Indonesia International Institute for Life Sciences

Liquid Dosage Form I : Solution and Suspension

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Learning Outcomes

Comprehend definition and types of solution and suspension

Comprehend and elaborate the advantages and dsadvantages of suspension and solution

Elaborate the preparation process, consideration and excipients needed for suspension and solution

Outline

Solution (Definition, types, advantages disadvantages)

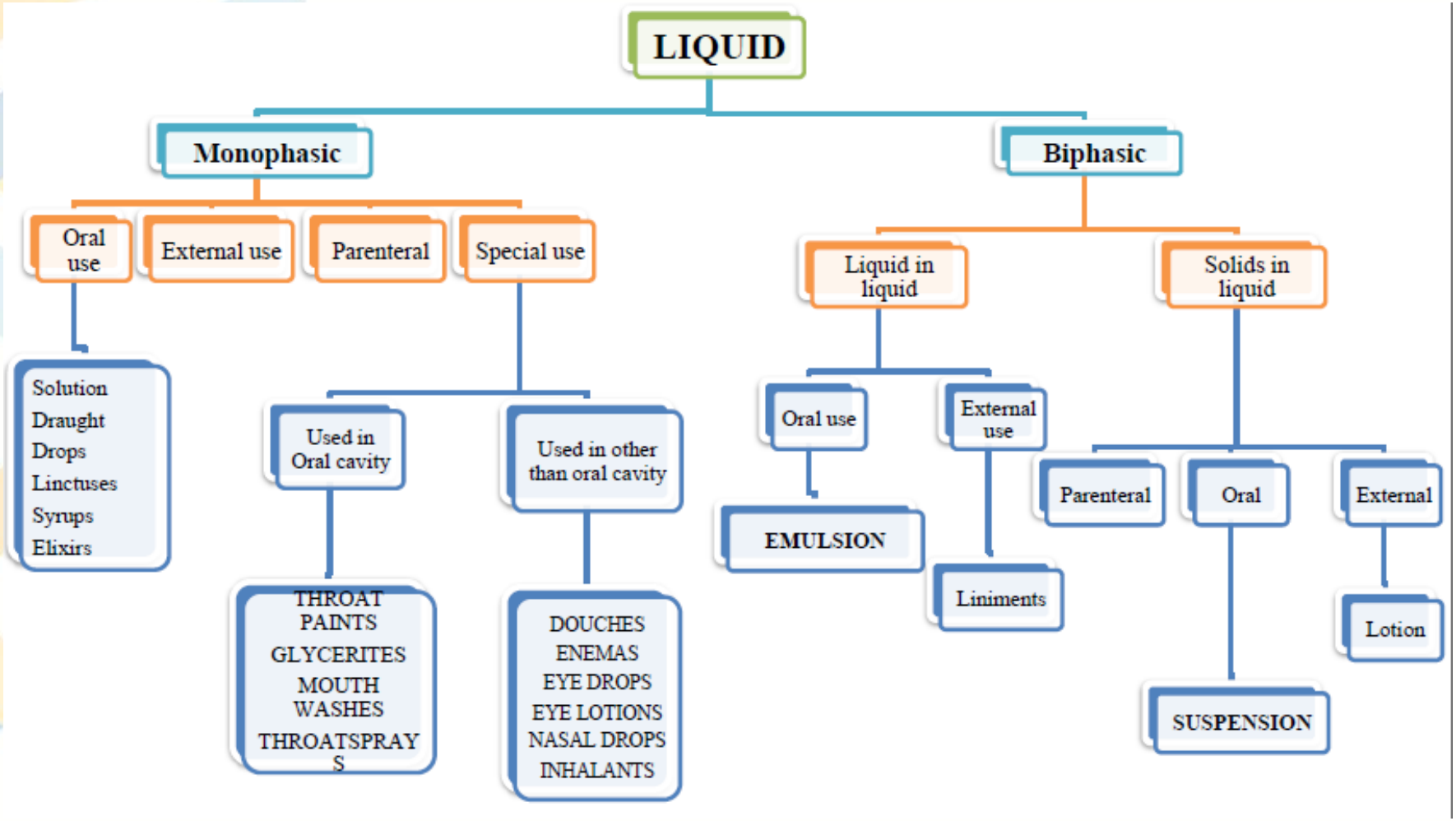
Solution preparation and consideration

Suspension (Definition, types, advantages disadvantages)

Suspension preparation and consideration

Packaging and Labeling

Classification of liquid dosage form



Solution – monophasic liquid

- A solution : preparation that contains one or more dissolved chemical substances in a suitable solvent or mixture of mutually miscible solvents.
- molecules of a drug substance in solution are uniformly dispersed, → assurance of uniform dosage upon administration and good accuracy during mixing and dilution
- can be administered by injection, inhalation, and the mucosal, topical/dermal, and gastrointestinal routes.

Disadvantages

- Shorter expiry date
- Stability is often reduced by solvolysis, hydrolysis, oxidation
- Stability of API
- Challenge to mask unpleasant taste
- Transport & breakages (bulky; packed in glass bottles) thus higher cost
- Technical accuracy is needed (measure the dose)
- Measuring device needed for administration
- Some drugs poorly soluble

Advantages

- Drug available immediately for absorption
- Flexible dosing
- May be designed for any route of administration (oral, parenteral, enemas, topical, ophthalmic)
- Uniform dosage (no need to shake the container) , accuracy during dilution or mixing
- Facilitate swallowing in difficult case

Things to consider

- Will the drug(s) dissolve in the solvent or a component of the solvent system?
- What quantity of drug will dissolve?
- How long will dissolution take?
- Will the drug(s) remain in solution and for how long?

Table 13.1 RELATIVE TERMS OF SOLUBILITY (2)

DESCRIPTIVE TERM	PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Very soluble	<1
Freely soluble	1–10
Soluble	10–30
Sparingly soluble	30–100
Slightly soluble	100–1,000
Very slightly soluble	1,000–10,000
Practically insoluble or insoluble	>10,000

Solubility

- Organic compounds → water soluble if they contain polar groups capable of forming hydrogen bonds with water.
- The greater the polar groups present, solubility >>>
- Polar groups include OH, CHO, COH, CHOH, CH2OH, COOH, NO2, CO, NH2, and SO3H.
- The introduction of halogen atoms → decrease water solubility due to increase in the molecular weight of the compound without a proportionate increase in polarity.
- An increase in the molecular weight of an organic compound without a change in polarity → reduces solubility in water.

