirrer using a magnetic bar and adjusting it 150 C and 250 rpm

4- Take 14 ml of glycerol then add to the soluble mixture of gelatin while it is on the hot plate stirrer

5- Ensure from complete dissolution of the mixture

6- Take a suppository mold, open it and lubricate with an oil to prevent sticking of the suppository inside the mold

7- Pour the mixture inside the mold

8- Put the mold in the refrigerator and wait until solidifying the suppositories inside the mold

9- Open the mold and take the prepared suppositories

Lab 3

Powder and granules

- **Powders** are subdivided solids which are classified according to the size of their constituent particles which can range from less than 1.2 µm to 1.7 mm in diameter.
- The term powder uses to describe a formulation in which a drug powder has been mixed with other powdered excipients to produce the final product. The function of the added excipients depends upon the intended use of the product. Diluting, colouring, flavouring, and sweetening agents for example may be added to powders for oral use.
- A single active ingredient may be presented as powders called a ***simple powder*** or may be blended with different ingredients. These are termed ***compound powders*** (e.g. compound tragacanth powder).
- **Granules** which are used as a dosage form consist of powder particles which have been aggregated to form a larger particle which is usually 2 – 4 mm in diameter.

- **Powders and granules are often dispensed as:**

1. Bulk powders or granules for internal use.

2. Divided powders or granules (i.e. individually wrapped doses) for internal use.

3. Dusting powders for external use.

4. Insufflations for ear, nose, or throat.

Examples for other preparations which may be presented as powders or granules:

1. Antibiotics which are reconstituted before use.

2. Powders for injection.

Advantages of powders and granules as a dosage form

1. The solid preparations are more stable than liquid preparations. Because the liquid vehicles are not present, many incompatibilities are avoided as well as deterioration in some cases.

2. When tablets and capsules are difficult for children and others to swallow, the powder form is often desirable.

3. Powders and granules are convenient form in which we can dispense drugs with large dose.

4. Orally administered powders and granules of soluble medicaments have a faster dissolution rate than tablets as these must first disintegrate before the drug dissolves.

Disadvantages of powders and granules as a dosage form

1. Not suitable for administering bitter and corrosive drugs and those which readily change on exposure to the air or moisture.

2. Bulk powders and granules are not a method of administering potent drugs with a low dose.

3. Powders and granules are not suitable method for the administration of drugs which are inactivated in the stomach. These should be presented as enteric coated dosage form.

Mixing powders

Powders should be divided finely before mixing. Ingredients of powders should be mixed thoroughly using doubling-up (geometrical dilution) technique to ensure even distribution.

There are three methods for mixing powders:

1. Trituration method (using mortar and pestle). Used when large amounts of powders are to be mixed or when powders have crystalline or coarse forms and must be grinded thoroughly.

2. Spatulation method (using spatula and slab). Used when the powders are smooth and don't require grinding.

3. Sifting method (using kitchen-type flour sieve). Used when the powders to be mixed need to have a uniform particle sizes.

Dispensing powders

1. Bulk powders or granules: The mixed ingredients are packed into suitable bulk container such as a wide mouthed glass jar. The constituents are usually non-potent and non-toxic which can be measured safely in a spoon by the patient. Example: Compound Magnesium Trisilicate Oral Powder BP and Methylcellulose Granules BP.

2. Divided powders or granules: These are similar formulations to bulk powders but individual doses are separately wrapped to make certain that the patient gets the proper dosage. They can be used to supply **some** potent drugs where the accuracy of dose is important. Example: Effervescent powders and granules.

3. Dusting powders: Dusting powders contain one or more substances in fine powder and may be dispensed in a single dose or multi-dose preparations. They are used to treat variety of skin conditions or to sooth the skin.

They are usually dispensed in sifter-top cans. The powder must flow well from such container so that it can be dusted over the affected area. Examples: Antifungal powder (Tinaderm®) for athlete's foot and talc dusting powder for the prevention of chafing and skin irritation. For open wounds, only sterile dusting powders should be used (e.g. Chlorhexidine Antiseptic Dusting Powder®).

