INTRODUCTION TO **PHARMACEUTICAL TECHNOLOGY**

3rd year pharmacy

Pharmaceutical technology

Ansel's pharmaceutical dosage forms and drug delivery systems

What is a DRUG

- **Drug** How does the law define a drug?
- The Federal Food, Drug, and Cosmetic Act FD&C Act defines drugs, in part, by their intended use, as
- "articles intended for use in the
- diagnosis,
- cure,
- mitigation(alleviation, modification),
- treatment,
- or prevention of disease“
- and "articles (other than food) intended to affect the structure or any function of the body of man or other animals"
- [FD&C Act, 1938 sec. 201(g)(1)]

DRUG

- This is pharmacologically active ingredient in the medicine
- Also called
- Medicinal agent
- Active ingredient
- Active pharmaceutical ingredient API

Pharmaceutics

- Converts a DRUG into a MEDICINE
- Pharmaceutics is the science and technology of the design and manufacture of dosage form
- This covers
- Physical pharmaceutics (the drug itself)
- Biopharmaceutics (therapeutic consideration)
- Dosage form design
- Manufacture of these medicines either on small scale (compounding) or on large scale (industrial)
- Avoidance and elimination of M.O

Pharmaceutical preparation (Medicine)

- Elegant pharmaceutical preparations must be:
- Safe
- Stable
- Palatable
- Therapeutically effective

Pharmacopeia

- The term comes from the Greek
- Pharmakon meaning drug
- Poiein meaning make
- Any recipe or formula or other standards required to make or prepare a drug
- Pharmacopeia , is a book containing directions for the identification of compound medicines, and published by the authority of a government or a medical or pharmaceutical society.
- Descriptions of preparations are called monographs. In a broader sense it is a reference work for pharmaceutical drug specifications

British Pharmacopeia BP

- The British Pharmacopeia is the official collection of standards for UK medicinal products and pharmaceutical substances
- The standards are established by the British Pharmacopeia Commission.
- Canada and Australia also use the BP as their official standard

The United States Pharmacopeia USP

- The United States Pharmacopeia (USP), established in 1820, contains legally recognized standards of identity, strength, quality, purity, packaging, and labeling for drug substances, dosage forms, and other therapeutic products, including nutritionals and dietary supplements.
- An official publication, issued first by the American Pharmaceutical Association and now yearly by the United States Pharmacopeial Convention, (a non profit organization) that sets the standards for the quality, purity, identity, and strengths of medicine, food ingredients, and dietary supplements manufactured, distributed, and consumed world wide
- The book contains two separate official compendia -- the USP and the NF.

National Formulary NF

- The National Formulary (NF), established in 1888 by the American Pharmaceutical Association, includes standards for excipients, botanicals, and other similar products, gives the composition, description, method of preparation, and dosage for drugs. USP purchased the NF in 1975, combining the two publications under one cover, creating the USP-NF
- United States Pharmacopeia and National Formulary (USP-NF).

Monograph

- USP-NF monographs contain specifications (tests, procedures, and acceptance criteria) that helps ensure the strength, quality, and purity of named items. The USP-NF also contains monographs and general approaches to ensure the quality of compounded preparations. USP-NF monographs, which are recognized worldwide, may be enforceable by the US Food and Drug Administration (FDA) and also by state agencies in the US.

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Solutions
Chapter 13

3rd year pharmacy

Pharmaceutical technology

Ansel's pharmaceutical dosage forms and drug delivery systems

Dispersion types

Molecular	Colloidal	Coarse
True solutions Molecules Ions	Intermediate 10^{-9} to 1 µ	Suspension Larger than 1 µ

Solutions

- Physicochemical terms
- One phase system
- 2 or more substances mixed together
- Physically homogeneous system
- Single phase system

- Prepared from any combination of
- solid liquid and gas

Pharmaceutical solutions

- Liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents.

Most common pharmaceutical solutions are **Aqueous solutions**

(also the biological systems are mostly aqueous)

Medicated solutions contain drugs that are usually soluble in water and their absorption is higher than from suspension or solid dosage forms because any drug must be molecular dispersed (in-solution), before they can be absorbed across the biological membrane and be effective

Classification of pharmaceutical solutions depending on the route of administration

Oral

Otic , nasal

Vaginal ,

rectal solutions

Ophthalmic

Topical

Oral topical (mouthwash)

Injectable

Irrigation

Pharmaceutical classification depending on the solution composition

Syrups	• Sweet thick oral solution • Contains sucrose
Elixirs	• Hydro-alcoholic oral solutions • Sweetened
Spirits, aromatic water	• Spirits are alcoholic or hydro-alcoholic solution of aromatic material • Aromatic water the solvent is water
Fluidextracts Tinctures	• Aqueous or hydroalcoholic or alcoholic extract • Plant or chemical origin • Differ in concentration of the extract
Injections	Must be sterile, isotonic and buffered Aqueous or non aqueous

Classification of solutions according to method of preparation

1-Solutions prepared by simple solution

- Gention violet solution1%in(10%alcohol) solution topical anti-infective

2-Solution prepared by chemical reaction

- Hydrogen peroxide solution 3% hydrolysis of persulfuric acid used as topical anti infective

3-Solutions prepared by simple solution with sterilization

- Atropine sulphate ophthalmic solution, also 0.9%w/v NaCl I.V. fluid

4- Solutions prepared by extraction

Ipecac, tolu

Solution dosage form

Advantages

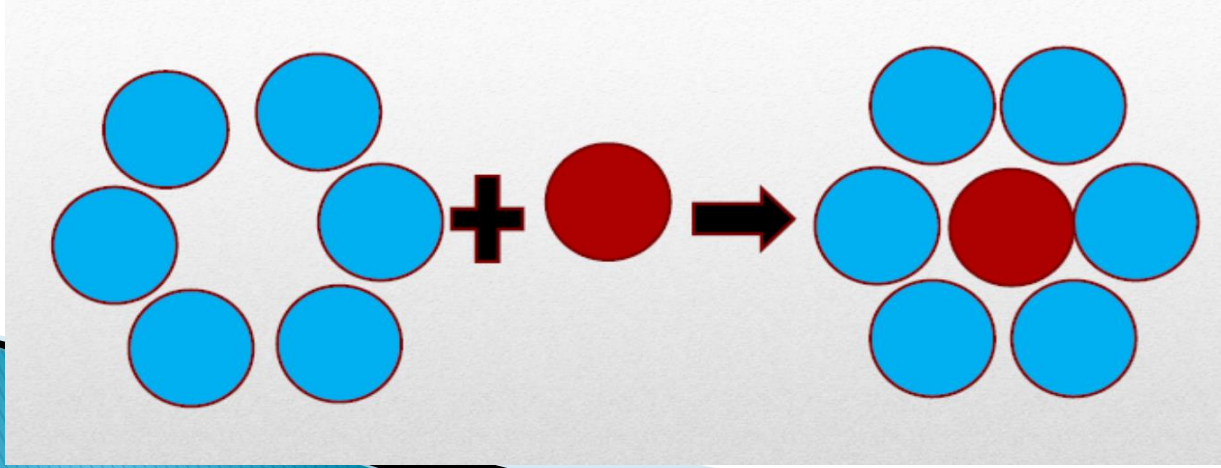
- Easy to swallow , flow, apply , spray
- Good absorption
- Homogeneous

Disadvantage

- Bulky, taste masking
- Stability
  M.O. growth
- Patient measurement

Solubility

- The solubility of an agent in a particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and that solvent.
- i.e, Amount of a solute dissolved in a solvent at a certain temperature(degree of solubility)



Solubility measurement

- **Saturated solubility**
- Excess amount of solid shaken at certain temperature, with a certain volume of liquid for a period of time
- **Super saturated solution**
- Heat the solution containing excess solid then filter and cool. No ppt of the excess solid
  Sodium thiosulfate
  Potassium acetate

Expression of solubility

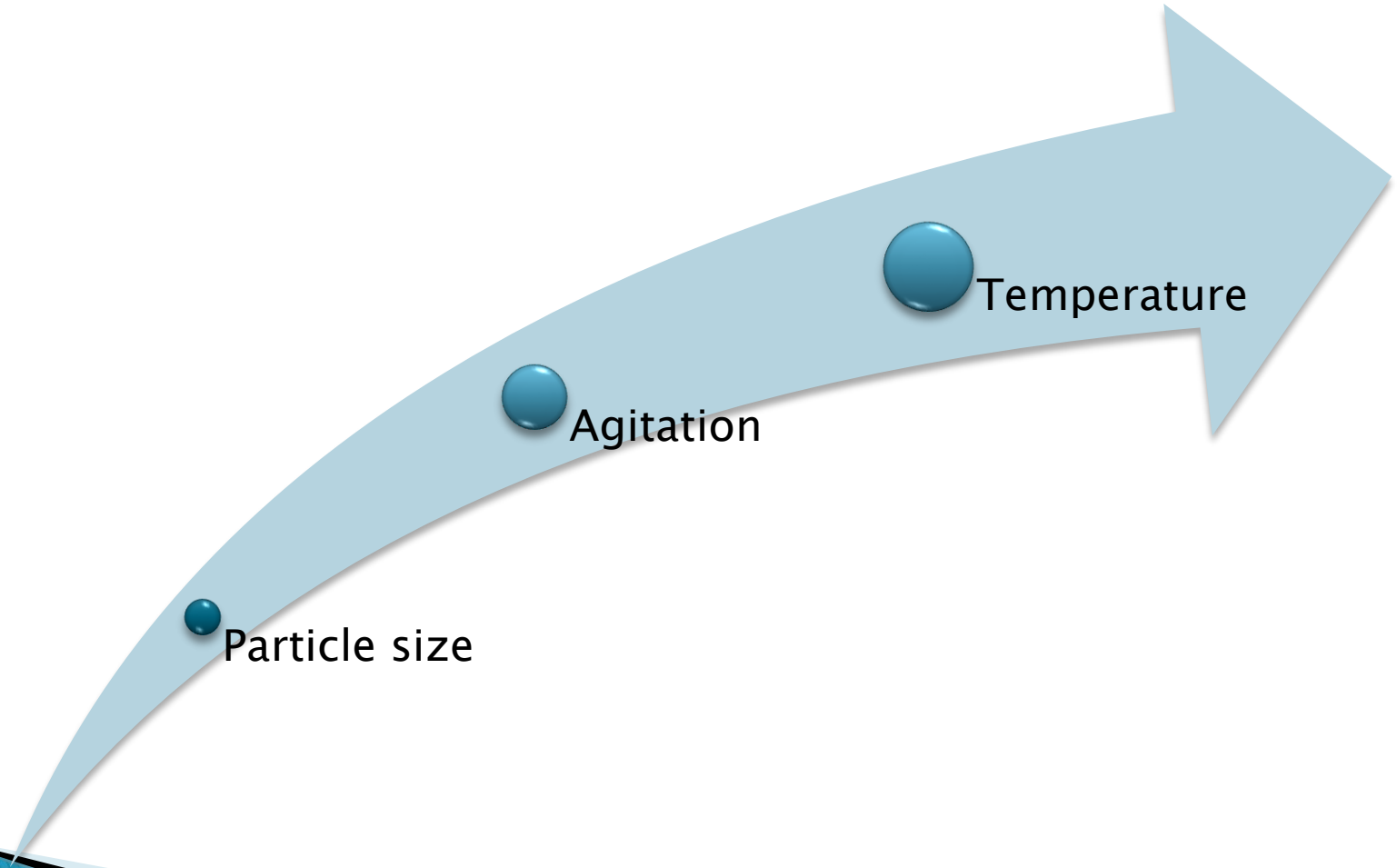
- Calcium Hydroxide Topical solution USP 140mg per 100ml of solution at 25°C
- Potassium iodide solution 100g per 100ml of solution

- The no. of ml. of a solvent required to dissolve 1 g of the solute (or 1 ml. of liquid)
- 1g of KI dissolves in 0.7 ml of water
- 0.5 ml boiling water
- Expressed using **physical units** w/w w/v, v/v
- Or **chemical units** milliequivalent
- Used to express concentration of electrolytes depending on their ionic charge and valence activity

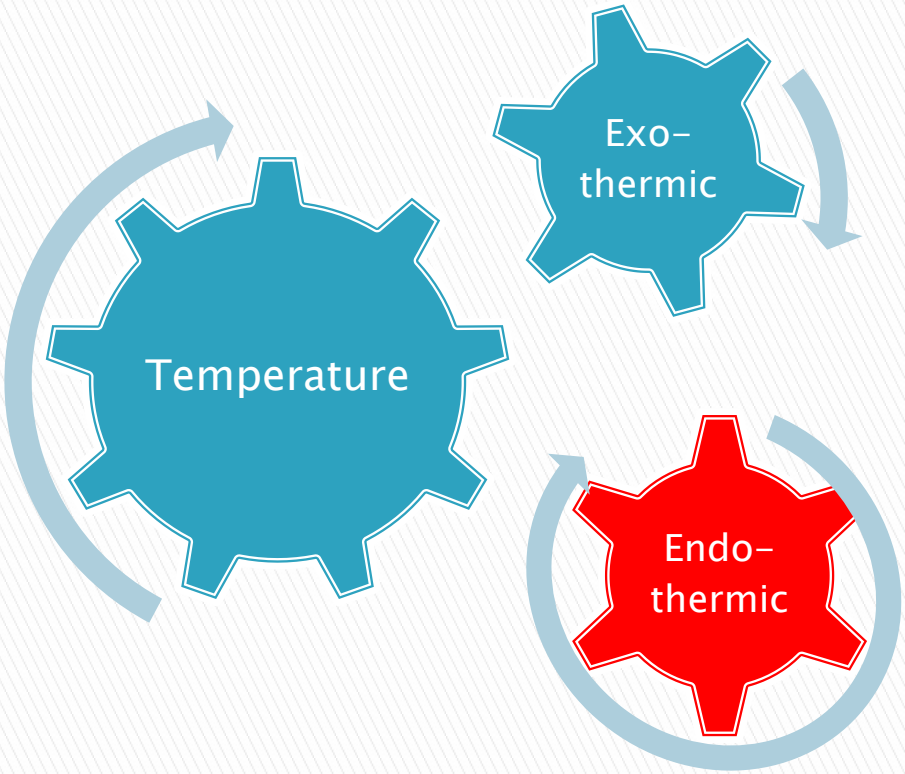
Relative terms of solubility

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	100-1000
Very slightly soluble	1000-10000
insoluble	>10000

Rate of solution(speed)



Factors that determine the extent of solubility



- Depend on the
- Nature of the solvent
- Like dissolves like
- Chemical nature of the solute (molecular structure and functional groups)

Temperature

Chemical Constitution

Water is a good solvent

polarity

- Dipole moment
- Electonegative difference

Hydrogen bonds

- Certain functional groups present
- Low molecular wt

Drugs of low water solubility

- Drugs with low aqueous solubility present problems in relation to the formulation and bioavailability
- Consider non- aqueous solutions for drugs of low solubility

Pharmaceutical Methods to increase solubility

1) Adjust the pH for drugs that are weak acids or bases. Weak acids and weak base solubility is effected by the pH of the solution.
   At a given pH the degree of ionization depends on the pKa .
2) Co-solvent change the polarity of water
3) Surfactant Micell formation
4) Complexation (chemical reaction),

(Lugol's solution) Iodine is slightly soluble in water(1g in 3000ml water) but freely soluble in solution of sodium iodide forming tri-iodide ion

Effect of added substance on solubility

- Salting –In ..addition of an electrolyte to a non electrolyte cause an increase in solubility
- Salting– out..decrease in solubility

- Addition of soluble salt to slightly soluble salt having a common ion will cause ppt. of the slightly soluble salt (according to the law of mass action)

How to predict solubility

Like dissolves like The more solvents and solutes are structurally alike the more rapid solution takes place

Polar solvents dissolve electo-valent substances readily

- But are poor solvents for non polar substances add the opposite is

3Polar liquids are usually miscible with other polar liquids

- Non polar liquids are slightly miscible with polar liquids

Complex organic substances which have polar and non polar groups may dissolve in polar liquids depending on the proportion of the polar groups to the non polar

Semi polar liquids (ethyl alcohol)posses the character of both polar and non polar solvents

Water and alcohol solubility of some weak acids, weak bases, and their salts

Drug (1g)	Water (ml)	Alcohol (ml)
Atropine	455	2
Atropine sulfate	0.5	5
Codeine	120	2
Codeine sulfate	30	1,280
Codeine phosphate	2.5	325
Morphine	5,000	210
Morphine sulfate	16	565
Phenobarbital	1,000	8
Phenobarbital sodium	1	10
Procaine	200	Slightly soluble
Procaine HCl	1	15
Sulfadiazine	13,000	Sparingly soluble
Sodium sulfadiazine	2	Soluble

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	C6H6	1430
Benzoic acid	C6H5COOH	275
Benzyl alcohol	C6H5CH2OH	25
Phenol	C6H5OH	15
Pyrocatechol	C6H4(OH)2	2.3
Pyrogallol	C6H3(OH)3	1.7

Water soluble inorganic salts

- Salts of alkali metals(Na, K, Li,)are usually water soluble except Li_2CO_3
- Ammonium and quaternary ammonium salts
- Nitrates ,nitrites, acetates, chlorates lactates except silver and mercurous acetate
- Sulfates ,sulfites and thiosulfates ,except calcium and barium salts
- Chlorides, bromides and iodides except salts of silver and mercurous ions

Water insoluble inorganic salts

- Hydroxides and oxides of compounds other than alkali metals cations and the ammonium ion
- Sulfides are water insoluble except for their alkali metal salts
- Phosphates ,carbonates ,silicates borates and hypochlorite are water insoluble except for their alkali metal salts and ammonium salt

Organic molecules

- Molecules of 5 carbon chain length and one polar gp are usually soluble
- Branched chains are more soluble than the corresponding straight chain
- Increasing molecular weight will usually decrease solubility
- Increased structure similarity between solute and solvent is accompanied by increase solubility
- Polar function groups include OH, CHO, COH, CHOH, CH_2OH, COOH, NO_2, CO, NH_2 and SO_3H .

Solution formulation

- The formulation additives used are according to
- the type of solution and
- the site of administration.

Solvents for pharmaceutical use

Water	• Purified water • Widely used
Alcohol ethyl alcohol Ethanol C_2H_5OH	• Dissolve polar and semi-polar substances • Miscible with water, used internally Antimicrobial activity
Isopropyl alcohol (70%)	• External use • Vehicle for topical preparations
Glycerin $CH_2OH\ CHOHCH_2OH$	Clear, viscous liquid with sweet taste miscible with water and alcohol
Propylene Glycol $CH_3CH(OH)CH_2OH$	Viscous liquid, miscible, substitute glycerin in pharmaceutical preparations
Corn oil ,Cotton seed oil Peanut oil and Sesame oil	Organic solvents for oleaginous injection

Additives: Buffers

- pH required
  (7.4 for injectable solutions, eye, nose)
- (5.5 for dermal application)(vaginal 4-5)
- Buffering capacity
- Compatible with other excipients
- Low toxicity
- Carbonates, citrates, gluconates, lactates phosphates and tartrates are widely used.
- Borates are used for external application but not to abraded skin or internally

Taste masking

Taste of product	Suitable masking flavor
Salty	Apricot, butterscotch, liquorice, peach vanilla
Bitter	Anise, chocolate, mint, passion fruit, wild cherry
Sweet	Vanilla, fruits, berries
Sour	Citrus fruits, liquorice, raspberry

Additives: Flavors and perfumes

Product use	Flavor preferred
Relief of indigestion	Mint
Antiseptic activity	Terpineol
Oral mucosa anesthetic	Clove oil (eugenol)
Children	Fruity taste and smell
Adult	Flowery odours, acid taste

Additives: Colors

- The colour of the product is associated with the flavor

Flavor	Colour
Mint	Green
Chocolate	Brown
Cherry , strawberry	Pink – red

- Product identification
- Safe, acceptable

Solvents :Water USP

- Drinking water must be clear, colorless, odorless, and neutral or only slightly acid or alkaline
- Not accepted for manufacture of aqueous pharmaceutical preparations because of chemical compatibility of the dissolved solids with the medicinal agents (ppt.,discoloration, effervescence)
- Used for washing, in extraction of the crude vegetable drugs

Purified Water USP

- Prepared from tap water complying with the Environmental Protection Agency for drinking water.
- Purified Water has fewer solids impurities than ordinary drinking water, when evaporated to dryness it must not yield more than 1mg solids per 100ml water
- Intended for use in preparation of aqueous dosage forms except those intended for parenteral administration.

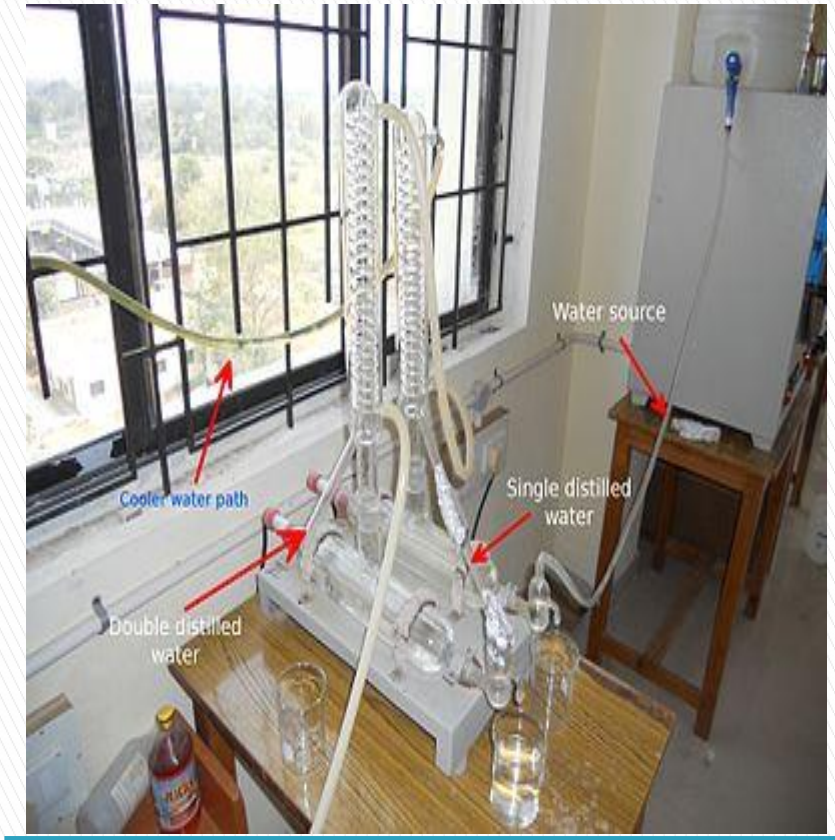
Purified water USP

- Used in preparation of all medications containing water except injectable preparation and other specialized products
- Purification of water is done by

1) Distillation
2) De-ionization (Ion exchange)
3) Reverse osmosis

Distillation Method

- **Distilled water** is water that has many of its impurities removed through distillation. Distillation involves boiling the water and then condensing the steam into a clean container



Definition

Typical laboratory distillation unit

Ion exchange method

- On a large or small scale, ion exchange for the preparation of purified water offers a number of advantages over distillation.

1. The requirement of heat is eliminated and with it,
2. The costly and troublesome maintenance frequently encountered in the operation of the more complex distillation apparatus.
3. Because of the simpler equipment and the nature of the method, ion exchange permits ease of operation, minimal maintenance, and a more mobile facility.

Water purified in this manner, referred to as demineralized or deionized water, may be used in any pharmaceutical preparation or prescription calling for distilled water

Ion exchange resin or polymer beads

Is an water insoluble, synthetic, polymeric resin of high molecular weight containing phenolic, carboxylic, amino, or sulfonated groups.

The beads are typically porous, providing a high surface area.

definition

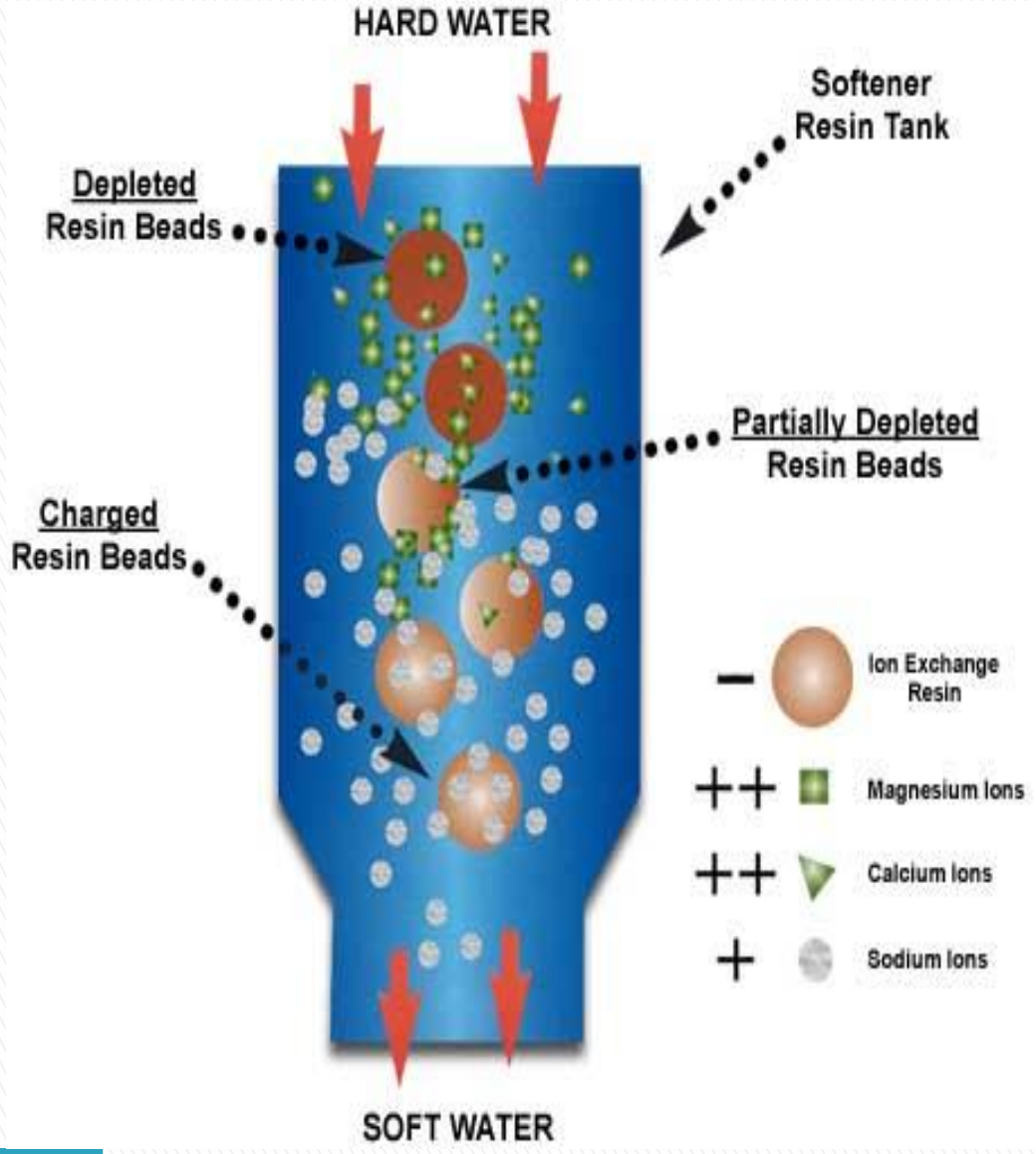
Ion exchange beads

Ion exchange polymer types

- 1-Acid or cationic exchanger
- which permit the exchange of the cations in solution with hydrogen ion from the resin;
- H- resin + M^+ + X^- + H_2O →
- M-resin + H^+ + X^- + H_2O (pure)
- 2- Base or anionic exchanger
- which permit the removal of anions
- Resin-NH_2 + H^+ + X^- + H_2O →
- Resin-NH_2 ◆ HX + H_2O (pure)

Water softener

- Ion exchange is a method widely used in water filters to produce soft water. The trapping of ions occurs with concomitant releasing of other ions; thus the process is called ion-exchange.
- Water purification is accomplished by exchanging calcium Ca^{2+} and magnesium Mg^{2+} cations against Na^{+} or H^{+} cations
- The most commercial resins are made of polystyrene sulfonate these polymers have a higher affinity to divalent cations than monovalent cations.



Principle

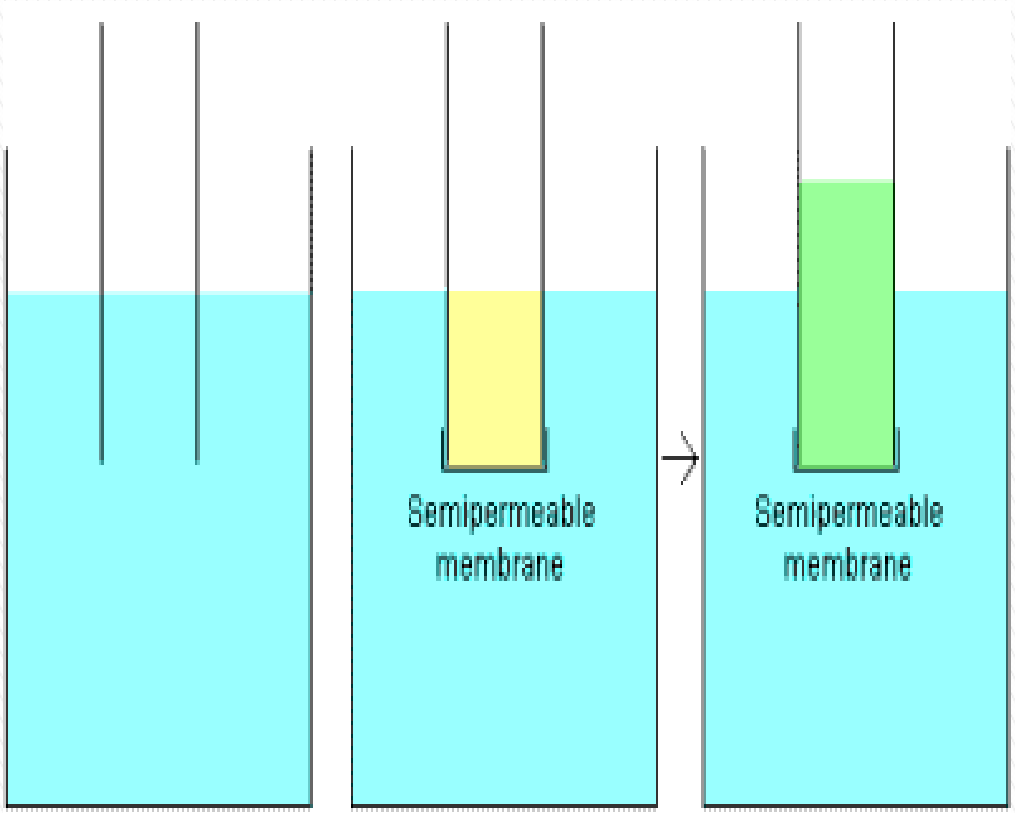
Water softener illustration

Reverse Osmosis

- Reverse osmosis is one of the processes referred to in the industry as cross-flow membrane filtration.
- In osmosis the flow through a semipermeable membrane is from a less concentrated solution to a more concentrated solution,
- The flow in this cross-flow system is from a more concentrated to a less concentrated solution; thus the term reverse osmosis.

Osmosis

- Osmosis is the passage or diffusion of water or other solvents through a semipermeable membrane that blocks the passage of dissolved solutes



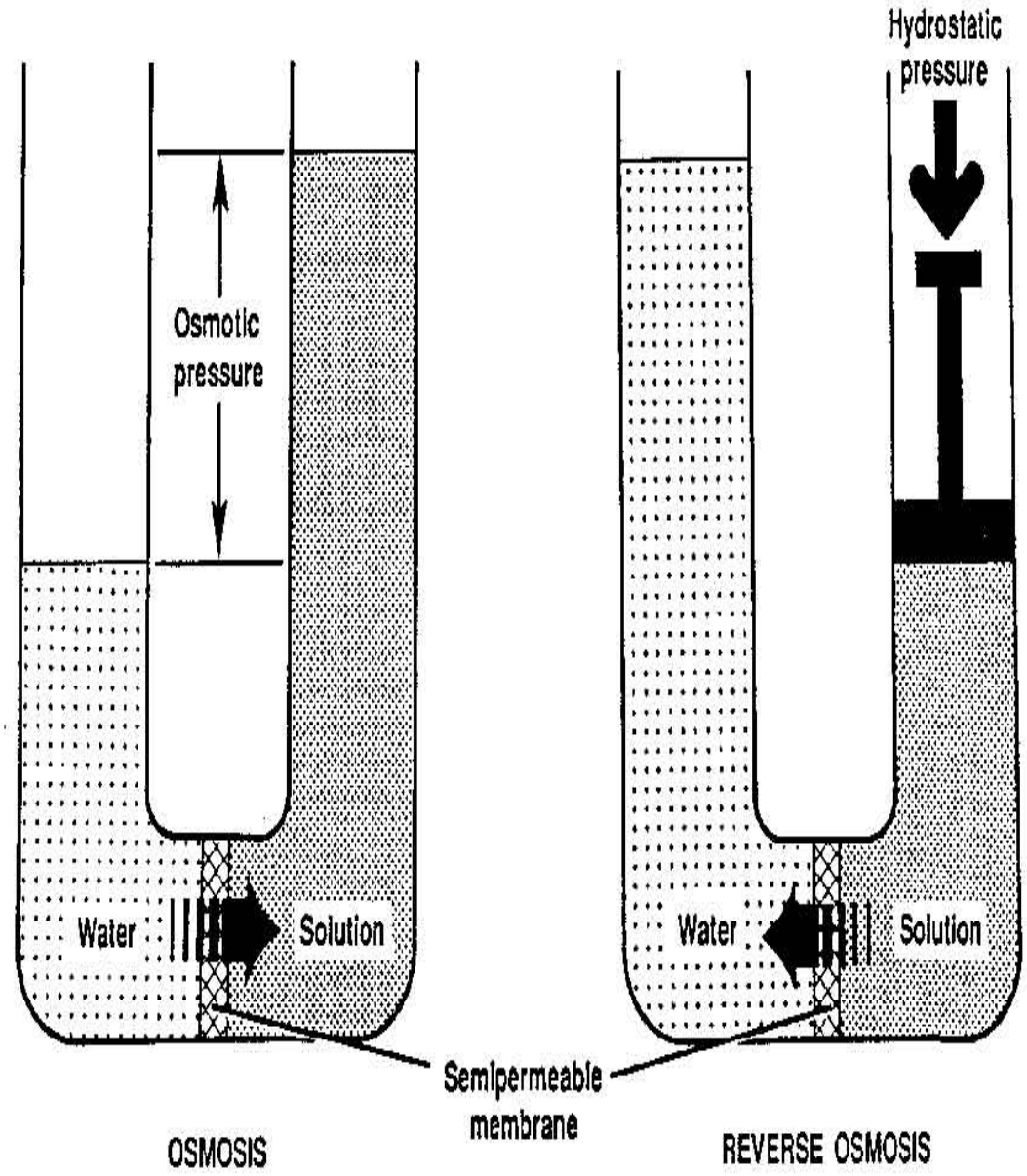
Principle

Osmosis

Reverse osmosis system

Principle

- In RO, an applied pressure is used to overcome osmotic pressure, a colligative property, that is driven by chemical potential, a thermodynamic parameter.
- The result is that the solute is retained on the pressurized side of the membrane and the pure solvent is allowed to pass to the other side.
- To be "selective," this membrane should not allow large molecules or ions through the pores (holes), but should allow smaller components of the solution (such as the solvent) to pass freely.



Reverse osmosis

- Depending on their pore size, cross-flow filter membranes can remove particles defined in the range of
- microfiltration (0.1 to 2 μm, e.g., bacteria);
- ultrafiltration (0.01 to 0.1 μm, e.g., virus);
- nanofiltration (0.001 to 0.01 μm, e.g., organic compounds
- in the molecular weight range of 300 to 1,000); and reverse osmosis (particles less than 0.001 μm).
- Reverse osmosis removes virtually all viruses, bacteria, pyrogen, and organic molecules and 90% to 99% of ions

Solutions
Water for injection

- Pyrogen free water (polysaccharide byproduct of bacterial origin)
- Purified by distillation and used within 24 hr. after collection.
- Intended to be used as a solvent for parental products preparation to be sterilized after preparation
- Sterilization is achieved by autoclave (steam under pressure)

Sterile solutions
Sterile water for injection USP

- Water for injection sterilized and packed in suitable single dose container preferably Type I glass and not larger than 1000ml size.
- This water is intended to be used as a solvent, vehicle, or diluent for already sterilized and packaged injectable medications.
- They are used to reconstitute of antibiotics

Sterile solutions
Bacteriostatic water for injection USP

- Sterile water for injection that contains bacteriostatic agent (benzyl alcohol)
- May be packed in single dose container (not larger than 5ml)or multiple dose containers (not larger than 30ml)
- Not used for neonates.

Other sterile diluents

- Sodium chloride injection USP
- Bacteriostatic sodium chloride injection USP
- Ringer injection USP
- Lactated Ringer injection USP
- Dextrose 5% solution

Ophthalmic solutions

Sterile

by autoclave or filtration

Isotonic

Preserved

(multi-dose)by phenyl ethyl-alcohol, chorobutanol, benzalkonium chloride, phenyl mercuric nitrate

Optimum pH

low buffer capacity

Oral solutions

Final solution
Drug
Sweetening agent
Flavoring agent
Preservative
Colors
Buffers
Density modifiers
Viscosity enhancers
Reducing agents

Types of oral solutions

Oral solutions

- Mostly used for small and old aged patients
- Cold remedies and bronchodilators
- vitamins
- Laxative solutions
- Mist Diuretic

Dry for reconstitution

1. Unstable in aqueous media
2. Uniform dose

- ORS
- Orodispersible tablet (Halazone) or powder Voltafast ®
- Effervescent tablets or powder

Oral rehydration solution

ORS

- Used for diarrhea to replenish electrolytes
- This equates to
- 45 mEq sodium,
- 35 mEq chlorine, and
- 20 mEq potassium
- 30mEq citrate
- 25g dextrose per liter of fluid.
- These formulation are available in liquid or powder packet form for reconstitution

Oral colonic lavage solution

- Used before bowel procedures (colonscopy)
- Balanced solutions of electrolytes with PEG-3350

- Lactulose is a colonic acidifier that works by increasing stool water content and softening the stool. It is a man-made sugar solution laxative used to treat constipation.

Topical solutions (infection)

	conc	Vehicle
Hydrogen peroxide	3%	Aqueous
Chlorhexidine gluconate	4%	Aqueous
Iodine tincture	2%	Alcohol, water
Povidone Iodine	7.5%, 10%	Aqueous
Clindamycin phosphate	1%	Isopropyl alcohol Water
Erythromycin	2%	PEG/acetone/alcohol
Clotrimazole	1%	PEG400
Ketoconazole	1%	Water
Tolnaftate	1%	PEG

Topical solutions

Drug	Conc	Vehicle	Use
Fluorouracil	2.5%	PG	antineoplastic
Minoxidil	2 ,5%	Alcohol, water, PG	Baldness
Hydroquinone		Water Alcohol ,PG	
Podophyllum		Benzoin tincture	Warts
Fluocinolone acetonide Betamethasone Mometasone		PG	Adrenocortical steroid

Mouthwashes and gargles

- Mouthwashes/gargles are designed for the treatment of infection and inflammation of the oral cavity. Formulations designed for this purpose employ water as the vehicle, although a co-solvent, e.g. alcohol, may be employed to solubilize the active agent.
- The use of alcohol as a co-solvent may act to enhance the antimicrobial properties of the therapeutic agent.
- Other formulation components are frequently required to enhance the palatability and acceptability of the preparation. These include preservatives, colors, flavoring agents and non-cariogenic sweetening agents.

Vaginal solutions (douches)

Powders for solution

Liquid solutions or concentrates

- Used for irrigation, cleansing of the vagina for hygienic effect
- Astringents
- Antimicrobials
- Adjusting pH

Vaginal preparations properties

1. Maintain optimal pH
2. Ease of application
3. May be used externally OR internally

Rectal solutions (Enemas)

Retention enemas

1. Local effect (hydrocortisone) as enemas for ulcerative colitis
2. Systemic absorption

(aminophylline) rectal administration minimizes the undesirable GIT reaction, effective blood levels within 30 min after rectal instillation

Viscosity-enhancing agents, e.g. glycerol, may be included to aid retention of the formulation within the rectum and to reduce the incidence of seepage.

Evacuation enemas

- Used to cleanse the bowel available in disposable plastic squeeze bottles containing a premeasured amount of enema solution

Evacuation Enemas

- Enemas are pharmaceutical solutions that are administered rectally and are employed to ensure clearance of the bowel,

1. Oil-based solutions and, in some formulations, the vehicle is the agent that promotes bowel evacuation, e.g. Arachis oil enema. **Softening the feces**
2. Aqueous formulations usually contain salts (e.g. phosphates) to alter the osmolality within the rectum, thereby increasing the movement of fluid to the rectal contents. Increasing the amount of water in the large bowel (**osmotic laxatives**).