Solubility : organic molecules

- Molecules having one polar functional group are usually soluble to total chain lengths of five carbons.
- Molecules having branched chains are more soluble than the corresponding straight-chain compound.
- **Water solubility decreases with an increase in molecular weight.**
- Increased structural similarity between solute and solvent is accompanied by increased solubility.

Solubility : inorganic molecules

- If both the cation and anion of an ionic compound are monovalent, → solute–solute attractive forces are overcome, → water soluble (e.g., NaCl, LiBr, KI, NH_4NO_3, and $NaNO_2$).
- If only one of the two ions in an ionic compound is monovalent, the solute–solute interactions are overcome → water soluble (e.g., $BaCl_2$, MgI_2, Na_2SO_4, and Na_3PO_4).
- If both the cation and anion are multivalent, the solute–solute interaction may be too great to be overcome by the solute–solvent interaction, → poor water solubility (e.g., $CaSO_4$, $BaSO_4$, and $BiPO_4$; exceptions: $ZnSO_4$, $FeSO_4$).
- Common salts of alkali metals (e.g., Na, K, Li, Cs, and Rb) are usually water soluble (exception: Li_2CO_3).
- Ammonium and quaternary ammonium salts are water soluble

Solubility

- Nitrates, nitrites, acetates, chlorates, and lactates are generally water soluble (exceptions: silver and mercurous acetate).
- Sulfates, sulfites, and thiosulfates are generally water soluble (exceptions: calcium and barium salts).
- Chlorides, bromides, and iodides are water soluble (exceptions: salts of silver and mercurous ions).
- Acid salts corresponding to an insoluble salt will be more water soluble than the original salt.
- Hydroxides and oxides of compounds other than alkali metal cations and the ammonium ion are generally water insoluble.
- Sulfides are water insoluble except for their alkali metal salts.
- Phosphates, carbonates, silicates, borates, and hypochlorites are water insoluble except for their alkali metal salts and ammonium salts.

Table 13.3 SOLUBILITIES OF SELECTED ORGANIC COMPOUNDS IN WATER AS A DEMONSTRATION OF CHEMICAL STRUCTURE-SOLUBILITY RELATIONSHIP

COMPOUND	FORMULA	MILLILITERS OF WATER REQUIRED TO DISSOLVE 1 G OF COMPOUND
Benzene	C_6H_6	1,430.0
Benzoic acid	C_6H_5COOH	275.0
Benzyl alcohol	$C_6H_5CH_2OH$	25.0
Phenol	C_6H_5OH	15.0
Pyrocatechol	$C_6H_4(OH)_2$	2.3
Pyrogallol	$C_6H_3(OH)_3$	1.7
Carbon tetrachloride	CCl_4	2,000.0
Chloroform	$CHCl_3$	200.0
Methylene chloride	CH_2Cl_2	50.0

Table 13.2 WATER AND ALCOHOL SOLUBILITIES OF SOME WEAK ACIDS, WEAK BASES, AND THEIR SALTS

DRUG	WATER	ALCOHOL
Atropine	455.0	2
Atropine sulfate	0.5	5
Codeine	120.0	2
Codeine sulfate	30.0	1,280
Codeine phosphate	2.5	325
Morphine	5,000.0	210
Morphine sulfate	16.0	565
Phenobarbital	1,000.0	8
Phenobarbital sodium	1.0	10
Procaine	200.0	Soluble
Procaine hydrochloride	1.0	15
Sulfadiazine	13,000.0	Sparingly soluble
Sodium sulfadiazine	2.0	Slightly soluble

Dissolution : Increasing dissolution rate

- **Smaller particle sizes (API)**
- **Effective stirring**
- **Lower viscosities**
- **pH**
  - Drugs : either weak acids or weak bases, solubility depends on pH
    - Weak bases : alkaloid (atropine, codeine, and morphine), antihistamines (diphenhydramine and promethazine); local anesthetics (cocaine, procaine, and tetracaine); other important drugs, are not very water soluble, but they are soluble in dilute solutions of acids.
  - acid salts of these organic bases are prepared to enable the preparation of aqueous solutions
- **Increased temperature**
  - Most chemicals absorb heat when they are dissolved, positive heat of solution, resulting in increased solubility with an increase in temperature
  - Few chemicals have a negative heat of solution and exhibit a decrease in solubility with a rise in temperature

Stability in solution

Physical stability (Crystallization etc)

- Temperature
- photosensitivity

Chemical stability & time period (Change of chemical structure)

- Assay
- impurities of API

Microbiological stability (Microbial contamination)

- Preservative

Consideration when preparing solution (compounding)

- To aid dissolution, high-viscosity liquid components should be added to those of lower viscosity.
- Completely dissolve salts in a small amount of water prior to the addition of other solvent elements.
- In complex solutions, *organic components should be dissolved in alcoholic solvents while water soluble components dissolved in aqueous solvents*.
- *Aqueous solutions should be added to alcoholic solutions with stirring to maintain the alcohol concentration as high as possible* – the reverse may result in separation of any dissolved components.

Table 13.5 EXAMPLES OF ORAL SOLUTIONS BY CATEGORY

ORAL SOLUTION	REPRESENTATIVE COMMERCIAL PRODUCTS	CONCENTRATION OF COMMERCIAL PRODUCT	COMMENTS
Antidepressants			
Escitalopram oxalate	Lexapro (Forest)	1 mg/mL	For major depressive disorder
Fluoxetine HCl	Prozac Liquid (Dista)	20 mg fluoxetine/ 5 mL	For depression, obsessive–compulsive disorder
Nortriptyline HCl	Pamelor Oral Solution (Mallinckrodt)	10 mg nortriptyline/5 mL	Tricyclic antidepressant
Antinauseant			
Ondansetron HCl	Zofran Oral Solution (GlaxoSmithKline)	4 mg/5 mL	For prevention of nausea and vomiting due to cancer-related therapies
Antiperistaltic			
Diphenoxylate HCl, atropine Sulfate	Lomotil Liquid (Pfizer)	2.5 mg diphenoxylate HCl, 0.025 mg atropine sulfate/5 mL	For diarrhea. Diphenoxylate is related structurally and pharmacologically to the opioid meperidine. Atropine sulfate in subtherapeutic amounts discourages (by virtue of side effects) deliberate overdosage.
Loperamide HCl	Imodium A-D Liquid (Ortho-McNeil)	1 mg loperamide HCl/5 mL	For diarrhea in adults and children aged 6 years and older. Structurally related to haloperidol