4. Insufflations: Are medicated powders which are blown into regions such as ear, nose, and throat using insufflator. Some potent drugs such as sodium cromoglycate are now present as insufflator because they are rapidly absorbed from the lungs when inhaled as a fine powder but poorly absorbed after oral or topical administration.

Preparing individually wrapped powders

1. Weighing method (accurate).

2. Blocking and dividing (less accurate).

3. Mechanical powder dividers (least accurate).

The minimum weight of individually wrapped powder is 100 mg. Dilution with a diluent (usually lactose) is often necessary to produce this weight.

The minimum amount that can be weighed in a balance is 65 mg (to avoid errors). So, the total weight of each individual active ingredient should be above 65 mg.

We calculate for extra 2 packets…

Manufactured tablets or capsules might be used as a source for powders. This involves crushing the tablet by mortar and pestle or opening the capsule shell into a mortar and then adding the diluent.

Lactose is frequently used as a diluent because it is colourless, odourless, cheap, available, inert, not hygroscopic, soluble, and generally harmless. It has a good flow property as well.

Rx

aspirin	gr IV
Phenacetin	gr IV
Codeine phosphate	gr 1/8

ft. pulv.

Mitt. XI packets

Calculations for 13 packets:

4 gr × 65 = **260** mg × 13 = 3380 mg for Aspirin (more than 65 mg)

4 gr× 65 = 260 mg × 13 = 3380 mg for phenacetin (more than 65 mg)

1/8 × 65 = **8.125** mg × 13 = 105.625 mg of Codeine phosphate (more than 65 mg)

Total weight of each packet is (260 +260 +8.125 = 528.125) mg (more than 100 mg).

Then, No need for dilution.

Procedure:

Grind the powder individually if needed. Mix the powders geometrically, then weight individual packets (528.125 mg) and wrap them by paper.

Rx

Hyoscine bromide 0.1 mg

ft. pulv.

mitte IIX packets

Calculations for 10 packets:

Total amount of drug = 0.1 × 10 = 1 mg (less than 65 mg).

Total weight of drug in each packet is 0.1 mg (less than 100 mg).

Must double-dilute:

1. Minimum weight of packets (capacity) = 100 × 10 = 1000 mg

2. Minimum weighable amount of the drug = 65 mg

3. First dilution:

Weigh 65 mg of hyoscine bromide and dilute it to 1000 mg (mixture A).

Drug	Drug + Lactose (Mixture A)
65 mg	1000 mg
1 mg	X

X = 15.38 mg (also below 65 mg so we need second **dilution**)

4. Second dilution:

From mixture A, take 65 mg (which contain 4.23 mg of the drug) and dilute it to 1000 mg (mixture B)

Drug	Drug + Lactose (Mixture B)
4.23 mg	1000 mg
1 mg	X

X = 236 mg (more than 65 mg).

5. So, we take 236 mg from mixture B (will contain 1 mg of hyoscine bromide). Then complete the weight to 1000 mg by adding lactose (1000 – 236 = 764 mg).

6. Mix and divide into 10 packets, each of 100 mg in weight.

Rx

Codeine phosphate 1/6 gr

Ft. pulvis

Mitt. 11 packets

Calculations for 13 packets:

1/6 gr × 65 = **10.83** mg × 13 = 140.83 mg for Codeine phosphate (more than 65 mg)

Total weight of each packet is (10.83 mg) mg (less than 100 mg).

Therefore, need for dilution:

13 × 100 = 1300 mg total weight of 13 packets

1300 – 140.83 = 1159.17 mg needed lactose.

Lab 4

Semisolid Dosage Forms: Ointments

Ointments: are greasy semisolid preparations for external application. They are usually anhydrous containing dissolved or dispersed medicaments.

Ointments can be medicated on non-medicated. The non-medicated ointments are also called ointment bases and used as such for emollient, protective, or lubricating effect or as a vehicle in the preparation of medicated ointments.

Preparation of ointments

1. Incorporation method (trituration method)

Insoluble solids or liquids medicaments are incorporated into bases using the technique called (mixing by trituration) which can be carried out by 3 ways:

a) Using ointment slab and spatula when small quantities of ointment are to be prepared.

b) Using mortar and pestle when large quantities of ointment are to be prepared or when large quantities of liquids are to be incorporated in to a base.

c) Using an ointment mill for large quantities of ointment (a pound or more).