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- Physically homogeneous system
- Single phase system

- Prepared from any combination of
- solid liquid and gas

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Most common pharmaceutical solutions are **Aqueous solutions**

(also the biological systems are mostly aqueous)

Medicated solutions contain drugs that are usually soluble in water and their absorption is higher than from suspension or solid dosage forms because any drug must be molecular dispersed (in-solution), before they can be absorbed across the biological membrane and be effective

Classification of pharmaceutical solutions depending on the route of administration

Oral

Otic , nasal

Vaginal ,

rectal solutions

Ophthalmic

Topical

Oral topical (mouthwash)

Injectable

Irrigation

Pharmaceutical classification depending on the solution composition

Syrups	• Sweet thick oral solution • Contains sucrose
Elixirs	• Hydro-alcoholic oral solutions • Sweetened
Spirits, aromatic water	• Spirits are alcoholic or hydro-alcoholic solution of aromatic material • Aromatic water the solvent is water
Fluidextracts Tinctures	• Aqueous or hydroalcoholic or alcoholic extract • Plant or chemical origin • Differ in concentration of the extract
Injections	Must be sterile, isotonic and buffered Aqueous or non aqueous

Classification of solutions according to method of preparation

1-Solutions prepared by simple solution

- Gention violet solution1%in(10%alcohol) solution topical anti-infective

2-Solution prepared by chemical reaction

- Hydrogen peroxide solution 3% hydrolysis of persulfuric acid used as topical anti infective

3-Solutions prepared by simple solution with sterilization

- Atropine sulphate ophthalmic solution, also 0.9%w/v NaCl I.V. fluid

4- Solutions prepared by extraction

Ipecac, tolu

Solution dosage form

Advantages

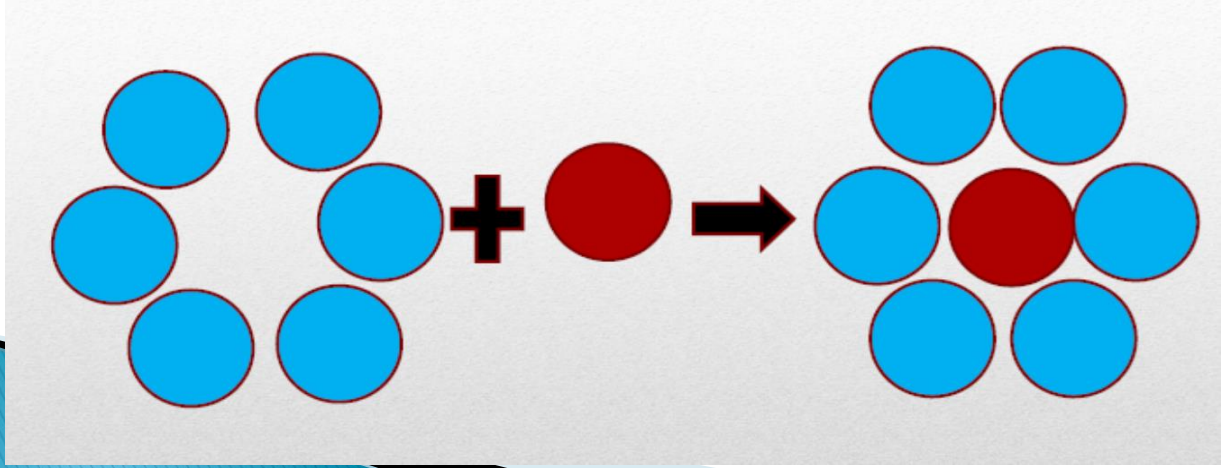
- Easy to swallow , flow, apply , spray
- Good absorption
- Homogeneous

Disadvantage

- Bulky, taste masking
- Stability
  M.O. growth
- Patient measurement

Solubility

- The solubility of an agent in a particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and that solvent.
- i.e, Amount of a solute dissolved in a solvent at a certain temperature(degree of solubility)



Solubility measurement

- **Saturated solubility**
- Excess amount of solid shaken at certain temperature, with a certain volume of liquid for a period of time
- **Super saturated solution**
- Heat the solution containing excess solid then filter and cool. No ppt of the excess solid
  Sodium thiosulfate
  Potassium acetate

Expression of solubility

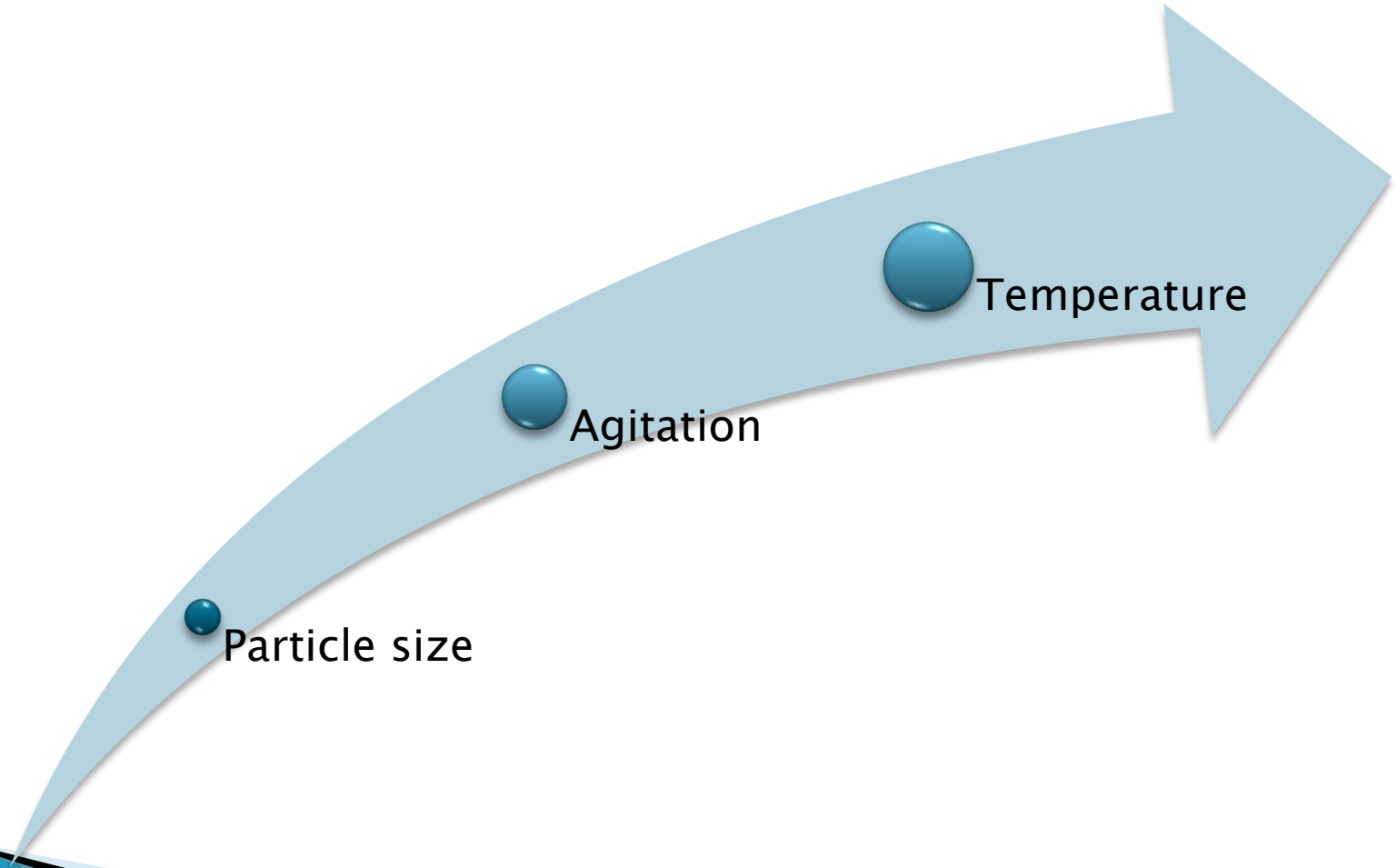
- Calcium Hydroxide Topical solution USP 140mg per 100ml of solution at 25°C
- Potassium iodide solution 100g per 100ml of solution

- The no. of ml. of a solvent required to dissolve 1 g of the solute (or 1 ml. of liquid)
- 1g of KI dissolves in 0.7 ml of water
- 0.5 ml boiling water
- Expressed using **physical units** w/w w/v, v/v
- Or **chemical units** milliequivalent
- Used to express concentration of electrolytes depending on their ionic charge and valence activity

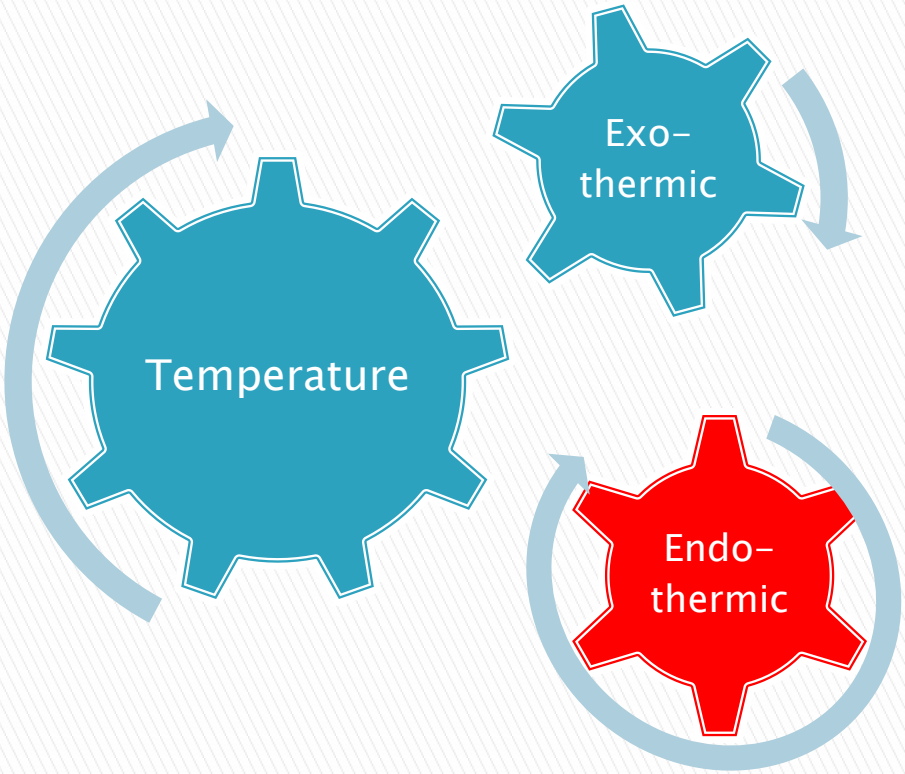
Relative terms of solubility

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	100-1000
Very slightly soluble	1000-10000
insoluble	>10000

Rate of solution(speed)



Factors that determine the extent of solubility



- Depend on the
- Nature of the solvent
- Like dissolves like
- Chemical nature of the solute (molecular structure and functional groups)

Temperature

Chemical Constitution

Water is a good solvent

polarity

- Dipole moment
- Electonegative difference

Hydrogen bonds

- Certain functional groups present
- Low molecular wt

Drugs of low water solubility

- Drugs with low aqueous solubility present problems in relation to the formulation and bioavailability
- Consider non- aqueous solutions for drugs of low solubility

Pharmaceutical Methods to increase solubility

1) Adjust the pH for drugs that are weak acids or bases. Weak acids and weak base solubility is effected by the pH of the solution.
   At a given pH the degree of ionization depends on the pKa .
2) Co-solvent change the polarity of water
3) Surfactant Micell formation
4) Complexation (chemical reaction),

(Lugol's solution) Iodine is slightly soluble in water(1g in 3000ml water) but freely soluble in solution of sodium iodide forming tri-iodide ion

Effect of added substance on solubility

- Salting –In ..addition of an electrolyte to a non electrolyte cause an increase in solubility
- Salting– out..decrease in solubility

- Addition of soluble salt to slightly soluble salt having a common ion will cause ppt. of the slightly soluble salt (according to the law of mass action)

How to predict solubility

Like dissolves like The more solvents and solutes are structurally alike the more rapid solution takes place

Polar solvents dissolve electo-valent substances readily

- But are poor solvents for non polar substances add the opposite is

3Polar liquids are usually miscible with other polar liquids

- Non polar liquids are slightly miscible with polar liquids

Complex organic substances which have polar and non polar groups may dissolve in polar liquids depending on the proportion of the polar groups to the non polar

Semi polar liquids (ethyl alcohol)posses the character of both polar and non polar solvents

Water and alcohol solubility of some weak acids, weak bases, and their salts

Drug (1g)	Water (ml)	Alcohol (ml)
Atropine	455	2
Atropine sulfate	0.5	5
Codeine	120	2
Codeine sulfate	30	1,280
Codeine phosphate	2.5	325
Morphine	5,000	210
Morphine sulfate	16	565
Phenobarbital	1,000	8
Phenobarbital sodium	1	10
Procaine	200	Slightly soluble
Procaine HCl	1	15
Sulfadiazine	13,000	Sparingly soluble
Sodium sulfadiazine	2	Soluble

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	C6H6	1430
Benzoic acid	C6H5COOH	275
Benzyl alcohol	C6H5CH2OH	25
Phenol	C6H5OH	15
Pyrocatechol	C6H4(OH)2	2.3
Pyrogallol	C6H3(OH)3	1.7

Water soluble inorganic salts

- Salts of alkali metals(Na, K, Li,)are usually water soluble except Li_2CO_3
- Ammonium and quaternary ammonium salts
- Nitrates ,nitrites, acetates, chlorates lactates except silver and mercurous acetate
- Sulfates ,sulfites and thiosulfates ,except calcium and barium salts
- Chlorides, bromides and iodides except salts of silver and mercurous ions

Water insoluble inorganic salts

- Hydroxides and oxides of compounds other than alkali metals cations and the ammonium ion
- Sulfides are water insoluble except for their alkali metal salts
- Phosphates ,carbonates ,silicates borates and hypochlorite are water insoluble except for their alkali metal salts and ammonium salt

Organic molecules

- Molecules of 5 carbon chain length and one polar gp are usually soluble
- Branched chains are more soluble than the corresponding straight chain
- Increasing molecular weight will usually decrease solubility
- Increased structure similarity between solute and solvent is accompanied by increase solubility
- Polar function groups include OH, CHO, COH, CHOH, CH_2OH, COOH, NO_2, CO, NH_2 and SO_3H .

Solution formulation

- The formulation additives used are according to
- the type of solution and
- the site of administration.

Solvents for pharmaceutical use

Water	• Purified water • Widely used
Alcohol ethyl alcohol Ethanol C_2H_5OH	• Dissolve polar and semi-polar substances • Miscible with water, used internally Antimicrobial activity
Isopropyl alcohol (70%)	• External use • Vehicle for topical preparations
Glycerin $CH_2OH\ CHOHCH_2OH$	Clear, viscous liquid with sweet taste miscible with water and alcohol
Propylene Glycol $CH_3CH(OH)CH_2OH$	Viscous liquid, miscible, substitute glycerin in pharmaceutical preparations
Corn oil ,Cotton seed oil Peanut oil and Sesame oil	Organic solvents for oleaginous injection

Additives: Buffers

- pH required
  (7.4 for injectable solutions, eye, nose)
- (5.5 for dermal application)(vaginal 4-5)
- Buffering capacity
- Compatible with other excipients
- Low toxicity
- Carbonates, citrates, gluconates, lactates phosphates and tartrates are widely used.
- Borates are used for external application but not to abraded skin or internally

Taste masking

Taste of product	Suitable masking flavor
Salty	Apricot, butterscotch, liquorice, peach vanilla
Bitter	Anise, chocolate, mint, passion fruit, wild cherry
Sweet	Vanilla, fruits, berries
Sour	Citrus fruits, liquorice, raspberry

Additives: Flavors and perfumes

Product use	Flavor preferred
Relief of indigestion	Mint
Antiseptic activity	Terpineol
Oral mucosa anesthetic	Clove oil (eugenol)
Children	Fruity taste and smell
Adult	Flowery odours, acid taste

Additives: Colors

- The colour of the product is associated with the flavor

Flavor	Colour
Mint	Green
Chocolate	Brown
Cherry , strawberry	Pink – red

- Product identification
- Safe, acceptable

Solvents :Water USP

- Drinking water must be clear, colorless, odorless, and neutral or only slightly acid or alkaline
- Not accepted for manufacture of aqueous pharmaceutical preparations because of chemical compatibility of the dissolved solids with the medicinal agents (ppt.,discoloration, effervescence)
- Used for washing, in extraction of the crude vegetable drugs

Purified Water USP

- Prepared from tap water complying with the Environmental Protection Agency for drinking water.
- Purified Water has fewer solids impurities than ordinary drinking water, when evaporated to dryness it must not yield more than 1mg solids per 100ml water
- Intended for use in preparation of aqueous dosage forms except those intended for parenteral administration.

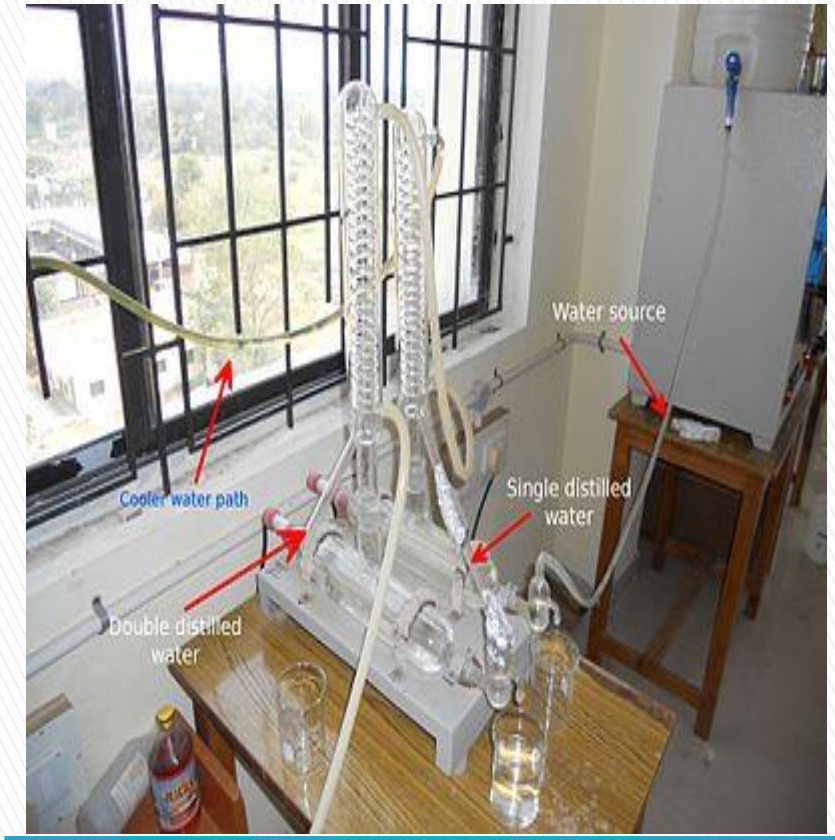
Purified water USP

- Used in preparation of all medications containing water except injectable preparation and other specialized products
- Purification of water is done by

1) Distillation
2) De-ionization (Ion exchange)
3) Reverse osmosis

Distillation Method

- **Distilled water** is water that has many of its impurities removed through distillation. Distillation involves boiling the water and then condensing the steam into a clean container



Definition

Typical laboratory distillation unit

Ion exchange method

- On a large or small scale, ion exchange for the preparation of purified water offers a number of advantages over distillation.

1. The requirement of heat is eliminated and with it,
2. The costly and troublesome maintenance frequently encountered in the operation of the more complex distillation apparatus.
3. Because of the simpler equipment and the nature of the method, ion exchange permits ease of operation, minimal maintenance, and a more mobile facility.

Water purified in this manner, referred to as demineralized or deionized water, may be used in any pharmaceutical preparation or prescription calling for distilled water

Ion exchange resin or polymer beads

Is an water insoluble, synthetic, polymeric resin of high molecular weight containing phenolic, carboxylic, amino, or sulfonated groups.

The beads are typically porous, providing a high surface area.

definition

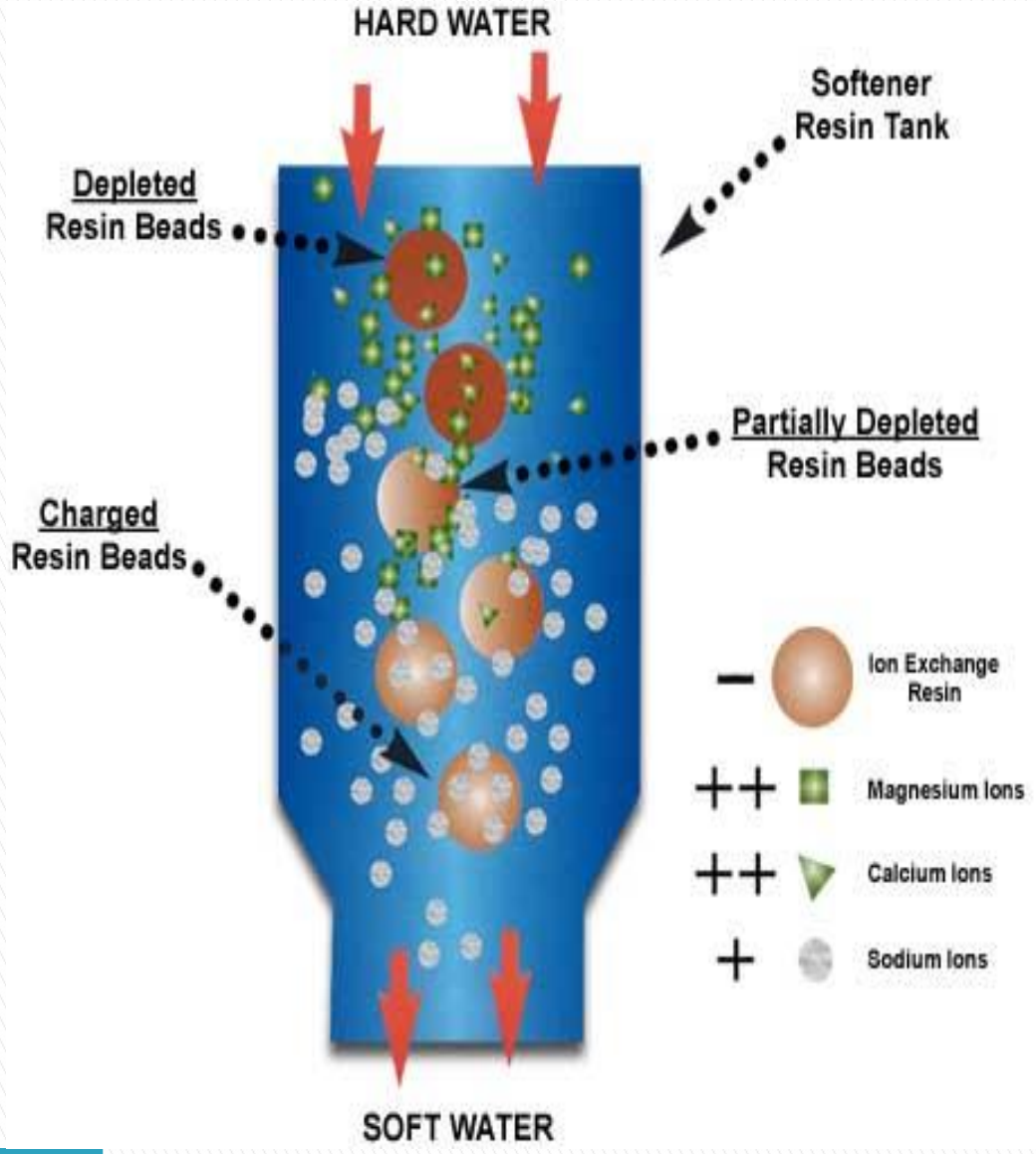
Ion exchange beads

Ion exchange polymer types

- 1-Acid or cationic exchanger
- which permit the exchange of the cations in solution with hydrogen ion from the resin;
- H- resin + M^+ + X^- + H_2O →
- M-resin + H^+ + X^- + H_2O (pure)
- 2- Base or anionic exchanger
- which permit the removal of anions
- Resin-NH_2 + H^+ + X^- + H_2O →
- Resin-NH_2 ◆ HX + H_2O (pure)

Water softener

- Ion exchange is a method widely used in water filters to produce soft water. The trapping of ions occurs with concomitant releasing of other ions; thus the process is called ion-exchange.
- Water purification is accomplished by exchanging calcium Ca^{2+} and magnesium Mg^{2+} cations against Na^{+} or H^{+} cations
- The most commercial resins are made of polystyrene sulfonate these polymers have a higher affinity to divalent cations than monovalent cations.



Principle

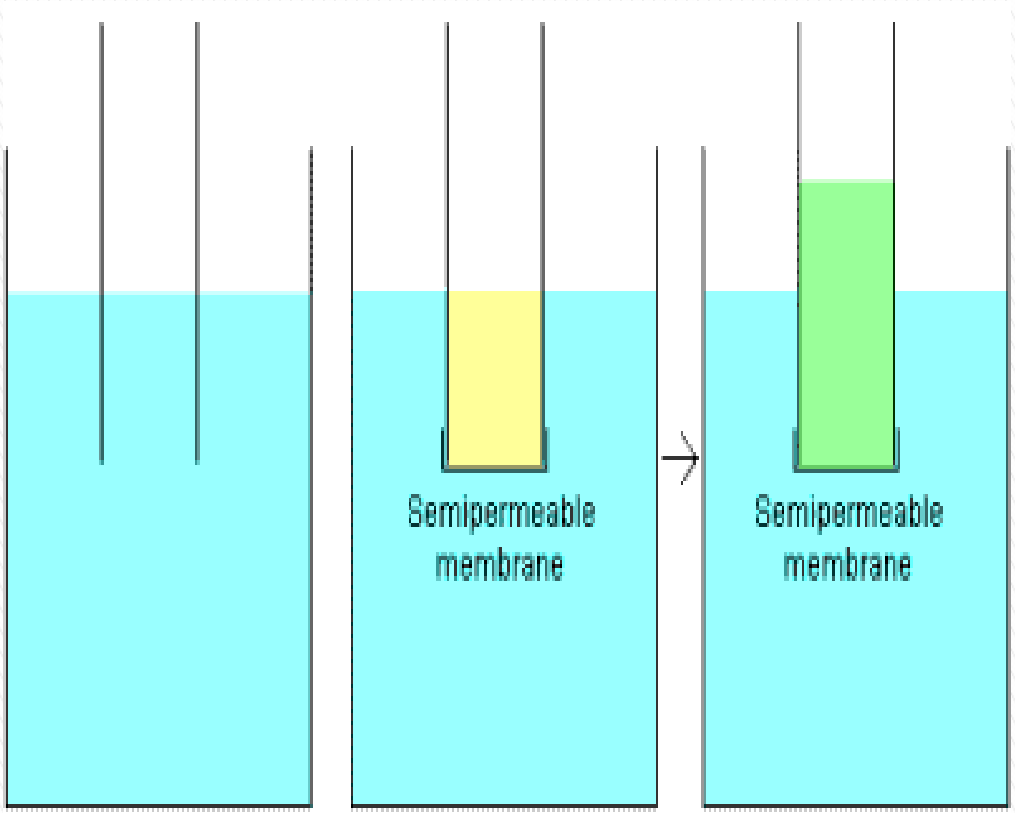
Water softener illustration

Reverse Osmosis

- Reverse osmosis is one of the processes referred to in the industry as cross-flow membrane filtration.
- In osmosis the flow through a semipermeable membrane is from a less concentrated solution to a more concentrated solution,
- The flow in this cross-flow system is from a more concentrated to a less concentrated solution; thus the term reverse osmosis.

Osmosis

- Osmosis is the passage or diffusion of water or other solvents through a semipermeable membrane that blocks the passage of dissolved solutes



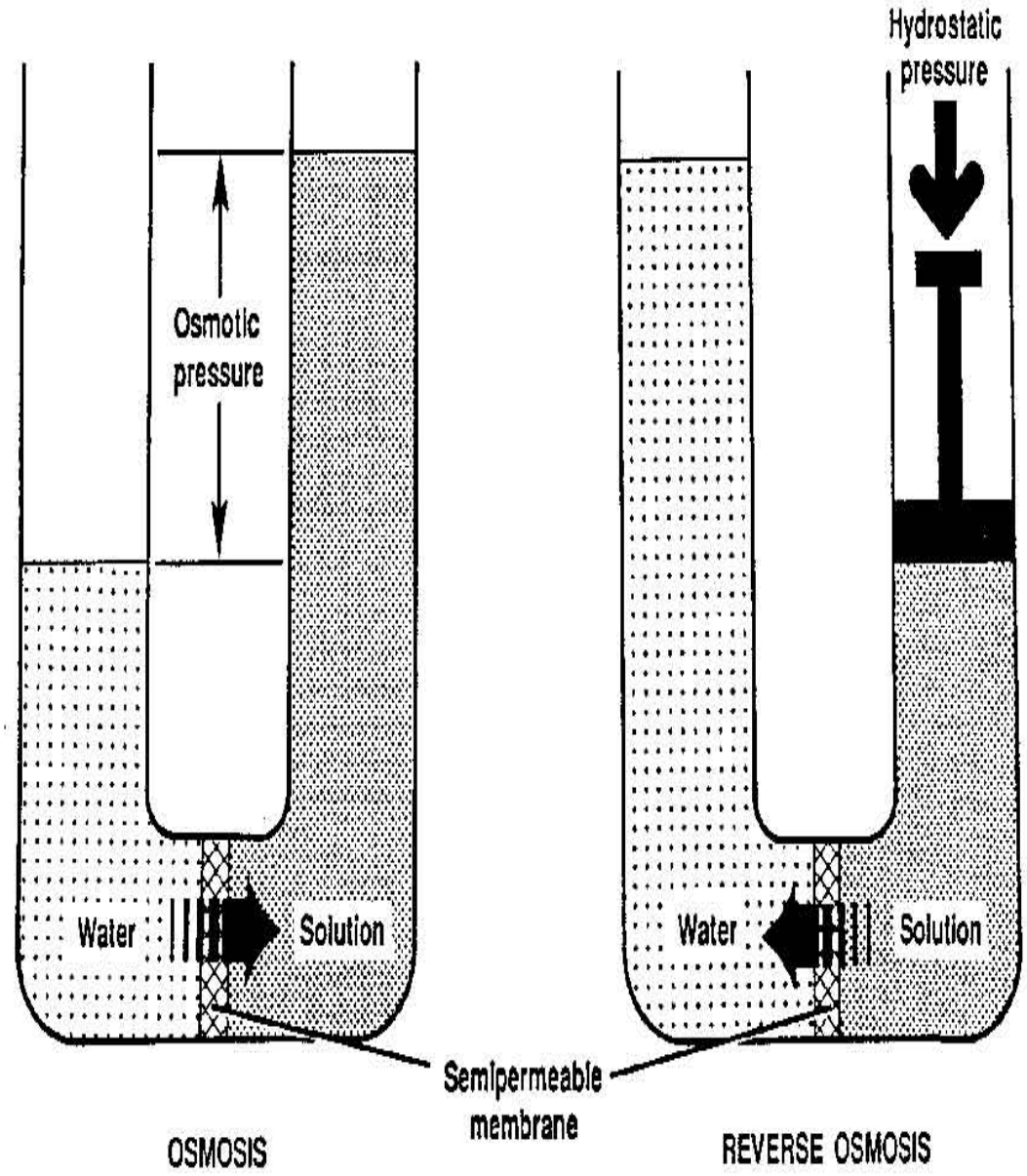
Principle

Osmosis

Reverse osmosis system

Principle

- In RO, an applied pressure is used to overcome osmotic pressure, a colligative property, that is driven by chemical potential, a thermodynamic parameter.
- The result is that the solute is retained on the pressurized side of the membrane and the pure solvent is allowed to pass to the other side.
- To be "selective," this membrane should not allow large molecules or ions through the pores (holes), but should allow smaller components of the solution (such as the solvent) to pass freely.



Reverse osmosis

- Depending on their pore size, cross-flow filter membranes can remove particles defined in the range of
- microfiltration (0.1 to 2 μm, e.g., bacteria);
- ultrafiltration (0.01 to 0.1 μm, e.g., virus);
- nanofiltration (0.001 to 0.01 μm, e.g., organic compounds
- in the molecular weight range of 300 to 1,000); and reverse osmosis (particles less than 0.001 μm).
- Reverse osmosis removes virtually all viruses, bacteria, pyrogen, and organic molecules and 90% to 99% of ions

Solutions
Water for injection

- Pyrogen free water (polysaccharide byproduct of bacterial origin)
- Purified by distillation and used within 24 hr. after collection.
- Intended to be used as a solvent for parental products preparation to be sterilized after preparation
- Sterilization is achieved by autoclave (steam under pressure)

Sterile solutions
Sterile water for injection USP

- Water for injection sterilized and packed in suitable single dose container preferably Type I glass and not larger than 1000ml size.
- This water is intended to be used as a solvent, vehicle, or diluent for already sterilized and packaged injectable medications.
- They are used to reconstitute of antibiotics

Sterile solutions
Bacteriostatic water for injection USP

- Sterile water for injection that contains bacteriostatic agent (benzyl alcohol)
- May be packed in single dose container (not larger than 5ml)or multiple dose containers (not larger than 30ml)
- Not used for neonates.

Other sterile diluents

- Sodium chloride injection USP
- Bacteriostatic sodium chloride injection USP
- Ringer injection USP
- Lactated Ringer injection USP
- Dextrose 5% solution

Ophthalmic solutions

Sterile

by autoclave or filtration

Isotonic

Preserved

(multi-dose)by phenyl ethyl-alcohol, chorobutanol, benzalkonium chloride, phenyl mercuric nitrate

Optimum pH

low buffer capacity

Oral solutions

Final solution
Drug
Sweetening agent
Flavoring agent
Preservative
Colors
Buffers
Density modifiers
Viscosity enhancers
Reducing agents

Types of oral solutions

Oral solutions

- Mostly used for small and old aged patients
- Cold remedies and bronchodilators
- vitamins
- Laxative solutions
- Mist Diuretic

Dry for reconstitution

1. Unstable in aqueous media
2. Uniform dose

- ORS
- Orodispersible tablet (Halazone) or powder Voltafast ®
- Effervescent tablets or powder

Oral rehydration solution

ORS

- Used for diarrhea to replenish electrolytes
- This equates to
- 45 mEq sodium,
- 35 mEq chlorine, and
- 20 mEq potassium
- 30mEq citrate
- 25g dextrose per liter of fluid.
- These formulation are available in liquid or powder packet form for reconstitution

Oral colonic lavage solution

- Used before bowel procedures (colonscopy)
- Balanced solutions of electrolytes with PEG-3350

- Lactulose is a colonic acidifier that works by increasing stool water content and softening the stool. It is a man-made sugar solution laxative used to treat constipation.

Topical solutions (infection)

	conc	Vehicle
Hydrogen peroxide	3%	Aqueous
Chlorhexidine gluconate	4%	Aqueous
Iodine tincture	2%	Alcohol, water
Povidone Iodine	7.5%, 10%	Aqueous
Clindamycin phosphate	1%	Isopropyl alcohol Water
Erythromycin	2%	PEG/acetone/alcohol
Clotrimazole	1%	PEG400
Ketoconazole	1%	Water
Tolnaftate	1%	PEG

Topical solutions

Drug	Conc	Vehicle	Use
Fluorouracil	2.5%	PG	antineoplastic
Minoxidil	2 ,5%	Alcohol, water, PG	Baldness
Hydroquinone		Water Alcohol ,PG	
Podophyllum		Benzoin tincture	Warts
Fluocinolone acetonide Betamethasone Mometasone		PG	Adrenocortical steroid

Mouthwashes and gargles

- Mouthwashes/gargles are designed for the treatment of infection and inflammation of the oral cavity. Formulations designed for this purpose employ water as the vehicle, although a co-solvent, e.g. alcohol, may be employed to solubilize the active agent.
- The use of alcohol as a co-solvent may act to enhance the antimicrobial properties of the therapeutic agent.
- Other formulation components are frequently required to enhance the palatability and acceptability of the preparation. These include preservatives, colors, flavoring agents and non-cariogenic sweetening agents.

Vaginal solutions (douches)

Powders for solution

Liquid solutions or concentrates

- Used for irrigation, cleansing of the vagina for hygienic effect
- Astringents
- Antimicrobials
- Adjusting pH

Vaginal preparations properties

1. Maintain optimal pH
2. Ease of application
3. May be used externally OR internally

Rectal solutions (Enemas)

Retention enemas

1. Local effect (hydrocortisone) as enemas for ulcerative colitis
2. Systemic absorption

(aminophylline) rectal administration minimizes the undesirable GIT reaction, effective blood levels within 30 min after rectal instillation

Viscosity-enhancing agents, e.g. glycerol, may be included to aid retention of the formulation within the rectum and to reduce the incidence of seepage.

Evacuation enemas

- Used to cleanse the bowel available in disposable plastic squeeze bottles containing a premeasured amount of enema solution

Evacuation Enemas

- Enemas are pharmaceutical solutions that are administered rectally and are employed to ensure clearance of the bowel,

1. Oil-based solutions and, in some formulations, the vehicle is the agent that promotes bowel evacuation, e.g. Arachis oil enema. **Softening the feces**
2. Aqueous formulations usually contain salts (e.g. phosphates) to alter the osmolality within the rectum, thereby increasing the movement of fluid to the rectal contents. Increasing the amount of water in the large bowel (**osmotic laxatives**).

Syrups

Syrups

- Syrups are concentrated aqueous preparations of a sugar or sugar substitute

- Sweet(sugar or sugar substitute)
- Viscous
- Concentrated
- Aqueous preparations(solution)

Advantage of syrups

- Syrups provide a pleasant means of administrating a liquid form of a disagreeable tasting drug
- Useful for administration of drugs for young patients, because the pleasant taste usually dissipates any reluctance on the part of the child to take the medication
- No or low content of alcohol

Main features of syrups

sweet

- Sweet so it mask the unpleasant taste of drugs

viscous

- Viscous will ensure physical concealment of the taste due to covering of the taste buds ,also the thick viscous nature of the medicine will sooth the irritated tissue of the throat as it passes over it (especially in case of antitussive syrups)

flavored

- Flavored will also aid in taste masking

Classification

medicated

- Antihistamine
- Antitussives
- sedatives
- vitamins

Flavored(non medicated)

- Pleasant tasting vehicle for drugs not available as solution
- Used in extemporaneous compounding
- For children and elderly who have difficulty swallowing tablet or capsule

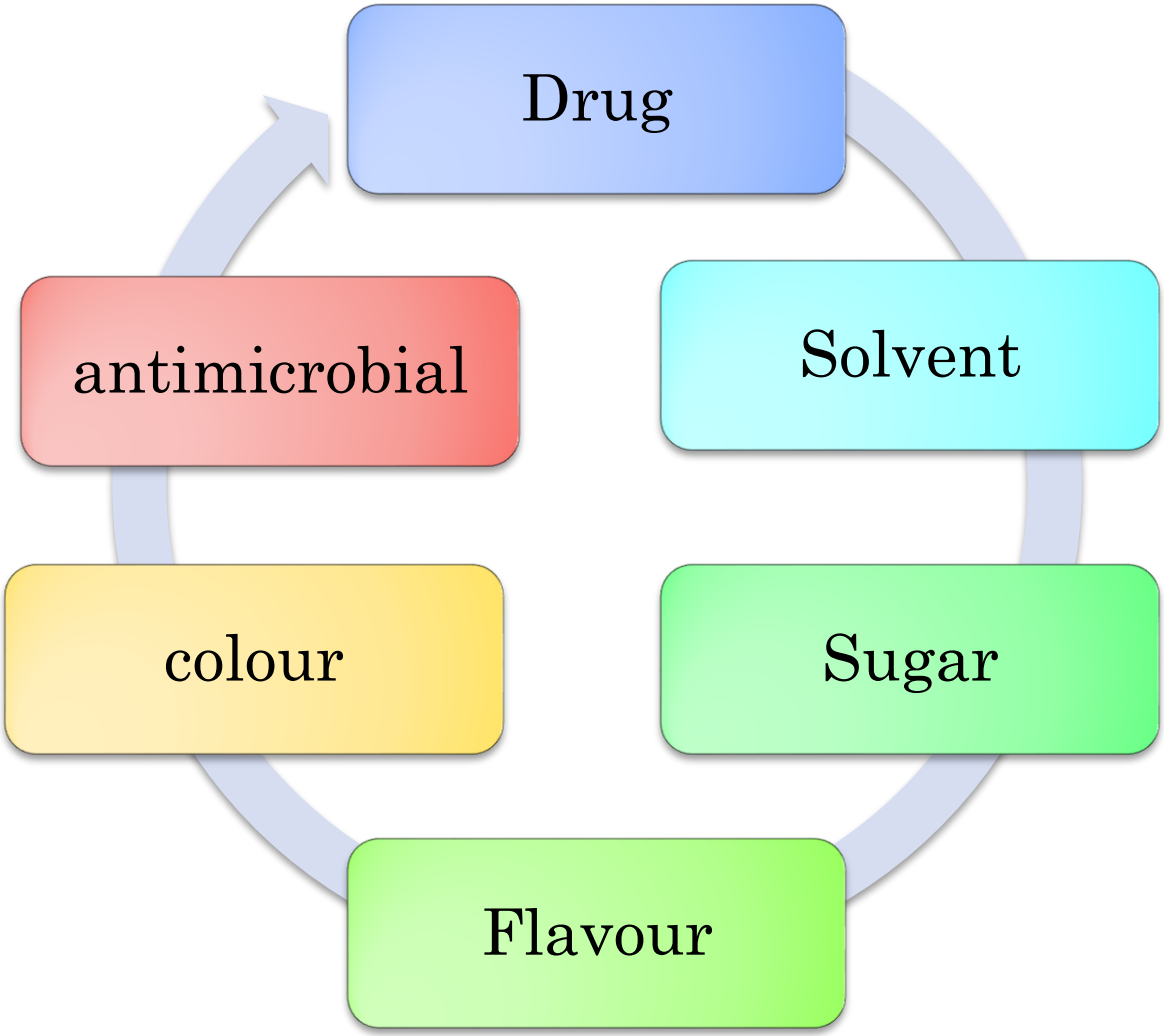
Examples of Non medicated syrups

Syrup	Comments
Cherry syrup	Sucrose-based syrup with cherry juice about 47% by volume. Tart fruit flavor is attractive to most patients and acidic pH makes it useful as a vehicle for drugs requiring an acid medium
Cocoa syrup	Suspension of cocoa powder in aqueous vehicle sweetened and thickened with sucrose, liquid glucose, glycerin; flavored with vanilla, sodium chloride. Particularly effective in administering bitter-tasting drugs to children
Orange syrup	Sucrose-based syrup uses sweet orange peel tincture, citric acid as the source of flavor and tartness. Resembles orange juice in taste; good vehicle for drugs stable in acidic medium
Ora-Sweet, Ora-Sweet SF	Commercial vehicles for extemporaneous compounding of (Paddock Laboratories) syrups. Both have a pH of 4-4.5 and are alcohol free. Ora-Sweet SF is sugar free
Syrup	85% sucrose in purified water. Simple syrup may be used as the basis for flavored or medicated syrups

EXAMPLE CAPTOPRIL ORAL LIQUID

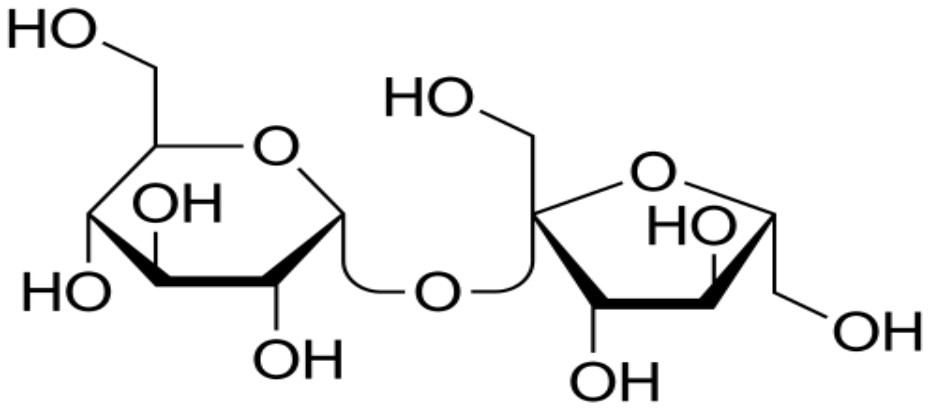
- Preferred formula
- Using a typical strength of 1 mg/mL as an example:
- * 4 captopril tablets 25 mg
- * Ora-Plus to 50mL
- * Ora-Sweet to 100 ml
- Method guidance
- Tablets can be ground to a fine, uniform powder in a pestle and mortar. A small amount of Ora-Plus may be added to form a paste, before adding further portions of Ora-Plus up to 50% of the final volume. Transfer to a measuring cylinder. The Ora-Sweet can be used to washout the pestle and mortar before making the suspension up to 100%volume. Transfer to an amber medicine bottle.
- Shelf-life
- 7 days refrigerated in amber glass. Shake the bottle

Syrup components



1. Sugar usually sucrose or sugar substitutes.
2. Antimicrobial preservative
3. Flavoring agent
4. Co solvent
5. Purified water, Solvents, solubility agent, thicker, stabilizer
6. Drug

Sucrose



- Purest compound commercially available
- sweet
- Lack of color
- Easy to handle

Simple syrup NF

Rχ	
Sucrose	85 g
Purified water q.s.	100 ml

- Sucrose 85% w/v
- This concentration requires no additional preservatives if the syrup is used soon and not stored.

Saturated sucrose solution

- Saturated solution of sucrose might crystallize from solution upon cooling
- Thereby acting as nuclei that initiate chain reaction which result in separation of an amount of sucrose disproportionate to it's solubility at the storage temperature
- The syrup will be less concentrated so it will be prone to micro organism growth .

Saturated vs. concentrated

- Each 100ml of syrup weighs 131.3g
- 131.3-85=46.3g water
- 46.3 ml water dissolves 85g sucrose
- Solubility of sucrose is expressed as 1g in 0.5ml water
- To dissolve 85g of sucrose 42.5ml of water is needed
- 46.3-42.5=3.8ml /100ml syrup excess water

Syrups containing sucrose

- Most syrups contain about 60-80% sucrose
- Desirable sweetness and viscosity, also because of stability factors (dilute sucrose solution are prone to microbial growth which result in turbidity, fermentation ,change in color)
- Concentrated sugar solution (85%w/v) are resistant to microbial growth (no free water)
- Syrups containing less than (85%w/v) sucrose, preservatives must be added.

Anti- microbial preservative

preservative	Concentration used as %
Benzoic acid	0.1-0.2
Sod benzoate	0.1-0.2
Butyl paraben (butyl p-hydroxybenzoate)	0.02
Propyl paraben 4-hydroxybenzoic acid propyl ester	0.05
Methyl paraben 4-hydroxybenzoic acid methyl ester	0.1
Sorbic acid	0.1
Alcohol 99%	15-20 (18)
Glycerin	45

Preservatives

- The benzoates and the parabenes (hydroxyl-benzoic acids) and sorbic acid are most effective in acid solution
- Mixture of parabens are frequently employed to take advantage of their potentiating effect
- The amount of added preservative needed in syrups containing sucrose less than 85% w/v is estimated according to the calculated free water.
- If the syrups are diluted with water preservatives must be added

Calculate the amount of preservative

- Calculate the preservative action of the sucrose present knowing that 85%w/v sucrose will preserve 100ml solution (syrup)

- 65/v=85/100 v=76.5ml volume of solution preserved by 65%w/v sucrose.
- 100-76.5=23.5ml free water (not preserved)
- The amount of preservative added is calculated according to the volume of the free water

Q CALCULATE THE VOLUME OF ETHANOL

Drug	5ml
Solids	3ml
Glycerin	15ml
Sucrose	25g
Ethanol 95%	q.s.
Purified water q.s.	100ml

Answer

- 85/100=25/v v=29.4ml volume of solution preserved
- 100-29.4=70.6ml volume of solution not preserved by sucrose
- Glycerin can preserve an equal amount of water 15×2 =30ml
- 70.6-30=40.6ml
- Volume occupied by other components 5+3=8
- 40.6-8=32.6ml
- 0.18×32.6=5.868 ≈5.9ml of alcohol(99%) required
- 5.9/0.95=6.21ml of alcohol95%will be required

Another method for calculations

- Simple syrup 85g /100ml solution weighs 131.3g
- 131.3-85=46.3 wt. or volume of water
- 100-46.3=53.7 volume occupied by sucrose
- 85g sucrose preserves 46.3 ml of water so that:
- 1g of sucrose preserves 0.54ml of water
- Also 85g of sucrose will occupy a volume of 53.7ml so that :
- 1g of sucrose will occupy 0.63ml

Alcohol

- In some syrups alcohol is present in small amount as a solvent for alcohol soluble ingredients
- Although the concentration of alcohol is not sufficient for preservative effect but the alcohol concentrates in vapor above the syrup thus preventing the growth of surface molds
- In sealed containers vaporization of water from the syrup and condensation will create a dilute solution of sucrose on the surface ,which supports mold growth
- Syrups can withstand 10%of alcohol not more.