Elixir

- An elixir is a clear, sweetened hydroalcoholic solution intended for oral use and usually flavored to enhance palatability
- Non medicated elixirs : for vehicle; Medicated elixirs : for therapy
- Paediatric elixirs are usually formulated with a fruit syrup as a base flavouring agent.
- In general, non-aqueous solvents (alcohol, glycerin or propylene glycol) form a significant proportion of the vehicle used in elixirs, or alternatively solubilizing agents are included

Elixir

- The proportion of alcohol in elixirs varies depend on solubility characteristics.
- For elixirs containing agents with poor water solubility, the proportion of alcohol required is greater than for elixirs prepared from components having good water solubility.
- In addition to alcohol and water, other solvents, such as glycerin and propylene glycol, are frequently employed in elixirs as adjunctive solvents.
- Usually less sweet that syrup (less glucose/sucrose concentration)

Elixir : excipient used

- Other excipient :
- Sweetener : sucrose, sorbitol, other artificial sweeteners (Saccharine, aspartame) esp when formulated elixirs have high alcoholic content
- Flavor & coloring agent
- Self preserving (antimicrobial agent): 10-12% alcohol

Elixir : Preparation

- by simple solution with agitation and/or by admixture of two or more liquid ingredients.
- Alcohol soluble and water-soluble components are dissolved separately
- aqueous solution added to the alcoholic solution, rather than the reverse,
  - to maintain the highest possible alcoholic strength at all times so that minimal separation of the alcohol-soluble components occurs.
- When mixed, made up the volume.
- If final mixture become cloudy, (likely flavoring oils separate because alcohol % reduced)→ removed with filtration after setting it for a while (could also use talc to absorb oil)

Theophylline Elixir

Theophylline	5.3 g
Citric acid	10.0 g
Liquid glucose	44.0 g
Syrup	132.0 mL
Glycerin	50.0 mL
Sorbitol solution	324.0 mL
Alcohol	200.0 mL
Saccharin sodium	5.0 g
Lemon oil	0.5 g
FD&C Yellow No. 5	0.1 g
Purified water, to make	1,000.0 mL

Phenobarbital Elixir

Phenobarbital	4.0 g
Orange oil	0.25 mL
Propylene glycol	100.0 mL
Alcohol	200.0 mL
Sorbitol solution	600.0 mL
Color	q.s.
Purified water, to make	1,000.0 mL

Mfg. by:
Nostrum Laboratories, Inc.
Bryan, OH 43506

7230L04 Iss. 07/16

NDC 70408-644-34

ELIXOPHYLLIN®
ELIXIR

(Theophylline
Oral Solution, USP)

(THEOPHYLLINE ANHYDROUS)

80 mg / 15 mL

Rx only

16 OUNCES
(473 mL)

Each 15 mL (tablespoonful) contains 80 mg theophylline anhydrous.

Alcohol 20%.

Dosage: Should be individualized. See package insert.

Store at controlled room temperature 15°–30° C (59°–86° F).

Dispense in a tight, light-resistant container. Avoid exposure to excessive heat.

NOSTRUM
LABORATORIES, INC.

NDC 0603-1508-58

PHENOBARBITAL ELIXIR, USP CIV

Manufactured for:
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PHENOBARBITAL ELIXIR, USP CIV

Each 5 mL (teaspoonful) contains:
Phenobarbital ..... 20 mg
Alcohol 15%
Inactive Ingredients: FD&C Red #40, flavors, glycerin, sucrose, and water.

USUAL DOSAGE: See package insert.

DISPENSE in a tight, light-resistant container as defined in the USP/NF with a child-resistant closure.

STORE at 20°- 25°C (68°- 77°F) [see USP Controlled Room Temperature]. Keep tightly closed.

Rx only

NET: 1 PINT (473 mL)

Qualitest®

Syrup

- Syrups are concentrated solutions of sucrose or other sugars at a concentration of at least 45%.
- high concentrations of sucrose prevented the decomposition of matter extracted from vegetable drugs.
- exerted an osmotic pressure → prevent the growth of bacteria, fungi
- Sucrose also retards oxidation because it is partly hydrolysed into the reducing sugars glucose and fructose.
- Medicated syrups are made of ingredients used in extemporaneous dispensing and thus form a stock solution of certain drugs (e.g. Tolu Syrup BP).
- Flavoured syrups contain aromatic or pleasantly flavoured substances and are designed to be used as flavourings or vehicles for extemporaneous preparations.

Syrup : Components

- **Purified water**
- **API**
- **Sugar**: sucrose or Sugar substitute: sweetness & viscosity
- **Antimicrobial preservatives**
- **Flavorants**: synthetic/natural
- **Colorants**: green with mint, brown with chocolate
- **Special solvents** (including alcohol)
- **Solubilizing agents**
- **Thickeners or stabilizers**

Acetaminophen Syrup

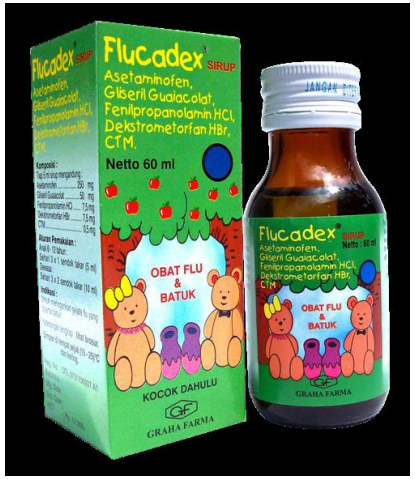
Acetaminophen	24.0 g
Benzoic acid	1.0 g
Disodium calcium EDTA	1.0 g
Propylene glycol	150.0 mL
Alcohol	150.0 mL
Saccharin sodium	1.8 g
Purified water	200.0 mL
Flavor	qs

Antihistamine Syrup

Chlorpheniramine maleate	0.4 g
Glycerin	25.0 mL
Syrup	83.0 mL
Sorbitol solution	282.0 mL
Sodium benzoate	1.0 g
Alcohol	60.0 mL
Color and flavor	qs
Purified water, to make	1,000.0 mL