Mixing by trituration is carried out on an ointment slab and spatula:

1. Any powders should be reduced to a fine state before weighing to avoid grittiness. If there are more than one ingredient, they should be finely powdered and mixed by geometrical dilution method.

2. Powders are placed on the slab, rubbed with small amount of base to give concentrated ointment.

3. Then, incorporating this concentrated ointment into the reminder of the base using doubling-up method.

4. Liquids (if present) are to be incorporated into the base:

(Aqueous solution is easily mixed with absorption, water-removable, and water-soluble bases.

For **hydrophobic base**, it requires replacement of a portion of the hydrophobic base with hydrophilic base. The aqueous solution is to be incorporated into this hydrophilic base and then mixing the product with the original base.

Pulverization by intervention:

This is the process of reducing the state of subdivision of solids with the aid of an additional material that can be removed easily after the pulverization has been completed. This technique often is applied to substances that are gummy and tend to re-agglomerate or that resist grinding. A prime example is camphor, which cannot be pulverized easily by trituration because of its gummy properties; however, on the addition of a small amount of alcohol or other volatile solvent, this compound can be reduced readily to a fine powder. Similarly, iodine crystals may be comminuted with the aid of a small quantity of ether. In both instances the solvent is permitted to evaporate and the powdered material is recovered.

Levigation: In this process a paste is first formed by the addition of a suitable non-solvent to the solid material. Particle-size reduction then is accomplished by rubbing the paste in a mortar with a pestle or on an ointment slab using a spatula. Levigation is used to incorporate solids into ointments and suspensions.

2. Fusion method (melting method)

- All or some of the components of an ointment are combined by being melted together and cooled with constant stirring until congealed.
- Medicated ointments and ointment bases containing components such as beeswax, paraffin, stearyl alcohol, and high molecular weight PEGs, which do not lend themselves well to mixture by incorporation, are prepared by fusion.

Steps are:

1. Place the base constituents in evaporating dish or beaker on a water bath and melt.

2. When all the ingredients are melted, remove the beaker from the water bath and gently stir.

3. Medicaments that are soluble in the melted base should be added to the base before it congeals.

4. Insoluble medicaments should be levigated with small quantity of the melted base. After the reminder of the base is congealed, the levigated medicament can be incorporated with it (doubling-up method)

5. Water and water-soluble ingredients such as glycerin and PEG must be heated approximately the same temperature as the melted base before mixing to avoid crystallization of high melting point substances.

NOTES

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

Practical part

Rx

Sulphur Ointment USP

Sulphur	1 g
Vaseline	9 g

Method

dissolve 1 gm of the Sulphur in the glycerin then add small portion of Sulphur to the small amount of Vaseline and mix, then continue adding until complete the mixture.

Zinc Oxide Ointment BP

Zinc Oxide, finely sifted 1.5 g

Vaseline 8.5 g

BP: Triturate the Zinc Oxide (1.5 gm) with a portion of the Vaseline until smooth, gradually add the remainder of the Vaseline and mix thoroughly.

Salicylic acid (30% w/w)

Salicylic acid 1 gm

Vaseline 9 gm

Method: because salicylic acid is un soluble so we first dissolve it (1 gm) by glycerin then mix gradually with small portion of Vaseline until smooth mixture formed then add the reminder amount of the Vaseline and mix thoroughly.

Lab 5

Semisolid cream, gels and paste

Creams are semisolid emulsions for external application. O/W emulsions (aqueous creams) are most useful as water-washable bases whereas W/O emulsions (oily creams) are emollient and cleansing.

Creams are soft, easy to apply, cool the skin, and less greasy than ointments.

Gels (Jellies) are non-greasy semisolid preparations intended for internal or external application, it could be transparent or not. They are used for medication, lubrication, and other uses.

Gels are semisolids consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jellylike by the addition of a **gelling agent**.