Preparation of syrups

Syrups are prepared by 4 different methods depending on the physical and chemical characteristics of the ingredients

1. Solution of ingredients with the aid of heat
   Simple Syrup USP
2. Solution of ingredients by agitation without heat (simple admixture of liquid component
   Ephedrine Sulphate Syrup USP.
3. Addition of sucrose to a prepared medicated liquid or to a flavored liquid Orange Syrup USP
4. Percolation of either the source of the medicating substance or of the sucrose. Wild Cherry Syrup USP, Licorice syrup USP, Ipecac Syrup USP

1. Solution with the aid of heat

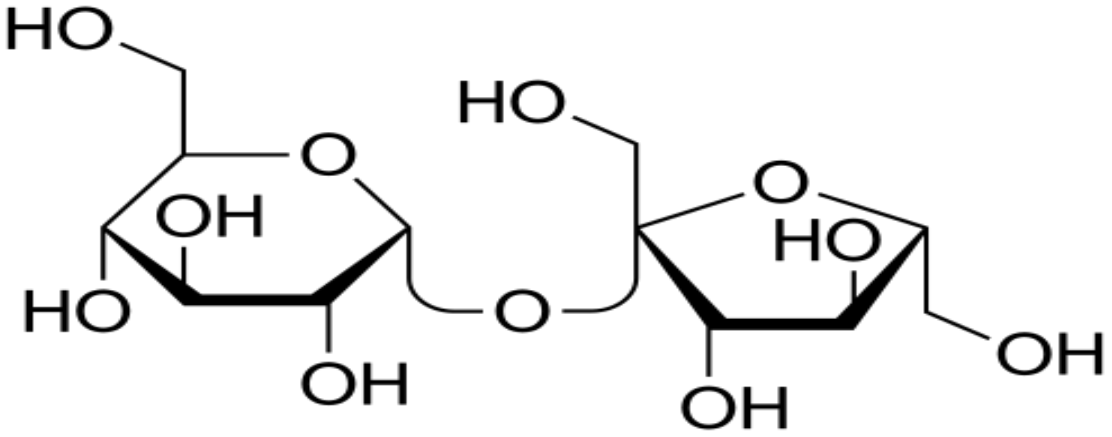
1. Quick method
2. Syrup ‘s components are not damaged or volatilized by heat
3. Sugar added to purified water and the heat applied until the sucrose is dissolved ,the other heat stable ingredients are added the hot syrup, cooled ,adjust the volume with purified water

Solubility of sucrose in water vs. temperature

T (°C)	S (g/mL)
50	2.59
55	2.73
60	2.89
65	3.06
70	3.25
75	3.46
80	3.69
85	3.94
90	4.20

Precautions

- The use of excessive heat cause hydrolytic decomposition of sucrose to glucose and fructose (invert sugar)
- Inversion is increased by the presence of acids
- Invert sugar is sweeter
  darker in color (carmalization) and more susceptible to fermentation



HYDROLYSIS OF SUCROSE(SPECIFIC ACID CATALYZED) CALLED INVERSION

Sucrose →	Glucose (dextrose) +	Fructose (laevulose)
Dextro -rotation	Dextro- rotation	Levo rotation of the light more pronounced than dextrose
Degrees of sweetness 100 (1)	74 (0.5-0.9)	173 (1.2)
Colorless liquid	Solution of invert sugar are more prone to microbial growth	Degradation leads to brown discoloration (caramelization)

Solution by agitation

- To avoid heat induced inversion
- Sucrose and other ingredients are placed in a vessel larger than the volume of the syrup to be prepared
- More time consuming than the use of heat
- But the product has maximum stability
- Miscible Liquid ingredients are incorporated during mixing
- Solid ingredients are dissolved in small volume of purified water than added(viscous nature of the syrup retards the dissolution of solids , also amount of free water is limited)

Example of medicated syrup

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	q.s.
Purified water, to make	1000.0 mL

Addition of Sucrose to a Medicated Liquid or to a Flavored Liquid

- Tincture or fluidextract, is employed as the source of medication in the preparation of a syrup.
- Many such tinctures and fluidextracts contain alcohol-soluble constituents and are prepared with alcoholic or hydroalcoholic vehicles. If the alcohol-soluble components are desired medicinal agents, some means of rendering them water soluble is employed.
- However, if the alcohol-soluble components are undesirable or unnecessary components of the corresponding syrup, they are generally removed by mixing the tincture or fluidextract with water, allowing the mixture to stand until separation of the water-insoluble agents is complete, and filtering them from the mixture. The filtrate is the medicated liquid to which the sucrose is added in preparation of the syrup.
- If the tincture or fluidextract is miscible with aqueous preparations, it may be added directly to simple syrup or to a flavored syrup.

PERCOLATION METHOD

- In the percolation method, either
- sucrose may be percolated to prepare the syrup
- or the source of the medicinal component may be percolated to form an extractive to which sucrose or syrup may be added.
- This latter method really is two separate procedures: first the preparation of the extractive of the drug and then the preparation of the syrup.

Ipecac syrup USP

- Ipecac syrup, which is prepared by adding glycerin and syrup to an extractive of powdered ipecac obtained by percolation.
- The drug ipecac, which consists of the dried rhizome and roots of *Cephaëlis ipecacuanha*, contains the medicinally active alkaloids emetine, cephaeline, and psychotrine.
- These alkaloids are extracted from the powdered ipecac by percolation with a hydroalcoholic solvent.
- The syrup is categorized as an emetic with a usual dose of 15 mL.

Non- sucrose based syrups

- **Diabetic simple syrup**
- **Artificial syrups**
- **Non nutritive syrups**
  - Used for patient who must control their caloric intake
  - Substitute for the sucrose
  - sweetness, artificial sweetener
  - viscous, viscosity builder
  - and self preserving at 85% preservative

Formulation

Early formulas contained glycerin and propylene glycol
But they are also glycogenic

Rχ		
Sodium CMC (medium viscosity)	1.5%	Viscosity builder
Saccharin	q.s.	Sweetening agent
Methyl paraben	q.s.	Preservative
Purified water	100 ml	

Non- sucrose based syrups

Viscosity builders

- Non-glycogenic
  - Natural
  - Semi synthetic
- Glycogenic
  - Polyols

VISCOSITY BUILDERS

- 1-Glycogenic (Polyols) sorbitol (64%), glycerin, propylene glycol

- 2- Non- glycogenic ,

a) Natural (Gums) Tragacanth, Acacia

b) Semi synthetic Polymers

Methylcellulose MC (nonionic , exothermic)

Hydroxypropylmethylcellulose HPMC (nonionic)

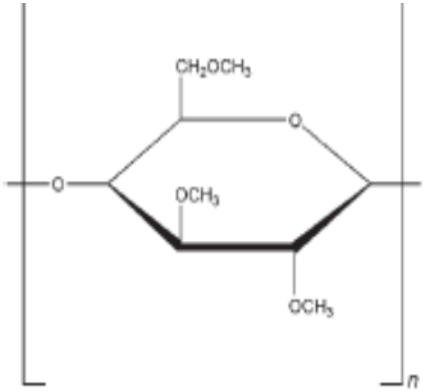
Sodium Carboxymethylcellulose Sod CMC(anionic),

Sod Alginate(anionic) ,

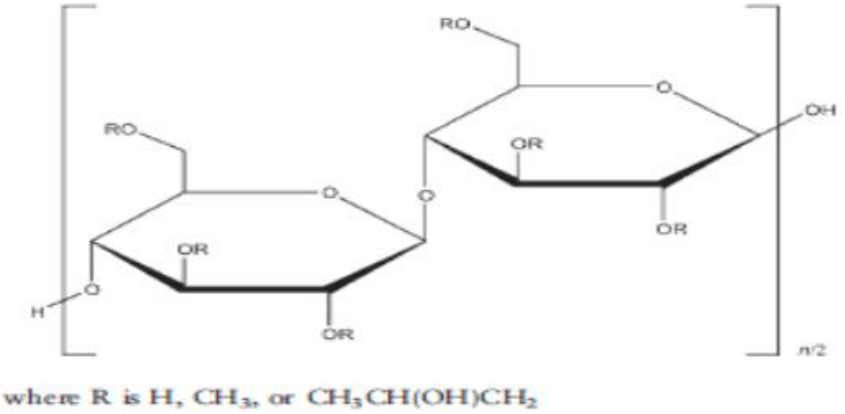
Tragacanth and Acacia

- Tragacanth
  - Naturally occurring dried gum consists of a mixture of water-insoluble and water soluble polysaccharides.
  - Bassorin, which is the main water-insoluble portion, while the remainder of the gum consists of the water-soluble material tragacanthin.
  - On hydrolysis, tragacanthin yields L-arabinose, L-fucose, D-xylose, D-galactose, and D-galacturonic acid.
- Acacia
  - Complex, loose aggregate of sugars and hemicelluloses
  - The aggregate consists essentially of an **arabic acid** nucleus to which are connected calcium, magnesium, and potassium along with the sugars arabinose, galactose, and rhamnose.

Structures of semisynthetic polymers (nonionic)



Methylcellulose MC

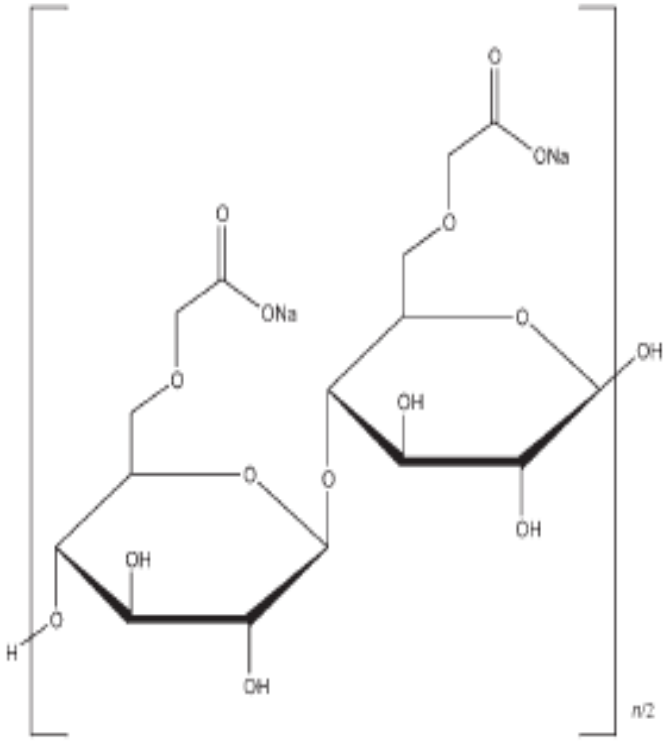


where R is H, CH_3, or $CH_3CH(OH)CH_2$

Hydroxpropylmethyl cellulose HPMC

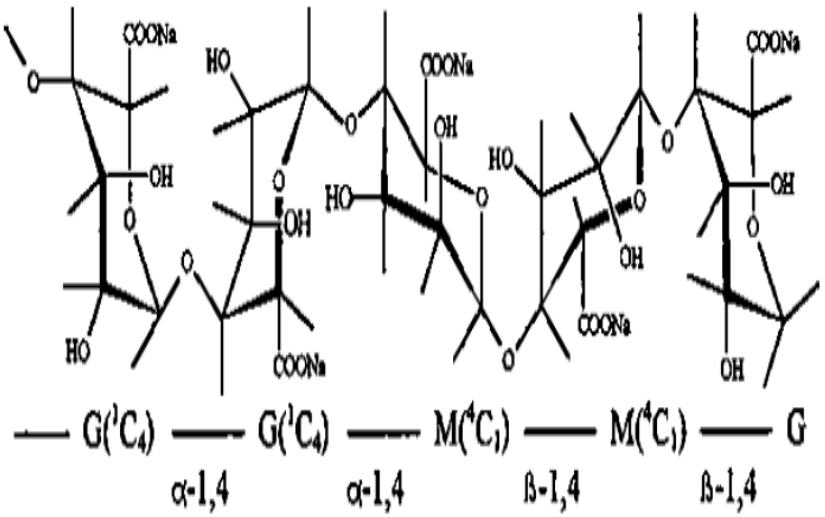
Structures of semisynthetic polymers (anionic)

Carboxymethylcellulose Sodium



Structure shown with a degree of substitution (DS) of 1.0.

Sodium Alginate



The number and sequence of the Mannuronate M and Glucuronate G residues shown above vary in the naturally occurring alginate

Natural and semi-synthetic viscosity builder

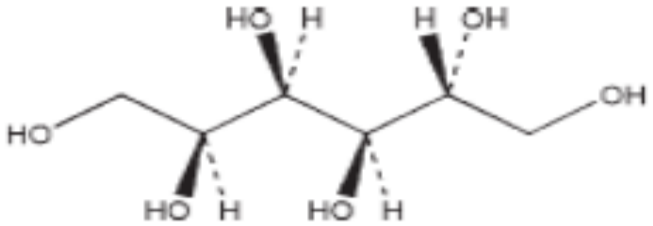
- Natural
- Acacia
- Tragacanth
- Opalescent (not colorless)
- Change characteristics upon aging
- Differ according to the plant source

- Synthetic (semi-synthetic)
- Non glycogenic
- Colorless
- MC is exothermic

Special precautions

1. Anionic polymers are incompatible with cationic drugs or other formulation ingredients.
2. Strong dehydrating agents cause coagulation of aqueous dispersion of both natural or semisynthetic polymers.
3. Incompatible with excessive amounts of alcohol and electrolytes.

Sorbitol based syrup



Hexa-hydric alcohol	• $C_6H_{14}O_6$ • Glucose hydrogenation
Crystalline sorbitol	• White ,odorless • Non volatile
70%w/w	• Substitute for sucrose • Diabetic patients

Advantage of sorbitol solution over simple syrup

mouth

- Sorbitol solution is not irritating to the membranes of the mouth and throat, and lacks the acrid characteristics of some polyols, half as sweet as sucrose , overall pleasant taste
- Don't cause dental caries

G.I.T

- Not absorbed from the G.I.T
- Excessive amount has a laxative effect

Sorbitol

- 60% as sweet as sucrose ,half as viscous as simple syrup
- Chemically stable ,inert with respect to drugs and other ingredients
- Sorbitol based solution have extended shelf lives

Advantage of sorbitol solution addition to simple syrup

Compatible with other polyols

Can be added (30%)to simple syrup to reduce crystallization

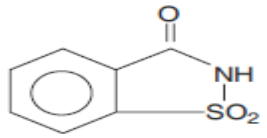
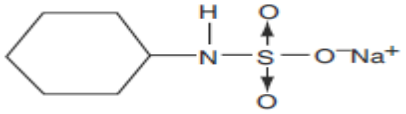
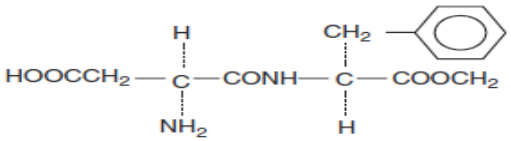
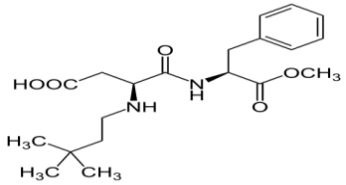
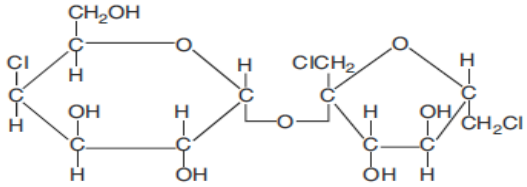
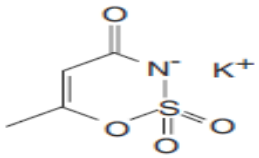
Sorbitol inhibits the sticking or locking of bottle caps which occur with high concentrations of sucrose

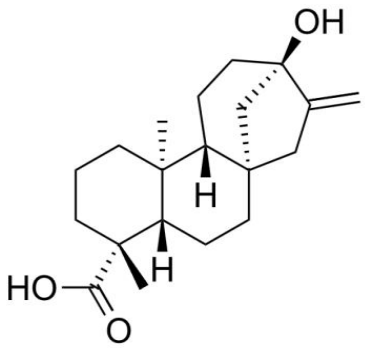
Formulation

- Artificial sweeteners are added to intensify the mild sweetness
- Sorbitol(60%w/v) can resist microbial growth
  If the concentration of sorbitol is less we add preservative.

Linctuses

- Linctuses are viscous preparations that contain the therapeutic agent dissolved in a vehicle composed of a high percentage of sucrose and, if required, other sweetening agents. (honey or glucose syrup)
- Linctuses are often used when the drug has a bitter taste
- These formulations are administered orally and are primarily employed for the treatment of cough, due to their soothing actions on the inflamed mucous membranes.
- Linctuses may also be formulated as sugar-free alternatives in which sucrose is replaced by sorbitol and the required concentration of sweetening agent

Sweetener	Degree of sweetness	Chemical structure	Comment
Saccharin Sweet "N" Low®	500		Bitter after taste
Sod cyclamate	30		Banned in USA
Aspartame Aspartyl phenylalanine methyl ester Canderel®	200		Unstable in hot solution,(PKU)
Neotame (N-[N-(3,3-dimethylbutyl)-L--aspartyl]-L-phenylalanine 1-methyl ester) Nutrasweet®	8000		
Sucralose Splenda®	600		Stable over a broad pH range
Acesulfame –K Nutrinova®	200		Heat stable

Natural Sweetener	Degree of sweetness	Chemical structure	Comments
Stevia	250		Extracts known as rebiana, Truvia, Pure Via; mainly containing rebaudioside A, a steviol glycoside
Sorbitol	0.6		
Xylitol	1.0		
Mannitol	0.5		Derived from Mannose

Syrups

Syrups

- Syrups are concentrated aqueous preparations of a sugar or sugar substitute

- Sweet(sugar or sugar substitute)
- Viscous
- Concentrated
- Aqueous preparations(solution)

Advantage of syrups

- Syrups provide a pleasant means of administrating a liquid form of a disagreeable tasting drug
- Useful for administration of drugs for young patients, because the pleasant taste usually dissipates any reluctance on the part of the child to take the medication
- No or low content of alcohol

Main features of syrups

sweet

- Sweet so it mask the unpleasant taste of drugs

viscous

- Viscous will ensure physical concealment of the taste due to covering of the taste buds ,also the thick viscous nature of the medicine will sooth the irritated tissue of the throat as it passes over it (especially in case of antitussive syrups)

flavored

- Flavored will also aid in taste masking

Classification

medicated

- Antihistamine
- Antitussives
- sedatives
- vitamins

Flavored(non medicated)

- Pleasant tasting vehicle for drugs not available as solution
- Used in extemporaneous compounding
- For children and elderly who have difficulty swallowing tablet or capsule

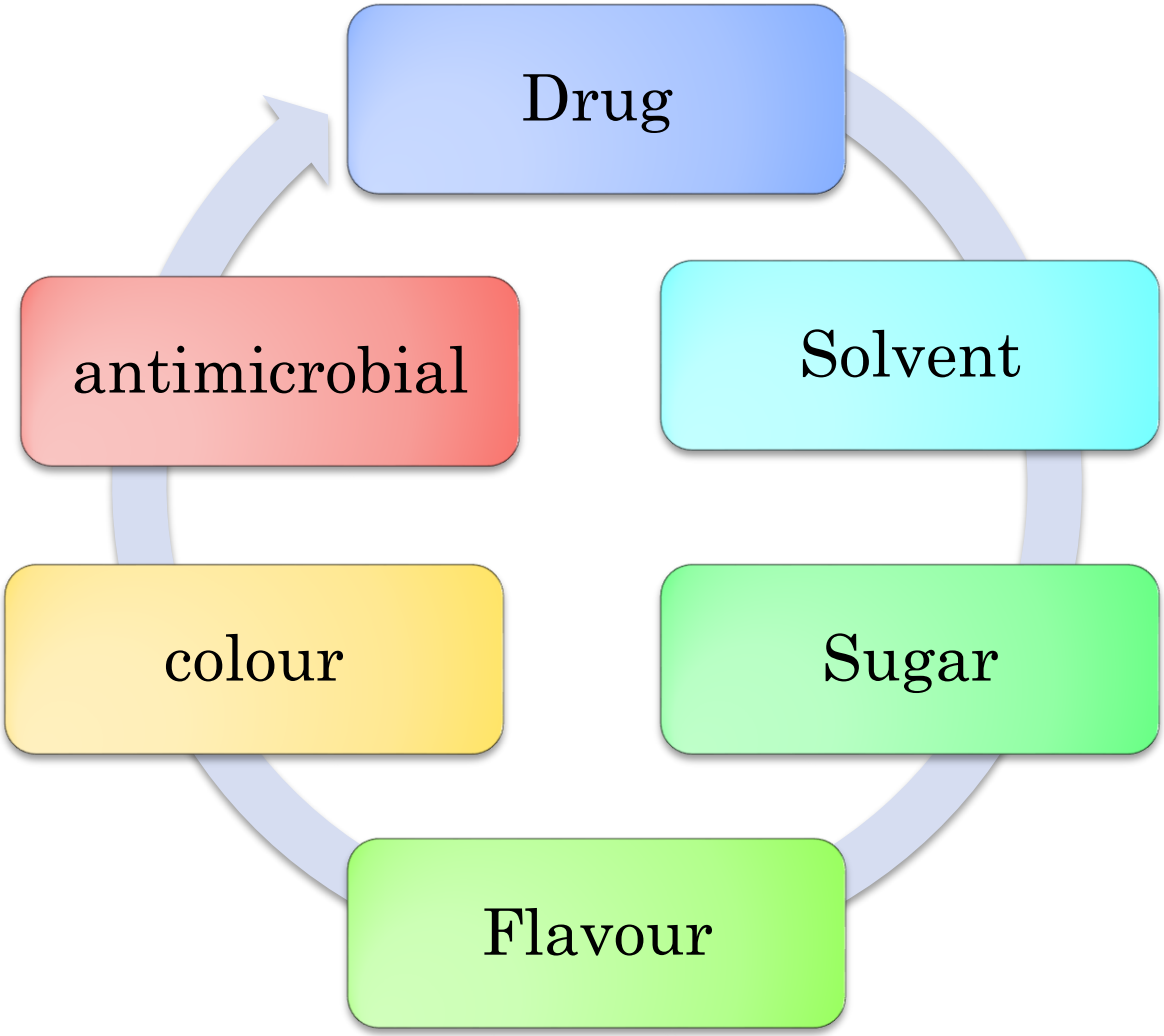
Examples of Non medicated syrups

Syrup	Comments
Cherry syrup	Sucrose-based syrup with cherry juice about 47% by volume. Tart fruit flavor is attractive to most patients and acidic pH makes it useful as a vehicle for drugs requiring an acid medium
Cocoa syrup	Suspension of cocoa powder in aqueous vehicle sweetened and thickened with sucrose, liquid glucose, glycerin; flavored with vanilla, sodium chloride. Particularly effective in administering bitter-tasting drugs to children
Orange syrup	Sucrose-based syrup uses sweet orange peel tincture, citric acid as the source of flavor and tartness. Resembles orange juice in taste; good vehicle for drugs stable in acidic medium
Ora-Sweet, Ora-Sweet SF	Commercial vehicles for extemporaneous compounding of (Paddock Laboratories) syrups. Both have a pH of 4-4.5 and are alcohol free. Ora-Sweet SF is sugar free
Syrup	85% sucrose in purified water. Simple syrup may be used as the basis for flavored or medicated syrups

EXAMPLE CAPTOPRIL ORAL LIQUID

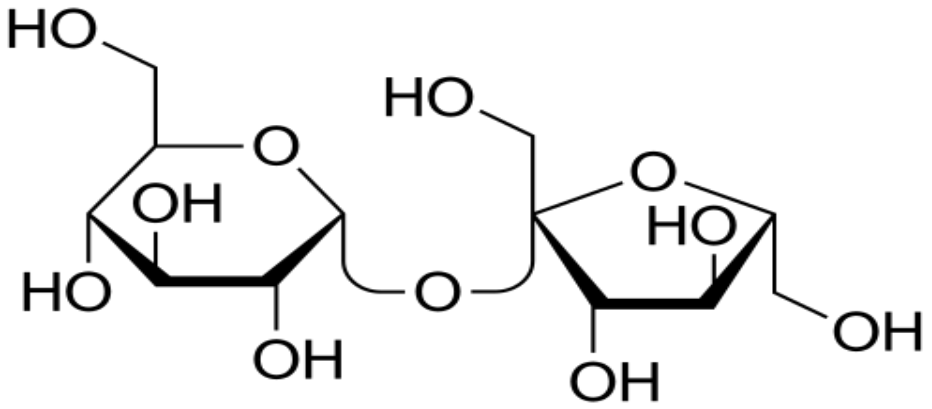
- Preferred formula
- Using a typical strength of 1 mg/mL as an example:
- * 4 captopril tablets 25 mg
- * Ora-Plus to 50mL
- * Ora-Sweet to 100 ml
- Method guidance
- Tablets can be ground to a fine, uniform powder in a pestle and mortar. A small amount of Ora-Plus may be added to form a paste, before adding further portions of Ora-Plus up to 50% of the final volume. Transfer to a measuring cylinder. The Ora-Sweet can be used to washout the pestle and mortar before making the suspension up to 100%volume. Transfer to an amber medicine bottle.
- Shelf-life
- 7 days refrigerated in amber glass. Shake the bottle

Syrup components



1. Sugar usually sucrose or sugar substitutes.
2. Antimicrobial preservative
3. Flavoring agent
4. Co solvent
5. Purified water, Solvents, solubility agent, thicker, stabilizer
6. Drug

Sucrose



- Purest compound commercially available
- sweet
- Lack of color
- Easy to handle

Simple syrup NF

Rχ	
Sucrose	85 g
Purified water q.s.	100 ml

- Sucrose 85% w/v
- This concentration requires no additional preservatives if the syrup is used soon and not stored.

Saturated sucrose solution

- Saturated solution of sucrose might crystallize from solution upon cooling
- Thereby acting as nuclei that initiate chain reaction which result in separation of an amount of sucrose disproportionate to it's solubility at the storage temperature
- The syrup will be less concentrated so it will be prone to micro organism growth .

Saturated vs. concentrated

- Each 100ml of syrup weighs 131.3g
- 131.3-85=46.3g water
- 46.3 ml water dissolves 85g sucrose
- Solubility of sucrose is expressed as 1g in 0.5ml water
- To dissolve 85g of sucrose 42.5ml of water is needed
- 46.3-42.5=3.8ml /100ml syrup excess water

Syrups containing sucrose

- Most syrups contain about 60-80% sucrose
- Desirable sweetness and viscosity, also because of stability factors (dilute sucrose solution are prone to microbial growth which result in turbidity, fermentation ,change in color)
- Concentrated sugar solution (85%w/v) are resistant to microbial growth (no free water)
- Syrups containing less than (85%w/v) sucrose, preservatives must be added.

Anti- microbial preservative

preservative	Concentration used as %
Benzoic acid	0.1-0.2
Sod benzoate	0.1-0.2
Butyl paraben (butyl p-hydroxybenzoate)	0.02
Propyl paraben 4-hydroxybenzoic acid propyl ester	0.05
Methyl paraben 4-hydroxybenzoic acid methyl ester	0.1
Sorbic acid	0.1
Alcohol 99%	15-20 (18)
Glycerin	45

Preservatives

- The benzoates and the parabenes (hydroxyl-benzoic acids) and sorbic acid are most effective in acid solution
- Mixture of parabens are frequently employed to take advantage of their potentiating effect
- The amount of added preservative needed in syrups containing sucrose less than 85% w/v is estimated according to the calculated free water.
- If the syrups are diluted with water preservatives must be added

Calculate the amount of preservative

- Calculate the preservative action of the sucrose present knowing that 85%w/v sucrose will preserve 100ml solution (syrup)

- 65/v=85/100 v=76.5ml volume of solution preserved by 65%w/v sucrose.
- 100-76.5=23.5ml free water (not preserved)
- The amount of preservative added is calculated according to the volume of the free water

Q CALCULATE THE VOLUME OF ETHANOL

Drug	5ml
Solids	3ml
Glycerin	15ml
Sucrose	25g
Ethanol 95%	q.s.
Purified water q.s.	100ml

Answer

- 85/100=25/v v=29.4ml volume of solution preserved
- 100-29.4=70.6ml volume of solution not preserved by sucrose
- Glycerin can preserve an equal amount of water 15×2 =30ml
- 70.6-30=40.6ml
- Volume occupied by other components 5+3=8
- 40.6-8=32.6ml
- 0.18×32.6=5.868 ≈5.9ml of alcohol(99%) required
- 5.9/0.95=6.21ml of alcohol95%will be required

Another method for calculations

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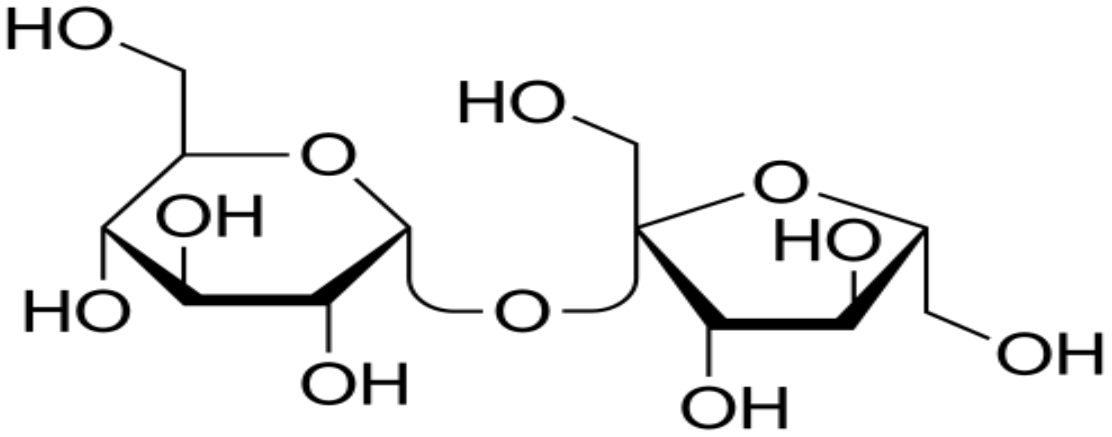

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Degrees of sweetness 100 (1)	74 (0.5-0.9)	173 (1.2)
Colorless liquid	Solution of invert sugar are more prone to microbial growth	Degradation leads to brown discoloration (caramelization)

Solution by agitation

- To avoid heat induced inversion
- Sucrose and other ingredients are placed in a vessel larger than the volume of the syrup to be prepared
- More time consuming than the use of heat
- But the product has maximum stability
- Miscible Liquid ingredients are incorporated during mixing
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Example of medicated syrup

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	q.s.
Purified water, to make	1000.0 mL

Addition of Sucrose to a Medicated Liquid or to a Flavored Liquid

- Tincture or fluidextract, is employed as the source of medication in the preparation of a syrup.
- Many such tinctures and fluidextracts contain alcohol-soluble constituents and are prepared with alcoholic or hydroalcoholic vehicles. If the alcohol-soluble components are desired medicinal agents, some means of rendering them water soluble is employed.
- However, if the alcohol-soluble components are undesirable or unnecessary components of the corresponding syrup, they are generally removed by mixing the tincture or fluidextract with water, allowing the mixture to stand until separation of the water-insoluble agents is complete, and filtering them from the mixture. The filtrate is the medicated liquid to which the sucrose is added in preparation of the syrup.
- If the tincture or fluidextract is miscible with aqueous preparations, it may be added directly to simple syrup or to a flavored syrup.

PERCOLATION METHOD

- In the percolation method, either
- sucrose may be percolated to prepare the syrup
- or the source of the medicinal component may be percolated to form an extractive to which sucrose or syrup may be added.
- This latter method really is two separate procedures: first the preparation of the extractive of the drug and then the preparation of the syrup.

Ipecac syrup USP

- Ipecac syrup, which is prepared by adding glycerin and syrup to an extractive of powdered ipecac obtained by percolation.
- The drug ipecac, which consists of the dried rhizome and roots of *Cephaëlis ipecacuanha*, contains the medicinally active alkaloids emetine, cephaeline, and psychotrine.
- These alkaloids are extracted from the powdered ipecac by percolation with a hydroalcoholic solvent.
- The syrup is categorized as an emetic with a usual dose of 15 mL.

Non- sucrose based syrups

- **Diabetic simple syrup**
- **Artificial syrups**
- **Non nutritive syrups**
  - Used for patient who must control their caloric intake
  - Substitute for the sucrose
  - sweetness, artificial sweetener
  - viscous, viscosity builder
  - and self preserving at 85% preservative

Formulation

Early formulas contained glycerin and propylene glycol
But they are also glycogenic

Rχ		
Sodium CMC (medium viscosity)	1.5%	Viscosity builder
Saccharin	q.s.	Sweetening agent
Methyl paraben	q.s.	Preservative
Purified water	100 ml	

Non- sucrose based syrups

Viscosity builders

- Non-glycogenic
  - Natural
  - Semi synthetic
- Glycogenic
  - Polyols

VISCOSITY BUILDERS

- 1-Glycogenic (Polyols) sorbitol (64%), glycerin, propylene glycol

- 2- Non- glycogenic ,

a) Natural (Gums) Tragacanth, Acacia

b) Semi synthetic Polymers

Methylcellulose MC (nonionic , exothermic)

Hydroxypropylmethylcellulose HPMC (nonionic)

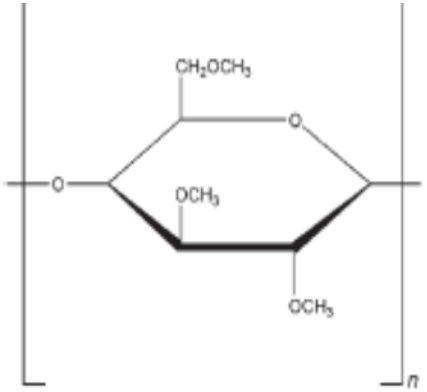
Sodium Carboxymethylcellulose Sod CMC(anionic),

Sod Alginate(anionic) ,

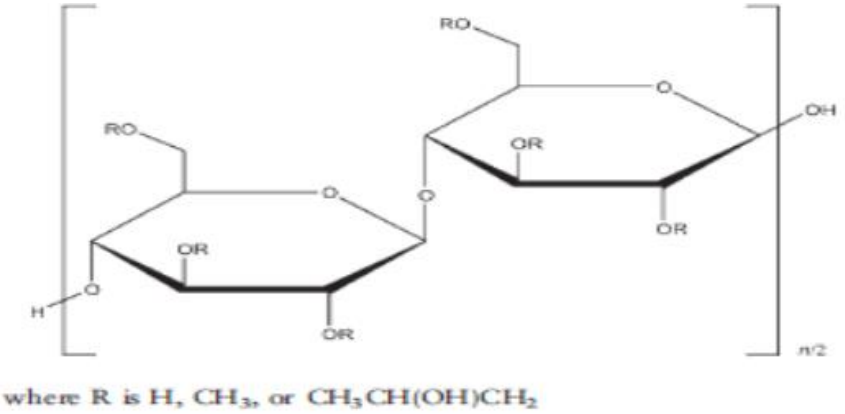
Tragacanth and Acacia

- Tragacanth
  - Naturally occurring dried gum consists of a mixture of water-insoluble and water soluble polysaccharides.
  - Bassorin, which is the main water-insoluble portion, while the remainder of the gum consists of the water-soluble material tragacanthin.
  - On hydrolysis, tragacanthin yields L-arabinose, L-fucose, D-xylose, D-galactose, and D-galacturonic acid.
- Acacia
  - Complex, loose aggregate of sugars and hemicelluloses
  - The aggregate consists essentially of an **arabic acid** nucleus to which are connected calcium, magnesium, and potassium along with the sugars arabinose, galactose, and rhamnose.

Structures of semisynthetic polymers (nonionic)



Methylcellulose MC

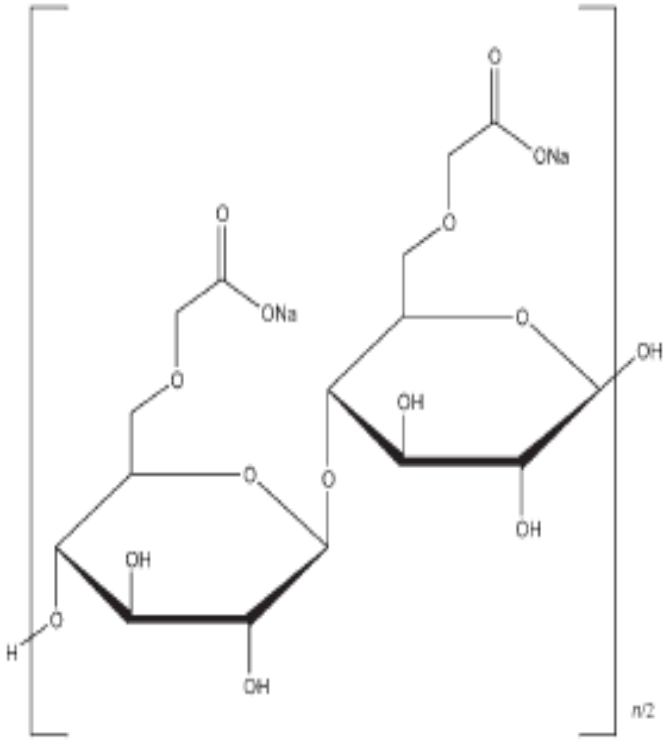


where R is H, CH_3, or $CH_3CH(OH)CH_2$

Hydroxpropylmethyl cellulose HPMC

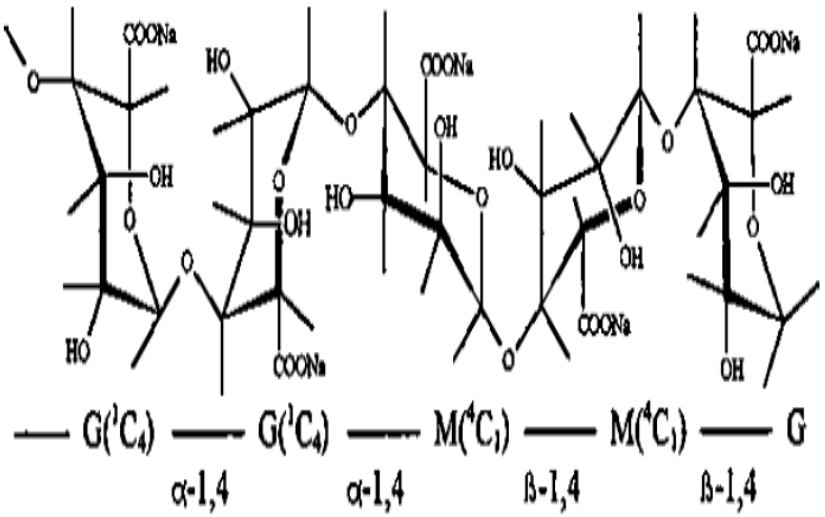
Structures of semisynthetic polymers (anionic)

Carboxymethylcellulose Sodium



Structure shown with a degree of substitution (DS) of 1.0.

Sodium Alginate



The number and sequence of the Mannuronate M and Glucuronate G residues shown above vary in the naturally occurring alginate

Natural and semi-synthetic viscosity builder

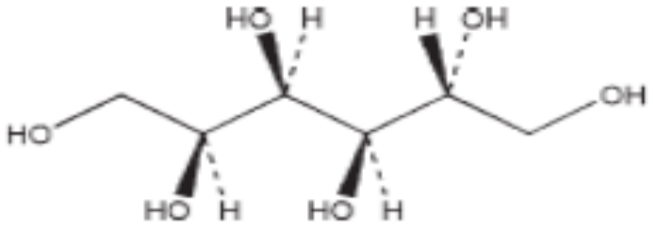
- Natural
- Acacia
- Tragacanth
- Opalescent (not colorless)
- Change characteristics upon aging
- Differ according to the plant source

- Synthetic (semi-synthetic)
- Non glycogenic
- Colorless
- MC is exothermic

Special precautions

1. Anionic polymers are incompatible with cationic drugs or other formulation ingredients.
2. Strong dehydrating agents cause coagulation of aqueous dispersion of both natural or semisynthetic polymers.
3. Incompatible with excessive amounts of alcohol and electrolytes.

Sorbitol based syrup



Hexa-hydric alcohol	• $C_6H_{14}O_6$ • Glucose hydrogenation
Crystalline sorbitol	• White ,odorless • Non volatile
70%w/w	• Substitute for sucrose • Diabetic patients

Advantage of sorbitol solution over simple syrup

mouth

- Sorbitol solution is not irritating to the membranes of the mouth and throat, and lacks the acrid characteristics of some polyols, half as sweet as sucrose , overall pleasant taste
- Don't cause dental caries

G.I.T

- Not absorbed from the G.I.T
- Excessive amount has a laxative effect

Sorbitol

- 60% as sweet as sucrose ,half as viscous as simple syrup
- Chemically stable ,inert with respect to drugs and other ingredients
- Sorbitol based solution have extended shelf lives

Advantage of sorbitol solution addition to simple syrup

Compatible with other polyols

Can be added (30%)to simple syrup to reduce crystallization

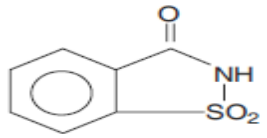
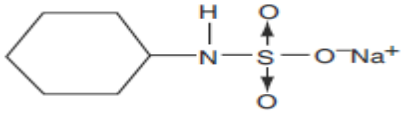
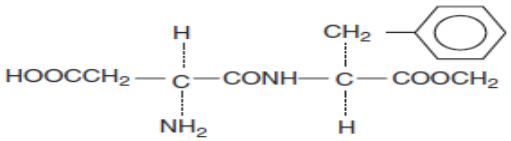
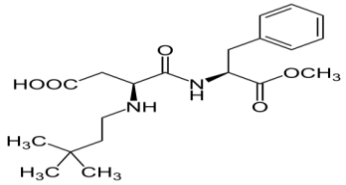
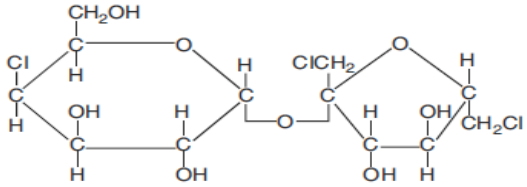
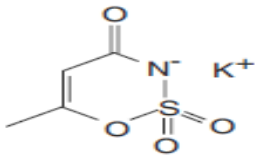
Sorbitol inhibits the sticking or locking of bottle caps which occur with high concentrations of sucrose

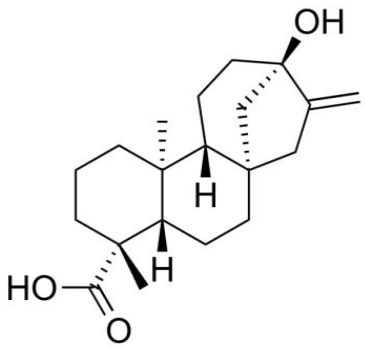
Formulation

- Artificial sweeteners are added to intensify the mild sweetness
- Sorbitol(60%w/v) can resist microbial growth
  If the concentration of sorbitol is less we add preservative.

Linctuses

- Linctuses are viscous preparations that contain the therapeutic agent dissolved in a vehicle composed of a high percentage of sucrose and, if required, other sweetening agents. (honey or glucose syrup)
- Linctuses are often used when the drug has a bitter taste
- These formulations are administered orally and are primarily employed for the treatment of cough, due to their soothing actions on the inflamed mucous membranes.
- Linctuses may also be formulated as sugar-free alternatives in which sucrose is replaced by sorbitol and the required concentration of sweetening agent

Sweetener	Degree of sweetness	Chemical structure	Comment
Saccharin Sweet "N" Low®	500		Bitter after taste
Sod cyclamate	30		Banned in USA
Aspartame Aspartyl phenylalanine methyl ester Canderel®	200		Unstable in hot solution,(PKU)
Neotame (N-[N-(3,3-dimethylbutyl)-L--aspartyl]-L-phenylalanine 1-methyl ester) Nutrasweet®	8000		
Sucralose Splenda®	600		Stable over a broad pH range
Acesulfame –K Nutrinova®	200		Heat stable

Natural Sweetener	Degree of sweetness	Chemical structure	Comments
Stevia	250		Extracts known as rebiana, Truvia, Pure Via; mainly containing rebaudioside A, a steviol glycoside
Sorbitol	0.6		
Xylitol	1.0		
Mannitol	0.5		Derived from Mannose

Aromatic water

Aromatic water

* Aromatic waters are clear, aqueous solutions saturated with volatile oils or other aromatic or volatile substances.
* They are saturated solutions usually of volatile oils or similar substances in distilled water.
* Aromatic waters are not therapeutically potent because of the very small proportion of the active ingredient present in them.