Cough and Cold Syrup

Dextromethorphan hydrobromide	2.0 g
Guaifenesin	10.0 g
Chlorpheniramine maleate	0.2 g
Phenylephrine hydrochloride	1.0 g
Sodium benzoate	1.0 g
Saccharin sodium	1.9 g
Citric acid	1.0 g
Sodium chloride	5.2 g
Alcohol	50.0 mL
Sorbitol solution	324.0 mL
Syrup	132.0 mL
Liquid glucose	44.0 mL
Glycerin	50.0 mL
Color	qs
Flavor	qs
Purified water, to make	1,000.0 mL



Tinctures

- Alcohol: 15 – 80%
- Tinctures are alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances.
- They vary in *method of preparation, strength of the active ingredient, alcoholic content, and intended use* in medicine or pharmacy.
- When they are prepared from chemical substances (e.g., iodine, thimerosal), tinctures are prepared by *simple solution of the chemical agent in the solvent*.
  - Examples:
    - Opium Tincture (10% opium ~ 1% morphine)
    - Camphorated Tincture of opium (0.4% opium ~ 0.04% morphine)

Linctuses

- A linctus is a **liquid oral preparation** that is chiefly used for a demulcent, expectorant or sedative purpose, principally in the treatment of cough.
- As such, a linctus is intended to be sipped slowly and allowed to trickle down the throat in an undiluted form.
- Consequently, linctuses are formulated as viscous solutions which contain sugars.
- Could be considered as elixir or syrup too

Mixture/Oral Solution

- Simple liquid preparations intended for oral use containing dissolved medicaments may be described as oral solutions or mixtures, although the term ‘mixture’ may also be applied to a suspension.

Draughts

- A draught is an older term used to describe a liquid preparation formulated as a single dose, in a volume which is larger than generally utilised in traditional mixture formulations.
- Each draught was usually supplied in a 50mL unit dose container.

Spirits

- Spirits are solutions containing one or more API dissolved in either absolute or dilute ethanol.

Pediatric drops

- These are an oral liquid formulation of potent drugs usually in solution, intended for administration to paediatric patients, though they may be useful in other patients with swallowing difficulties.
- The formulation is designed to have very small dose volumes which must be administered with a calibrated dropper.

Gargles and Mothwashes

- Gargles and mouthwashes are aqueous solutions that are intended for treatment of the throat (gargles) and mouth (mouthwashes) and are generally formulated in a concentrated form
- These preparations usually will be diluted before use and care should be taken to ensure that appropriate instructions are included on the label and that the container used will be easily distinguishable from those containing preparations intended to be swallowed.

Enema and Douches

- These liquid preparations are often formulated as solutions (though they may be presented as an emulsion or suspension) and are intended for instillation into the rectum (enema) or other orifice, such as the vagina or nasal cavity (douche).
- The volumes of these preparations may vary from 5mL to much larger volumes. When the larger volumes are used it is important that the liquid is warmed to body temperature before administration.

Lotio or lotions

- Lotions are solutions, but may also be suspensions or emulsions, that are intended to be applied to the skin without friction on a carrier fabric such as lint and covered with a waterproof dressing.
- In some cases lotions are applied to the scalp, where the vehicle for the medication is alcohol based, allowing for rapid drying of the hair and thus making the product more acceptable to the patient (e.g. Salicylic Acid Lotion2% BPC).
- In these cases, problems of flammability are addressed by suitable labelling.
- High content of water

Liniments

- Liniments are alcoholic or oleaginous solutions or emulsions of various medicinal substances intended to be rubbed on the skin.
- Liniments with an alcoholic or hydroalcoholic vehicle are useful when rubefacient, counterirritant, or penetrating action is desired; oleaginous liniments are employed primarily when massage is desired. By their nature, oleaginous liniments are less irritating to the skin than alcoholic liniments.
- Liniments should not be used on broken skin.
- Usually solution but may be formulated as emulsions.
- Oleaginous liniments such as almond oil, peanut oil, sesame oil, or cottonseed oil or a volatile substance such as wintergreen oil or turpentine, or it may be a combination of fixed and volatile oils
- All liniments should bear a label indicating that they are suitable only for external use and must never be taken internally
- Label “Shake Well” and Store in tight containers

Collodions

- Collodions are liquid preparations composed of pyroxylin dissolved in a solvent mixture usually composed of alcohol and ether with or without added medicinal substances.
- Pyroxylin (i.e., nitrocellulose, soluble gun cotton, collodion cotton), obtained by the action of a mixture of nitric and sulfuric acids on cotton, consists chiefly of cellulose tetranitrate.
- It has the appearance of raw cotton when dry but is harsh to the touch. It is frequently available commercially moistened with about 30% alcohol or other similar solvent.
- Collodions are highly volatile and highly flammable and care should be taken to label any preparation appropriately.
- Labeled “for external use only”

Sprays

- Sprays may be defined as aqueous or oleaginous solutions in the form of coarse droplets or as finely divided solids to be applied topically, most usually to the nasopharyngeal tract or to the skin.
- Many commercial sprays are used intranasally to relieve nasal congestion and inflammation and to combat infection and contain antihistamines, sympathomimetic agents, and antibiotic substances.
- Examples:
- Nasal spray

Typical Oral/ Dental Solution

- A variety of medicinal substances are employed topically in the mouth for a number of purposes and in a wide range of dosage forms.
- Among the drugs and preparations included in this group are the following:
  - Benzocaine: topical anesthetic
  - Camphorated parachlorophenol: dental anti-infective
  - Eugenol: dental analgesic
  - Lidocaine oral spray: topical anesthetic , etc

Others

- Aromatic water: perfuming/ flavoring
  - Orange flower oil
  - Peppermint oil
  - Rose oil
  - Anise oil
  - Spearmint oil
  - Wintergreen oil
  - Camphor
  - Chloroform
- Diluted acids: anti bacterial effects
  - Acetic acid 0.25%: irrigating solution to the bladder
  - Acetic acid 1% : surgical dressing

Packaging and Labelling

- 'Not to be taken' and 'Do not swallow in large amounts' – This warning must be added to gargles and mouthwashes.
- 'Not to be taken' – This warning should be added to inhalations and nasal drops.
- 'For rectal use only' and 'Warm to body temperature before administration' – These warnings should be added to large-volume enemas.
- 'For external use only' – This warning must be added to the label of any other preparation that is not intended for administration via the oral route.