Gels are easily applied and evaporation of their water content produces a pleasant cooling effect. The residual film usually adheres well and gives protection. However, it is easily removed by washing with water.

Pastes are semisolid preparations for external application. They have high content of powder (20-50%) dispersed in either an aqueous or oily vehicle.

Pastes usually stiffer and less greasy than ointments and are more difficult to apply and remove.

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.
- The solid excipients are melted at the time of preparation. Emulsifying agents include nonionic surfactants, detergents, and soaps.
- Preparation usually involves separating the formula components into two portions: lipid and aqueous.
- The lipid portion contains all water-insoluble components and the aqueous portion the water-soluble components.
- Both phases are heated to a temperature above the melting point of the highest melting component.
- The phases then are mixed, and the mixture is stirred until reaching ambient temperature or the mixture has congealed.
- Mixing generally is continued during the cooling process to promote uniformity.

NOTES

- Traditionally, the aqueous phase is added to the lipid phase, but comparable results have been obtained with the reverse procedure.
- High-shear homogenization may be employed to reduce particle or droplet size and improve the physical stability of the resultant dosage form.
- Creams usually require the addition of a preservative(s) unless they are compounded immediately prior to use and intended to be consumed in a relatively short period of time.

Preparation of gels

Gels formed with large organic molecules may be formed by:

1. Dispersing the molecule in the continuous phase (e.g., by heating starch).

2. By cross-linking the dispersed molecules by changing the pH (as for carbomers).

3. By reducing the continuous phase (as for jellies formed with sucrose).

- Care should be taken to ensure uniformity of the APIs by dispersing them by vigorous mixing or milling or by shaking if the preparation is less viscous.
- Gels should be stored in tight containers to prevent water loss. Avoid freezing gels.

Preparation of pastes

- 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, a portion of the base is often used rather than a liquid, which would soften the paste.
- It is important to stir the product thoroughly during cooling process to prevent settling of the solids.

Zinc Gelatin (Glycero-gelatin Jelly)

Zinc Oxide	15 g
Gelatin	15 g
Glycerin	35 g
P.W.	35 g

- Triturate ZnO to fine powder.
- Soften the gelatin by soaking in warm water then heat it.
- Heat the glycerin and add it to gelatin.
- Remove from water bath and upon congealing, add ZnO part by part with stirring.

Bentonite Gel

Zinc Oxide	10 g
Glycerin	10 g
Bentonite	10 g
P.W. qs	100 g

- Triturate ZnO and bentonite in mortar.

- Add glycerin with continuous trituration.
- Add water part by part with trituration.

Lab 6

Capsules and flow properties of the powders and granules

Capsules are solid preparations intended for oral administration made with a hard or soft gelatin shell. One or more medicaments are enclosed within this gelatin container.

Soft shell capsules

Consist of a flexible solid shell containing powders, non-aqueous liquids, solutions, suspension, or pastes. Such capsules allow liquids to be given as solid dosage form (e.g. cod-liver oil). They also offer accurate dosage, improved stability and overcome some of the problems of dealing with powders.

They are formed, filled, and sealed on one manufacturing process.