History

* Aromatic waters such as rose water were used in Egypt as early as the 4th century.
* Distilled waters containing volatile oils reached their therapeutic peak in the early sixteenth century in Europe .
* Although their therapeutic use declined in modern times, they continued to be used as flavorings.
* Hamamelis water (witch hazel) has lingered on as an aftershave and astringent.

Examples of Aromatic Waters

* Aromatic waters were prepared from a number of volatile substances, including
* orange oil
* flower oil,
* Peppermint oil,
* rose oil,
* anise oil,
* spearmint oil,
* wintergreen oil,
* camphor,
* and chloroform.

Aromatic water uses

1. Aromatic Waters are used as Intermediate solutions for manufacturing of other preparations and also used as the liquid phase of emulsions and suspensions.
2. Aromatic water is used as a flavoring agent. Aromatic waters provide a pleasantly flavored medium for administration of water –soluble drugs when taste masking of undesirable taste is not a problem. The odors and tastes of aromatic waters are of the volatile substances from which they are prepared.
3. Aromatic water prepared from essential oils like peppermint and anise waters have some carminative properties.

Topical Aromatic Water

Aromatic water	Use
Rose Water	Perfume
Hamamelis Water (Witch Hazel)	Astringent
Camphor Water	Rubefacient (dilate skin vessels) Reduce skin itching Eye wash

Preparation of aromatic water

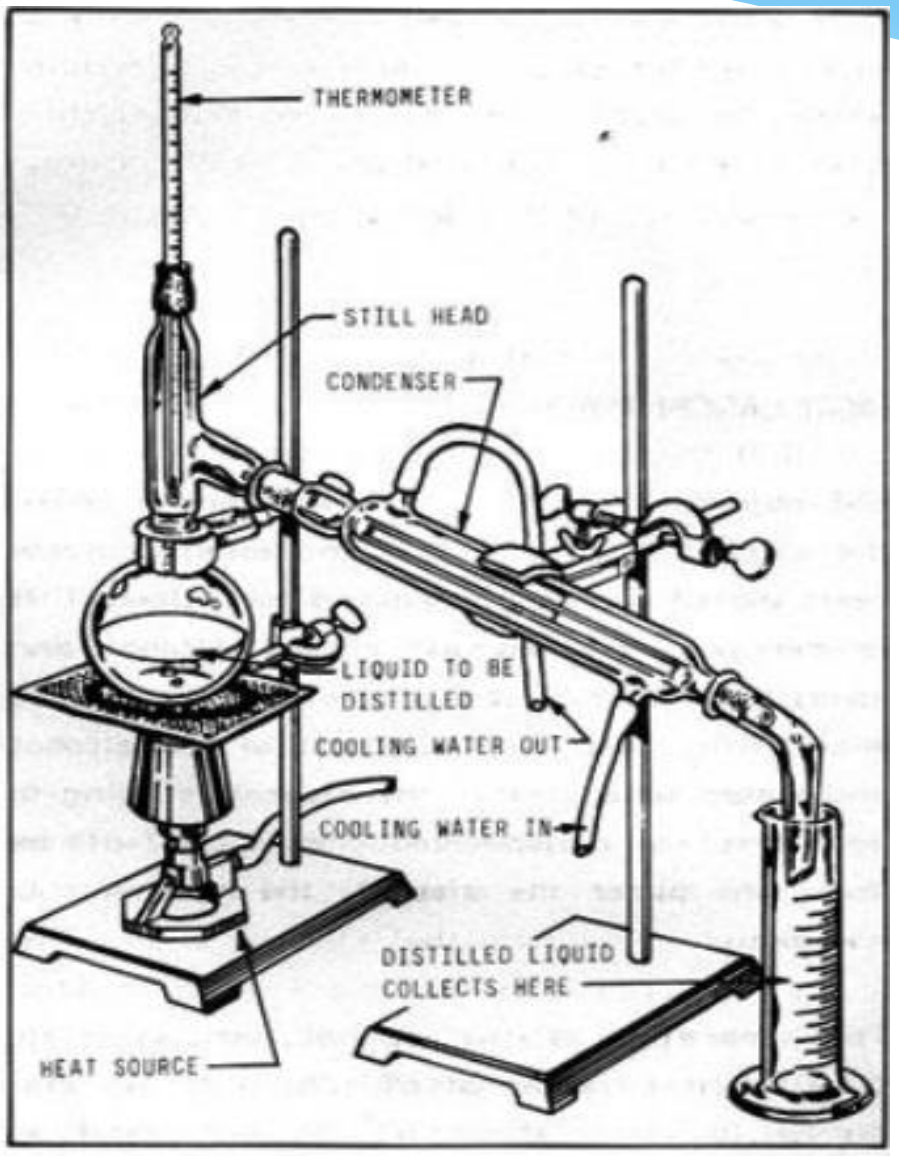
* Most of the aromatic substances in the preparation of aromatic waters have very low solubility in water, and even though the water may be saturated, its concentration of aromatic material is still rather small.

The official method of preparation of aromatic water are:

1. Distillation 2. Solution 3. Alternate solution

Formulas for concentrates of the aromatic principles containing either alcohol or solubilizing agent have been developed, or are manufactured as concentrated waters. To prepare an aromatic water the concentrates are diluted with water before use.

Distillation method



The distillation method consists of placing the odoriferous portion of the plant or the drug in a suitable still with sufficient purified water and then distilling most of the water, avoiding charring or scorching (burning) of the substance.

The excess oil is separated from the distillate .

The label of commercial witch hazel contain one or more X , each X represent one distillation

Distillation

Advantage

* Most of the aromatic waters are prepared by distillation.
* Used for preparation of aromatic water from fresh plants ex
* Stronger Rose water
* Orange flower water
* Hamamelis water
* These cannot be prepared by other methods

Disadvantage

* Not practical or economically feasible to use this method in most cases

Solution method

* The volatile substance is agitated with purified water for a period of 15 minutes.
* The mixture is set aside for at least 12 hours to ensure saturation before it is filtered through wetted filter paper
* A large excess of solute is used 2g or 2ml /liter solution in order to obtain the maximal rate of solution
* The filter paper must be wet to prevent the passage of excess oil in to the filtrate and eliminate absorption of the dissolved aromatics by the filter.
* Not necessary to make up to volume through the filter , since a saturated solution is sought.

Solution method

Advantage

* Easy method
* Simple equipment

Disadvantage

* In spite of repeated filtration it is difficult to obtain a brilliantly clear preparation owing to formation of extremely fine particles.
* This can be obviated by using boiling purified water
* Time consuming method

Chloroform water N.F

* Prepared by solution method
* No clarification is needed because the excess chloroform must remain in the bottle because chloroform is heavier than water
* The high volatility of chloroform creates an equilibrium of loss and restoration of strength by evaporation
* When dispensed the bottle must be shaken vigorously and only the supernatant liquid should be used

Alternant solution method

* The volatile material is mixed with 15g purified talc or with sufficient quantity of purified siliceous earth (silica) or pulped filter paper. (an adsorbent)
* The mixture is agitated with a liter of purified water for 10 minutes prior to filtration.
* The talc or other inert material functions as both a
* 1-filter aid which facilitates the clarification of the solution
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Alternate solution method

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Disadvantage

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Peppermint water

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* The (aroma carriers) alcohols, ethers, aldehydes and ketones
* The terpenes are the least water soluble which are mostly removed by filtration
* Terpeneless oils are prepared by fractional distillation and or extraction are stronger in aroma and more soluble and more stable than the natural essential oil , but are of higher expense

Dilution

* Concentrated aromatic are prepared to obviate the difficulties involved in the clarification of aromatic water
* Which are designed to be diluted with an appropriate volume of purified water when needed.
* Dilute rose water prepared from strong rose water with an equal volume of water .

Preparation of concentrated aromatic water

* An alcoholic solution (50-55% alcohol)of the essential oil is mixed with water and talc , the Mixture is agitated ; after several hours it is filtered .
* The diluted aromatic water is prepared by diluting 2ml of the concentrated aromatic solution to 100ml with water. The resultant contains less than 1.5% of alcohol.

Dilution method

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* Separation of volatile material when the temperature decrease causing cloudiness.
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Special care

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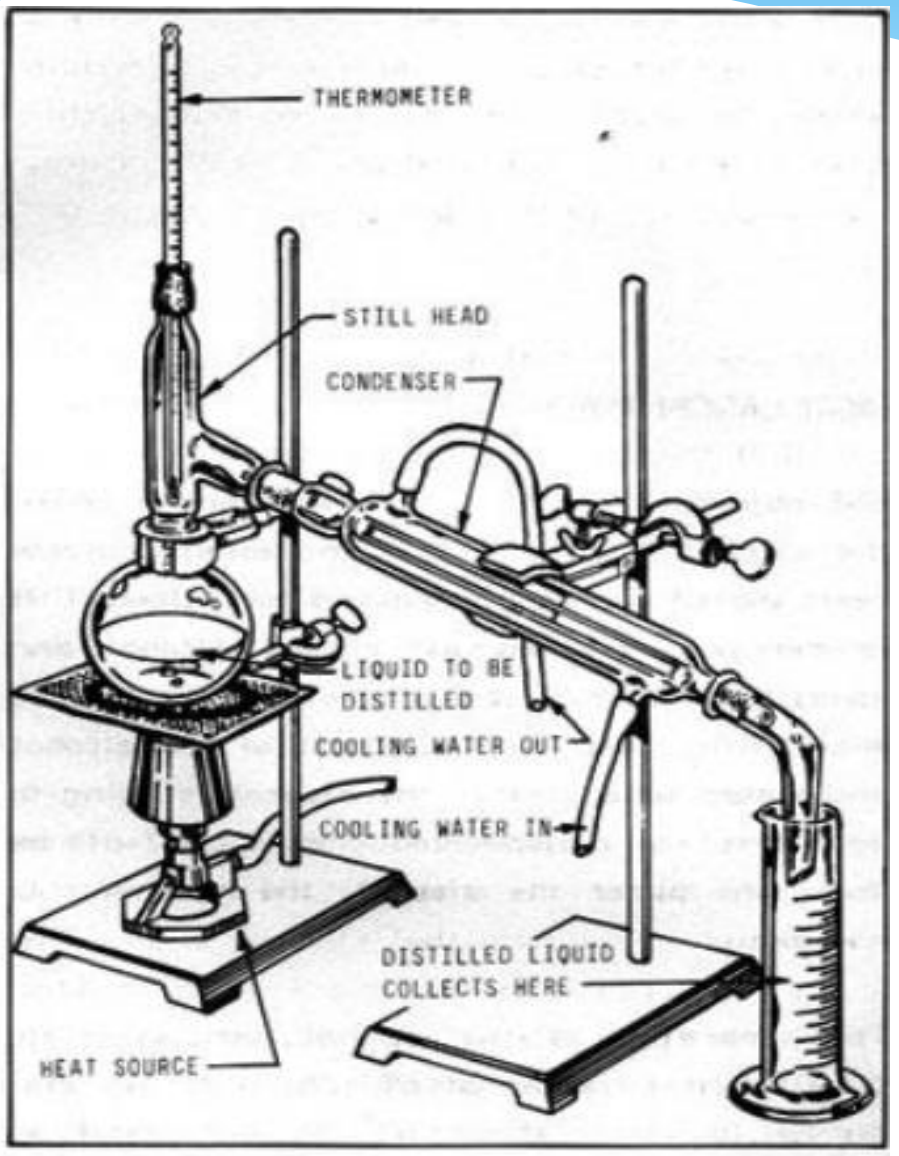

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Colloidal dispersions
Introduction- properties

Aulton's Pharmaceutics The Design and Manufacture of Medicines 3rd Ed Ch. 6

Ansel's Pharmaceutical dosage form 9th Ed. Ch. 14

American Pharmacy

What is a Colloidal Dispersion?

- Colloid from the Greek word
- Kolla= glue
- Introduced by Thomas Graham
- Discovered that certain substances (e.g., glue, gelatin, or starch) could be separated from certain other substances (e.g., sugar or salt) by dialysis.
- He gave the name *colloid* to substances that do not diffuse through a semipermeable membrane (e.g., parchment or cellophane) and the name ***crystalloid*** to those which do diffuse and which are therefore in true solution

Colloidal Dispersion

- Colloidal system or colloidal dispersion is a heterogeneous system which is made up of Dispersed phase and Dispersion medium(Continuous phase).
  In colloidal dispersion one substance is dispersed as very fine particles in another substance called dispersion medium.

Classification of colloidal dispersions

1. Physical state of the dispersion phase and the continuous medium
2. Interaction between the dispersion phase and the continuous medium
3. Particle size

Medium / Phases	Dispersed phase: Gas	Dispersed phase: Liquid	Dispersed phase: Solid
Continuous medium: Gas	**NONE** (All gases are mutually miscible)	**Liquid aerosol** Examples: fog, mist, hair sprays 	**Solid aerosol** Examples: smoke, dust particulates 
Liquid	**Foam** Example: whipped cream, Shaving cream, carbonated soft drinks 	**Emulsion** Examples: milk, mayonnaise, hand cream ,lotions 	**Sol** Examples blood, antacid suspensions 
Solid	**Solid foam** Examples: aerogel, styrofoam, pumice	**Gel** Examples: agar, gelatin, jelly, 	**Solid sol** Example: colored glass, pastes like toothpastes 

Particle size

- Size of colloidal particles are in range of 1–1000nm while size of true solution suspension is >1000nm and that of true solution is < 1nm. **Thus size of colloids lies between that of true solution and suspension.** The colloidal particles can’t be seen with naked eye. This is why, colloidal system appears as homogeneous mixtures, but in reality are heterogeneous mixtures.

Differentiation according to particle size

Solution	Colloidal dispersion	Suspension
<1nm	1-1000nm (0.5µm)	>1000nm (0.5µm)
Electron microscope(lower limit)	Visible in electron microscope ultra microscope	Ordinary microscope
High rate of diffusion	Low rate of diffusion (Brownian motion)	No diffusion nor Brownian motion
Pass through 1. filter paper , 2. dialysis membrane a)collodion; cellulose nitrate b)cellophane ultrafiltration (with suction) or electro dialysis (electric current)	Pass filter paper	Retained by filter paper Settle down or cream
High osmotic pressure	Low osmotic pressure	No osmotic pressure
Do not scatter light	Scatter light (Tyndall effect)	
NaCl, glucose	Surfactant micelle	Pharmaceutical Suspensions

Particle size and size distribution

Particle size can affect absorption behavior

Solid aerosols particle size must be in the range of 1-5µm and no particle above 10µm

Measured by osmotic pressure (no. of particles)

Measured by sedimentation or light scattering the weight rather than no. is important

- Spherical particles The size is determined by the diameter

-Asymmetrical particles are measured by Stoke's diameter d_{st} which describes an equivalent sphere undergoing sedimentation at the same rate as sample particle

Interaction between dispersion phase and dispersion medium

lyophilic

- Liquid loving

lyophobic

- Liquid hating

Association colloids

Surfactant

Dispersion medium is water

Hydrophilic

- Disperse spontaneously
- High affinity (swell)

Hydrophobic

- Un stable dispersions
- Need stabilizing agent

Lyophobic	Association(Amphiphilic)	Lyophilic
Weak interaction/ Liquid hating Lyophobic colloid is a colloidal dispersion in which there are little interaction between the dispersed phase and the continuous phase Dispersed phase in lyophobic colloids is not solvated by the dispersion media If the continuous phase is water, it is also called hydrophobic colloids	Dispersed phase consists of Aggregates (*micelles*) of small organic molecules or ions whose size *individually* is below the colloidal range Hydrophilic or lipophilic portion of the molecule is solvated, depending on whether the dispersion medium is aqueous or Non-aqueous	Strong forces of interaction /Liquid loving, Lyophilicity is the tendency of particles, surfaces, or functional groups to become extensively wetted, solvated, swollen, or dissolved by solvents Molecules of dispersed phase are solvated, i.e., they are associated with the molecules comprising the dispersion medium
Water based colloids with inorganic dispersed phase are lyophobic ex: Gold Au198 injection USP Mild silver protein NF Sulfur Some of lyophobic colloids possess lyophilic properties (eg. hydrosols of silica and alumina).	Tween Span	Dispersed phase consists generally of large Organic *molecules* lying within colloidal size range Poly saccharides Proteins

Lyophobic	Association(Amphiphilic)	Lyophilic
Viscosity of the dispersion medium is not greatly increased by the presence of lyophobic colloidal particles, which tend to be **Un-solvated** and **symmetrical** Sols of low viscosity, even at high concentration, because of low solvation and low attraction between the particles compared to high repulsion Lyophobic colloidal particles are not readily solvated because the continuous phase prefer to interact with one another than be involved in solvating the dispersed particles	Viscosity of the system increases as the concentration of the amphiphile increases, as micelles increase in number and **become asymmetric**	Viscosity of the dispersion medium ordinarily is increased greatly by the presence of the dispersed phase; at sufficiently high concentrations, the sol may become a gel; viscosity and gel formation are related to solvation effects and to the shape of the molecules, which are usually **highly asymmetric** Usually high at sufficiently high concentration of disperse phase a gel may be formed. Lyophilicity is the tendency of particles, surfaces, or functional groups to become extensively **wetted, solvated, swollen**, or dissolved by solvents

Lyophobic	Association(Amphiphilic)	Lyophilic
Material does not disperse spontaneously, and special procedures therefore must be adopted to produce colloidal dispersion	Colloidal aggregates are formed spontaneously when the concentration of amphiphile exceeds the critical micelle concentration	Molecules disperse spontaneously to form colloidal solution
Lyophobic sols with high net inter-particle attraction leads to coagulation forming distinct granules and the system cannot easily be restored to its colloidal state. At high concentration lyophobic systems turn into pastes		lyophilic sols form **gels** on coagulation

Lyophobic preparation

Cannot be prepared directly by mixing colloid with liquid.
Special methods are employed to prepare them need stabilizers like SAA
Preparation may be either

1. Mechanical reduction of larger particles to colloidal size by either
   a) Colloidal mill, hammer, ball jet, roller, which is required because of high interfacial energy of the dispersed particles.
   b) Ultrasonic vibration and electric arcs inside liquids which cause evaporation of the electrode material followed by condensation

2. Condensation nucleation and particle growth, rapid production of supersaturated solution of colloidal material which is deposited in the medium as colloidal particles and not as ppt. Condensation of smaller particles to form a colloid usually involves

a) Physical (add hot water to acetone solution of ppt. sulfur)
b) Chemical (strong acid and sod thio-sulphate produce) typically displacement, hydrolysis, or oxidation and reduction

Lyophilic

Prepared directly by mixing colloid with liquid.
easy to prepare

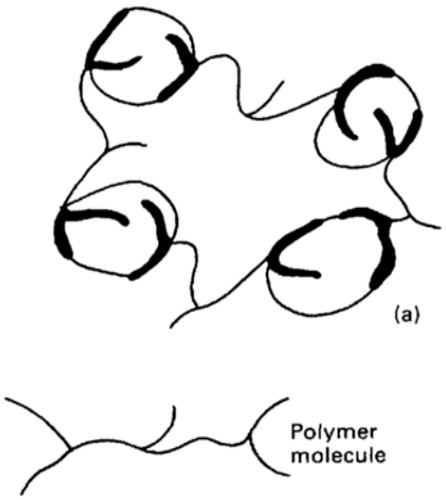
1) Disperse spontaneously in the appropriate solvent
2) The resultant dispersion are intrinsically stable
3) Molecularly dissolved lyophilic materials are in colloidal range

	Lyophobic	lyophilic
Formation of dispersion	Dispersions usually of metals, inorganic crystals etc., with a high interfacial surface-free energy due to large increase in surface area on formation. A positive ΔG of formation, dispersion will never form spontaneously and is thermodynamically unstable. Particles of sol remain dispersed due to electrical repulsion	Generally proteins, macromolecules etc., which disperse spontaneously in a solvent. Interfacial free energy is low. There is a large increase in entropy when rigidly held chains of a polymer in the dry state unfold in solution. The free energy of formation is negative, a stable thermodynamic system
Stability	Controlled by charge on particles. The particles in such sols are stabilized only by the presence of electric charges on their surfaces. The like charges produce a repulsion that prevents coagulation of the particles, it can be Stabilized by additives such as surfactant (lowering the interfacial energy of the system) or by protective colloids (Steric stabilization - protective colloid action)	Controlled by charge and solvation of particles Surrounding each particle with a protective solvent sheath that prevents mutual adherence when the particles collide as a result of Brownian movement

	Lyophobic	Lyophilic
Effect of electrolytes addition	Very sensitive to added electrolyte, leading to aggregation in an irreversible manner. Depends on the Schulze-Hardy rule (a) The type and valency of counter ion of electrolyte, e.g. with a negatively charged sol, $La^{3+} > Ba^{2+} > Na^{+}$ (10^{-4}, 10^{-3}, 10^{-1} mol /ml) (b) Concentration of electrolyte. At a particular concentration sol passes from disperse to aggregated state.	Dispersions are stable generally in the presence of electrolytes. If sufficient salt is added, agglomeration and sedimentation of the particles may result. This phenomenon, referred to as "salting out," . Effect is due to desolvation of the lyophilic molecules and depends on the tendency of the electrolyte ions to become hydrated. According to the Hofmeister (lyotropic) series, which ranks cations and anions in order of coagulation of hydrophilic sols For anionic colloids $Ba^{2+} < Ca^{2+} < Mg^{2+} < NH_4^{+} < K^{+} < Na^{+} < Li^{+}$ and for cationic colloid $I^{-} < Br^{-} < ClO_3^{-} < NO_3^{-} < Cl^{-} <$ acetate $< CO_4^{2-} <$ tartrate < citrate The precipitating power is directly related to the hydration of the ion and hence to its ability to separate water molecules from the colloidal particles Proteins are more sensitive to electrolytes at their isoelectric points. Lyophilic colloids when salted out may appear as amorphous droplets known as a coacervate

Effect of addition of macromolecular material to lyophobic colloidal sols

Diagram of flocs



Polymer bridging

- 1- When added in **small amounts**, many polyelectrolyte and polymer molecules(lyophilic colloids) can adsorb simultaneously on to two particles and are long enough to **bridge** across the energy barrier between the particles. This can even occur with neutral polymer when the lyophobic particles have a high zeta potential
- 2-(Steric stabilization - protective colloid action) if larger amounts of polymer are added, sufficient to cover the surface of the particles, then a lyophobic sol may be stabilized to coagulation even in the absence of significant zeta potential.

Properties of colloids

- ***1-Kinetic properties***
- **Thermal motion** manifests itself in the form of Brownian motion, diffusion and osmosis. **Brownian motion :**Colloidal particles are subject to random collisions with the molecules of the dispersion medium, with the result that each particle pursues an irregular and complicated zigzag path. Responsible for the **diffusion** of colloidal particles.
- **Gravity** (or a centrifugal field) leads to sedimentation, by **ultra-centrifugal** force about $10^6 g.$
- Viscous flow is the result of an **externally applied force**.
- However, the usefulness of **osmotic pressure** measurement is limited to a molecular weight range of about 10^4-10^6; below10^4 the membrane may be permeable to the molecules under consideration and above 10^6 the osmotic pressure will be too small to permit accurate measurement.
- Measurement of these properties enables molecular weight or particle size to be determined.

2-Optical properties

- When a strong beam of light is passed through a colloidal sol, a visible cone, resulting from the scattering of light by the colloidal particles, is formed. This is the Faraday–Tyndall effect.
- The **ultra-microscope**, developed by Zsigmondy, allows one to examine the light points responsible for the Tyndall cone.
- An intense light beam is passed through the sol against a dark background at right angles to the plane of observation, and, although the particles cannot be seen directly, the bright spots corresponding to particles can be observed and counted
- Low solvation of the lyophobic colloidal dispersion leads to large difference in refractive index between the liquid medium and the dispersed phase which produces marked light scattering and **strong Tyndall beams**

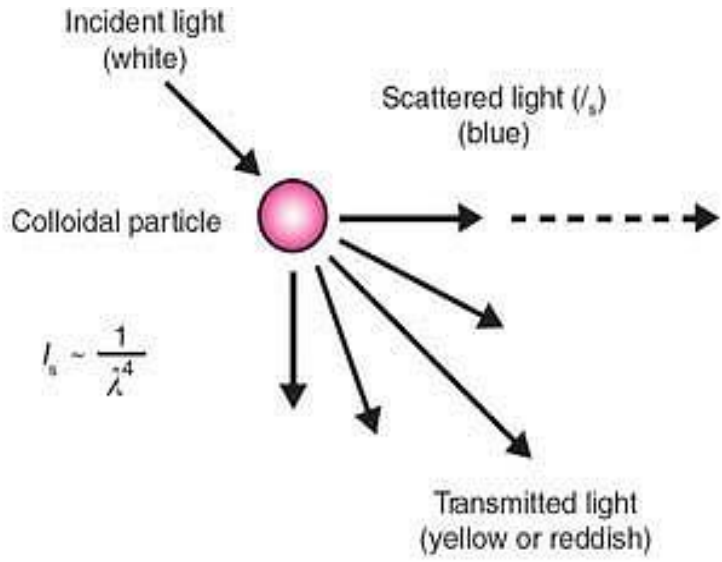
2- Optical properties

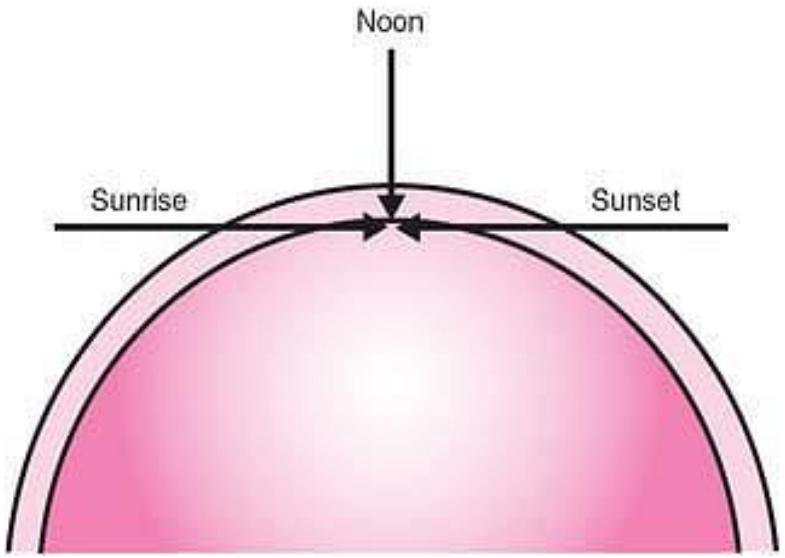
(Tyndall effect) why is the sky blue ?

- When a beam of light passes through a colloid, colloidal particles scatter the light. The intensity of scattered, I_s, light is inversely proportional to the fourth power of the wavelength, λ (Rayleigh law):

$$I_s \sim \frac{1}{\lambda^4}$$

- Thus, shorter-wavelength light (blue) (λ=450nm) is scattered more intensely than longer-wavelength light (yellow and red), (λ=650 nm) and so the scattered light is mostly blue, whereas transmitted light has a yellow or reddish color
- The scattering of short-wavelength light gives the sky its blue color. In contrast, transmitted light has a yellow color. At sunrise and sunset, sunlight has to travel a longer distance through the atmosphere than at noon.

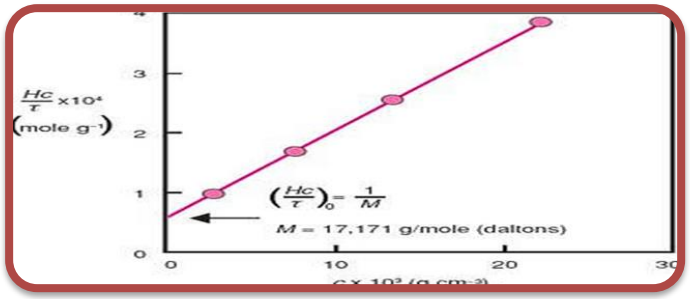




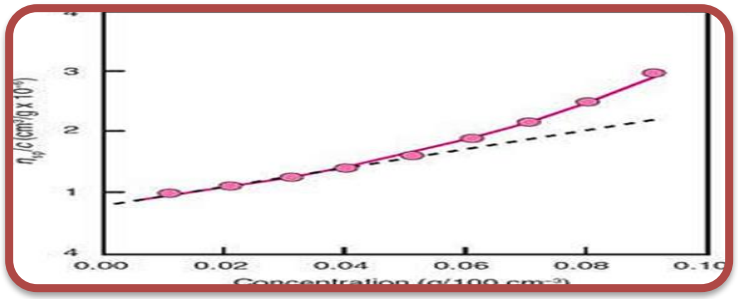
Microscopy

- Colloidal particles are too small to be seen in the optical microscope
- The electron microscope, capable of yielding pictures of the actual particles, even those approaching molecular dimensions, is now widely used to observe the size, shape, and structure of colloidal particles.
- The success of the electron microscope is due to its high resolving power, which can be defined in terms of d, the smallest distance by which two objects are separated and yet remain distinguishable.
- The smaller the wavelength of the radiation used, the smaller is d and the greater is the resolving power.
- The optical microscope uses visible light as its radiation source and is able to resolve only two particles separated by about 20 nm
- The radiation source of the electron microscope is a beam of high-energy electrons having wavelengths in the region of 0.01 nm

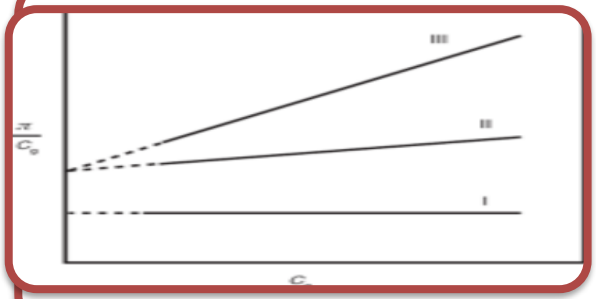
Colloid properties used for measuring the molecular weight determination



Tyndall effect



Viscosity



Osmotic pressure

3- Electrical property of colloids

- Most surfaces acquire a surface electric charge when brought in contact with an aqueous medium due to

1. Ion dissolution e.g. AgI dispersion , $Mg(OH)_2$
2. Ionization of the surface grouping -COO^- and NH_3^+ ions net charge depend on the pH like proteins
   insulin may be precipitated from aqueous alcohol at pH 5.2.
   Erythrocytes and bacteria usually acquire their charge by ionization of surface chemical groups such as sialic acid.
3. Ion adsorption at the interfaces SAA

- The particles of a colloid selectively <u>adsorb</u> ions and acquire an electric charge.
- All of the particles of a given colloid take on the same charge (either positive or negative) and thus are repelled by one another.
- **If the charge on the particles is neutralized, they may precipitate out of the dispersion.**

Electrophoresis

- If an electric potential is applied to a colloid through a liquid, the charged colloidal particles move toward the oppositely charged electrode; this migration is called electrophoresis.
- **Electrophoresis** movement of a charged particle plus attached ions relative to a stationary liquid under the influence of an applied electric field
- Used in measurement of zeta potential

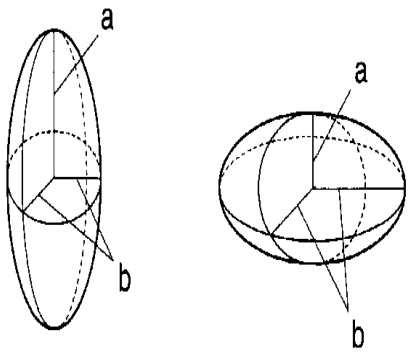
Terminology

- Imbibtion : taking up of certain amount of liquid like water without considerable increase in volume
- Swelling taking up of liquid by a gel with an increase in volume
- Syneresis great interaction between dispersed phase particles ,upon standing dispersed medium is squeezed out in droplets and gel shrink

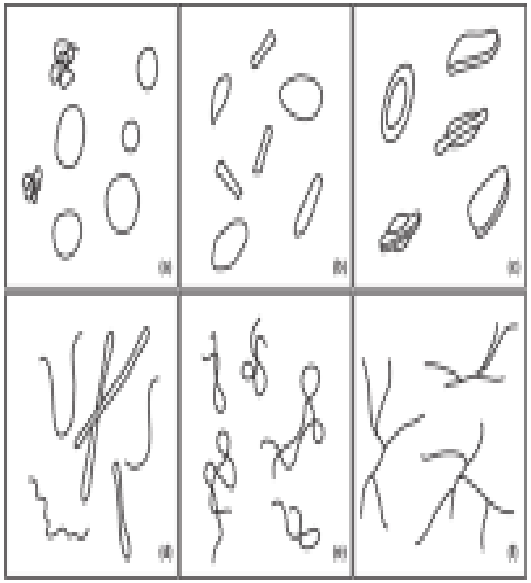
- ***Xerogels*** are gels in which the vehicle has been removed, leaving a polymer network, e.g. polymer films. Xerogel :formed when liquid removed from the gel and only framework remains
- Example .Sheet gelatin, acacia tears, Tragacanth flakes

Shape of colloidal particles(hydrophobic)

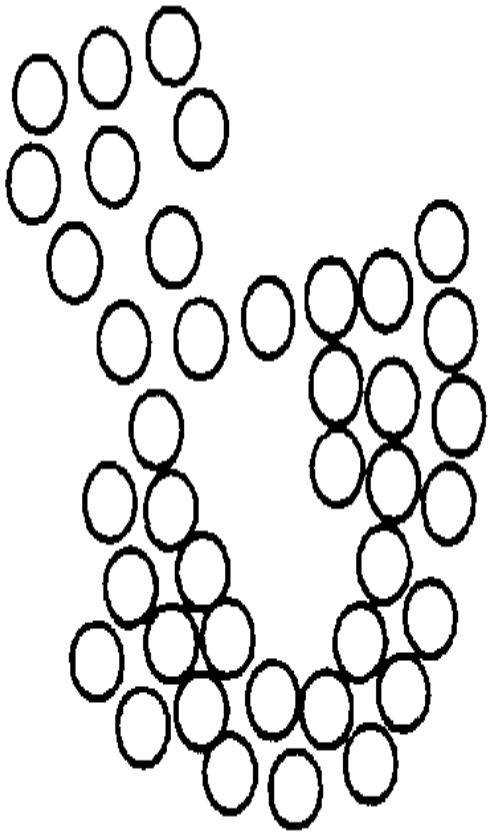
- Many colloidal systems, including emulsions, liquid aerosols and most dilute micellar solutions, contain **spherical particles**,
- Small deviations from sphericity are often treated using **ellipsoidal** models.
- Clay suspensions are examples of systems containing **plate-like** particles



Model representation of ellipsoids of revolution.



Dispersion of lyophobic sols

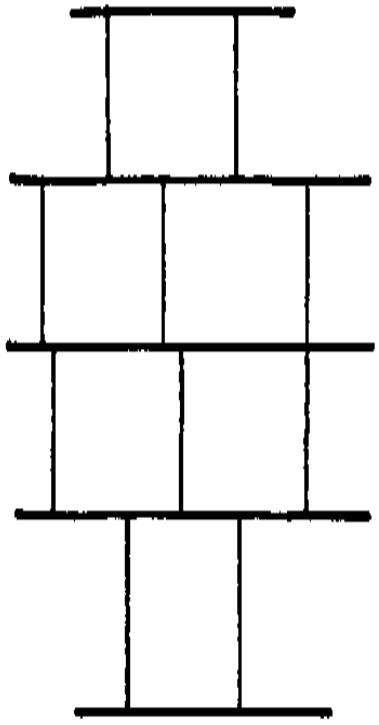


- Lyophobic sols may be flocculated , it is a 2 phase system
- where the **sol** can be looked upon as a **Continuous floccule** Examples are aluminum hydroxide
- Aluminum Hydroxide Gel, USP

and magnesium hydroxide gels

Milk of Magnesia

Dispersion of lyophobic sols



- Clays such as **bentonite**, aluminum magnesium silicate (**Veegum**) and to some extent **kaolin** form gels by flocculation in a special manner.
- They are hydrated aluminum **(aluminum/magnesium)** silicates whose crystal structure is such that they exist as flat plates; the flat part or 'face' of the particle carries a negative charge due to O~ atoms and the edge of the plate carries a positive charge due to Al3+/Mg2+ atoms.
- As a result of electrostatic attraction between the face and the edge of different particles a gel structure is built up, forming what is usually known as a **'card house floc**'
- Ex Bentonite Magma, NF
- The forces holding the particles together in this type of gel are relatively **weak - van der Waals** forces in the secondary minimum flocculation of aluminum hydroxide, **electrostatic attraction** in the case of the clays - and because of this these gels show the phenomenon of ***thixotropy***

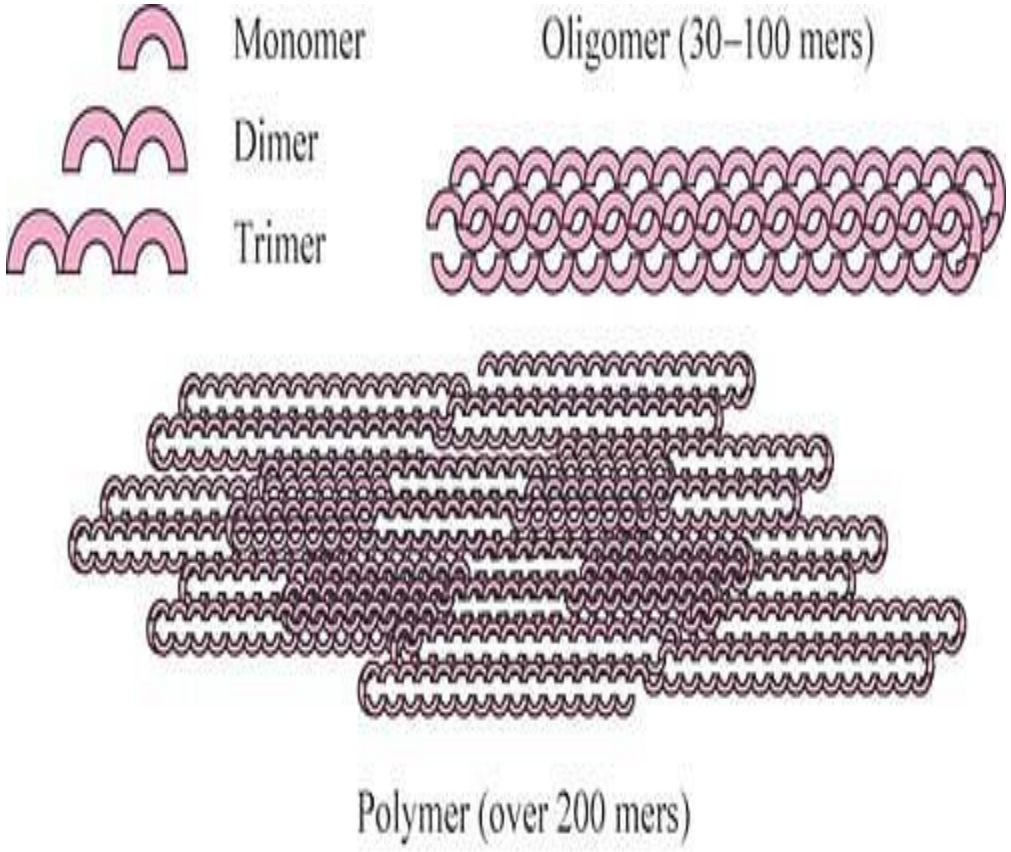
Shape of (hydrophilic) colloidal particles

- The shape adopted by colloidal particles in dispersion is important because the more extended the particle, the greater is its specific surface and the greater is the opportunity for attractive forces to develop between the particles of the dispersed phase and the dispersion medium.
- High molecular weight polymers and naturally occurring macromolecules often form random **coils** in aqueous solution.
- A colloidal particle is something like a hedgehog—in a friendly environment, it unrolls and exposes maximum surface area. Under adverse conditions, it rolls up and reduces its exposed area.
- Properties as flow, sedimentation, and osmotic pressure are affected by changes in the shape of colloidal particles. Particle shape may also influence pharmacological action.