Packaging and Labelling

Table 6.1 Summary of packaging for pharmaceutical solutions

		Typical sizes	Pharmaceutical product examples include
Oral liquids	Amber flat medical bottle	50 mL, 100 mL, 150 mL, 200 mL, 300 mL, 500 mL	Draughts Elixirs Linctuses Mixtures Spirits Syrups
	Amber round medical bottle with dropper top	10 mL	Paediatric drops
External liquids	Amber fluted medical bottle	50 mL, 100 mL, 200 mL	Applications Collodions Enemas and douches Gargles and mouthwashes Liniments Lotions
	Amber fluted medical bottle with dropper top	10 mL	Ear drops Nose drops

Packaging and Labelling

Table 5.10 Guide to auxiliary labels and discard dates for extemporaneous preparations

Preparation	Container	Important auxiliary labels	Suggested discard date
Emulsions	Plain amber medicine bottle with CRC	Shake the bottle	4 weeks
Enemas	Amber fluted bottle with CRC	For rectal use only[a] Warm to body temperature before use	4 weeks
Gargles and mouthwashes	Amber fluted bottle with CRC	Not to be taken[a] Do not swallow in large amounts	4 weeks
Inhalations	Amber fluted bottle with CRC	Not to be taken[a] Shake the bottle	4 weeks
Linctuses	Plain amber medicine bottle with CRC		4 weeks
Liniments and lotions	Amber fluted bottle with CRC	For external use only Shake the bottle Avoid broken skin	4 weeks
Mixtures and suspensions	Plain amber medicine bottle with CRC	Shake the bottle	4 weeks
Nasal drops	Hexagonal amber fluted glass bottle with a rubber teat and dropper closure	Not to be taken[a]	4 weeks

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SUSPENSION

Suspension

- A suspension is a biphasic preparation consisting of solid particles dispersed throughout a liquid phase.
- Routes of administration : *oral, topical, inhalation, ophthalmic, otic, and injection*.
- Some suspensions are prepared and ready for use, and others are prepared as solid mixtures intended for reconstitution with an appropriate vehicle just before use.
- Inhalation suspensions, ophthalmic suspensions, injectable suspensions, and some otic suspensions are prepared in sterile form.

Suspension

- Suspensions are generally not injected intravenously, epidurally, or intrathecally unless the product labeling clearly specifies these routes of administration.
- Some suspensions are designed to form a mass in situ. These suspensions comprise polymer, drug substance, and solvent for the polymer. The polymer solvent can be water or an organic solvent.
- After administration of the suspension to a patient by subcutaneous or intramuscular administration, it forms a gel or a solid polymeric matrix that traps the drug substance and extends the drug substance release for days or months.

Why Formulate into Suspension

- Limited aqueous solubility could be made into liquid dosage form
- taste masking thus improved patient compliance
- compared to solutions, suspensions have better chemical stability.
- When the liquid form is preferred to the solid form of the same drug because of the ease of swallowing liquids and the flexibility in administration of a range of doses → for elderly or infants

Suspension : Consideration

- Ideally, a suspension should contain small uniform particles that are readily suspended and easily redispersed following **settling**.
- Unless the dispersed solid is colloidal, the particulate matter in a suspension will likely **settle to the bottom of the container** upon standing. Such sedimentation may lead to caking and solidification of the sediment and difficulty in redispersing the suspension upon agitation.
  - To prevent such problems, manufacturers commonly add ingredients to increase viscosity and the gel state of the suspension or flocculation, including **clays, surfactants, polyols, polymers, or sugars.**

Suspension : Consideration

- Must be easily poured and redispersed
- Density of the dispersed phase and continuous phase may be modified to further control settling rate.
- topical suspensions, rapid drying upon application is desirable
- Temperature can influence the viscosity (and thus suspension properties and the ease of removing the dose from the bottle),
- temperature cycling can lead to changes in the particle size of the dispersed phase via Ostwald ripening.(freeze/thaw) could be done to investigate temperature effects.
- suspension for multiple doses must contain antimicrobial

Other type of Suspension

- **Suspensions for reconstitution** are dry powder or granular mixtures that require the addition of water or a supplied formulated diluent before administration.
- This formulation approach is frequently used when the chemical or physical stability of the drug substance or suspension does not allow sufficient shelf life for a preformulated suspension.
- Typically, these suspensions are refrigerated after reconstitution to increase their shelf life.
- For this type of suspension, the powder blend is uniform and the powder readily disperses when reconstituted.

Other type of Suspension

- **Injectable suspensions** are generally intended for either subcutaneous or intramuscular routes of administration and should have a controlled particle size, (5 µm or smaller)
- Developed due to ***poor drug substance solubility, improved chemical stability, prolonged duration of action, and avoidance of first-pass metabolism***.
- Care is needed in selecting the sterilization technique because it may affect product stability or alter the physical properties of the material.

Suspension : Preparation

- **suspending agents or other excipients and purified water or oil are added to solid drug substances** and mixing to achieve uniformity.
- the characteristics of both the dispersed phase and the dispersion medium should be considered.
- define an appropriate particle size distribution for the suspended material (to minimize the likelihood of particle size changes during storage)
- Some dispersed phase has an affinity for the vehicle and is readily wetted upon its addition while some others not really thus the displacement of air from the solid surface is difficult, and the solid particles may **clump together** or float on top of the vehicle. → need to add wetting agent to **facilitate displacement of air from the powder surface.**