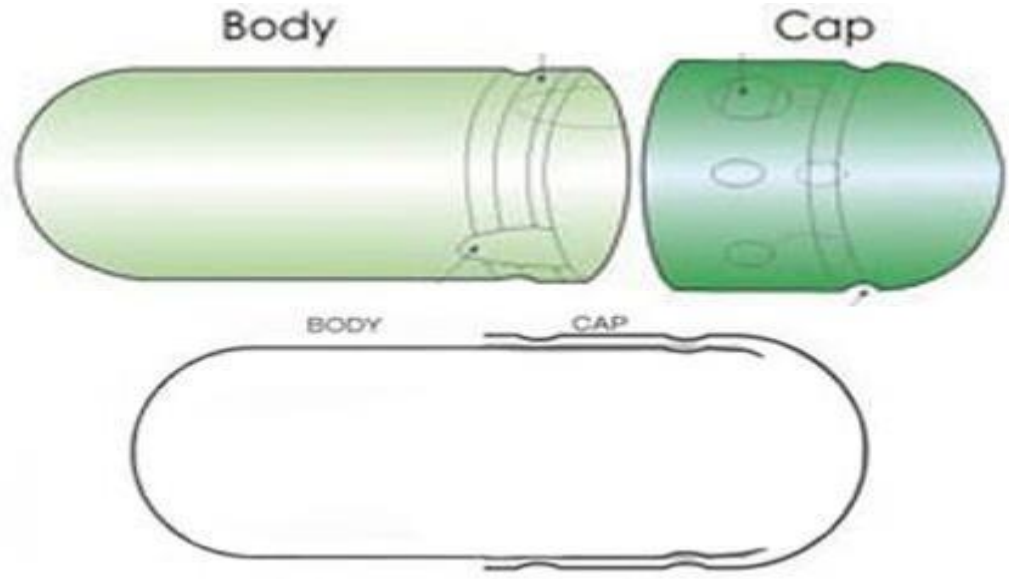
Hard shell capsule

Empty capsule shells are made from a mixture of gelatin, acacia, sugar, and water. They are clear, and essentially tasteless.

The hard gelatin capsule consists of 2 pieces: They body and the cap that fit one inside the other.

They are produced empty and are filled in a separate operation.

Powders or granules can be placed in the body and the capsule closed by bringing the body and cap together.



Advantages of capsules

1. **To the patient**: Capsules mask the taste and the odors of drugs. The gelatin shell rapidly dissolved in the stomach, and the contents are absorbed more readily than tablets because there are no excipients.

2. **To the physician**: He may prescribe different combinations of drugs and vary the proportion to suit the patient needs.

3. **To the pharmacist**: Convenience quick filling. They can be dispensed with confidence provided that each filled capsule is weighed.

4. **To make solutions**: Solutions of a defined strength are made by adding the contents of a capsule to a given volume of water

Disadvantages of capsules

1. Capsules are undesirable dosage form for aqueous or hydro-alcoholic liquids which would dissolve the gelatin.

2. They are unsuitable for very soluble salts. Such compounds, upon released in the stomach would make irritation concentrated solutions (e.g. bromides, iodides, chloral hydrates, etc.).

Flow properties of the powders and granules

Angle of Repose

The frictional force between granules or powder particles can be measured by repose angle which was measured by the following equation

$\tan \Theta = h/r$

Θ is the repose angle, h is the elevation of the pile, r is the radius of the base of the pile.

The method according to USP is called drained angle of repose: excesses amount of the sample poured over a funnel on a well-known stable diameter base with a retaining lip during this processes the funnel should move carefully to stay above the pile formed in about 2 to 4 cm permitted to decrease the influence of the sample dropping on the landfill of the pile formed. The height of the pile taken and used with known diameter of the base for calculating the angle of repose according to equation. The results compared with table which contains different sorts of followability in relation to the angle of repose.

Angle of Repose Degree	Flow Property
(25–30)	Excellent
(31–35)	Good
(36–40)	Fair (aid not needed)
(41–45)	Passable- might hung up
(46–55)	Poor (must agitate or vibrate)
(56–65)	Very poor
More than 66	Very very poor

Carr's Index and Haunser ratio

The measurement of compressibility index and Haunser ratio is a fast and simple test for predicting the flow properties of materials also it is indirectly measures bulk density, surface area, size and shape, moisture content, and cohesiveness of elements subsequently all of them affect the compressibility of the substances.

The method according to USP: Bulk density measured by computing the size of known amount of a sample (granules or powder) in a 10 ml graduated cylinder then the cylinder was tapped until no more reduction in the volume of the mass was detected the tapped density was calculated using the volume of the sample after tapping. Carr's compressibility index (CI) was determined according to the following formula.

Carr's Index=(V0-Vf)/V0 *100……

V0 is apparent volume

Vf is tapped volume

Flow properties of the samples evaluated according to Carr's, index as shown in the table.

of Compressibility%	**Flow property**	**Haunser ratio**
Less or equal to 10	**Excellent**	**100-1.11**
11-15	**Good**	**1.12-1.18**

16-20	**Fair**	**1.19-1.25**
21-25	**Passable**	**1.26-1.34**
26-31	**poor**	**1.35-1.45**
32-37	**Very poor**	**1.46-1.59**
More than 38	**Very, very poor**	**More than 1.6**

Dispensing capsules

1. Preparing the powder.
2. Choosing the correct size and color of the capsules' shell.
3. Filling the capsules.
4. Cleaning the filled capsules.
5. Packaging.