Polymers

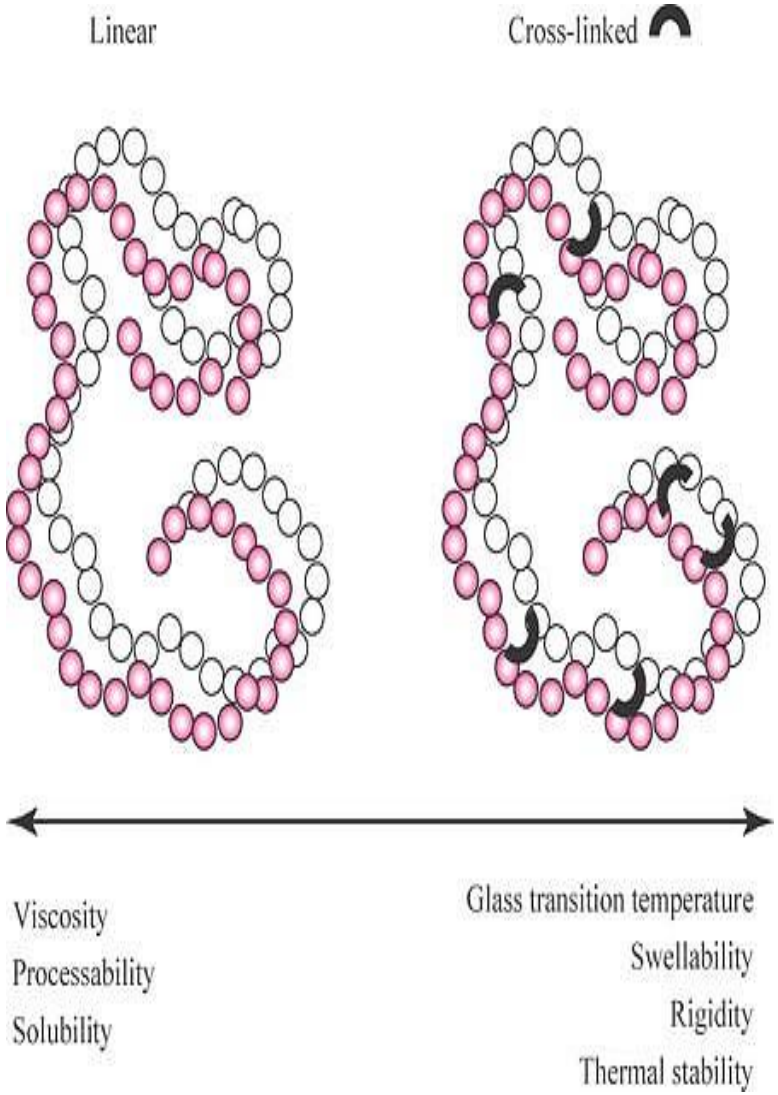
The word “polymer” means “many parts.” A polymer is a large molecule made up of many small repeating units

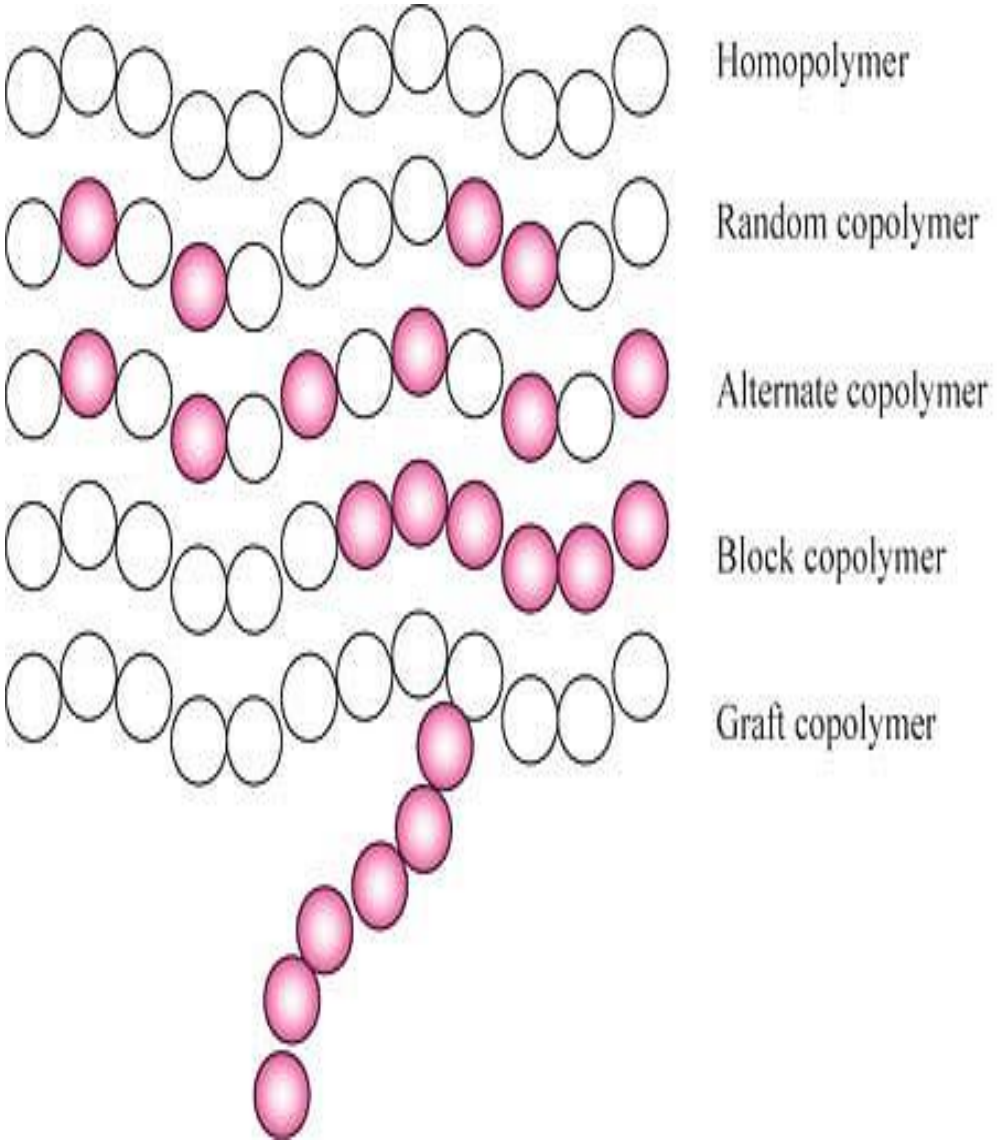
- Polymer anatomy



Degree of Polymerization (DP) = Number of monomers in a chain

Polymers made of two or more monomer units

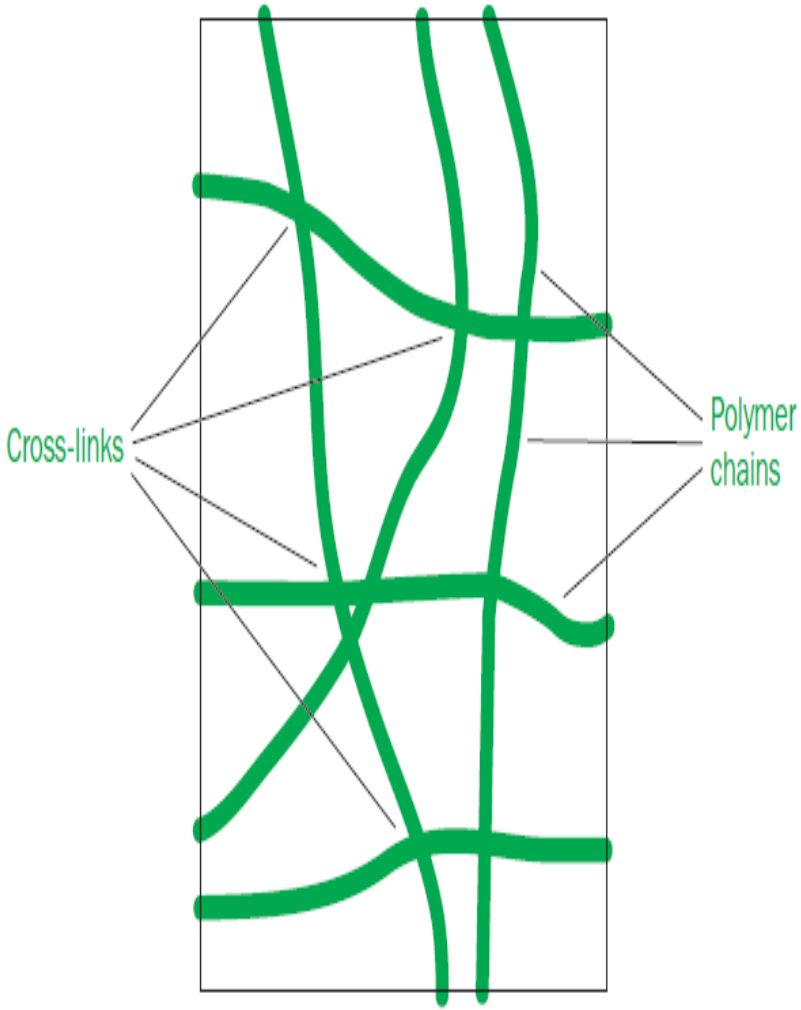




Gelation of lyophilic sols

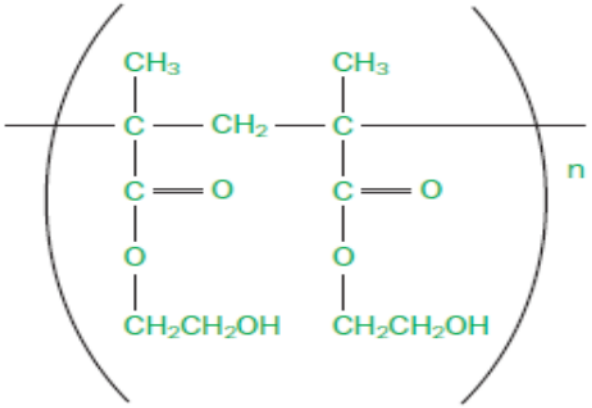
- Gels formed by lyophilic sols can be divided into groups depending on the nature of the bonds between the chains of the network.
- Pharmaceutical gels are most commonly (but not exclusively) manufactured by dispersing hydrophilic polymers within an appropriate **aqueous vehicle**. When dissolved within an aqueous phase, hydrophilic polymers behave as lyophilic colloids and their unique physical properties result from the self-association of the dissolved polymer and its interaction with the aqueous medium.
- There are two types of self-association (termed irreversible and reversible) that may be demonstrated by lyophilic colloids and this allows gels that are manufactured from lyophilic colloids to be classified as either type 1 or type 2 gels.

Type 1 gels

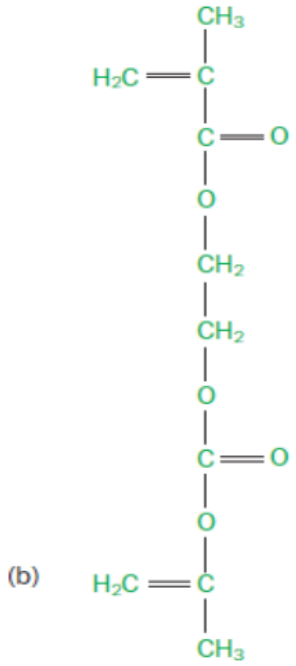


- Gels of ***type 1 (chemical gel)***
- These gels (often termed *hydrogels*) are **irreversible** systems with a three-dimensional network formed by covalent bonds between the macro-polymers in the presence of a **crosslinking agent**, forms a three-dimensional structure that swells in water but cannot dissolve because the crosslinks are stable.

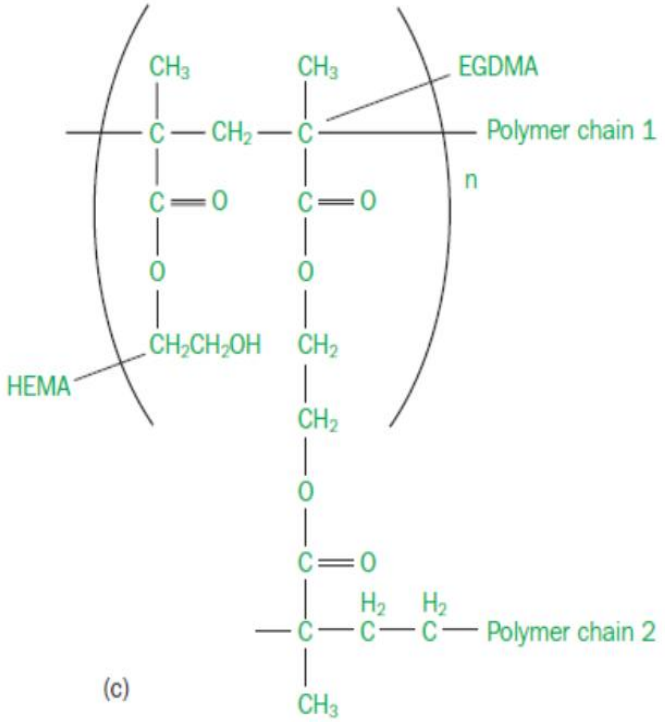
Gelation of lyophilic sols type 1



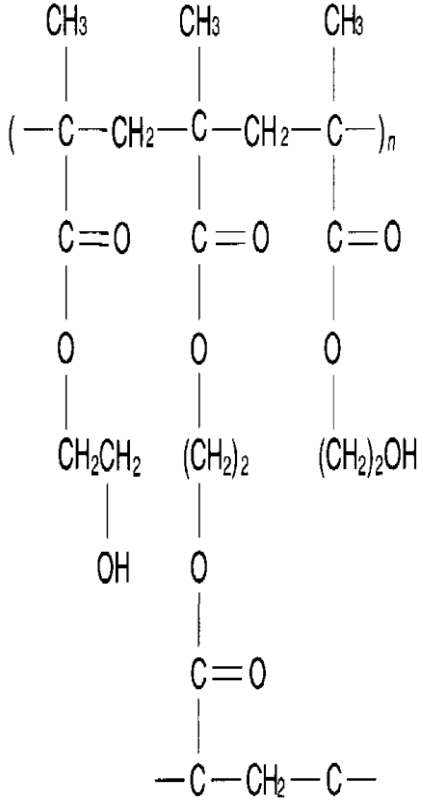
A) Hydroxyethylmethacrylate HEMA



B) Ethyleneglycol dimethacrylate EGDMA



C)Poly(hydroxyethlmethacrylate)HEMA cross-linked with ethyleneglycol dimethacrylate EGDMA



Poly (HEMA):poly (2-hydroxyethyl methacrylate) cross-linked with ethylene glycol dimethacrylate (EGDMA)

Type 1 gels (hydrogels)physicochemical properties

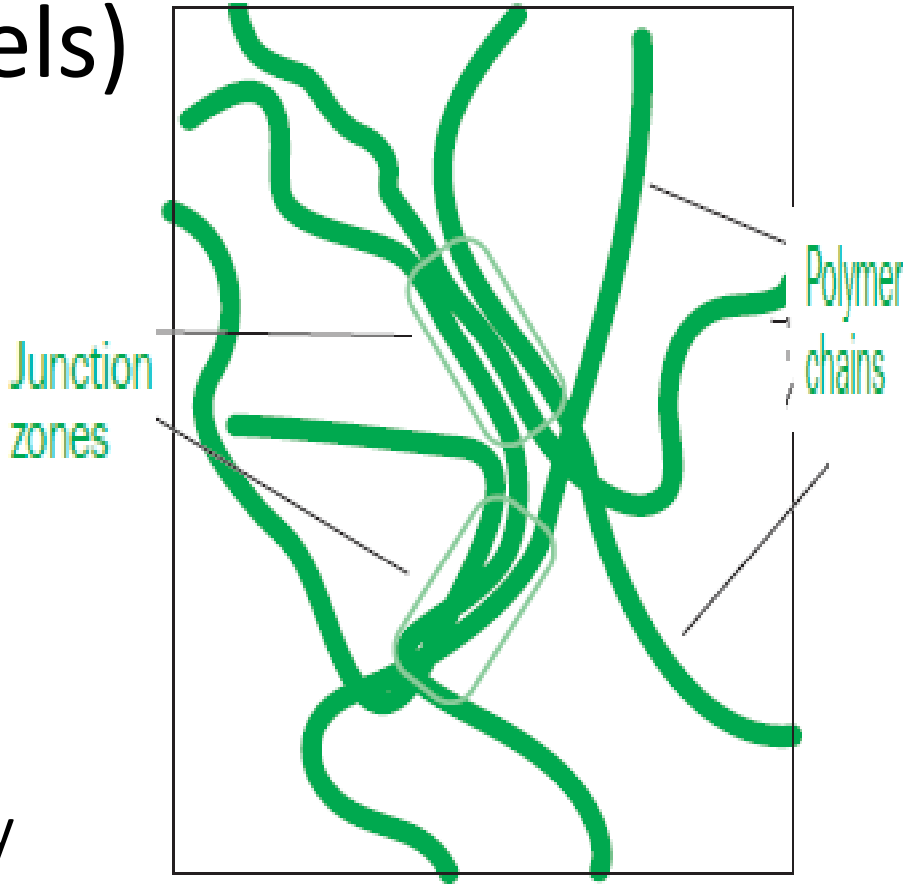
1. The ability to **absorb** a considerable mass of aqueous fluid (often 100 times the original mass) whilst still retaining a three-dimensional structure. Xerogels (hydrogels from which the aqueous phase has been removed by drying) are brittle. In this case the absorbed solvent acts as a plasticizer.
2. Hydrogels exhibit robust **mechanical** properties, being resistant to fracture following exposure to stresses frequently up to 1 kPa. Type 1 gels do not exhibit flow when exposed to an applied stress due to the inability of the stress to overcome(destroy) the covalent bonds.
3. Moreover, hydrogels exhibit excellent **flexibility**. Under these conditions, the elastic properties of type 1 gels enable the applied energy to be stored and utilized (after the stress is removed) to return the polymer chains to their equilibrium position.

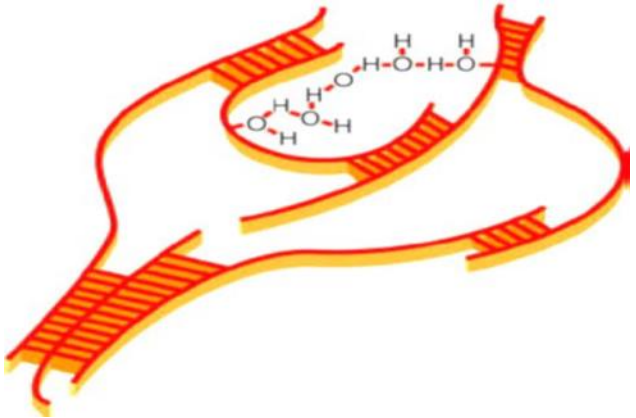
Type 1 gel uses

- Due to this ability to absorb a large mass of fluid (whilst retaining their mechanical properties), hydrogels are clinically used
- As wound dressings,
- as lubricious coatings on urethral catheters
- and as soft contact lenses.
- In addition, hydrogels may be used for the controlled delivery of therapeutic agents at the site of implantation

Type 2 gel (physical gels)

- A diagrammatic representation of the interactions that occur in type 2 (physical) gels is shown
- The areas where adjacent polymer chains interact are referred to as junction zones and, in practice, a substantial fraction of the polymer is involved in polymer–polymer interactions at these zones.
- ***Type 2*** gels are held together by much weaker intermolecular bonds such as hydrogen bonds.
- These gels are heat reversible, a transition from the sol to gel occurring on either heating or cooling.





Type 2 lyophilic gels

- In type 2 gels the interactions between the polymer chains are **reversible** and are facilitated by weaker bonds, e.g. hydrogen bonding, ionic association or van der Waals interactions.
- The application of stresses to type 2 gels will end in the temporary destruction of these bonds, thereby enabling the formulation to **flow**.
- As a result, type 2 gels are rheologically referred to as *pseudoplastic (shear-thinning)* systems. Following the removal of the stress, the inter-macromolecular bonds are reformed and the viscosity of the formulation returns to its equilibrium value.

Types of reversible hydrophilic gels

- The overwhelming majority of pharmaceutical gels are type 2 gels and typically the following polymers are employed in the formulation of these systems:
- (1) cellulose derivatives; methylcellulose MC, hydroxyethylcellulose HEC, hydroxypropylcellulose HPC, Sodium carboxymethylcellulose.
- (2) polysaccharides derived from natural sources; carrageenan; alginic acid/sodium alginate; and pectin
- (3) synthetic polymers like polyacrylic acid, poloxamers , polyvinyl alcohol,

Factors affecting gelation of type 2 gels

- Gelation in type 2 gels occurs whenever a sufficient number of polymer–polymer interactions (junction zones) occur.
- However, both the mechanism of gelation and the number (frequency) of interactions are affected by physicochemical and environmental factors,

Concentration of hydrophilic polymer

- At low concentrations, solutions of hydrophilic polymers exhibit Newtonian flow due to the limited number of polymer–polymer interactions. As the concentration of polymer increases, the number of polymer–polymer interactions increases and eventually, at a defined polymer concentration, the flow properties of these systems become non-Newtonian (**termed the gel point**).
- Further increases in the concentration of polymer lead to an increase in the number of junction zones and hence the resistance to deformation from an applied stress (the viscosity) increases.
- Therefore, the physicochemical and rheological properties of a pharmaceutical gel may be readily manipulated by altering the concentration of hydrophilic polymer.

Molecular weight of the polymer

- As the molecular weight of the hydrophilic polymer increases (at a defined concentration of polymer), there are a greater number of available sites on the polymer chains that may engage in polymer–polymer interactions.
- As a result the viscosity of the formulation increases.

Nature of the solvent

- In solvents that are described as ‘good solvents’, the chains of a polymer will exist in the expanded state.
- Conversely, in the presence of a poor solvent, the polymer chains will exist in a non-expanded (coiled) state.
- Lyophilic become lyophobic by addition of solvents like acetone or alcohol particles become desolvated
- The viscosity of a polymer solution is dependent on the expansion of the polymer chains.
- Therefore, the concentration of polymer that results in gel formation and the physicochemical (rheological) properties of the gel are dependent on the solvent system into which the hydrophilic polymer is dissolved. In poor solvents gelation will not occur.

pH of the solvent

- The pH of the solvent directly affects the ionization of acidic or basic polymers which, in turn, affects the conformation (expansion) of the polymer chains.
- In the non-ionized state acidic and basic polymers exist in a coiled (non-expanded) state and gelation does not occur.
- The rheological properties of ionic polymers are optimal with a range of pH values at which maximum expansion of the polymer chains occurs.
- The rheological properties of non-ionic polymers are unaffected by the pH of the solvent, usually over a large pH range (circa 4–10).

Ionic strength of the solvent phase

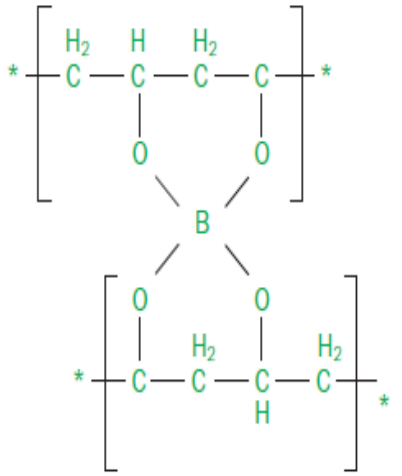
- **Ionic Strength** The rheological properties of both non-ionic and (in particular) ionic polymers are affected by the ionic strength of the solvent.
- At high concentrations of electrolytes (and hence large ionic strength), non-ionic polymers may be ‘salted out’ of solution due to desolvation of the polymer chains.
- This will therefore reduce the capacity of the polymer to interact with the solvent and hence the rheological properties of the gel will be compromised. If the concentration of electrolyte is sufficiently large, salting out of the ionic polymer will result.

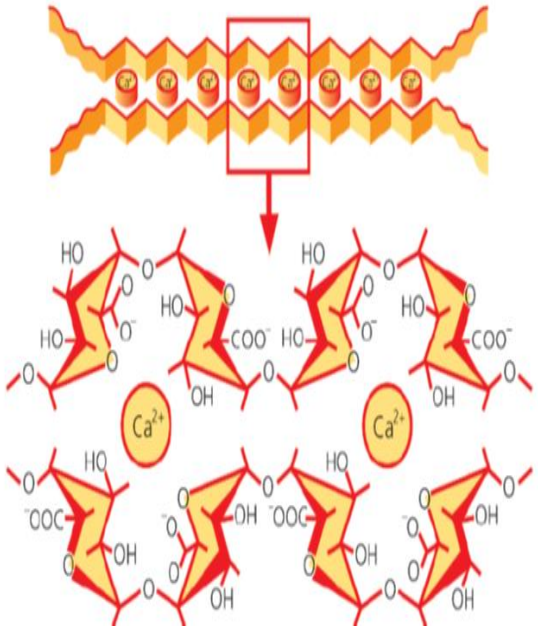
Temperature (Phase separation)

- Certain hydrophilic polymers may undergo a thermally induced transition that results in an increase in the rheological properties.
- Two examples of this are solutions of methylcellulose and hydroxypropylcellulose HPC which have been reported to undergo gelation at elevated temperatures (circa 50–60C). Whilst this transition has limited biological relevance, one polymer system, poly(oxyethylene)-poly(oxypropylene) block co-polymers (the Pluronic) undergoes a thermal transition within a biologically useful temperature range (37C). At temperatures below this (sol–gel) transition temperature (*T*sol/gel), solutions of this polymer exhibit Newtonian flow and low viscosity (the sol state).
- Conversely, above *T*sol/gel the polymer sol is converted into a gel with pronounced elasticity and viscosity.
- In solution at temperatures below *T*sol/gel and above the critical micelle concentration, the polymer exists in the micellar state.
- Elevation of the temperature (to above the *T*sol/gel) results in the further production of micelles and (close) intermicellar aggregation. This results in a gel of pronounced rheological structure. Lowering the temperature of the system to below the *T*sol/gel will result in deaggregation of the micelles and the reemergence of the sol (low-viscosity) state.
- The ability to modulate the rheological structure of these gels in the manner described has led to an interest in their use as drug delivery systems within the oral cavity and rectum. (In situ gel)

Ionic gelation

- Certain hydrophilic polymers may undergo gelation in the presence of inorganic metal ions. Examples of these include:
- ■ Cross-LinkingThe gelation of poly-hydroxy polymers, e.g. poly(vinyl alcohol) may occur in the presence of suitable anions, e.g. borate, permanganate. Poly(vinyl alcohol) is known to form structured gels in the presence of borate anions.
- ■ Salting out Addition of High concentration of a strongly hydrated electrolyte, colloidal material loses its water of solvation to these ions and coagulate
- Gelation of alginic acid occurs in the presence of positively charged di/trivalent ions, e.g. Mg^{2+}, Ca^{2+}, Al^{3+}. Also pectin in the presence of Ca^{2+} ions



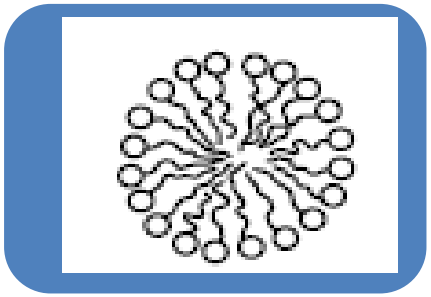


Coacervation

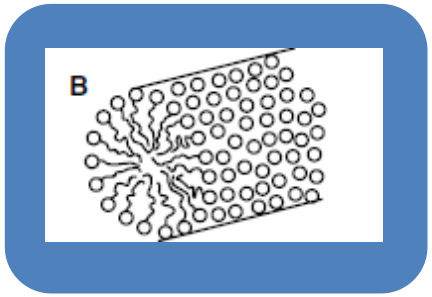
When negatively and positively charged hydrophilic colloids are mixed, the particles may separate from the dispersion to form a layer rich in the colloidal aggregates.

- The colloid-rich layer is known as a **coacervate**, and the phenomenon in which macromolecular solutions separate into two liquid layers is referred to as coacervation.
- As an example, consider the mixing of gelatin and acacia. Gelatin at a pH below 4.7 (its isoelectric point) is positively charged; acacia carries a negative charge that is relatively unaffected by pH in the acid range.
- When solutions of these colloids are mixed in a certain proportion, coacervation results. The viscosity of the upper layer, now poor in colloid, is markedly decreased below that of the coacervate, and in pharmacy this is considered to represent a physical incompatibility. Cationic SAA (+) and Anionic dyes(-)
- Coacervation need not involve the interaction of charged particles; the coacervation of gelatin may also be brought about by the addition of alcohol, sodium sulfate, or a macromolecular substance such as starch
- This method is the basic method for **MICROENCAPSULATION**

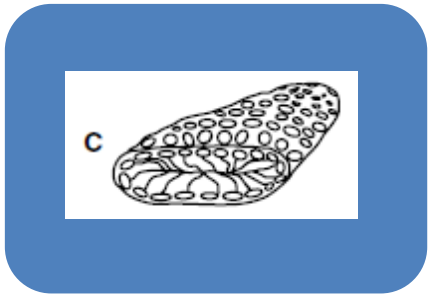
Association Colloids Shape



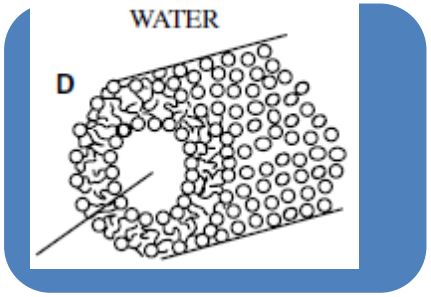
Spherical micelle



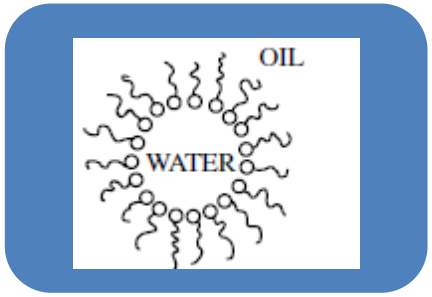
Cylindrical micelle



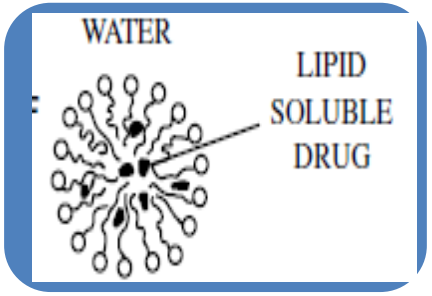
Flattened disc micelle



Micro tubular micelle



Inverted micelle



Swollen micelle in presence of Lipid soluble drug

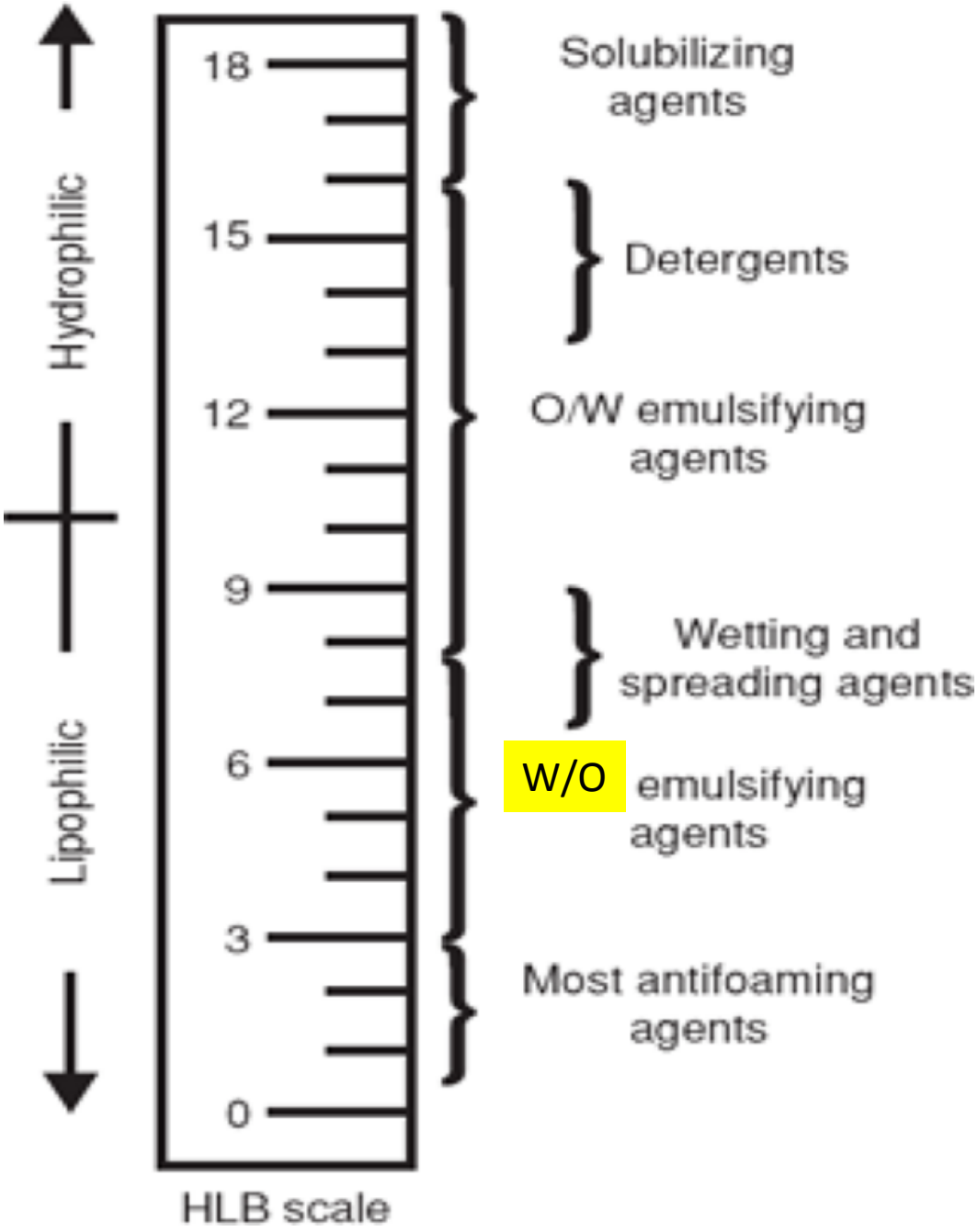
Amphiphilic colloids (Surfactant)

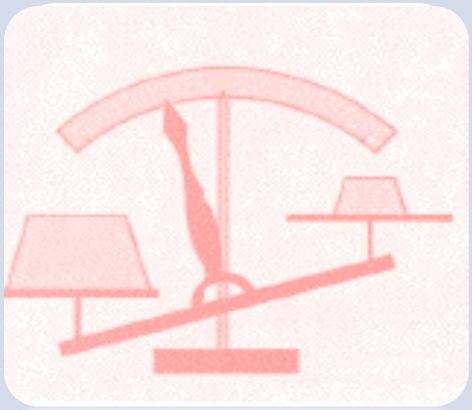
- **Surfactants** are compounds that lower the surface tension of a liquid, the interfacial tension between two liquids, or that between a liquid and a solid.
- Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants .Also as solubilizing agent.

Systems of Hydrophilic–Lipophilic Classification HLB

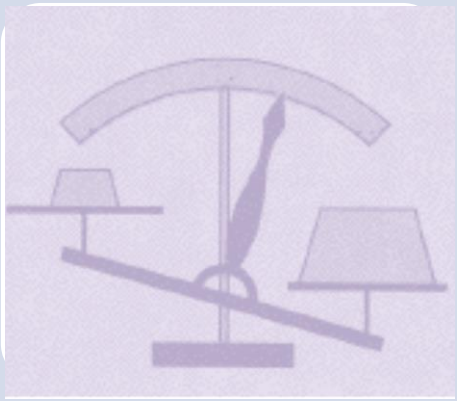
Griffin devised an arbitrary scale of values to serve as a measure of the hydrophilic–lipophilic balance of surface-active agents.

By means of this number system, it is possible to establish an HLB range of optimum efficiency for each class of surfactant, The higher the HLB of an agent, the more hydrophilic it is.





When oil-loving groups in surfactant are predominant, HLB is low... For producing water-in-oil emulsions (less than 9)



When water-loving groups predominate, the surfactant has high HLB and is used for oil-in-water emulsions (more than 10)

When oil-loving and water-loving groups are fairly well balanced, HLB is intermediate (around 10).

Hydrophilic–Lipophilic Balance (HLB) Values of Some Amphiphilic Agents

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

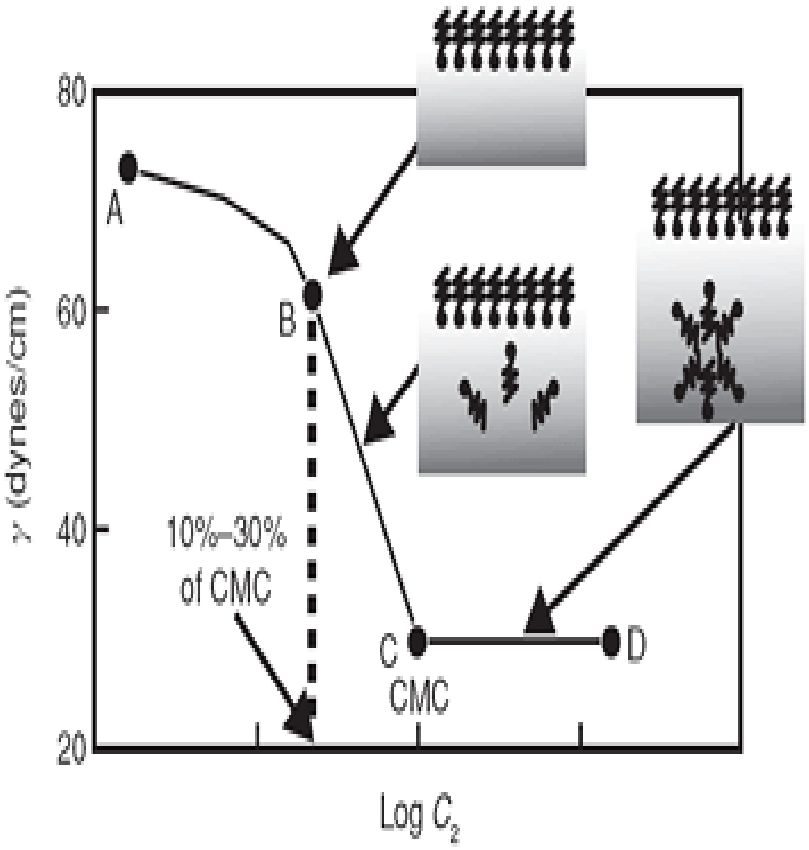
Effect of the concentration of soluble monolayer adsorbed (surfactant) on surface tension

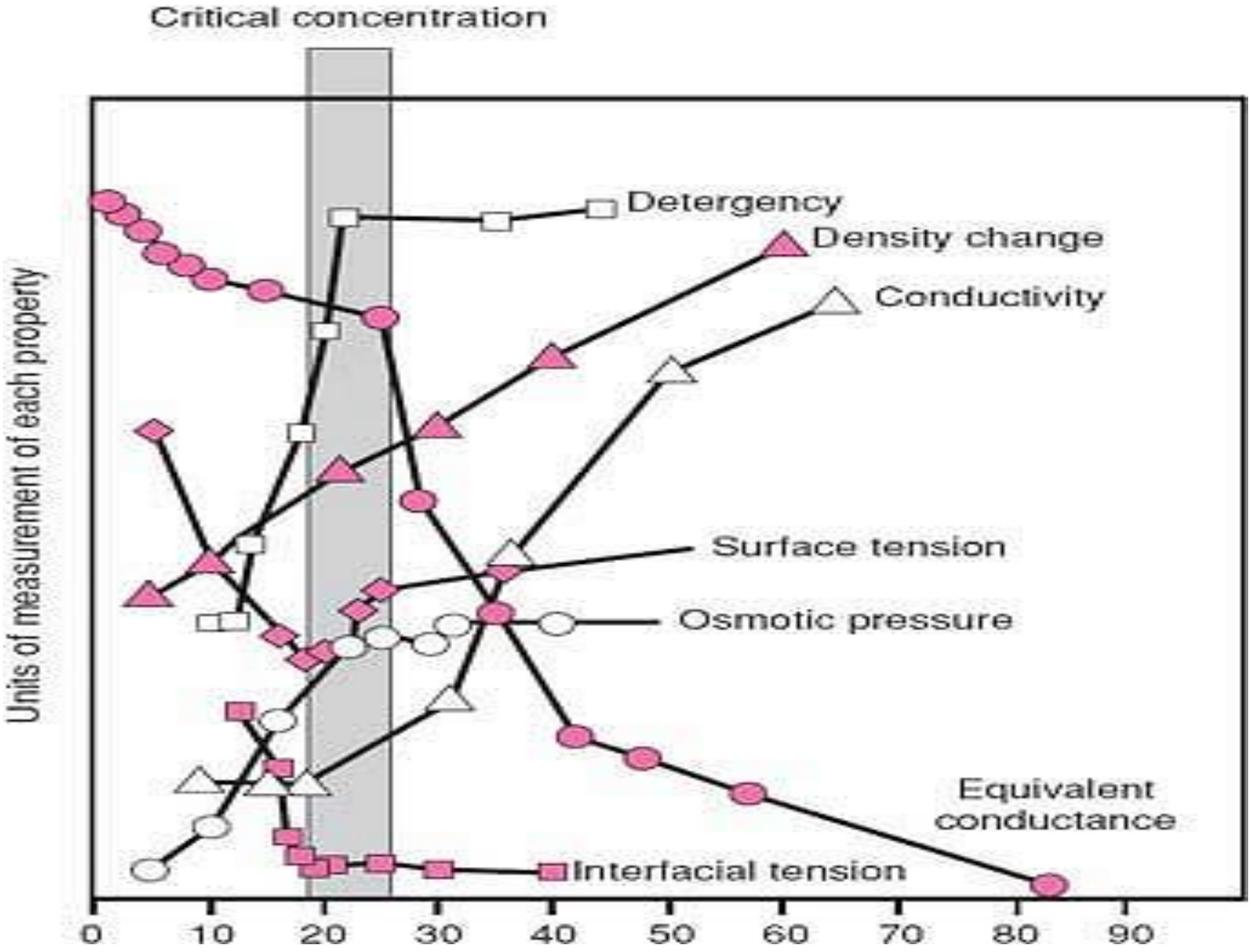
The initial curved segment A–B is followed by a linear segment, B–C, along which there is a sharp decrease in surface tension as log c_2 increases.

The point C corresponds to the critical micelle concentration (CMC), the concentration at which micelles form in the solution.

Beyond the CMC, the line becomes horizontal because further additions of surfactant are no longer being accompanied by a decrease in surface tension.

Along the linear segment B–C, the surface excess Γ is constant

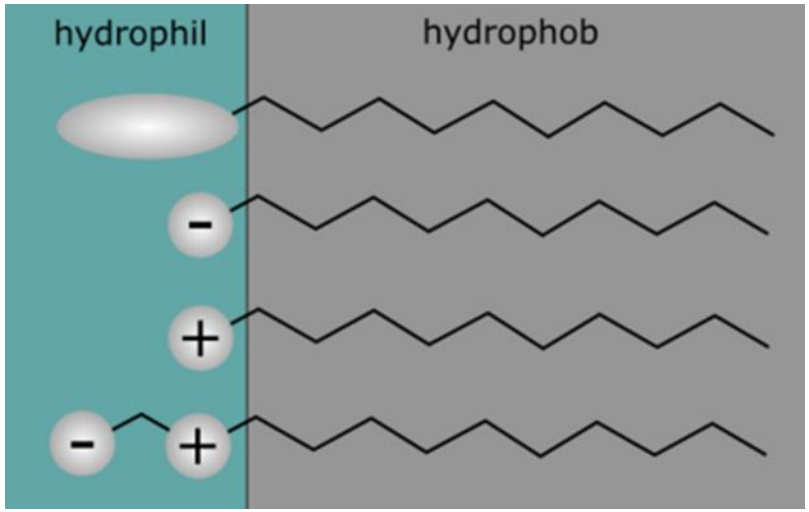



Critical concentration
Detergency
Density change
Conductivity
Surface tension
Osmotic pressure
Equivalent conductance
Interfacial tension
Units of measurement of each property
0
10
20
30
40
50
60
70
80
90

Surfactant structure

hydrophilic

Hydrophobic



Classification of surfactants

According to the composition of their tail

- The tail of surfactants can be:
- A hydrocarbon chain: aromatic hydrocarbons (arenes), alkanes (alkyl), alkenes, cycloalkanes, alkyne-based
- An alkyl ether chain:
  - Ethoxylated surfactants: polyethylene oxides are inserted to increase the hydrophilic character of a surfactant
  - Propoxylated surfactants: polypropylene oxides are inserted to increase the lipophilic character of a surfactant
- A fluorocarbon chain: fluorosurfactants
- A siloxane chain: siloxane surfactants.

According to the composition of their head

Non ionic

- A non-ionic surfactant has no charge groups in its head.

Cationic

- The head of an ionic surfactant carries
- Positive charge

Anionic

- The head of an ionic surfactant carries
- Negative charge

Zwitterionic

If a surfactant contains a head with two oppositely charged groups

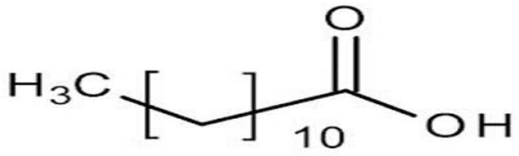
Anionic surfactant

- based on permanent anions (sulfate, sulfonate, phosphate)
- or pH-dependent anions (carboxylate):
  - Sulfates
    - Alkyl sulfates: ammonium lauryl sulfate, sodium lauryl sulfate (SDS, sodium dodecyl sulfate, another name for the compound)
    - Alkyl ether sulfates: sodium laureth sulfate, also known as sodium lauryl ether sulfate (SLES), sodium myreth sulfate
  - Sulfonates:
    - Docusates: dioctyl sodium sulfosuccinate
    - Sulfonate fluorosurfactants: perfluorooctanesulfonate (PFOS), perfluorobutanesulfonate
    - Alkyl benzene sulfonates
  - Phosphates:
    - Alkyl aryl ether phosphate
    - Alkyl ether phosphate
  - Carboxylates:
    - **Alkyl carboxylates: Fatty acid salts (soaps):** sodium stearate;
    - Sodium lauroyl sarcosinate
    - Carboxylate fluorosurfactants: perfluorononanoate, perfluorooctanoate (PFOA or PFO)

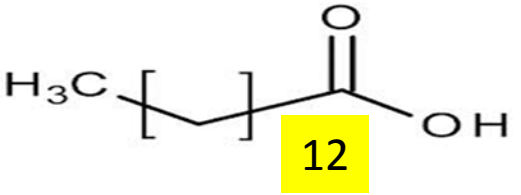
Metal salts of long chain fatty acid

Cations : sodium ,potassium ,triethanolamine

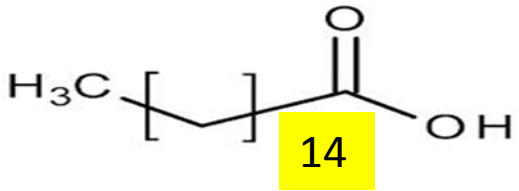
Lauric acid (n=10)
Bay leaf oil



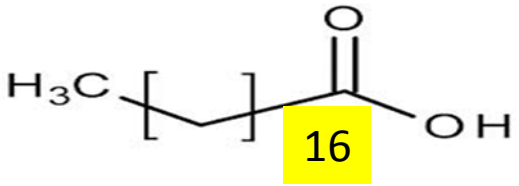
Myristic acid (n=12)
Nutmeg oil



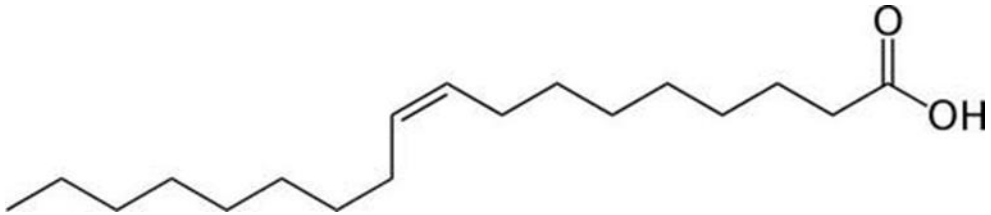
Palmitic acid (n=14)
Palm kernel oil



Stearic acid (n=16)
Animal fat , coca butter



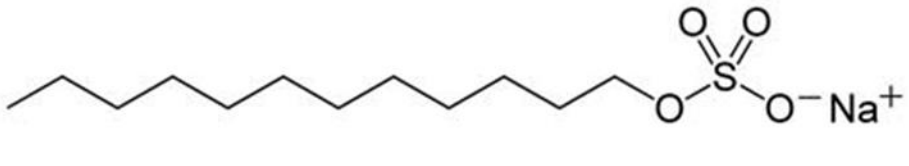
Oleic acid (olive oil)
(n=16,monounsaturated)



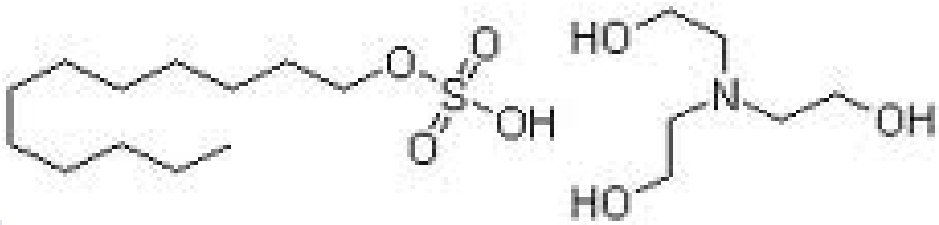
Anionic surfactants examples

Green soap N.F.
Potassium salt of oleic acid with glycerin

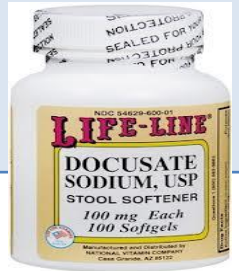
Sodium Lauryl Sulfate U.S.P.
Toothpaste ,ointments

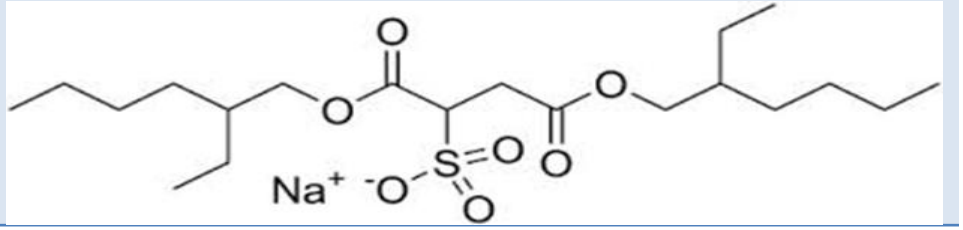


Triethanolamine dodecyl sulfate
Shampoo cosmetics



Dioctyl Sodium Sulfosuccinate U.S.P.
Fecal softener





Acne treatment

- A variety of cleansers are useful in removing sebum

- **Soaps** are some of the major cleansers used in acne treatment. These include true soaps that are composed of long chain fatty acid alkali salts, with a pH of 9–10.