Suspension : Preparation

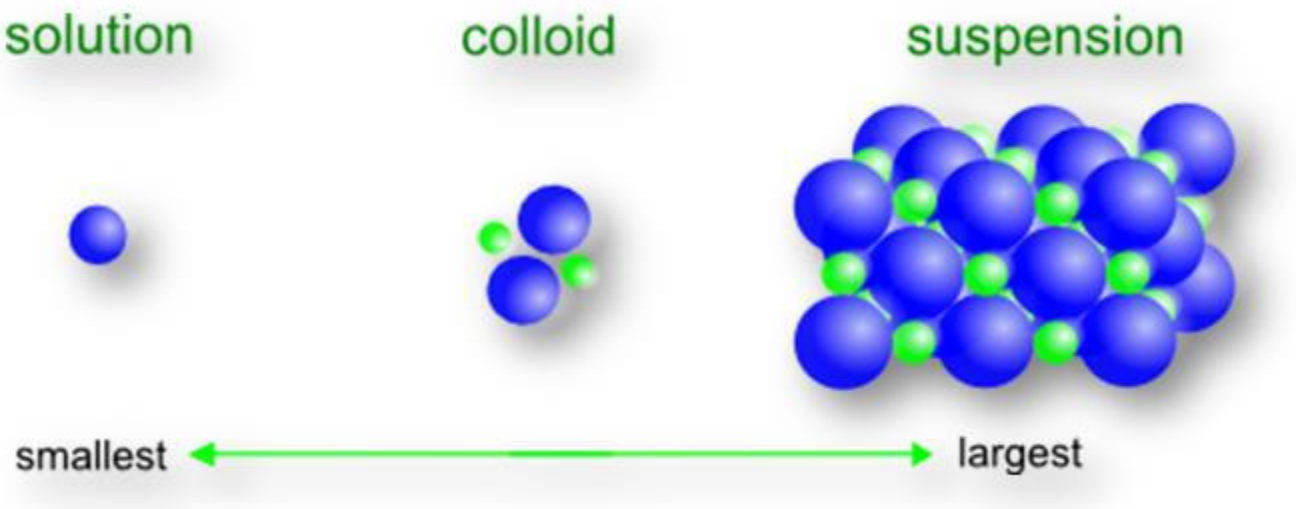
- Surfactants, alcohol, glycerin, and other hydrophilic liquids can be used as wetting agents when an aqueous vehicle (water) will be used as the dispersion phase.
  - These agents function by displacing the air in the crevices of the particles and dispersing the particles.
  - In the large-scale preparation of suspensions, **wetting of the dispersed phase** may be aided by the use of high-energy mixing equipment such as **colloid mills** or other rotor–stator mixing devices.
  - After the powder has been wetted, the dispersion medium (containing the soluble formulation components such as colorants, flavorings, and preservatives) is added in portions to the powder, and the mixture is thoroughly blended before subsequent additions of the vehicle.

Suspension : Preparation

- A portion of the vehicle is used to wash the mixing equipment free of suspended material, and this portion is used to bring the suspension to final volume and ensure that the suspension contains the desired concentration of solid matter.
- The final product may be passed through a colloid mill or other blender or mixing device to ensure uniformity.
- Suspensions are resuspended before the dose is dispensed. Because of the viscosity of many suspension vehicles, air entrainment may occur during dosing.
- The formulation process allows evaluation of this possibility; adjustments in vehicle viscosity or the incorporation of low levels of antifoaming agents are common approaches to minimize air entrainment.
- Alternatively, specific instructions for resuspending the formulation may be provided to minimize air incorporation and ensure accurate dosing.

Suspension : Preparation

- Ear drops
- Enemas
- Inhalations
- Lotions
- Mixture for oral use



Disperse System

- Molecular dispersion (particle size < 1nm)
  - Invisible in electron microscope
  - Pass through ultrafilter and semipermeable membrane
  - Rapid diffusion
  - Eg: oxygen molecules, ordinary ions, glucose
- Colloidal dispersion (particle size 1 nm - 0.5 um)
  - Might be detected under ultra microscope
  - Pass through filter paper, do not pass semipermeable membrane
  - Diffuse very slowly
  - Eg: natural & synthetic polymer, cheese, butter, jelly, paint, milk, shaving cream, etc
- Coarse dispersions dispersion (particle size > 0.5um)
  - Visible under microscope
  - Do not pass through normal filter paper
  - Do not dialyze through semipermeable membrane
  - Do not diffuse
  - Eg: grain of sand, most pharma emulsions, suspensions, red blood cells
  - Dispersions containing coarse particles, usually 10 to 50 µm, are referred to as *coarse dispersions*; they include the *suspensions* and *emulsions*.

Pharmaceutical Suspension : Requirements

- A properly prepared pharmaceutical suspension should settle slowly and should be readily redispersed upon gentle shaking of the container.
- The particle size of the suspensoid should remain fairly constant throughout long periods of undisturbed standing (1-50um)
- The suspension should pour readily and evenly from its container.

Pharmaceutical Suspension

Advantages

- Insoluble drugs may be more palatable
- Insoluble drugs may be more stable
- Suspended insoluble powders are easier to swallow
- Enables easy administration of bulk insoluble powders (Kaolin BP & Chalk BP) – act as adsorbents of toxins in the GI tract
- Absorption will be quicker than solid dosage forms
- Lotions will leave a cooling layer of medicament on the skin (Calamine lotion)
- Theoretically possible to formulate sustained-release preparations