Compounding of capsules

- Hand filling of capsules may be required for small-scale production (in the pharmacy).
- A suitable shell should be selected so that the finished capsule looks reasonably full.
- Hard-shell capsules are available in different sizes. These are listed in the following table with the corresponding approximate capacity (based on aspirin).

Capsule no.	**000**	**00**	**0**	**1**	**2**	**3**	**4**	**5**
Content (mg)	**1000**	**650**	**500**	**320**	**250**	**200**	**150**	**100**

The capacity varies according to the density and compressibility of the powder mixture.

Calculations

- The recommended minimum weight for filling a capsule is 100 mg.
- If the required weight of the drug is smaller than this, a diluent should be added by trituration. Lactose is usually used as a diluent.
- If the quantity of the drug for a batch of capsules is smaller than the minimum weighable amount (65 mg), double-dilution method will be required.
- The calculations are done for the entire batch and a small excess should be calculated (extra 2 capsules).

Filling the capsules

- The number of capsules to be filled should firstly be taken and set aside.
- The powder to be encapsulated should be prepared and finely sifted.
- If there are more than 1 ingredient, the powders must be mixed by geometrical dilution method.
- Various methods of filling capsules on small-scale are possible:

1. The prepared powder can be placed on a clean tile or paper and the powder is pushed into the capsule body with the aid of spatula until the required weight has been enclosed.

2. The empty capsule body could also be punched into a heap of powder until filled (**punching method**).

3. A small funnel of white paper may be used to fill the capsule body with the required weight.

Practical part

1- Preparation of capsule in the laboratory

Rx

Paracetamol 300 mg

Ft. Cap

Mitt 8 Cap.

Calculation

1- The calculation based on the preparation of 10 capsules (8 +2)

2- Weight 3000 mg of paracetamol (300 mg which is the weight of one capsule ×10 which is the number of all capsules)

3- The capsule number 0 is suitable because it is filled with approximately 500 mg

4- Weight the lactose (additive) needed so we will take 2000 mg to complete the total weight of 5000 mg of 10 capsules.

5- Mix the paracetamol 3000 mg with 2000 mg of additive (lactose) with trituration by mortar and pestle

6- Evaluate the powder formed with angle of repose and tapped density tests to know their flow properties

7- Fill the powder in the capsules by dipping method

2- Preparation of capsule in the pharmacy

Rx

Paracetamol 250 mg

Prepare 8 cap.

1- Prepare 10 capsule (8+2)

2- Choose a suitable paracetamol tablet from these (1000 mg, **500 mg** ,650 mg ,665 mg), of course the suitable one is 500 mg tablet. Why??????

Answer (because the active part (paracetamol) is 500 mg which is easily divided into 2 part to give 250 mg which is the weight needed for preparation, also the whole weight of the tablet is about 700 mg that is will be suitable for cap number 0 that is available currently in the pharmacies.

3- We need 10 capsules with final weight of 500 mg for each capsule so we need 10 ×500 mg =5000 mg (active part which is paracetamol additive)

4- Weight of each paracetamol tablet is 700 mg (500 mg active part + 200 mg additives)

5- The weight active part of 10 capsules is 250 mg × 10 = 2500 mg so

500 mg (wt of paracetamol in each tab 700 mg (whole wt. of the tablet)

2500 mg X

X = 700 ×2500/ 500 = 3500 mg that is mean 5 tablet of paracetamol we need.

6- The whole weight of 10 capsule is 500 mg × 10 cap = 5000 mg so we need

5000 – 3500 (weight of 5 tablet used) = 1500 mg which is the weight of additive (lactose)

7- Triturate 5 tablet of paracetamol by mortar and pestle until fine powder prepared then add a diluent with continues trituration until a homogenous fine powder performed

8- Fill the capsules by dipping method