They may contain triclosan,

or **Sulfur Soap** Sulfur is a known bacteriostatic and antifungal agent, It has a characteristic foul odor and unusual yellow color.

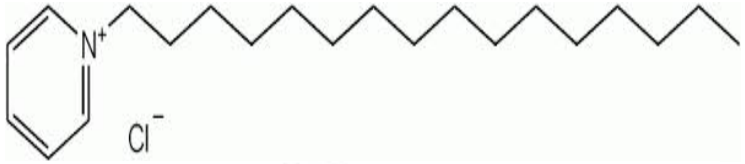
- Synthetic detergents, known as **syndets**. (milder detergent) These cleansers contain less than 10% soap with a more neutral pH adjusted to 5.5–7.0, called cleansing or dermatological bars

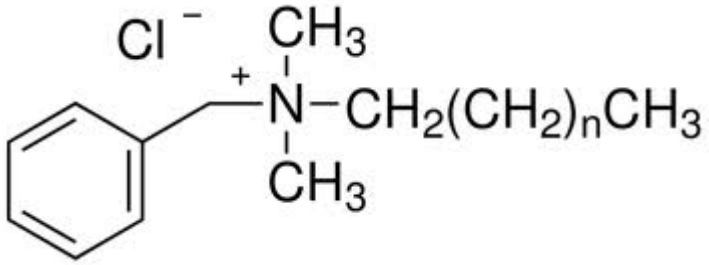
Dandruff Shampoo

- **Ketoconazole Shampoo** - a very effective anti-fungal.

Cationic surfactant

- Have bacteriostatic activity because they combine with the carboxyl in the cell walls of microorganisms by cation exchange , causing lysis.
- pH-dependent primary, secondary, or tertiary amines: Primary amines become positively charged at pH < 10, secondary amines become charged at pH < 4: Octenidine dihydrochloride;
- Permanently charged quaternary ammonium cation: Alkyltrimethylammonium salts:
- cetyl trimethylammonium bromide (CTAB)
- cetyl trimethylammonium chloride (CTAC)
- Cetylpyridinium chloride (CPC) Cetrimide





- Benzalkonium chloride (BAC)
- Benzethonium chloride (BZT)
- 5-Bromo-5-nitro-1,3-dioxane
- Dimethyldioctadecylammonium chloride
- Dioctadecyldimethylammonium bromide DODAB

Zwitterionic (amphoteric)

- based on primary, secondary, or tertiary amines or quaternary ammonium cation with: Sulfonates:
  - CHAPS (3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate);
  - Sultaines: cocamidopropyl hydroxysultaine;
- Carboxylates:
  - Amino acids
  - Imino acids
  - Betaines: cocamidopropyl betaine;
- Phosphates: lecithin

Nonionic

1. *Fatty alcohols*:

- Cetyl alcohol, $CH_3(CH_2)_{15}OH$ or **palmityl alcohol**
- Stearyl alcohol, $CH_3(CH_2)_{16}CH_2OH$ *octadecyl alcohol*
- Cetostearyl alcohol (consisting predominantly of cetyl and stearyl alcohols)
- Oleyl alcohol $CH_3(CH_2)_7$-CH=CH-$(CH_2)_8OH$.

2. *Polyoxyethylene glycol alkyl ethers (Brij)*:

$$CH_3–(CH_2)_{10–16}–(O\text{-}C_2H_4)_{1–25}–OH$$

- Octaethylene glycol monododecyl ether
- Pentaethylene glycol monododecyl ether

3. *Polyoxypropylene glycol alkyl ethers*:

$$CH_3–(CH_2)_{10–16}–(O\text{-}C_3H_6)_{1–25}–O$$

Non ionic

4. Glucoside alkyl ethers:

$CH_3–(CH_2)_{10–16}–(O\text{-Glucoside})_{1–3}–OH$:

- Decyl glucoside,
- Lauryl glucoside
- Octyl glucoside

5. Polyoxyethylene glycol octylphenol ethers:

$C_8H_{17}–(C_6H_4)–(O\text{-}C_2H_4)_{1–25}–OH$: Triton X-100

6. Polyoxyethylene glycol alkylphenol ethers:

$C_9H_{19}–(C_6H_4)–(O\text{-}C_2H_4)_{1–25}–OH$: Nonoxynol-9

7. Glycerol alkyl esters:

Glyceryl laurate

Non ionic

8. Polyoxyethylene glycol sorbitan alkyl esters: Polysorbate

9 Sorbitan alkyl esters:

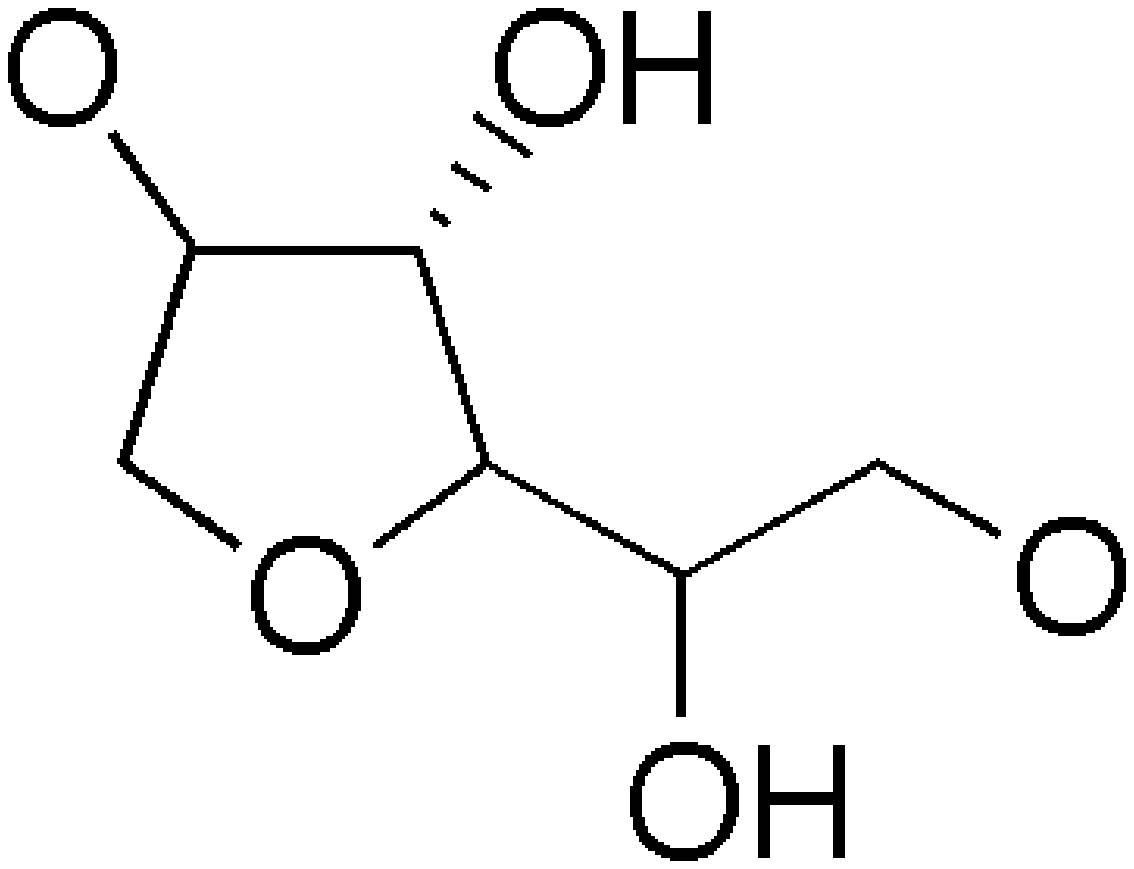
- Spans

10 Cocamide MEA, cocamide DEA

11 Dodecyldimethylamine oxide

12 Block copolymers of polyethylene glycol and polypropylene glycol: Poloxamers

13 Polyethoxylated tallow amine (POEA).



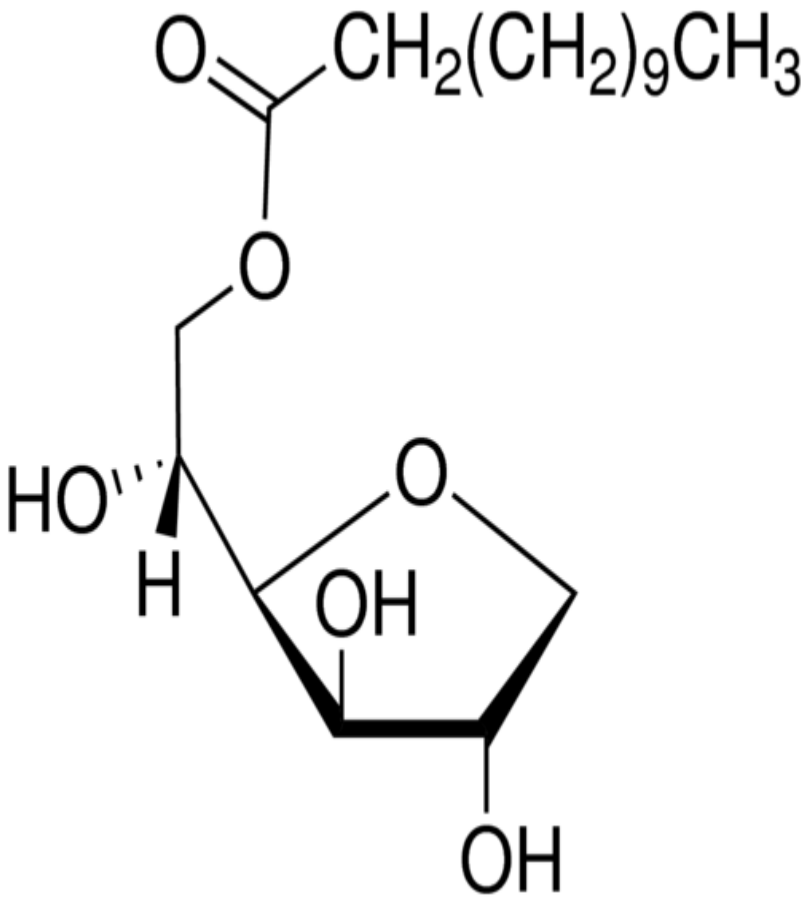
Sorbitan

Sorbitan is a mixture of chemical compounds derived from the dehydration of sorbitol

Sorbitan esters (Spans)

- **Sorbitan esters** (also known as Spans) are lipophilic non ionic surfactants that are used as emulsifying agents in the preparation of emulsions, creams, and ointments for pharmaceutical and cosmetic use.
- Sorbitan Monolaurate is indicated by 20
- Sorbitan monopalmitate is indicated by 40,
- Sorbitan monostearate by 60 and
- Sorbitan monooleate by 80.

Sorbitan monolaurate (Span 20)

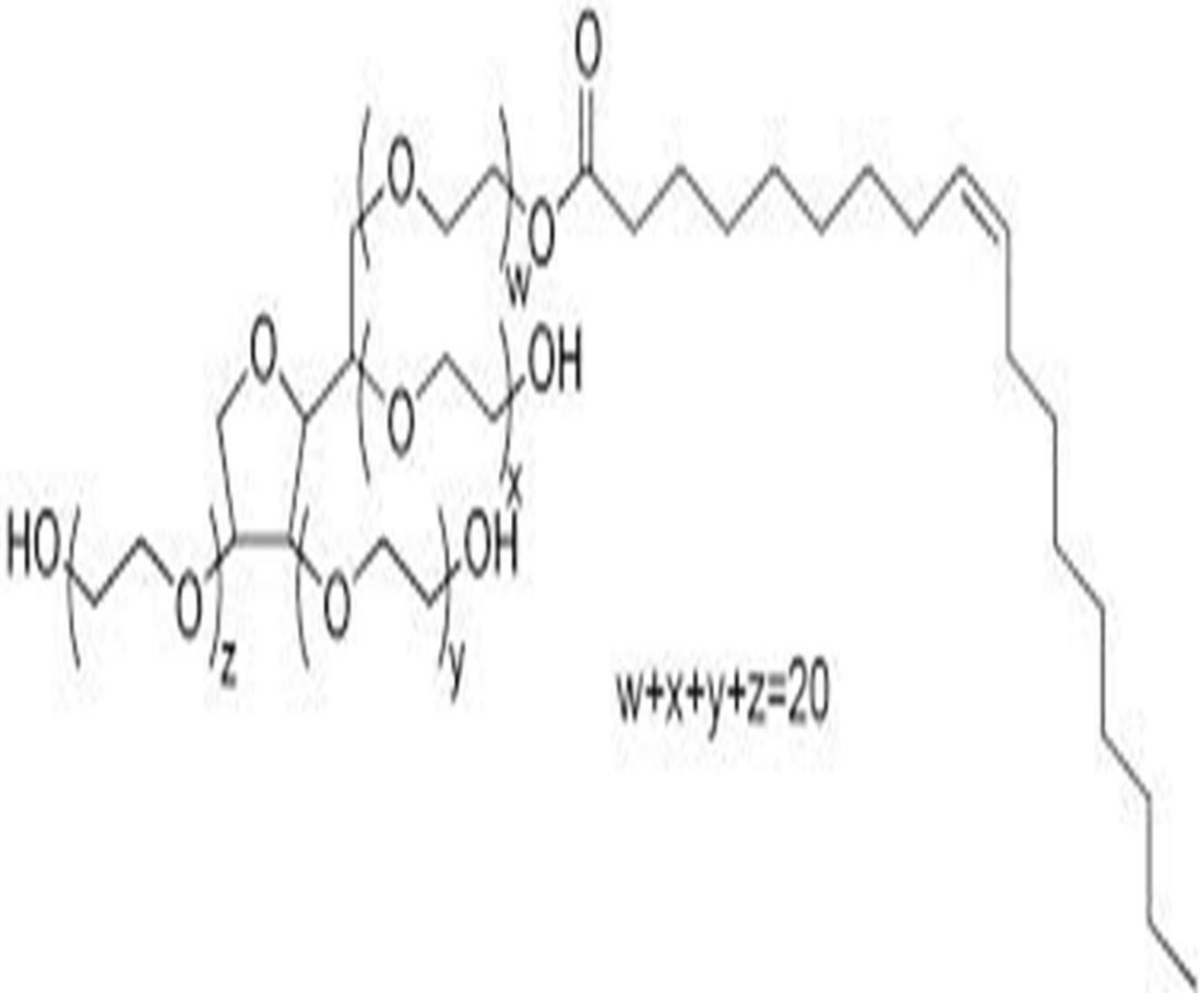


- **Sorbitan monolaurate**
- A lipophilic detergent liquid and monoester of lauric acid and hexitol anhydrides derived from sorbitol

Polysorbates (Tweens)

- Polysorbates are oily liquids derived from PEG-ylated sorbitan
- (a derivative of sorbitol) esterified with fatty acids.
- The hydrophilic groups in this compound are polyethers also known as polyoxyethylene groups which are polymers of ethylene oxide.
- Polysorbate 20 (Polyoxyethylene (20) sorbitan monolaurate)
- Polysorbate 40 (Polyoxyethylene (20) sorbitan monopalmitate)
- Polysorbate 60 (Polyoxyethylene (20) sorbitan monostearate)
- Polysorbate 80 (Polyoxyethylene (20) sorbitan monooleate)
- The number 20 following the *polyoxyethylene* part refers to the total number of oxyethylene -(CH_2CH_2O)- groups found in the molecule. The number following the *polysorbate* part is related to the type of fatty acid associated with the polyoxyethylene sorbitan part of the molecule

Polysorbate 80
Tween 80



- Polysorbate 80 is a viscous, water-soluble yellow liquid. It is a nonionic
- surfactant and emulsifier derived from polyethoxylated sorbitan and oleic acid

Colloidal dispersions
Introduction- properties

Aulton's Pharmaceutics The Design and Manufacture of Medicines 3rd Ed Ch. 6

Ansel's Pharmaceutical dosage form 9th Ed. Ch. 14

American Pharmacy

What is a Colloidal Dispersion?

- Colloid from the Greek word
- Kolla= glue
- Introduced by Thomas Graham
- Discovered that certain substances (e.g., glue, gelatin, or starch) could be separated from certain other substances (e.g., sugar or salt) by dialysis.
- He gave the name *colloid* to substances that do not diffuse through a semipermeable membrane (e.g., parchment or cellophane) and the name ***crystalloid*** to those which do diffuse and which are therefore in true solution

Colloidal Dispersion

- Colloidal system or colloidal dispersion is a heterogeneous system which is made up of Dispersed phase and Dispersion medium(Continuous phase).
  In colloidal dispersion one substance is dispersed as very fine particles in another substance called dispersion medium.

Classification of colloidal dispersions

1. Physical state of the dispersion phase and the continuous medium
2. Interaction between the dispersion phase and the continuous medium
3. Particle size

Medium / Phases	Dispersed phase: Gas	Dispersed phase: Liquid	Dispersed phase: Solid
Continuous medium: Gas	**NONE** (All gases are mutually miscible)	**Liquid aerosol** Examples: fog, mist, hair sprays 	**Solid aerosol** Examples: smoke, dust particulates 
Liquid	**Foam** Example: whipped cream, Shaving cream, carbonated soft drinks 	**Emulsion** Examples: milk, mayonnaise, hand cream ,lotions 	**Sol** Examples blood, antacid suspensions 
Solid	**Solid foam** Examples: aerogel, styrofoam, pumice	**Gel** Examples: agar, gelatin, jelly, 	**Solid sol** Example: colored glass, pastes like toothpastes 

Particle size

- Size of colloidal particles are in range of 1–1000nm while size of true solution suspension is >1000nm and that of true solution is < 1nm. **Thus size of colloids lies between that of true solution and suspension.** The colloidal particles can’t be seen with naked eye. This is why, colloidal system appears as homogeneous mixtures, but in reality are heterogeneous mixtures.

Differentiation according to particle size

Solution	Colloidal dispersion	Suspension
<1nm	1-1000nm (0.5µm)	>1000nm (0.5µm)
Electron microscope(lower limit)	Visible in electron microscope ultra microscope	Ordinary microscope
High rate of diffusion	Low rate of diffusion (Brownian motion)	No diffusion nor Brownian motion
Pass through 1. filter paper , 2. dialysis membrane a)collodion; cellulose nitrate b)cellophane ultrafiltration (with suction) or electro dialysis (electric current)	Pass filter paper	Retained by filter paper Settle down or cream
High osmotic pressure	Low osmotic pressure	No osmotic pressure
Do not scatter light	Scatter light (Tyndall effect)	
NaCl, glucose	Surfactant micelle	Pharmaceutical Suspensions

Particle size and size distribution

Particle size can affect absorption behavior

Solid aerosols particle size must be in the range of 1-5µm and no particle above 10µm

Measured by osmotic pressure (no. of particles)

Measured by sedimentation or light scattering the weight rather than no. is important

- Spherical particles The size is determined by the diameter

-Asymmetrical particles are measured by Stoke's diameter d_{st} which describes an equivalent sphere undergoing sedimentation at the same rate as sample particle

Interaction between dispersion phase and dispersion medium

lyophilic

- Liquid loving

lyophobic

- Liquid hating

Association colloids

Surfactant

Dispersion medium is water

Hydrophilic

- Disperse spontaneously
- High affinity (swell)

Hydrophobic

- Un stable dispersions
- Need stabilizing agent

Lyophobic	Association(Amphiphilic)	Lyophilic
Weak interaction/ Liquid hating Lyophobic colloid is a colloidal dispersion in which there are little interaction between the dispersed phase and the continuous phase Dispersed phase in lyophobic colloids is not solvated by the dispersion media If the continuous phase is water, it is also called hydrophobic colloids	Dispersed phase consists of Aggregates (*micelles*) of small organic molecules or ions whose size *individually* is below the colloidal range Hydrophilic or lipophilic portion of the molecule is solvated, depending on whether the dispersion medium is aqueous or Non-aqueous	Strong forces of interaction /Liquid loving, Lyophilicity is the tendency of particles, surfaces, or functional groups to become extensively wetted, solvated, swollen, or dissolved by solvents Molecules of dispersed phase are solvated, i.e., they are associated with the molecules comprising the dispersion medium
Water based colloids with inorganic dispersed phase are lyophobic ex: Gold Au198 injection USP Mild silver protein NF Sulfur Some of lyophobic colloids possess lyophilic properties (eg. hydrosols of silica and alumina).	Tween Span	Dispersed phase consists generally of large Organic *molecules* lying within colloidal size range Poly saccharides Proteins

Lyophobic	Association(Amphiphilic)	Lyophilic
Viscosity of the dispersion medium is not greatly increased by the presence of lyophobic colloidal particles, which tend to be **Un-solvated** and **symmetrical** Sols of low viscosity, even at high concentration, because of low solvation and low attraction between the particles compared to high repulsion Lyophobic colloidal particles are not readily solvated because the continuous phase prefer to interact with one another than be involved in solvating the dispersed particles	Viscosity of the system increases as the concentration of the amphiphile increases, as micelles increase in number and **become asymmetric**	Viscosity of the dispersion medium ordinarily is increased greatly by the presence of the dispersed phase; at sufficiently high concentrations, the sol may become a gel; viscosity and gel formation are related to solvation effects and to the shape of the molecules, which are usually **highly asymmetric** Usually high at sufficiently high concentration of disperse phase a gel may be formed. Lyophilicity is the tendency of particles, surfaces, or functional groups to become extensively **wetted, solvated, swollen**, or dissolved by solvents

Lyophobic	Association(Amphiphilic)	Lyophilic
Material does not disperse spontaneously, and special procedures therefore must be adopted to produce colloidal dispersion	Colloidal aggregates are formed spontaneously when the concentration of amphiphile exceeds the critical micelle concentration	Molecules disperse spontaneously to form colloidal solution
Lyophobic sols with high net inter-particle attraction leads to coagulation forming distinct granules and the system cannot easily be restored to its colloidal state. At high concentration lyophobic systems turn into pastes		lyophilic sols form **gels** on coagulation

Lyophobic preparation

Cannot be prepared directly by mixing colloid with liquid.
Special methods are employed to prepare them need stabilizers like SAA
Preparation may be either

1. Mechanical reduction of larger particles to colloidal size by either
   a) Colloidal mill, hammer, ball jet, roller, which is required because of high interfacial energy of the dispersed particles.
   b) Ultrasonic vibration and electric arcs inside liquids which cause evaporation of the electrode material followed by condensation

2. Condensation nucleation and particle growth, rapid production of supersaturated solution of colloidal material which is deposited in the medium as colloidal particles and not as ppt. Condensation of smaller particles to form a colloid usually involves

a) Physical (add hot water to acetone solution of ppt. sulfur)
b) Chemical (strong acid and sod thio-sulphate produce) typically displacement, hydrolysis, or oxidation and reduction

Lyophilic

Prepared directly by mixing colloid with liquid.
easy to prepare

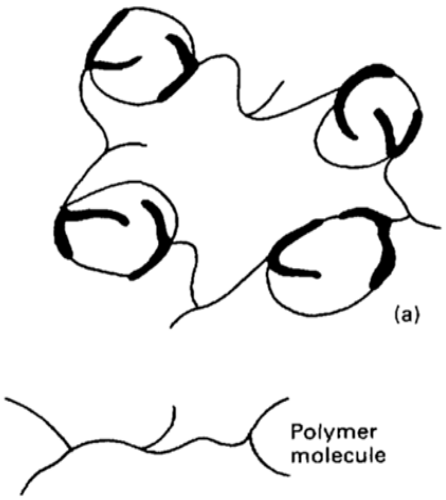
1) Disperse spontaneously in the appropriate solvent
2) The resultant dispersion are intrinsically stable
3) Molecularly dissolved lyophilic materials are in colloidal range

	Lyophobic	lyophilic
Formation of dispersion	Dispersions usually of metals, inorganic crystals etc., with a high interfacial surface-free energy due to large increase in surface area on formation. A positive ΔG of formation, dispersion will never form spontaneously and is thermodynamically unstable. Particles of sol remain dispersed due to electrical repulsion	Generally proteins, macromolecules etc., which disperse spontaneously in a solvent. Interfacial free energy is low. There is a large increase in entropy when rigidly held chains of a polymer in the dry state unfold in solution. The free energy of formation is negative, a stable thermodynamic system
Stability	Controlled by charge on particles. The particles in such sols are stabilized only by the presence of electric charges on their surfaces. The like charges produce a repulsion that prevents coagulation of the particles, it can be Stabilized by additives such as surfactant (lowering the interfacial energy of the system) or by protective colloids (Steric stabilization - protective colloid action)	Controlled by charge and solvation of particles Surrounding each particle with a protective solvent sheath that prevents mutual adherence when the particles collide as a result of Brownian movement

	Lyophobic	Lyophilic
Effect of electrolytes addition	Very sensitive to added electrolyte, leading to aggregation in an irreversible manner. Depends on the Schulze-Hardy rule (a) The type and valency of counter ion of electrolyte, e.g. with a negatively charged sol, $La^{3+} > Ba^{2+} > Na^{+}$ (10^{-4}, 10^{-3}, 10^{-1} mol /ml) (b) Concentration of electrolyte. At a particular concentration sol passes from disperse to aggregated state.	Dispersions are stable generally in the presence of electrolytes. If sufficient salt is added, agglomeration and sedimentation of the particles may result. This phenomenon, referred to as "salting out," . Effect is due to desolvation of the lyophilic molecules and depends on the tendency of the electrolyte ions to become hydrated. According to the Hofmeister (lyotropic) series, which ranks cations and anions in order of coagulation of hydrophilic sols For anionic colloids $Ba^{2+} < Ca^{2+} < Mg^{2+} < NH_4^{+} < K^{+} < Na^{+} < Li^{+}$ and for cationic colloid $I^{-} < Br^{-} < ClO_3^{-} < NO_3^{-} < Cl^{-} <$ acetate $< CO_4^{2-} <$ tartrate < citrate The precipitating power is directly related to the hydration of the ion and hence to its ability to separate water molecules from the colloidal particles Proteins are more sensitive to electrolytes at their isoelectric points. Lyophilic colloids when salted out may appear as amorphous droplets known as a coacervate

Effect of addition of macromolecular material to lyophobic colloidal sols

Diagram of flocs



Polymer bridging

- 1- When added in **small amounts**, many polyelectrolyte and polymer molecules(lyophilic colloids) can adsorb simultaneously on to two particles and are long enough to **bridge** across the energy barrier between the particles. This can even occur with neutral polymer when the lyophobic particles have a high zeta potential
- 2-(Steric stabilization - protective colloid action) if larger amounts of polymer are added, sufficient to cover the surface of the particles, then a lyophobic sol may be stabilized to coagulation even in the absence of significant zeta potential.

Properties of colloids

- ***1-Kinetic properties***
- **Thermal motion** manifests itself in the form of Brownian motion, diffusion and osmosis. **Brownian motion :**Colloidal particles are subject to random collisions with the molecules of the dispersion medium, with the result that each particle pursues an irregular and complicated zigzag path. Responsible for the **diffusion** of colloidal particles.
- **Gravity** (or a centrifugal field) leads to sedimentation, by **ultra-centrifugal** force about $10^6 g.$
- Viscous flow is the result of an **externally applied force**.
- However, the usefulness of **osmotic pressure** measurement is limited to a molecular weight range of about 10^4-10^6; below10^4 the membrane may be permeable to the molecules under consideration and above 10^6 the osmotic pressure will be too small to permit accurate measurement.
- Measurement of these properties enables molecular weight or particle size to be determined.

2-Optical properties

- When a strong beam of light is passed through a colloidal sol, a visible cone, resulting from the scattering of light by the colloidal particles, is formed. This is the Faraday–Tyndall effect.
- The **ultra-microscope**, developed by Zsigmondy, allows one to examine the light points responsible for the Tyndall cone.
- An intense light beam is passed through the sol against a dark background at right angles to the plane of observation, and, although the particles cannot be seen directly, the bright spots corresponding to particles can be observed and counted
- Low solvation of the lyophobic colloidal dispersion leads to large difference in refractive index between the liquid medium and the dispersed phase which produces marked light scattering and **strong Tyndall beams**

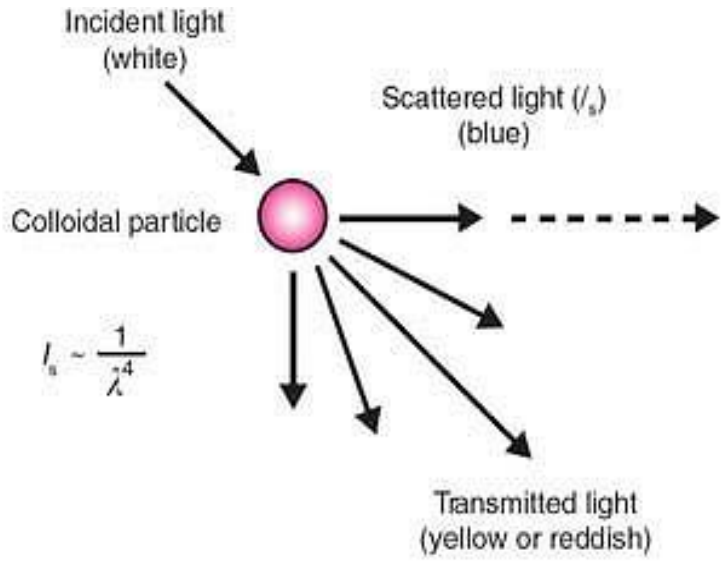
2- Optical properties

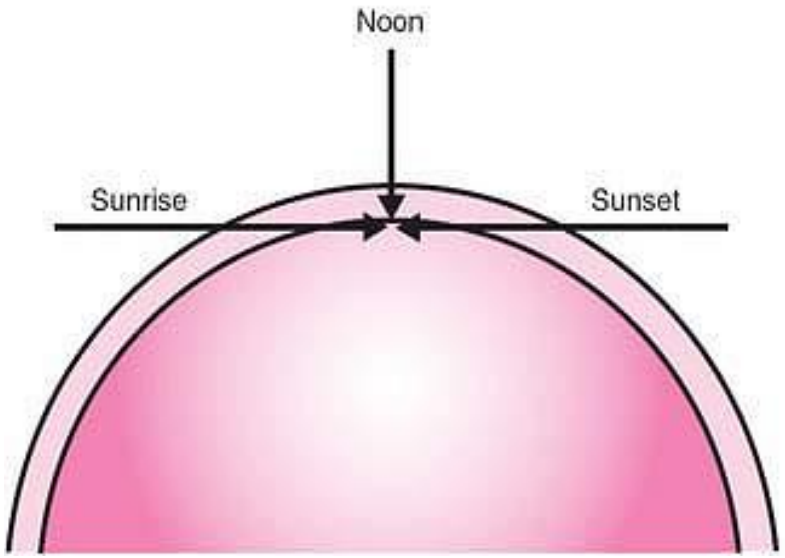
(Tyndall effect) why is the sky blue ?

- When a beam of light passes through a colloid, colloidal particles scatter the light. The intensity of scattered, I_s, light is inversely proportional to the fourth power of the wavelength, λ (Rayleigh law):

$$I_s \sim \frac{1}{\lambda^4}$$

- Thus, shorter-wavelength light (blue) (λ=450nm) is scattered more intensely than longer-wavelength light (yellow and red), (λ=650 nm) and so the scattered light is mostly blue, whereas transmitted light has a yellow or reddish color
- The scattering of short-wavelength light gives the sky its blue color. In contrast, transmitted light has a yellow color. At sunrise and sunset, sunlight has to travel a longer distance through the atmosphere than at noon.

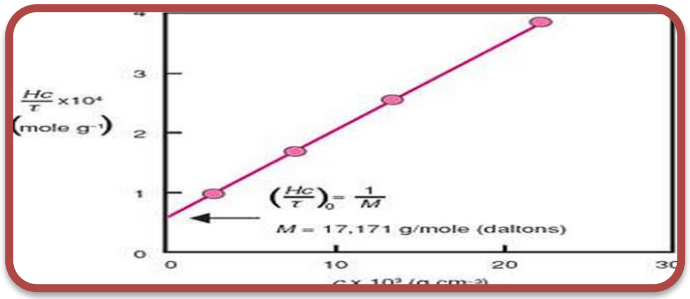




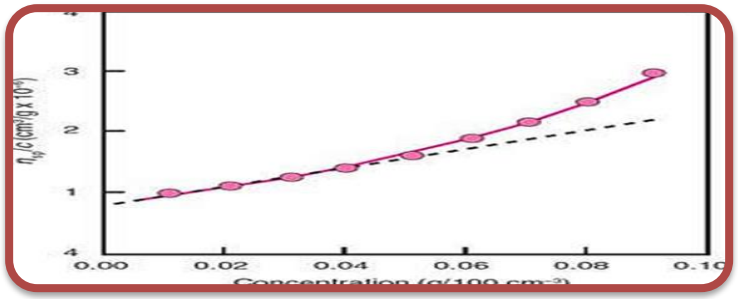
Microscopy

- Colloidal particles are too small to be seen in the optical microscope
- The electron microscope, capable of yielding pictures of the actual particles, even those approaching molecular dimensions, is now widely used to observe the size, shape, and structure of colloidal particles.
- The success of the electron microscope is due to its high resolving power, which can be defined in terms of d, the smallest distance by which two objects are separated and yet remain distinguishable.
- The smaller the wavelength of the radiation used, the smaller is d and the greater is the resolving power.
- The optical microscope uses visible light as its radiation source and is able to resolve only two particles separated by about 20 nm
- The radiation source of the electron microscope is a beam of high-energy electrons having wavelengths in the region of 0.01 nm

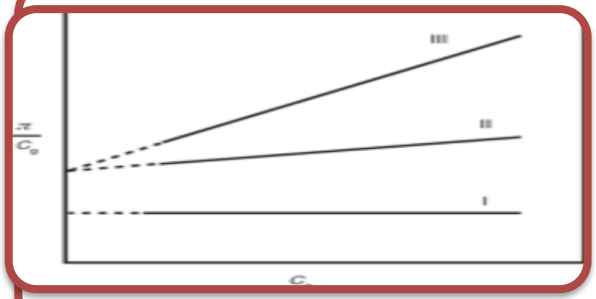
Colloid properties used for measuring the molecular weight determination



Tyndall effect



Viscosity



Osmotic pressure

3- Electrical property of colloids

- Most surfaces acquire a surface electric charge when brought in contact with an aqueous medium due to

1. Ion dissolution e.g. AgI dispersion , $Mg(OH)_2$
2. Ionization of the surface grouping -COO^- and NH_3^+ ions net charge depend on the pH like proteins
   insulin may be precipitated from aqueous alcohol at pH 5.2.
   Erythrocytes and bacteria usually acquire their charge by ionization of surface chemical groups such as sialic acid.
3. Ion adsorption at the interfaces SAA

- The particles of a colloid selectively <u>adsorb</u> ions and acquire an electric charge.
- All of the particles of a given colloid take on the same charge (either positive or negative) and thus are repelled by one another.
- **If the charge on the particles is neutralized, they may precipitate out of the dispersion.**

Electrophoresis

- If an electric potential is applied to a colloid through a liquid, the charged colloidal particles move toward the oppositely charged electrode; this migration is called electrophoresis.
- **Electrophoresis** movement of a charged particle plus attached ions relative to a stationary liquid under the influence of an applied electric field
- Used in measurement of zeta potential

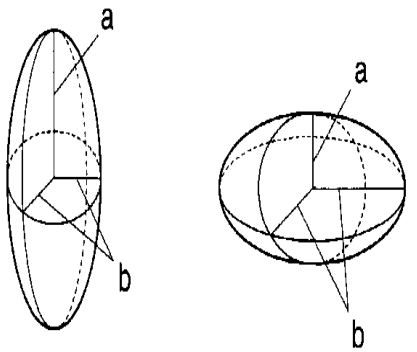
Terminology

- Imbibtion : taking up of certain amount of liquid like water without considerable increase in volume
- Swelling taking up of liquid by a gel with an increase in volume
- Syneresis great interaction between dispersed phase particles ,upon standing dispersed medium is squeezed out in droplets and gel shrink

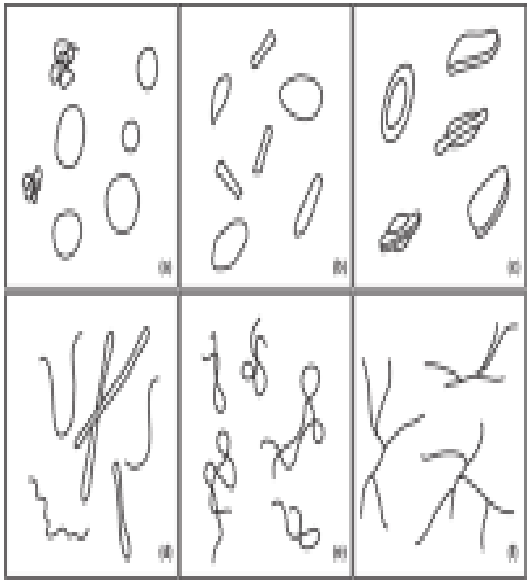
- ***Xerogels*** are gels in which the vehicle has been removed, leaving a polymer network, e.g. polymer films. Xerogel :formed when liquid removed from the gel and only framework remains
- Example .Sheet gelatin, acacia tears, Tragacanth flakes

Shape of colloidal particles(hydrophobic)

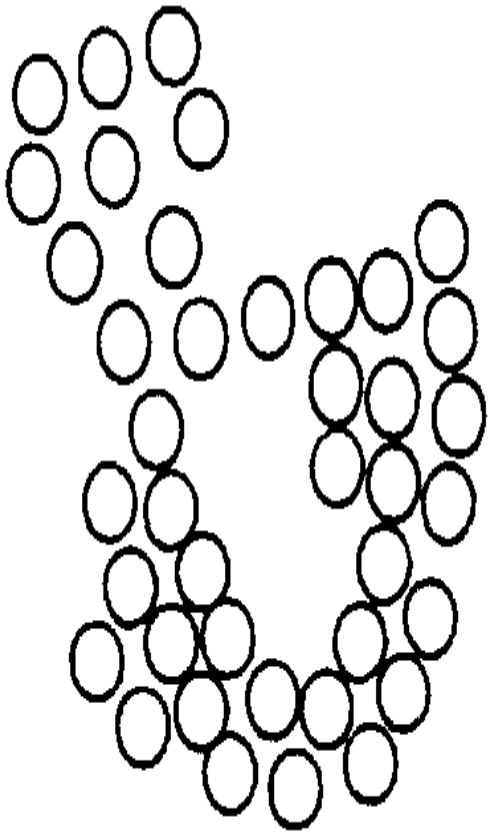
- Many colloidal systems, including emulsions, liquid aerosols and most dilute micellar solutions, contain **spherical particles**,
- Small deviations from sphericity are often treated using **ellipsoidal** models.
- Clay suspensions are examples of systems containing **plate-like** particles



Model representation of ellipsoids of revolution.



Dispersion of lyophobic sols

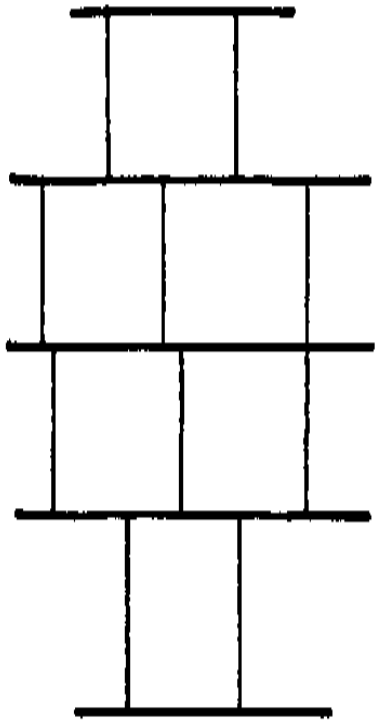


- Lyophobic sols may be flocculated , it is a 2 phase system
- where the **sol** can be looked upon as a **Continuous floccule** Examples are aluminum hydroxide
- Aluminum Hydroxide Gel, USP

and magnesium hydroxide gels

Milk of Magnesia

Dispersion of lyophobic sols



- Clays such as **bentonite**, aluminum magnesium silicate (**Veegum**) and to some extent **kaolin** form gels by flocculation in a special manner.
- They are hydrated aluminum **(aluminum/magnesium)** silicates whose crystal structure is such that they exist as flat plates; the flat part or 'face' of the particle carries a negative charge due to O~ atoms and the edge of the plate carries a positive charge due to Al3+/Mg2+ atoms.
- As a result of electrostatic attraction between the face and the edge of different particles a gel structure is built up, forming what is usually known as a **'card house floc**'
- Ex Bentonite Magma, NF
- The forces holding the particles together in this type of gel are relatively **weak - van der Waals** forces in the secondary minimum flocculation of aluminum hydroxide, **electrostatic attraction** in the case of the clays - and because of this these gels show the phenomenon of ***thixotropy***

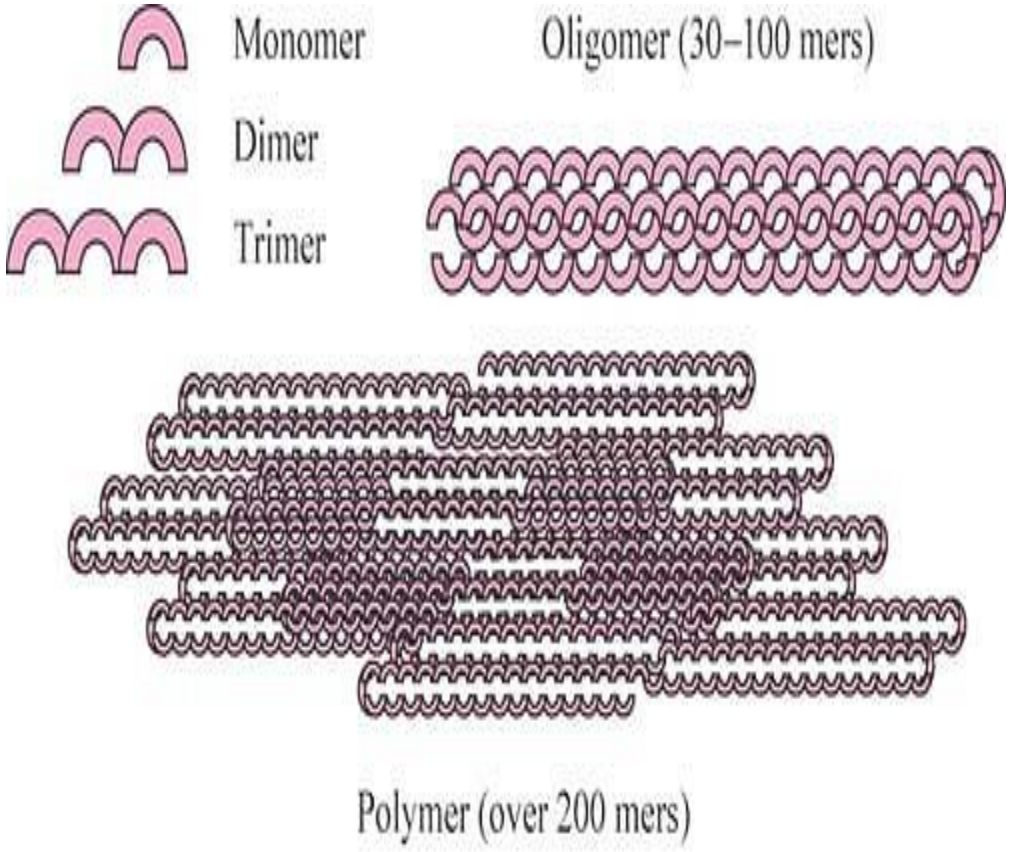
Shape of (hydrophilic) colloidal particles

- The shape adopted by colloidal particles in dispersion is important because the more extended the particle, the greater is its specific surface and the greater is the opportunity for attractive forces to develop between the particles of the dispersed phase and the dispersion medium.
- High molecular weight polymers and naturally occurring macromolecules often form random **coils** in aqueous solution.
- A colloidal particle is something like a hedgehog—in a friendly environment, it unrolls and exposes maximum surface area. Under adverse conditions, it rolls up and reduces its exposed area.
- Properties as flow, sedimentation, and osmotic pressure are affected by changes in the shape of colloidal particles. Particle shape may also influence pharmacological action.