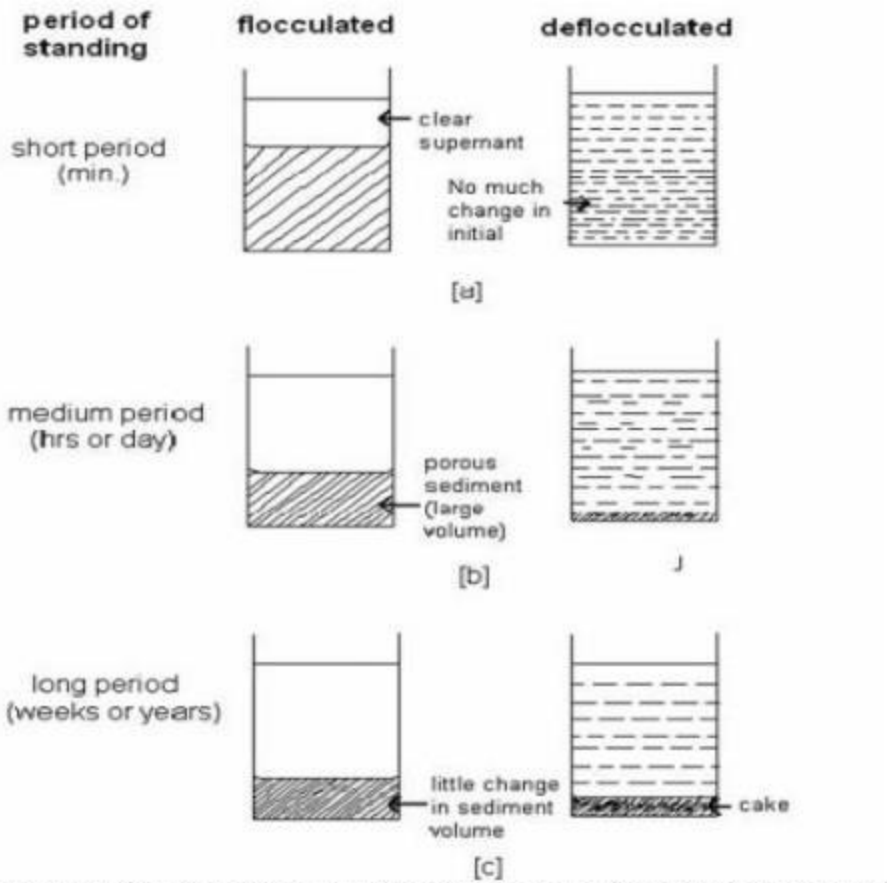
Pharmaceutical Suspension

Disadvantages

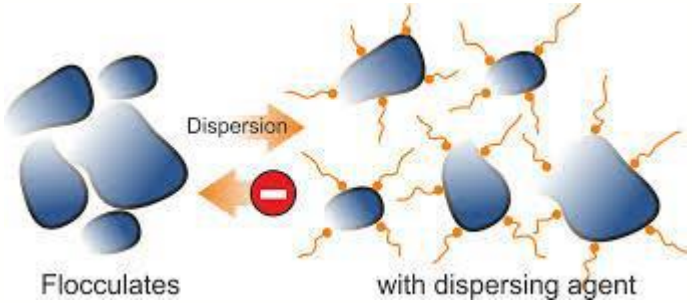
- Preparation requires shaking before use
- Accuracy of dose likely to be less than equivalent solution
- Conditions of storage may adversely affect the disperse system and in the case of indiffusible solids clumping may occur, leading to potential dosing inaccuracy.
- Bulky, difficult to transport and prone to container breakages

Flocculation

- To avoid formation of a cake, it is necessary to prevent agglomeration of the particles into larger crystals or into masses (flocculation).
- Such an aggregation of particles is termed a *floc* or a *floccule*, with flocculated particles forming a type of lattice that resists complete settling (although flocs settle more rapidly than fine, individual particles) and thus are less prone to compaction than unflocculated particles.



Sedimentation behaviour of flocculated and deflocculated suspensions



Excipient in Suspension

Suspending agents

- CMC: carboxymethylcellulose
- Methylcellulose
- Microcystalline cellulose
- Polyvinyl-pyrrolidone
- Xanthan gum
- Bentonite

Excipient in Suspension

- Wetting agent: alcohol, glycerin, propylenglycol, others

- Flavor & colorant

- Preservative

- Water

Equipment in making Suspension

Equipment

- Colloid mill
- Mortar and pestle

Diffusable Suspension

- Light powders that are insoluble, or only very slightly soluble, in the vehicle
- On shaking disperse evenly throughout the vehicle for long enough to allow an accurate dose
- Example:
  - Light Kaolin BP (insoluble in water)
  - Light Magnesium Carbonate BP (very slightly soluble in water)
  - Magnesium trisilicate BP (insoluble in water)

Indiffusable Suspension

- These are suspensions containing heavy powders that are insoluble in the vehicle
- On shaking do not disperse evenly throughout the vehicle long enough to allow an accurate dose to be poured.
- Examples
  - Aspirin BP
  - Calamine BP
  - Chalk BP
  - Zinc Oxide BP
- The main difference from diffusible suspensions is that the vehicle must be thickened to slow down the rate at which the powder settles.
- This is achieved by the addition of a suspending agent.

Formulation of Suspension

Vehicles

- Water
- Aqueous vehicle: addition of sucrose or glycerol

Thickening agent

- Increase viscosity means that the rate of sedimentation of the insoluble solid will be slower

Other additives

- Coloring & flavoring
- Preservatives: benzoic acid 0.1% (internal use); chlorocresol 0.1% w/v (external use)

Preparation of diffusible suspension

- 1. Check the solubilities, in the vehicle, of all solids in the mixture.
- 2. Calculate the quantities of vehicle required to dissolve any soluble solids.
- 3. Weigh all solids on a Class II or electronic balance.
- 4. Dissolve all soluble solids in the vehicle in a small glass beaker using the same procedures as outlined in the chapter on solutions
- 5.Mix any insoluble diffusible powders in a porcelain mortar using the 'doubling-up' technique to ensure complete mixing
- 6. Add a small quantity of the vehicle (which may or may not be a solution of the soluble ingredients) to the solids in the mortar and mix using a pestle to form a smooth paste.

Preparation of diffusable Suspension

- 7. Add further vehicle in small quantities, and continue mixing until the mixture in the mortar is of a pourable consistency.
- 8. Transfer the contents of the mortar to a conical measure of suitable size.
- 9. Rinse out the mortar with more vehicle and add any rinsings to the conical measure.
- 10. Add remaining liquid ingredients to the mixture in the conical measure. (These are added now, as some may be volatile and therefore exposure during mixing needs to be reduced to prevent loss of the ingredient by evaporation.)
- 11. Make up to final volume with vehicle.
- 12. Stir gently, transfer to a suitable container, ensuring that all the solid is transferred from the conical measure to the bottle, and label ready to be dispensed to the patient.

Preparation of indiffusable Suspension

- 1. Check the solubilities in the vehicle of all solids in the mixture.
- 2.Calculate the quantities of vehicle required to dissolve any soluble solids.
- 3.Prepare any Double Strength Chloroform Water BP required.
- 4.Weigh all solids on a Class II or electronic balance.
- 5.Dissolve all soluble solids in the vehicle in a small glass beaker.
- 6.Mix any insoluble indiffusible powders and the suspending agent in a porcelain mortar using the ‘doubling-up’ technique to ensure complete mixing

Preparation

- 7. Add a small quantity of the vehicle (which may or may not be a solution of the soluble ingredients) to the solids in the mortar and mix using a pestle to form a smooth paste.
- 8. Add further vehicle in small quantities, and continue mixing until the mixture in the mortar is a pourable consistency.
- 9. Transfer the contents of the mortar to a conical measure of suitable size.
- 10. Rinse out the mortar with more vehicle and add any rinsings to the conical measure.
- 11. Add remaining liquid ingredients to the mixture in the conical measure. (These are added now, as some may be volatile and therefore exposure during mixing needs to be reduced to prevent loss of the ingredient by evaporation.)
- 12.Make up to final volume with vehicle.
- 13. Stir gently, transfer to a suitable container, ensuring that all the solid is transferred from the conical measure to the bottle, and label ready to be dispensed to the patient.