Polymers

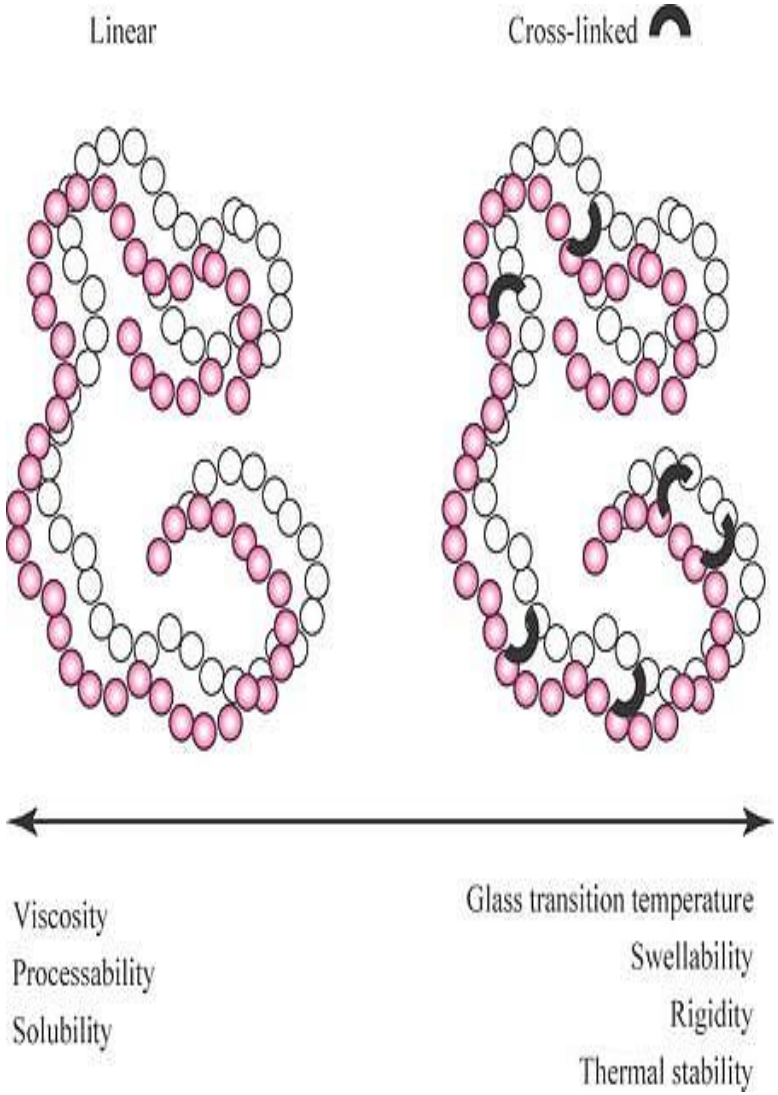
The word “polymer” means “many parts.” A polymer is a large molecule made up of many small repeating units

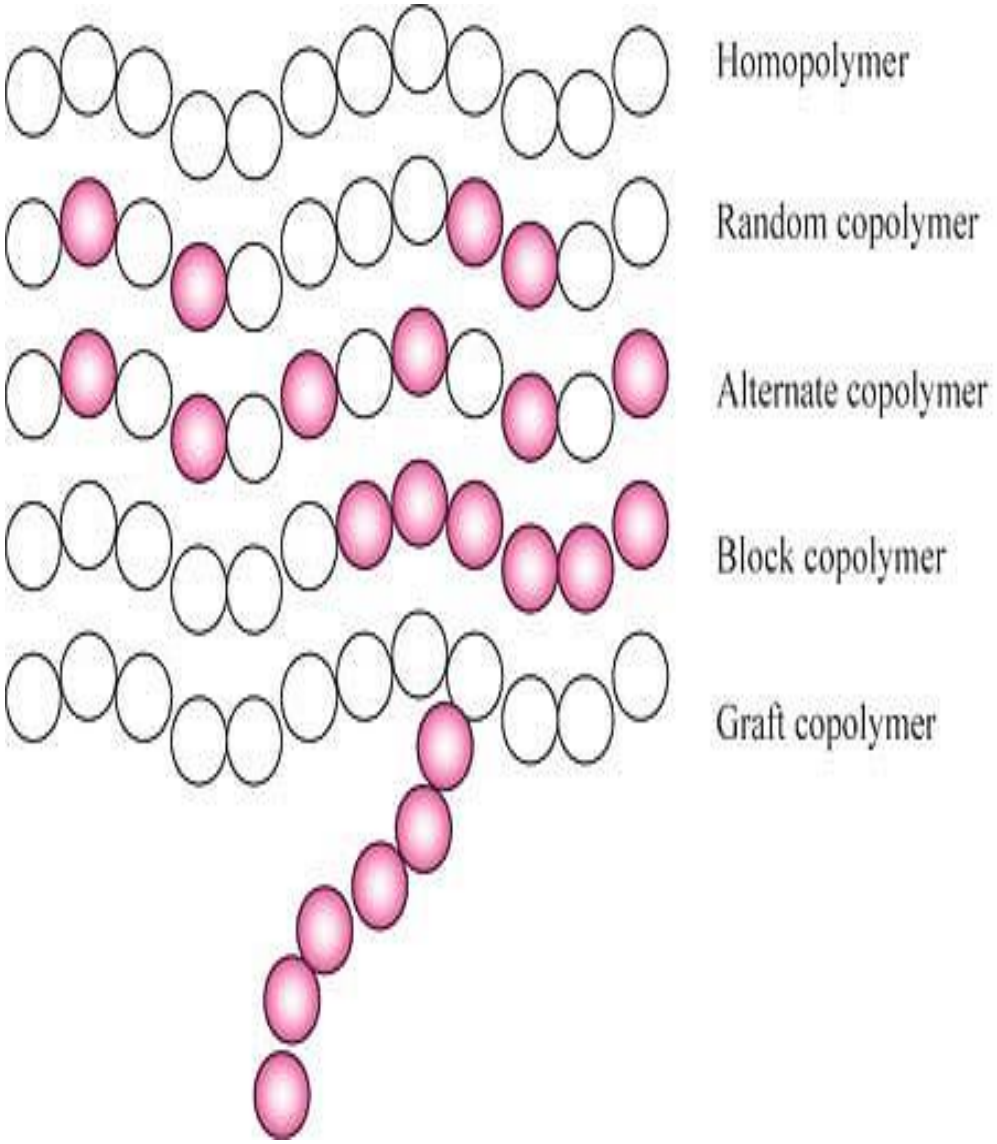
- Polymer anatomy



Degree of Polymerization (DP) = Number of monomers in a chain

Polymers made of two or more monomer units

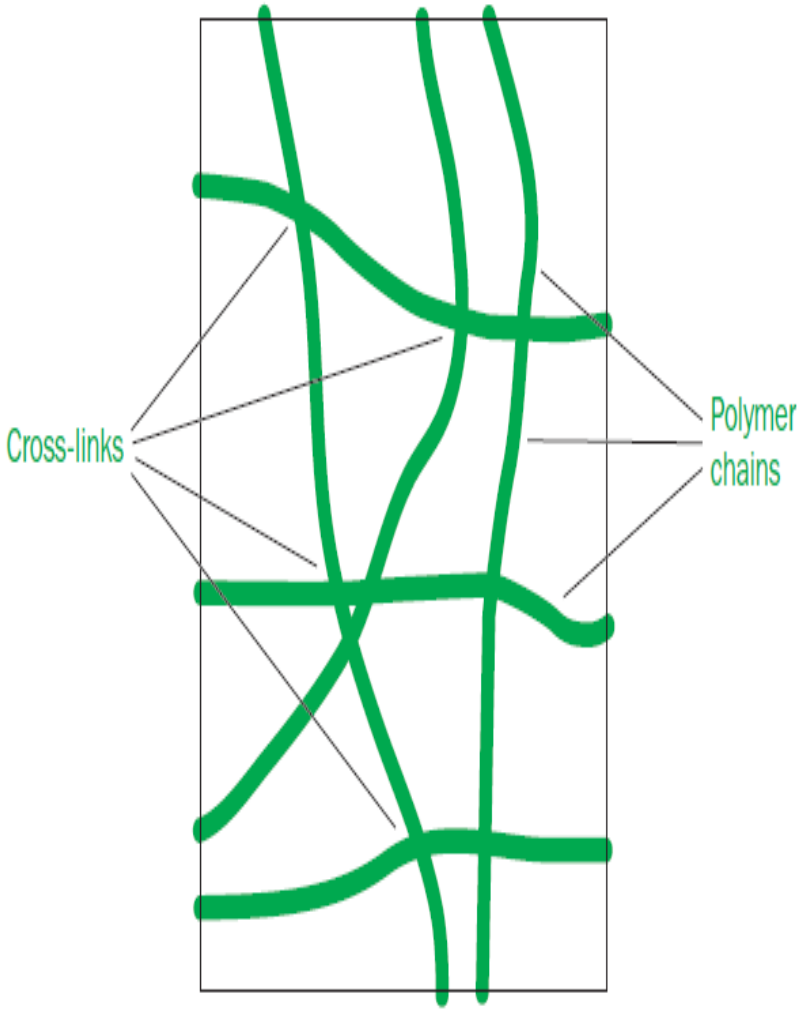




Gelation of lyophilic sols

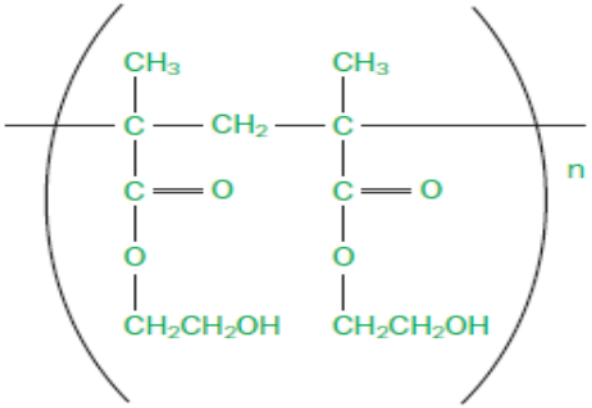
- Gels formed by lyophilic sols can be divided into groups depending on the nature of the bonds between the chains of the network.
- Pharmaceutical gels are most commonly (but not exclusively) manufactured by dispersing hydrophilic polymers within an appropriate **aqueous vehicle**. When dissolved within an aqueous phase, hydrophilic polymers behave as lyophilic colloids and their unique physical properties result from the self-association of the dissolved polymer and its interaction with the aqueous medium.
- There are two types of self-association (termed irreversible and reversible) that may be demonstrated by lyophilic colloids and this allows gels that are manufactured from lyophilic colloids to be classified as either type 1 or type 2 gels.

Type 1 gels

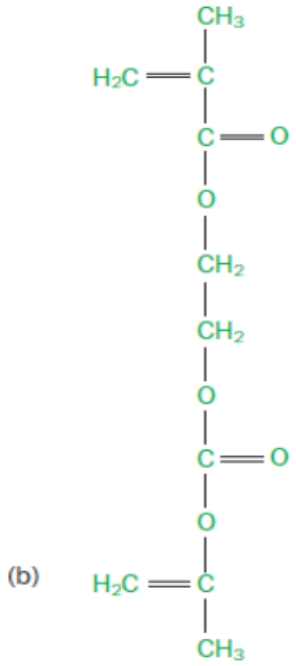


- Gels of ***type 1 (chemical gel)***
- These gels (often termed *hydrogels*) are **irreversible** systems with a three-dimensional network formed by covalent bonds between the macro-polymers in the presence of a **crosslinking agent**, forms a three-dimensional structure that swells in water but cannot dissolve because the crosslinks are stable.

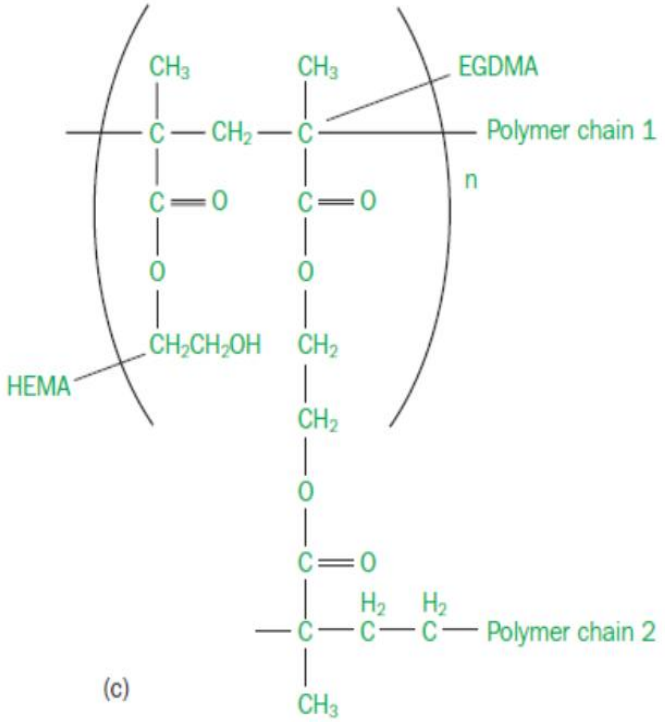
Gelation of lyophilic sols type 1



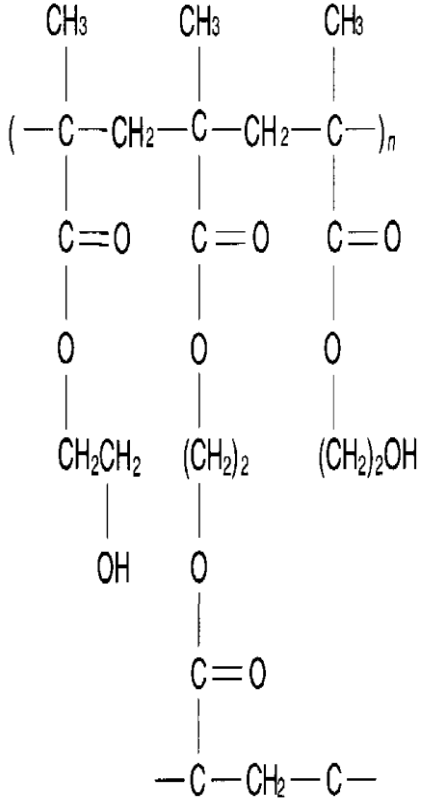
A) Hydroxyethylmethacrylate HEMA



B) Ethyleneglycol dimethacrylate EGDMA



C)Poly(hydroxyethlmethacrylate)HEMA cross-linked with ethyleneglycol dimethacrylate EGDMA



Poly (HEMA):poly (2-hydroxyethyl methacrylate) cross-linked with ethylene glycol dimethacrylate (EGDMA)

Type 1 gels (hydrogels)physicochemical properties

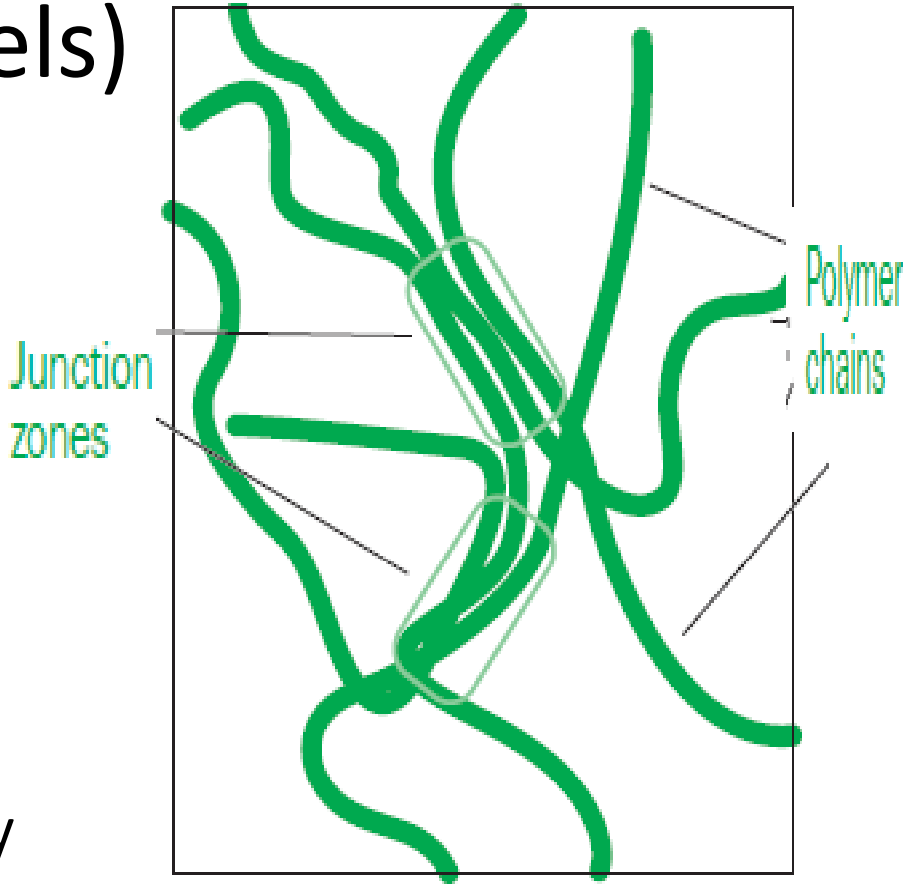
1. The ability to **absorb** a considerable mass of aqueous fluid (often 100 times the original mass) whilst still retaining a three-dimensional structure. Xerogels (hydrogels from which the aqueous phase has been removed by drying) are brittle. In this case the absorbed solvent acts as a plasticizer.
2. Hydrogels exhibit robust **mechanical** properties, being resistant to fracture following exposure to stresses frequently up to 1 kPa. Type 1 gels do not exhibit flow when exposed to an applied stress due to the inability of the stress to overcome(destroy) the covalent bonds.
3. Moreover, hydrogels exhibit excellent **flexibility**. Under these conditions, the elastic properties of type 1 gels enable the applied energy to be stored and utilized (after the stress is removed) to return the polymer chains to their equilibrium position.

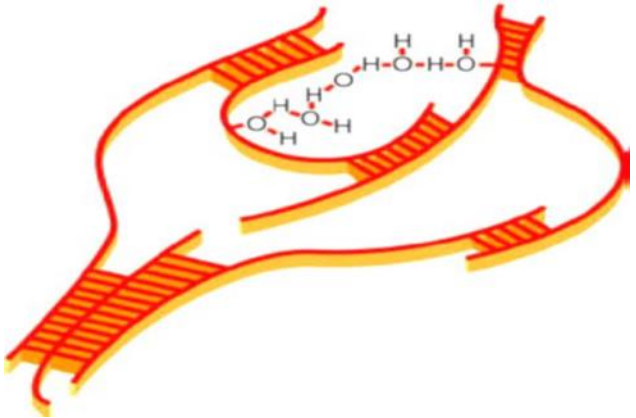
Type 1 gel uses

- Due to this ability to absorb a large mass of fluid (whilst retaining their mechanical properties), hydrogels are clinically used
- As wound dressings,
- as lubricious coatings on urethral catheters
- and as soft contact lenses.
- In addition, hydrogels may be used for the controlled delivery of therapeutic agents at the site of implantation

Type 2 gel (physical gels)

- A diagrammatic representation of the interactions that occur in type 2 (physical) gels is shown
- The areas where adjacent polymer chains interact are referred to as junction zones and, in practice, a substantial fraction of the polymer is involved in polymer–polymer interactions at these zones.
- ***Type 2*** gels are held together by much weaker intermolecular bonds such as hydrogen bonds.
- These gels are heat reversible, a transition from the sol to gel occurring on either heating or cooling.





Type 2 lyophilic gels

- In type 2 gels the interactions between the polymer chains are **reversible** and are facilitated by weaker bonds, e.g. hydrogen bonding, ionic association or van der Waals interactions.
- The application of stresses to type 2 gels will end in the temporary destruction of these bonds, thereby enabling the formulation to **flow**.
- As a result, type 2 gels are rheologically referred to as *pseudoplastic (shear-thinning)* systems. Following the removal of the stress, the inter-macromolecular bonds are reformed and the viscosity of the formulation returns to its equilibrium value.

Types of reversible hydrophilic gels

- The overwhelming majority of pharmaceutical gels are type 2 gels and typically the following polymers are employed in the formulation of these systems:
- (1) cellulose derivatives; methylcellulose MC, hydroxyethylcellulose HEC, hydroxypropylcellulose HPC, Sodium carboxymethylcellulose.
- (2) polysaccharides derived from natural sources; carrageenan; alginic acid/sodium alginate; and pectin
- (3) synthetic polymers like polyacrylic acid, poloxamers , polyvinyl alcohol,

Factors affecting gelation of type 2 gels

- Gelation in type 2 gels occurs whenever a sufficient number of polymer–polymer interactions (junction zones) occur.
- However, both the mechanism of gelation and the number (frequency) of interactions are affected by physicochemical and environmental factors,

Concentration of hydrophilic polymer

- At low concentrations, solutions of hydrophilic polymers exhibit Newtonian flow due to the limited number of polymer–polymer interactions. As the concentration of polymer increases, the number of polymer–polymer interactions increases and eventually, at a defined polymer concentration, the flow properties of these systems become non-Newtonian (**termed the gel point**).
- Further increases in the concentration of polymer lead to an increase in the number of junction zones and hence the resistance to deformation from an applied stress (the viscosity) increases.
- Therefore, the physicochemical and rheological properties of a pharmaceutical gel may be readily manipulated by altering the concentration of hydrophilic polymer.

Molecular weight of the polymer

- As the molecular weight of the hydrophilic polymer increases (at a defined concentration of polymer), there are a greater number of available sites on the polymer chains that may engage in polymer–polymer interactions.
- As a result the viscosity of the formulation increases.

Nature of the solvent

- In solvents that are described as ‘good solvents’, the chains of a polymer will exist in the expanded state.
- Conversely, in the presence of a poor solvent, the polymer chains will exist in a non-expanded (coiled) state.
- Lyophilic become lyophobic by addition of solvents like acetone or alcohol particles become desolvated
- The viscosity of a polymer solution is dependent on the expansion of the polymer chains.
- Therefore, the concentration of polymer that results in gel formation and the physicochemical (rheological) properties of the gel are dependent on the solvent system into which the hydrophilic polymer is dissolved. In poor solvents gelation will not occur.

pH of the solvent

- The pH of the solvent directly affects the ionization of acidic or basic polymers which, in turn, affects the conformation (expansion) of the polymer chains.
- In the non-ionized state acidic and basic polymers exist in a coiled (non-expanded) state and gelation does not occur.
- The rheological properties of ionic polymers are optimal with a range of pH values at which maximum expansion of the polymer chains occurs.
- The rheological properties of non-ionic polymers are unaffected by the pH of the solvent, usually over a large pH range (circa 4–10).

Ionic strength of the solvent phase

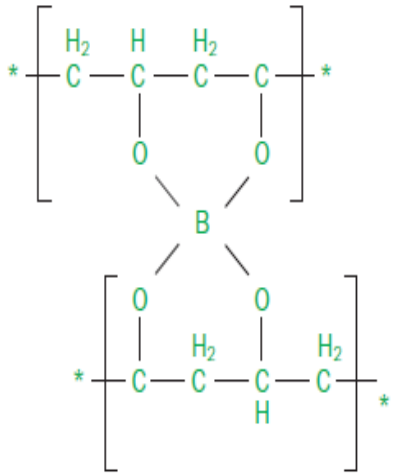
- **Ionic Strength** The rheological properties of both non-ionic and (in particular) ionic polymers are affected by the ionic strength of the solvent.
- At high concentrations of electrolytes (and hence large ionic strength), non-ionic polymers may be ‘salted out’ of solution due to desolvation of the polymer chains.
- This will therefore reduce the capacity of the polymer to interact with the solvent and hence the rheological properties of the gel will be compromised. If the concentration of electrolyte is sufficiently large, salting out of the ionic polymer will result.

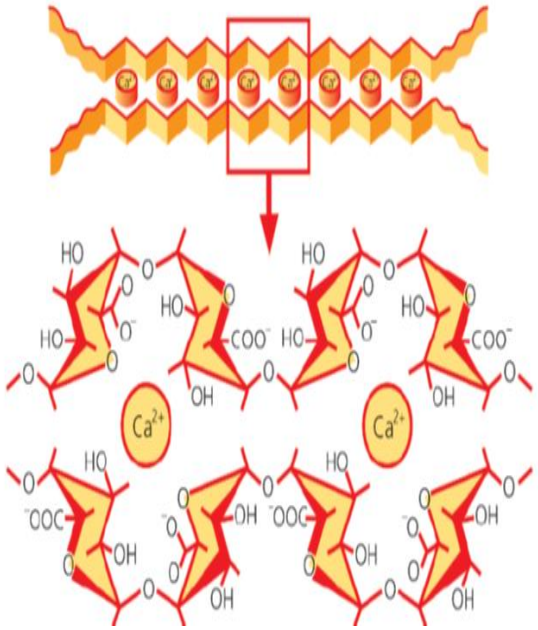
Temperature (Phase separation)

- Certain hydrophilic polymers may undergo a thermally induced transition that results in an increase in the rheological properties.
- Two examples of this are solutions of methylcellulose and hydroxypropylcellulose HPC which have been reported to undergo gelation at elevated temperatures (circa 50–60C). Whilst this transition has limited biological relevance, one polymer system, poly(oxyethylene)-poly(oxypropylene) block co-polymers (the Pluronic) undergoes a thermal transition within a biologically useful temperature range (37C). At temperatures below this (sol–gel) transition temperature (*T*sol/gel), solutions of this polymer exhibit Newtonian flow and low viscosity (the sol state).
- Conversely, above *T*sol/gel the polymer sol is converted into a gel with pronounced elasticity and viscosity.
- In solution at temperatures below *T*sol/gel and above the critical micelle concentration, the polymer exists in the micellar state.
- Elevation of the temperature (to above the *T*sol/gel) results in the further production of micelles and (close) intermicellar aggregation. This results in a gel of pronounced rheological structure. Lowering the temperature of the system to below the *T*sol/gel will result in deaggregation of the micelles and the reemergence of the sol (low-viscosity) state.
- The ability to modulate the rheological structure of these gels in the manner described has led to an interest in their use as drug delivery systems within the oral cavity and rectum. (In situ gel)

Ionic gelation

- Certain hydrophilic polymers may undergo gelation in the presence of inorganic metal ions. Examples of these include:
- ■ Cross-LinkingThe gelation of poly-hydroxy polymers, e.g. poly(vinyl alcohol) may occur in the presence of suitable anions, e.g. borate, permanganate. Poly(vinyl alcohol) is known to form structured gels in the presence of borate anions.
- ■ Salting out Addition of High concentration of a strongly hydrated electrolyte, colloidal material loses its water of solvation to these ions and coagulate
- Gelation of alginic acid occurs in the presence of positively charged di/trivalent ions, e.g. Mg^{2+}, Ca^{2+}, Al^{3+}. Also pectin in the presence of Ca^{2+} ions



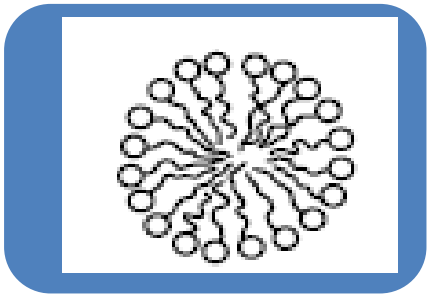


Coacervation

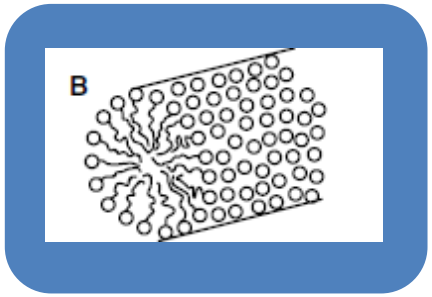
When negatively and positively charged hydrophilic colloids are mixed, the particles may separate from the dispersion to form a layer rich in the colloidal aggregates.

- The colloid-rich layer is known as a **coacervate**, and the phenomenon in which macromolecular solutions separate into two liquid layers is referred to as coacervation.
- As an example, consider the mixing of gelatin and acacia. Gelatin at a pH below 4.7 (its isoelectric point) is positively charged; acacia carries a negative charge that is relatively unaffected by pH in the acid range.
- When solutions of these colloids are mixed in a certain proportion, coacervation results. The viscosity of the upper layer, now poor in colloid, is markedly decreased below that of the coacervate, and in pharmacy this is considered to represent a physical incompatibility. Cationic SAA (+) and Anionic dyes(-)
- Coacervation need not involve the interaction of charged particles; the coacervation of gelatin may also be brought about by the addition of alcohol, sodium sulfate, or a macromolecular substance such as starch
- This method is the basic method for **MICROENCAPSULATION**

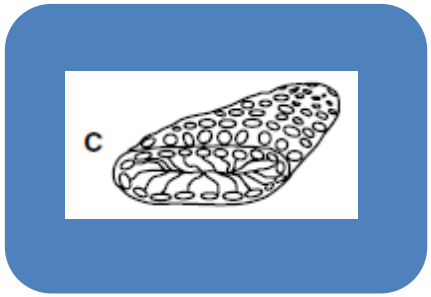
Association Colloids Shape



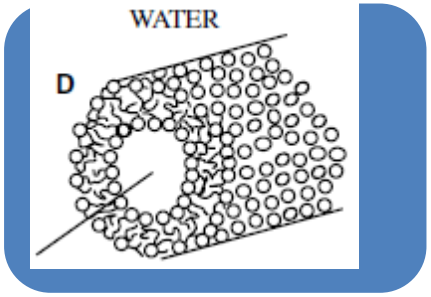
Spherical micelle



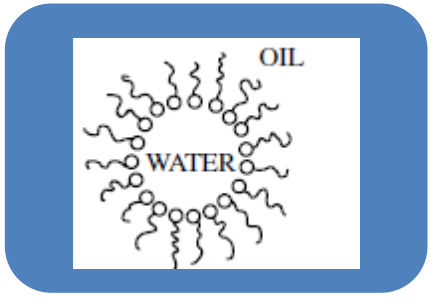
Cylindrical micelle



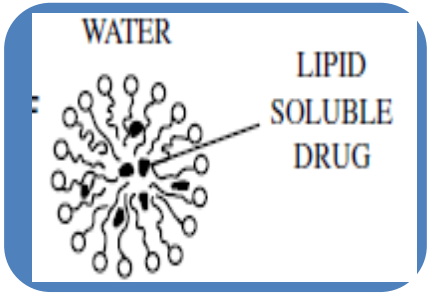
Flattened disc micelle



Micro tubular micelle



Inverted micelle



Swollen micelle in presence of Lipid soluble drug

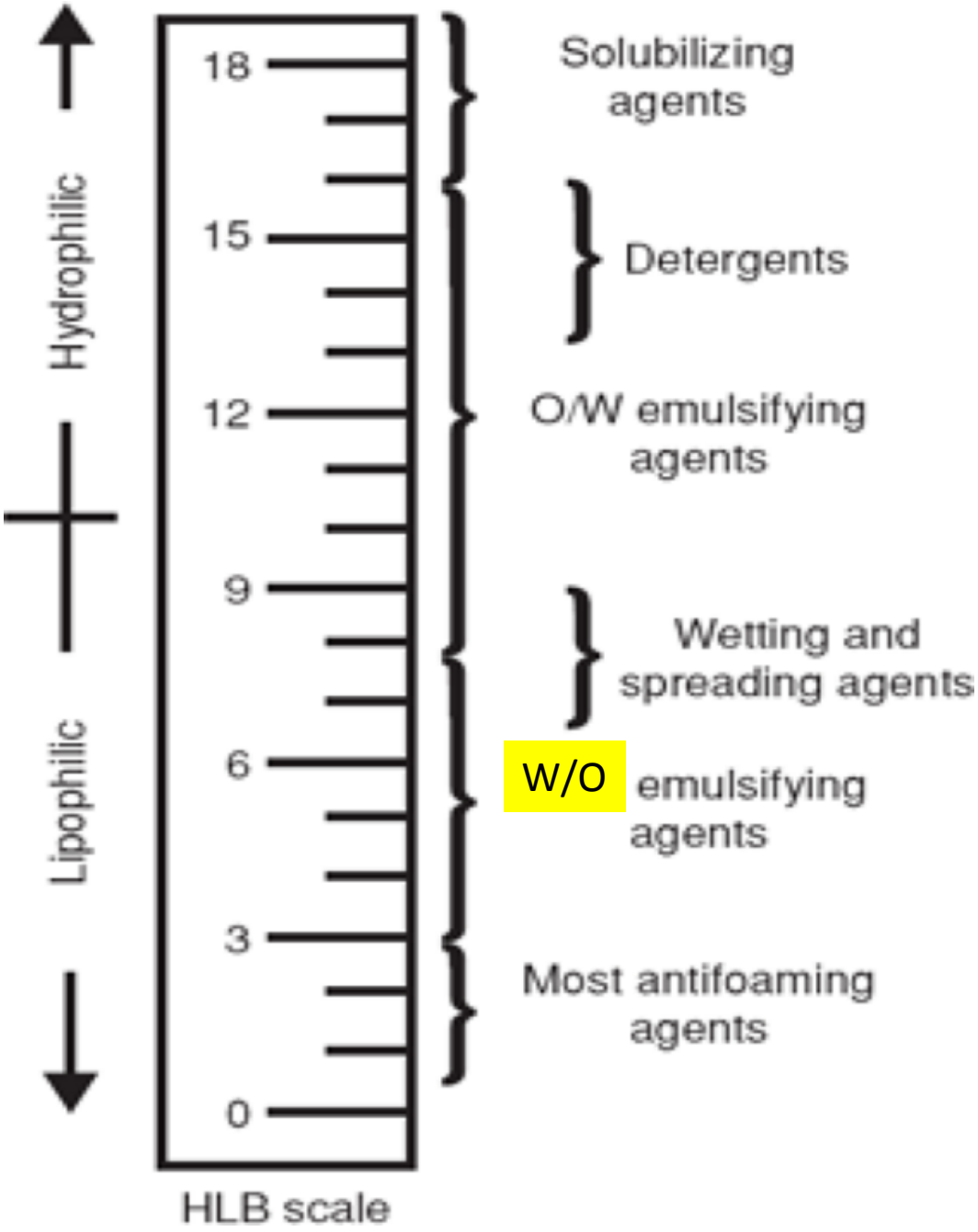
Amphiphilic colloids (Surfactant)

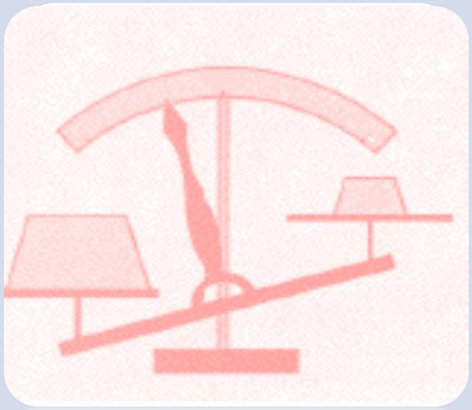
- **Surfactants** are compounds that lower the surface tension of a liquid, the interfacial tension between two liquids, or that between a liquid and a solid.
- Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants .Also as solubilizing agent.

Systems of Hydrophilic–Lipophilic Classification HLB

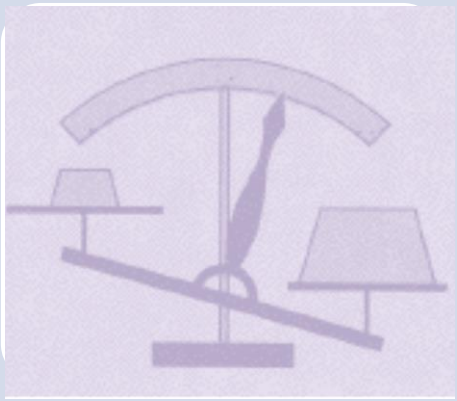
Griffin devised an arbitrary scale of values to serve as a measure of the hydrophilic–lipophilic balance of surface-active agents.

By means of this number system, it is possible to establish an HLB range of optimum efficiency for each class of surfactant, The higher the HLB of an agent, the more hydrophilic it is.





When oil-loving groups in surfactant are predominant, HLB is low... For producing water-in-oil emulsions (less than 9)



When water-loving groups predominate, the surfactant has high HLB and is used for oil-in-water emulsions (more than 10)

When oil-loving and water-loving groups are fairly well balanced, HLB is intermediate (around 10).

Hydrophilic–Lipophilic Balance (HLB) Values of Some Amphiphilic Agents

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

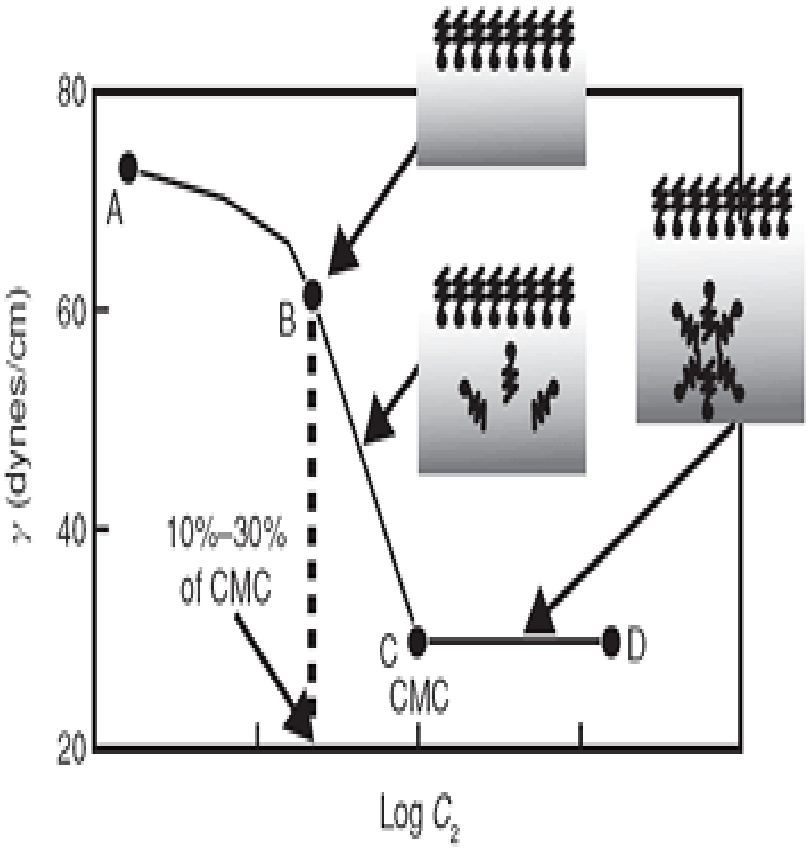
Effect of the concentration of soluble monolayer adsorbed (surfactant) on surface tension

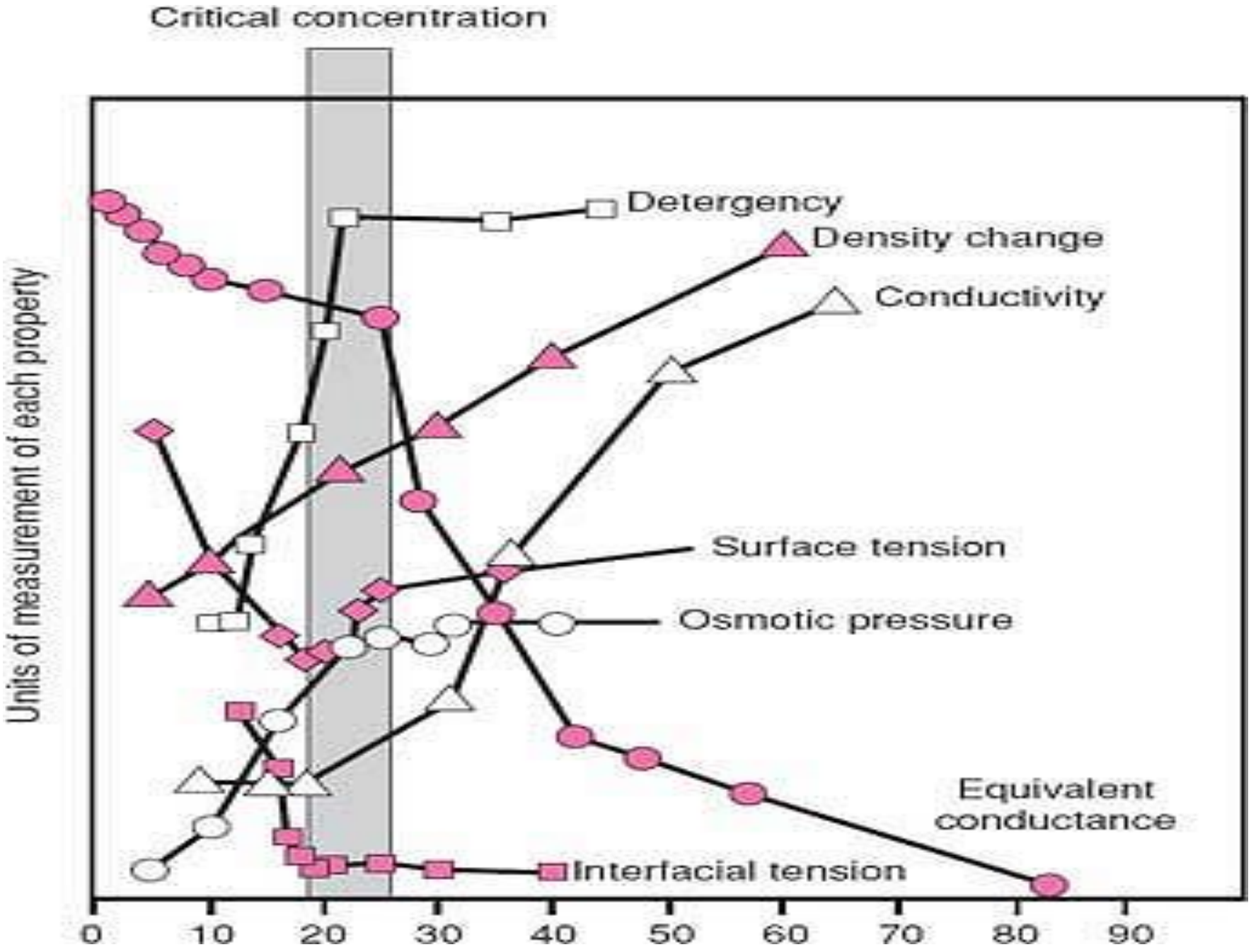
The initial curved segment A–B is followed by a linear segment, B–C, along which there is a sharp decrease in surface tension as log c_2 increases.

The point C corresponds to the critical micelle concentration (CMC), the concentration at which micelles form in the solution.

Beyond the CMC, the line becomes horizontal because further additions of surfactant are no longer being accompanied by a decrease in surface tension.