Preparation Suspension

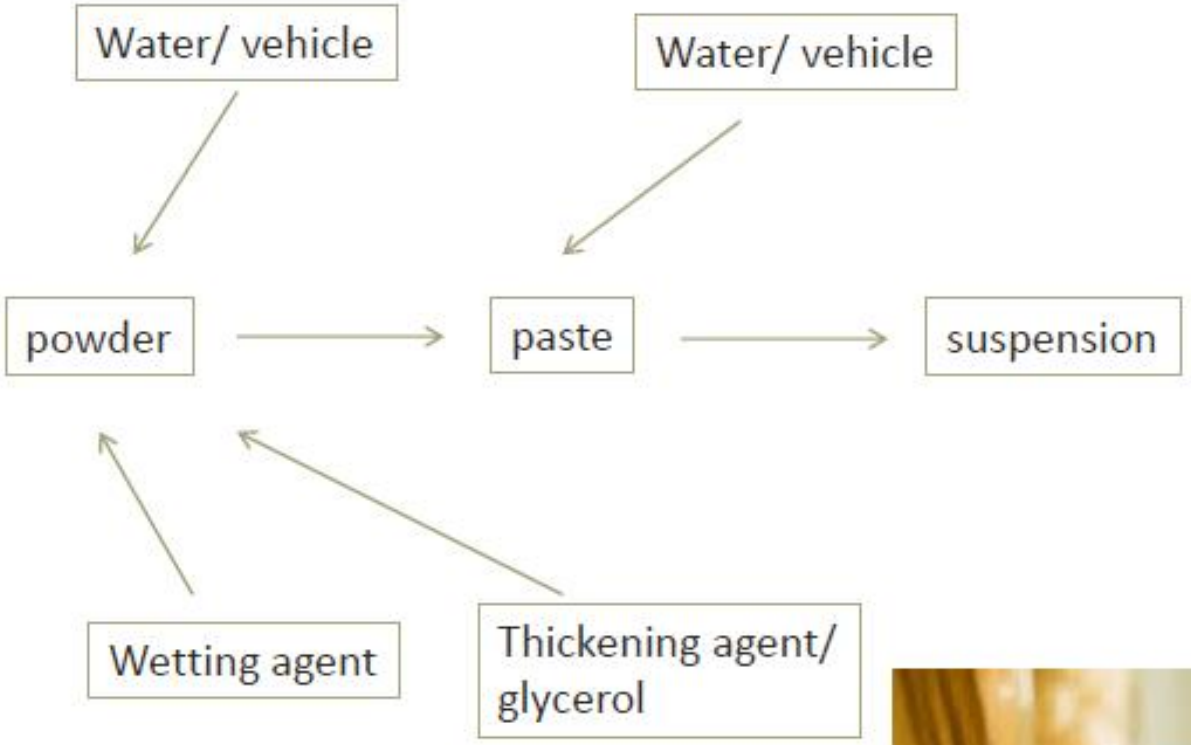


FIGURE 14.2 Commercial antibiotic preparation for oral suspension following reconstitution with purified water. *Left*, dry powder mixture. *Right*, suspension after reconstitution with the specified amount of purified water.

Preparation

Table 7.1 Summary of the different suspending agents used in extemporaneous formulation

Category of suspending agent	Example of suspending agent
Natural polysaccharides (page 85)	Acacia Gum BP Agar BP Carrageenan BP Compound Tragacanth Powder BP Guar Gum BP Powdered Tragacanth BP Sodium Alginate BP Starch BP
Semi-synthetic polysaccharides (page 86)	Hydroxyethylcellulose BP Methylcellulose BP Sodium Carboxymethylcellulose BP
Clays (page 86)	Aluminium Magnesium Silicate BP Bentonite BP Magnesium Aluminium Alginate BP
Synthetic agents (page 86)	Carbomer BP Polyvinyl Alcohol BP
Miscellaneous compounds	Gelatin BP

Key Skill 7.1 The 'doubling-up' technique

1. Weigh the powder present in the smallest volume (powder A) and place in the mortar.
2. Weigh the powder present in the next largest volume (powder B) and place on labelled weighing paper.
3. Add approximately the same amount of powder B, as powder A in the mortar.
4. Mix well with pestle
5. Continue adding an amount of powder B that is approximately the same as that in the mortar and mix with the pestle, i.e. doubling the amount of powder in the mortar at each addition.
6. If further powders are to be added, add these in increasing order of volume as in steps 3, 4 and 5 above.

Inhalation

- Inhalations are *liquid products that contain volatile ingredients intended to be released and brought into contact with the respiratory lining*.
- Suspensions are a particularly useful way of effecting this transfer as the volatile ingredient can be adsorbed onto a carrier powder (a diffusible solid) and formulated as a suspension which can then provide an accurate dose to be added to hot (about 65 C) but not boiling water, so that the volatile ingredient is released and inhaled by the patient.
- Alcoholic solutions are also suitable to use as a 'hot' inhalation. If ingredients are volatile at room temperature they may be inhaled directly from a handkerchief or absorbent pad.

Lotion

- Lotions can be suspensions, although they may also be solutions or emulsions
- They are intended to be applied to the skin, without friction, on a carrier fabric such as lint and covered with a waterproof dressing. In some cases, such as Calamine Lotion BP, they may be dabbed onto the skin surface and allowed to dry.

Packaging

Table 7.2 Summary of packaging for pharmaceutical suspensions	
Oral liquids	Amber flat medicine bottle (Typical sizes: 50 mL, 100 mL, 150 mL, 200 mL, 300 mL and 500 mL)
	Pharmaceutical product examples include:Mixtures (suspensions) for oral use
External liquids	Amber fluted medicine bottle (Typical sizes: 50 mL, 100 mL, 200 mL)
	Pharmaceutical product examples include: Applications Inhalations Lotions
	Amber fluted medicine bottle with dropper top (Typical sizes: 10 mL, 20 mL)
	Pharmaceutical product examples include: Ear drops Nose drops

Packaging/Storage

- All suspensions should be packaged in *widemouth containers having adequate airspace above the liquid to permit thorough mixing by shaking and ease of pouring*.
- Most suspensions should be stored in tight containers protected from freezing, excessive heat, and light.
- It is important that suspensions be shaken before each use to ensure a uniform distribution of solid in the vehicle and thereby uniform and proper dosage.

Labelling

- In addition to the standard requirements for the labeling of extemporaneous preparations, the following points need to be taken into consideration:
- ‘Shake the bottle’ – All suspensions will require this additional label.
- ‘Not to be taken’ – This warning must be added to the label of any inhalations.
- ‘For external use only’ – This warning must be added to the label of any other suspension not intended for administration via the oral route.

Review

- Different type of solution and suspension? Can you differentiate them? What is their Advantages and Disadvantages
- Consideration when making solution or suspension? Do you know how to prepare them? Common excipient?
- How about the packaging and labelling?