Along the linear segment B–C, the surface excess Γ is constant

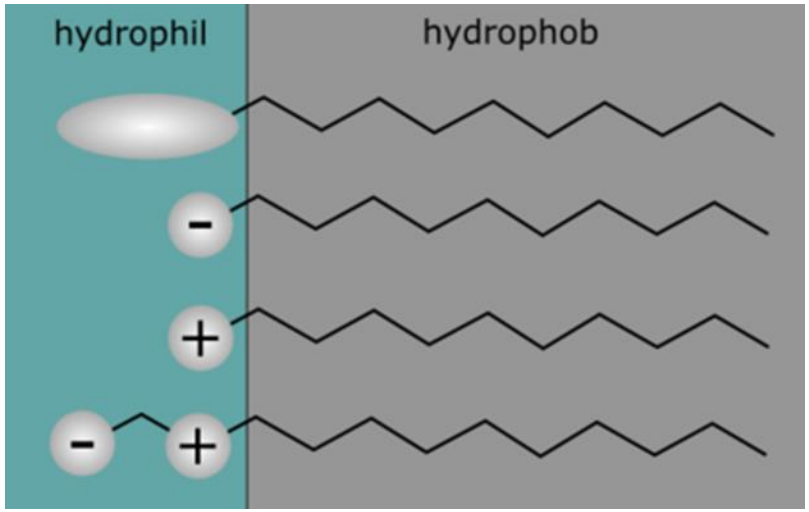



Critical concentration
Detergency
Density change
Conductivity
Surface tension
Osmotic pressure
Equivalent conductance
Interfacial tension
Units of measurement of each property
0
10
20
30
40
50
60
70
80
90

Surfactant structure

hydrophilic

Hydrophobic



Classification of surfactants

According to the composition of their tail

- The tail of surfactants can be:
- A hydrocarbon chain: aromatic hydrocarbons (arenes), alkanes (alkyl), alkenes, cycloalkanes, alkyne-based
- An alkyl ether chain:
  - Ethoxylated surfactants: polyethylene oxides are inserted to increase the hydrophilic character of a surfactant
  - Propoxylated surfactants: polypropylene oxides are inserted to increase the lipophilic character of a surfactant
- A fluorocarbon chain: fluorosurfactants
- A siloxane chain: siloxane surfactants.

According to the composition of their head

Non ionic

- A non-ionic surfactant has no charge groups in its head.

Cationic

- The head of an ionic surfactant carries
- Positive charge

Anionic

- The head of an ionic surfactant carries
- Negative charge

Zwitterionic

If a surfactant contains a head with two oppositely charged groups

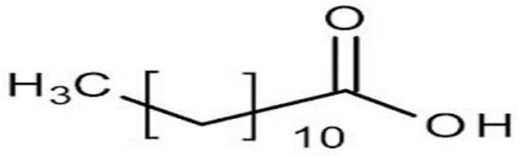
Anionic surfactant

- based on permanent anions (sulfate, sulfonate, phosphate)
- or pH-dependent anions (carboxylate):
  - Sulfates
    - Alkyl sulfates: ammonium lauryl sulfate, sodium lauryl sulfate (SDS, sodium dodecyl sulfate, another name for the compound)
    - Alkyl ether sulfates: sodium laureth sulfate, also known as sodium lauryl ether sulfate (SLES), sodium myreth sulfate
  - Sulfonates:
    - Docusates: dioctyl sodium sulfosuccinate
    - Sulfonate fluorosurfactants: perfluorooctanesulfonate (PFOS), perfluorobutanesulfonate
    - Alkyl benzene sulfonates
  - Phosphates:
    - Alkyl aryl ether phosphate
    - Alkyl ether phosphate
  - Carboxylates:
    - **Alkyl carboxylates: Fatty acid salts (soaps):** sodium stearate;
    - Sodium lauroyl sarcosinate
    - Carboxylate fluorosurfactants: perfluorononanoate, perfluorooctanoate (PFOA or PFO)

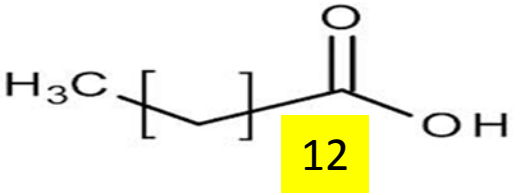
Metal salts of long chain fatty acid

Cations : sodium ,potassium ,triethanolamine

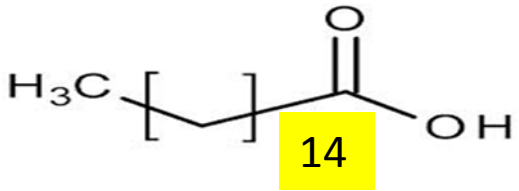
Lauric acid (n=10)
Bay leaf oil



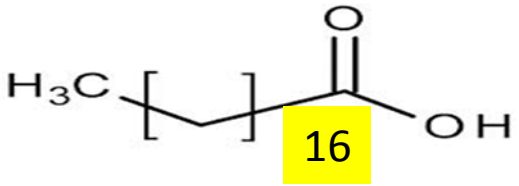
Myristic acid (n=12)
Nutmeg oil



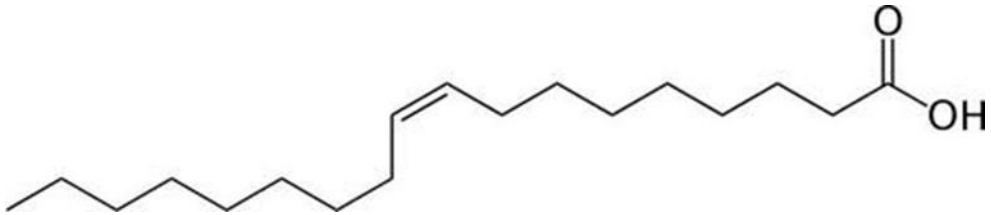
Palmitic acid (n=14)
Palm kernel oil



Stearic acid (n=16)
Animal fat , coca butter



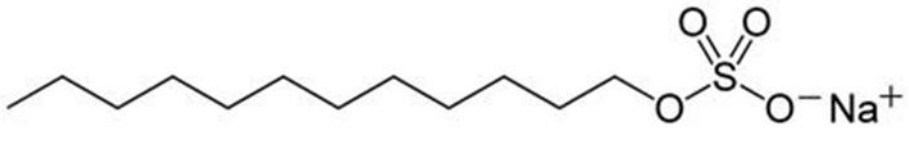
Oleic acid (olive oil)
(n=16,monounsaturated)



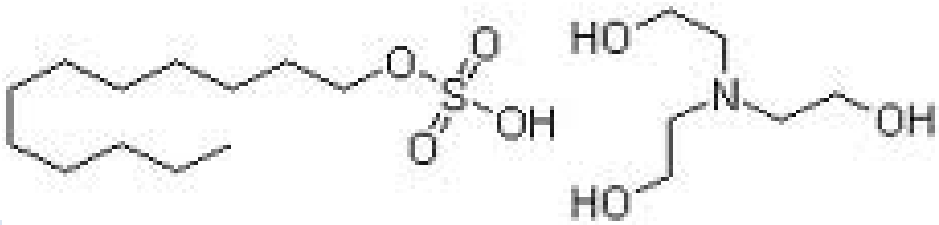
Anionic surfactants examples

Green soap N.F.
Potassium salt of oleic acid with glycerin

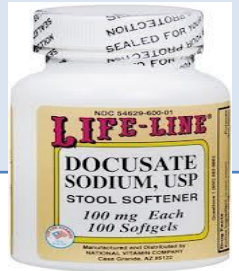
Sodium Lauryl Sulfate U.S.P.
Toothpaste ,ointments

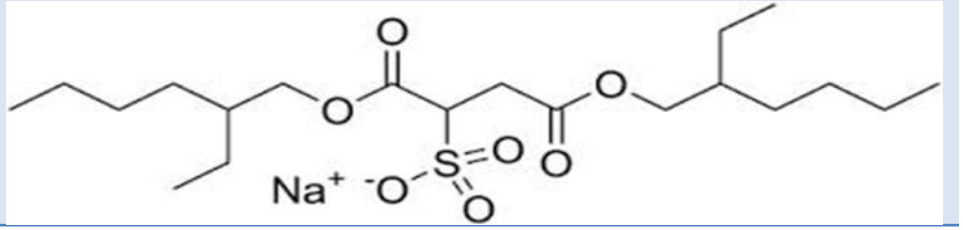


Triethanolamine dodecyl sulfate
Shampoo cosmetics



Dioctyl Sodium Sulfosuccinate U.S.P.
Fecal softener





Acne treatment

- A variety of cleansers are useful in removing sebum

- **Soaps** are some of the major cleansers used in acne treatment. These include true soaps that are composed of long chain fatty acid alkali salts, with a pH of 9–10.

They may contain triclosan,

or **Sulfur Soap** Sulfur is a known bacteriostatic and antifungal agent, It has a characteristic foul odor and unusual yellow color.

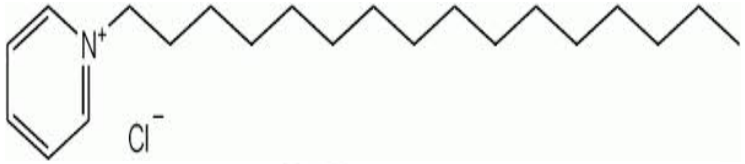
- Synthetic detergents, known as **syndets**. (milder detergent) These cleansers contain less than 10% soap with a more neutral pH adjusted to 5.5–7.0, called cleansing or dermatological bars

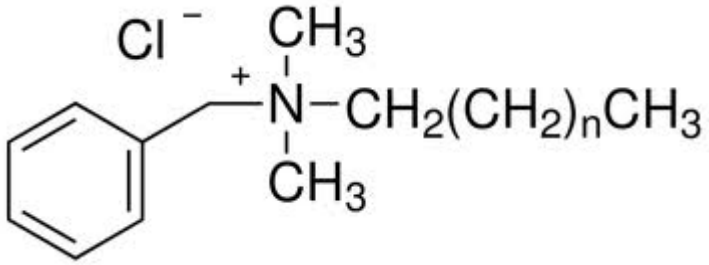
Dandruff Shampoo

- **Ketoconazole Shampoo** - a very effective anti-fungal.

Cationic surfactant

- Have bacteriostatic activity because they combine with the carboxyl in the cell walls of microorganisms by cation exchange , causing lysis.
- pH-dependent primary, secondary, or tertiary amines: Primary amines become positively charged at pH < 10, secondary amines become charged at pH < 4: Octenidine dihydrochloride;
- Permanently charged quaternary ammonium cation: Alkyltrimethylammonium salts:
- cetyl trimethylammonium bromide (CTAB)
- cetyl trimethylammonium chloride (CTAC)
- Cetylpyridinium chloride (CPC) Cetrimide





- Benzalkonium chloride (BAC)
- Benzethonium chloride (BZT)
- 5-Bromo-5-nitro-1,3-dioxane
- Dimethyldioctadecylammonium chloride
- Dioctadecyldimethylammonium bromide DODAB

Zwitterionic (amphoteric)

- based on primary, secondary, or tertiary amines or quaternary ammonium cation with: Sulfonates:
  - CHAPS (3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate);
  - Sultaines: cocamidopropyl hydroxysultaine;
- Carboxylates:
  - Amino acids
  - Imino acids
  - Betaines: cocamidopropyl betaine;
- Phosphates: lecithin

Nonionic

1. *Fatty alcohols*:

- Cetyl alcohol, $CH_3(CH_2)_{15}OH$ or **palmityl alcohol**
- Stearyl alcohol, $CH_3(CH_2)_{16}CH_2OH$ *octadecyl alcohol*
- Cetostearyl alcohol (consisting predominantly of cetyl and stearyl alcohols)
- Oleyl alcohol $CH_3(CH_2)_7$-CH=CH-$(CH_2)_8OH$.

2. *Polyoxyethylene glycol alkyl ethers (Brij)*:

$$CH_3–(CH_2)_{10–16}–(O\text{-}C_2H_4)_{1–25}–OH$$

- Octaethylene glycol monododecyl ether
- Pentaethylene glycol monododecyl ether

3. *Polyoxypropylene glycol alkyl ethers*:

$$CH_3–(CH_2)_{10–16}–(O\text{-}C_3H_6)_{1–25}–O$$

Non ionic

4. Glucoside alkyl ethers:

$CH_3–(CH_2)_{10–16}–(O\text{-Glucoside})_{1–3}–OH$:

- Decyl glucoside,
- Lauryl glucoside
- Octyl glucoside

5. Polyoxyethylene glycol octylphenol ethers:

$C_8H_{17}–(C_6H_4)–(O\text{-}C_2H_4)_{1–25}–OH$: Triton X-100

6. Polyoxyethylene glycol alkylphenol ethers:

$C_9H_{19}–(C_6H_4)–(O\text{-}C_2H_4)_{1–25}–OH$: Nonoxynol-9

7. Glycerol alkyl esters:

Glyceryl laurate

Non ionic

8. Polyoxyethylene glycol sorbitan alkyl esters: Polysorbate

9 Sorbitan alkyl esters:

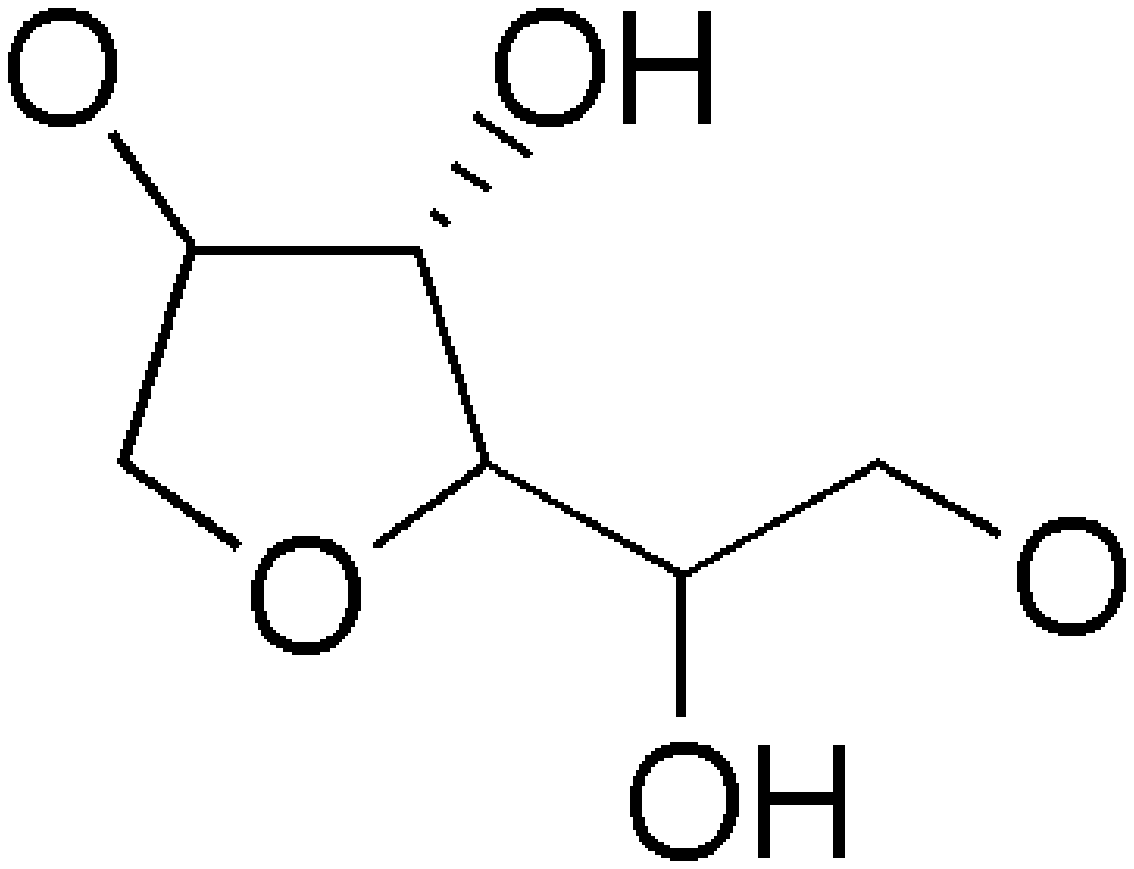
- Spans

10 Cocamide MEA, cocamide DEA

11 Dodecyldimethylamine oxide

12 Block copolymers of polyethylene glycol and polypropylene glycol: Poloxamers

13 Polyethoxylated tallow amine (POEA).



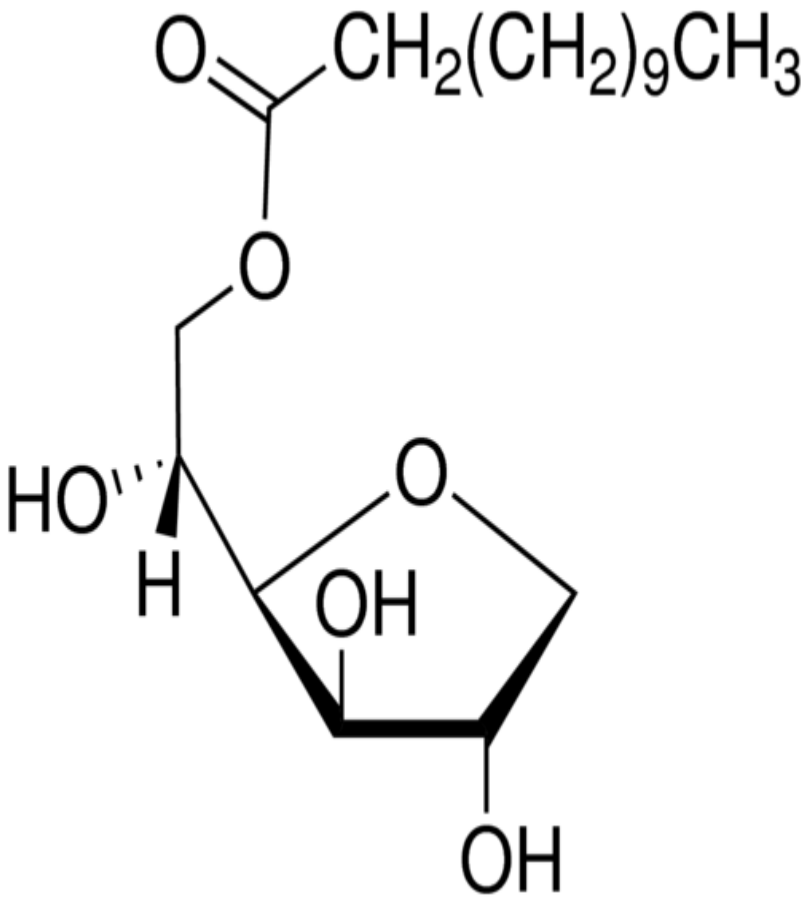
Sorbitan

Sorbitan is a mixture of chemical compounds derived from the dehydration of sorbitol

Sorbitan esters (Spans)

- **Sorbitan esters** (also known as Spans) are lipophilic non ionic surfactants that are used as emulsifying agents in the preparation of emulsions, creams, and ointments for pharmaceutical and cosmetic use.
- Sorbitan Monolaurate is indicated by 20
- Sorbitan monopalmitate is indicated by 40,
- Sorbitan monostearate by 60 and
- Sorbitan monooleate by 80.

Sorbitan monolaurate (Span 20)

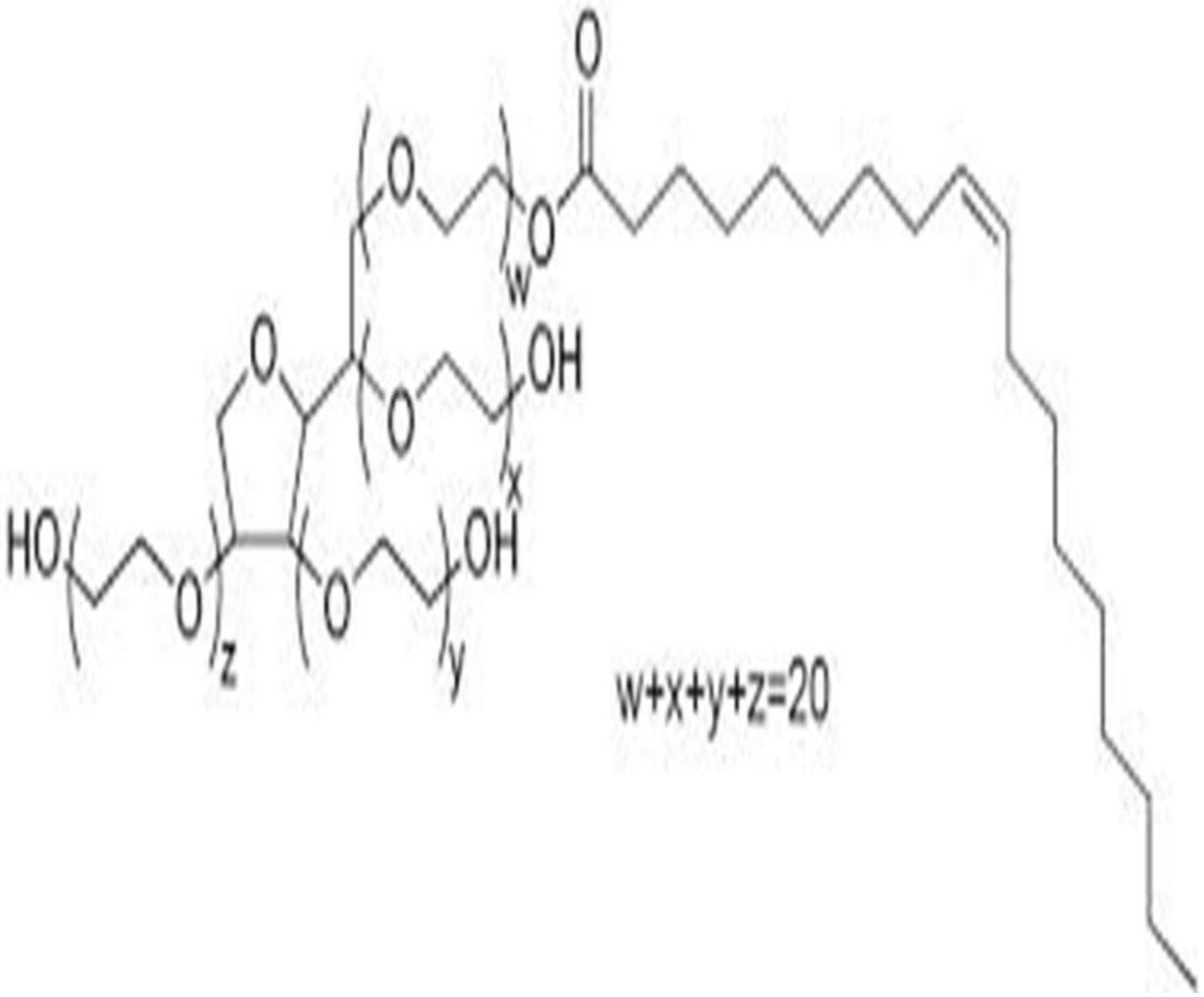


- **Sorbitan monolaurate**
- A lipophilic detergent liquid and monoester of lauric acid and hexitol anhydrides derived from sorbitol

Polysorbates (Tweens)

- Polysorbates are oily liquids derived from PEG-ylated sorbitan
- (a derivative of sorbitol) esterified with fatty acids.
- The hydrophilic groups in this compound are polyethers also known as polyoxyethylene groups which are polymers of ethylene oxide.
- Polysorbate 20 (Polyoxyethylene (20) sorbitan monolaurate)
- Polysorbate 40 (Polyoxyethylene (20) sorbitan monopalmitate)
- Polysorbate 60 (Polyoxyethylene (20) sorbitan monostearate)
- Polysorbate 80 (Polyoxyethylene (20) sorbitan monooleate)
- The number 20 following the *polyoxyethylene* part refers to the total number of oxyethylene -(CH_2CH_2O)- groups found in the molecule. The number following the *polysorbate* part is related to the type of fatty acid associated with the polyoxyethylene sorbitan part of the molecule

Polysorbate 80
Tween 80



- Polysorbate 80 is a viscous, water-soluble yellow liquid. It is a nonionic
- surfactant and emulsifier derived from polyethoxylated sorbitan and oleic acid

ELIXIRS

ELIXIRS

- Elixirs are clear, sweetened hydroalcoholic solutions intended for oral use and are usually flavored to enhance their palatability.

1. Non-medicated elixirs are employed as vehicles, and
2. Medicated elixirs are used for the therapeutic effect of the medicinal substances they contain.

SYRUPS AND ELIXIRS

- Syrups
- Sweet viscous contain sugar in high proportions
- Effective taste masking
- Face a problem in dissolving water insoluble material (not more than 10% alcohol)
- Stability problems
- Manufacture procedure either time consuming or needs heat

- Elixirs
- Sweetened hydroalcoholic solutions usually less sweet and less viscous because they contain a lower proportion of sugar
- Consequently are less effective than syrups in masking the taste of medicinal substances.
- However, because of their hydroalcoholic character, elixirs are better able than aqueous syrups to maintain both water-soluble and alcohol-soluble components in solution
- Also, because of their stable characteristics and the ease with which they are prepared (by simple solution), from a manufacturing standpoint, elixirs are preferred to syrups.

ELIXIR ALCOHOL CONTENT

- The proportion of alcohol in elixirs varies widely because the individual components of the elixirs have different water and alcohol solubility characteristics.
- Each elixir requires a specific blend of alcohol and water to maintain all of the components in solution.
- Naturally, 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.

ELIXIR SWEETENERS

- Although many elixirs are sweetened with sucrose or with a sucrose syrup, some use sorbitol, glycerin, and/or artificial sweeteners.
- Elixirs having a high alcoholic content usually use an artificial sweetener, such as saccharin, which is required only in small amounts, rather than sucrose, which is only slightly soluble in alcohol and requires greater quantities for equivalent sweetness.

OTHER ELIXIR COMPONENTS

- All elixirs contain flavorings to increase their palatability,
- Most elixirs have coloring agents to enhance their appearance.
- Elixirs containing more than 10% to 12% of alcohol are usually self-preserving and do not require the addition of an antimicrobial agent.

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
FDC Yellow No. 5	0.1 g
Purified water, to make	1,000.0 mL

COMPARISON BETWEEN ELIXIR AND SOLID DOSAGE FORMS

- One advantage of elixirs over their counterpart drugs in solid dosage forms is the flexibility of dosage
- For most elixirs, one or two teaspoonfuls (5 or 10 mL) provide the usual adult dose of the drug.
- Ease of dosage administration to patients who have difficulty swallowing solid forms.
- A disadvantage of elixirs for children and for adults who choose to avoid alcohol is their alcoholic content.

FDA REGULATIONS

- The U.S. Food and Drug Administration (FDA) has proposed that insofar as possible manufacturers of over-the-counter (OTC) oral drug products restrict the use of alcohol and include appropriate warnings in the labeling.
- For OTC oral products intended for children under 6 years of age, the recommended alcohol content limit is 0.5%;
- for products intended for children 6 to 12 years of age, the recommended limit is 5%; and for products recommended
- for children over 12 years of age and for adults, the recommended limit is 10%.

STORAGE CONDITIONS

- Because of their usual content of volatile oils and alcohol, elixirs should be stored in
- tight, light-resistant containers and
- protected from excessive heat.

PREPARATION OF ELIXIRS

- Elixirs are usually prepared by simple solution with agitation and/or by admixture of two or more liquid ingredients.
- Alcohol-soluble and water-soluble components are generally dissolved separately in alcohol and in purified water, respectively.
- Then the aqueous solution is 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 the two solutions are completely mixed, the mixture is made to the volume with the specified solvent or vehicle.

SPECIAL PRECAUTIONS

- Frequently, the final mixture will be cloudy, principally because of separation of some of the flavoring oils by the reduced alcoholic concentration. If this occurs, the elixir is usually permitted to stand for a prescribed number of hours to ensure saturation of the hydroalcoholic solvent and to permit the oil globules to coalesce so that they may be more easily removed by filtration.
- Talc, a frequent filter aid in the preparation of elixirs, absorbs the excessive amounts of oils and therefore assists in their removal from the solution.
- The presence of glycerin, syrup, sorbitol, and propylene glycol in elixirs generally contributes to the solvent effect of the hydroalcoholic vehicle, assists in the dissolution of the solute, and enhances the stability of the preparation. However, the presence of these materials adds to the viscosity of the elixir and slows the rate of filtration.

NONMEDICATED ELIXIRS

- (*a*) the addition of a therapeutic agent to a pleasant-tasting vehicle and
- (*b*) dilution of an existing medicated elixir.
- If a hydroalcoholic vehicle is selected for the drug, the proportion of alcohol should be only slightly above the amount needed to effect and maintain the drug's solution.
- The non medicated elixir selected as the diluent should have approximately the same alcoholic concentration as the elixir being diluted.
- Also, the flavor and color characteristics of the diluent should not be in conflict with those of the medicated elixir, and all components should be chemically and physically compatible.

NONMEDICATED ELIXIRS

- Aromatic elixir, USP

Sugar(31-42%w/v) Orange spirit , Alcohol (21-23%v/v)

(Orange oil 2.4ml,lemon oil 0.6ml,coriander oil 0.24ml, anise oil 0.06ml, syrup 375ml, talc 30g, alcohol 230ml and water to 1000ml)

- Iso-alcoholic elixir, NF is similar to aromatic elixir in flavor and is composed of 2 separate parts :low alcoholic content (8-10%) and high alcoholic content elixir (73-78%)
- Compound benzaldehyde elixir,

MEDICATED ELIXIRS

- Most official and commercial elixirs contain a single therapeutic agent.
- The main advantage of having only a single therapeutic agent is that the dosage of that single drug may be increased or decreased by simply taking more or less of the elixir,
- whereas when two or more therapeutic agents are present in the same preparation, it is impossible to increase or decrease the dose of one without an automatic and corresponding adjustment in the dose of the other, which may not be desired.

ANTIHISTAMINE ELIXIRS

- Most antihistaminic agents are basic amines. By forming salts through interaction with acid, the compounds are rendered water soluble. These salt forms are used in elixirs, so the elixirs of the antihistamines are not required to contain a large proportion of alcohol.
- The acid salts of the antihistamines are used, the pH of these elixirs is on the acid side and must remain so if the drugs are to remain freely soluble in water.

A pharmacist should keep this in mind when using one of these elixirs to compound a prescription with other components

ANTIHISTAMINE

- Diphenhydramine HCl Elixir 12.5 mg/5 mL
- Commercial product contains 5.6% alcohol

PHENOBARBITAL ELIXIR

Phenobarbital	4.0g
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	1000.0 mL

PHENOBARBITAL ELIXIR(0.4%)

- The official elixir contains about 14% alcohol, which is used to dissolve the phenobarbital. However, this amount is almost the very minimum required to keep the phenobarbital in solution.
- Therefore, glycerin is often added to enhance the solubility of phenobarbital.
- Phenobarbital is a long-acting barbiturate with a duration of action of about 4 to 6 hours, a usual adult dose as a sedative of about 30 mg and a hypnotic dose of about 100 mg.
- The strength of the elixir permits convenient adjustment of dosage to achieve the proper degree of sedation in the treatment of infants, children, and certain adults.

DIGOXIN ELIXIR

- Digoxin Elixir, USP; however, it is required to contain 4.5 to 5.25 mg of digoxin per 100 mL of elixir, or about 0.25 mg per 5 mL teaspoonful.
- The usual oral adult dose of digoxin as a cardio-tonic agent is about 1.5 mg on initial therapy and about 0.5 mg for maintenance therapy.
- The elixir is generally employed for children, and the commercial product available for this purpose is packaged with a calibrated dropper to facilitate accurate dosing.

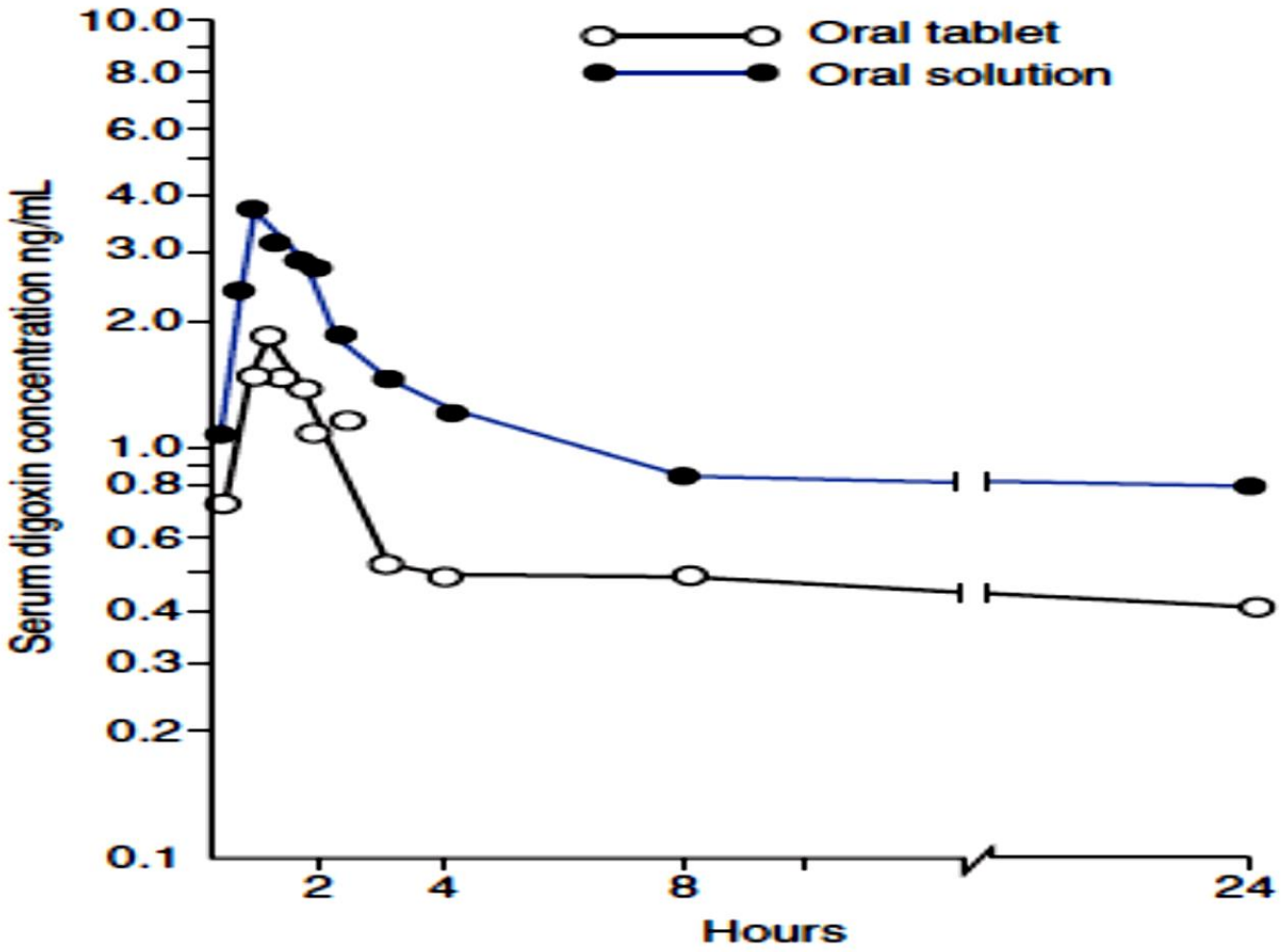


FIGURE 13.2 Serum digoxin concentrations following administration of digoxin 0.5 mg by oral tablet and elixir-like oral solution. (Adapted with permission from Huffman DH, Azarnoff DL. Absorption of orally given digoxin preparations. JAMA 1972;222:957. Copyright © 2010 American Medical Association. All rights reserved.)

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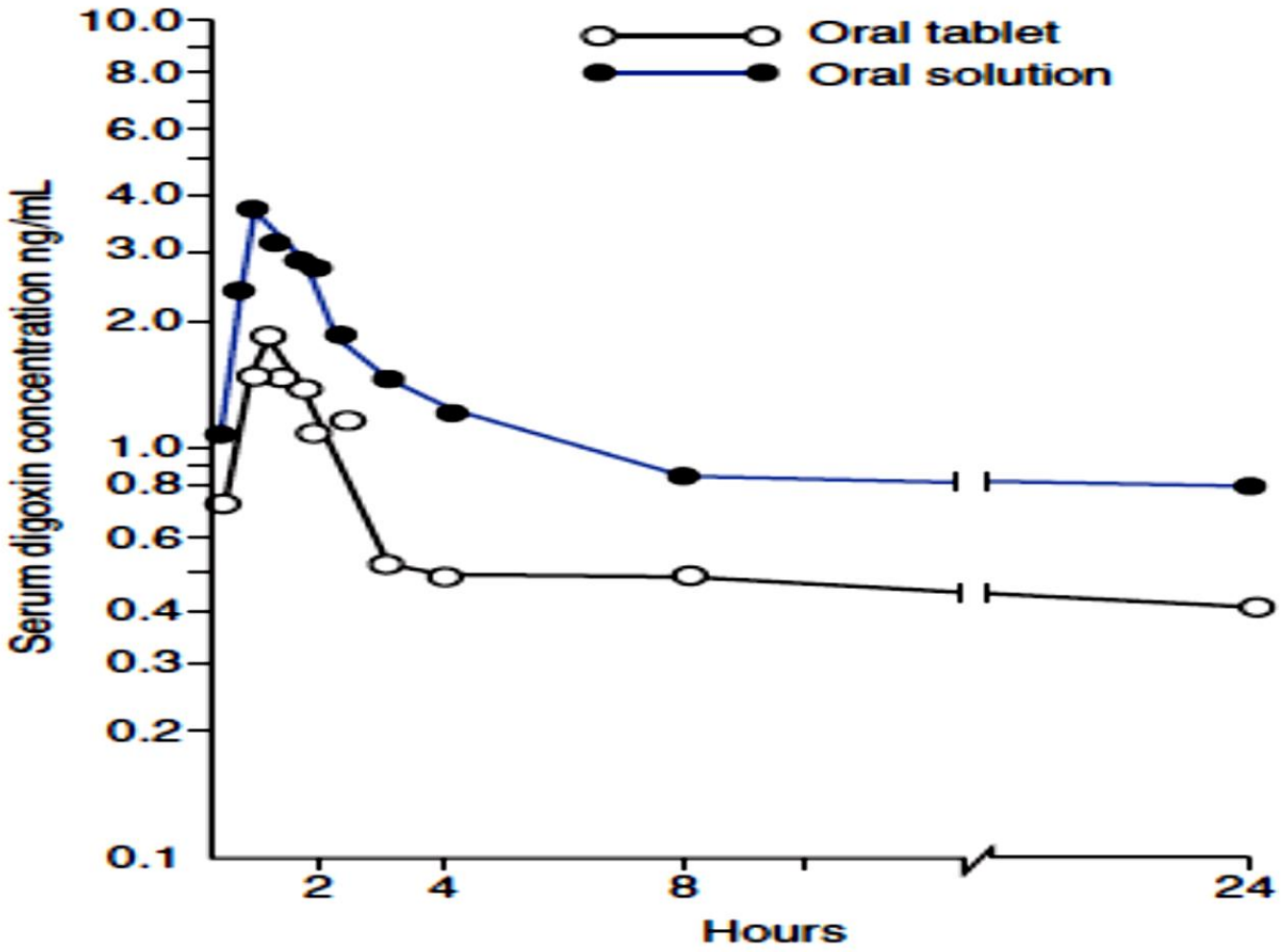

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Extracted products

Methods of extraction

Extraction

- Withdrawal of desired constituents from crude drugs through the use of selected solvents, in which the desired constituents are soluble
- Efficient extraction will obtain a potent palatable more conveniently administered dosage form

Crude drugs

- Are either plant or animal source which have collected , cleaned and dried to prevent fermentation
- Contain a number of constituents that may be soluble in a given solvent
- Plant materials are composed of heterogeneous mixture of constituents

1. Pharmacologically active e.g. alkaloids, glycosides ..etc
2. Pharmacologically inactive inert like tannins, gums, mucilage, pectin, fats

Efficient extraction

- Penetration of the solvent into the cellular material to dissolve the desired ingredients with minimum of undesired material
- Rate of penetration by diffusion of the solvent is enhanced by

1. increasing the surface area of exposure by comminution,
2. agitation and replacement the solvent will remove the saturated solution of the constituents that otherwise cause barrier to diffusion
3. Pre –soaking the dried cellular material will aid in the extraction which is also influenced by the surface tension of the liquid and it's wetting properties.
4. Increasing the time of exposure to the solvent

Solvents (menstrum)

1. **Water**

- Because of its ready availability, cheapness, and good solvent action for many plant constituents,
- Used for extraction in combination with other solvents. However, as a sole solvent, it has many disadvantages and is infrequently used alone. For one thing, most active plant constituents are complex organic chemical compounds that are less soluble in water than in alcohol.
- Although water has a great solvent action on such plant constituents as sugars, gums, starches, coloring principles, and tannins, most of these are not particularly desirable components of an extracted preparation.
- Water also tends to extract plant principles that separate upon standing in the extractive, leaving an undesired residue.
- Finally, unless preserved, aqueous preparations serve as excellent growth media for molds, yeasts, and bacteria. When water alone is employed as the menstrum, alcohol is frequently added to the extractive or to the final preparation as an antimicrobial preservative.

Solvents (menstrum)

2-Hydroalcoholic mixtures

the most versatile and most widely employed menstrua.

They combine the solvent effects of both water and alcohol, and the complete miscibility of these two agents permits flexible combining of the two agents to form solvent mixtures most suited to the extraction of the active principles from a particular drug.

A hydroalcoholic menstruum generally provides inherent protection against microbial contamination and helps to prevent the separation of extracted material on standing.

3-Alcohol is used alone as a menstruum only when necessary because it is more expensive than hydroalcoholic mixtures.

Solvents (menstrum)

4-Glycerin

Glycerin, a good solvent for many plant substances, is occasionally employed as a cosolvent with water or alcoholic menstrua because of its

A- ability to extract and then

B- prevent inert materials from precipitating upon standing.

It is especially useful in this regard in preventing separation of tannin and tannin oxidation products in extractives.

C-Because glycerin has preservative action, depending on its concentration in the final product, it may contribute to the stability of a pharmaceutical extractive.

Methods of extraction

1-Maceration

- the method of extraction selected for a given drug depends on several factors, including
- the nature of the crude drug,
- its adaptability to each of the various extraction methods,
- and the interest in obtaining complete or nearly complete extraction of the drug

2-Percolation

- Usually a combination of both is required

Maceration
Latin macerare, meaning to soak

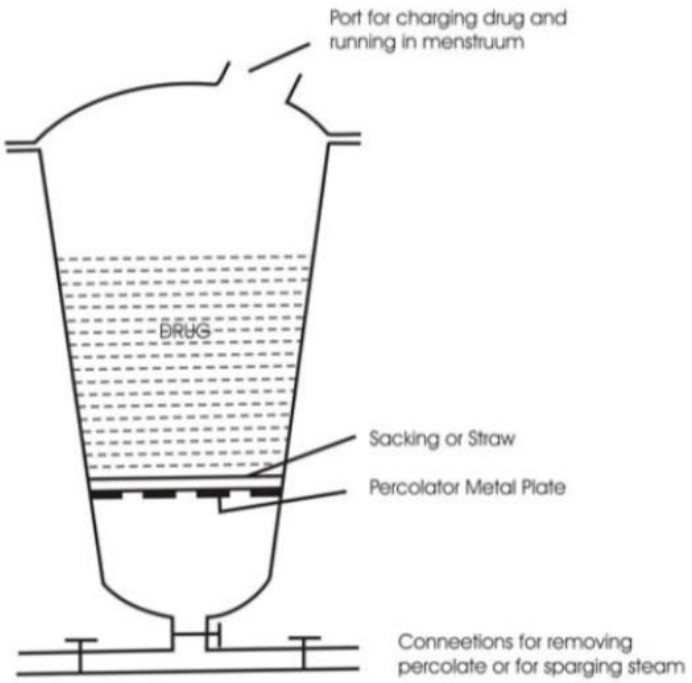
- Crude drug is placed into solvent system (menstrum) with or without heat
- Mixture allowed to stand with occasional agitation for an extended period to allow solvent penetration in closed wide containers
- Filtration to removed the un-dissolved material (marc)
- Bring the filtrate to volume with the solvent system
- Maceration is usually conducted at a temperature of 15°C to 20°C for 3 days or until the soluble matter is dissolved.(ranging from 2-14 days)

Maceration

- used for extraction of crude drugs containing little or no soft cellular tissue such as benzoin, tolu, aloe
- complete exhaustion of all the active principles is not possible because there is no agitation or replacement of solvent this can be overcome by placing the crude drug in a permeable membrane or sack as in a tea bag, the dissolved principles will falls away from the region of the crude drug due to its' greater specific gravity, and fresh solvent takes it's place

Percolation
Latin per, meaning through, and colare, meaning to strain

- Packing the crude drug into a column (percolator), slowly passing solvent through the column and then collecting the extracted material dissolved in the solvent .
- The flow rate of the menstrum is controlled by the orifice at the bottom of the percolator
- drawn by the force of gravity as well as the weight of the column of liquid
- In certain specialized and more sophisticated percolation apparatus, additional pressure on the column is exerted with positive air pressure at the inlet and suction at the outlet or exit.



Commercial scale (about 1 ton capacity) percolator

Percolation advantage

1. Extract principles exhaustively with a minimum solvent
2. Easier to bring a product to proper volume by adding solvent than by removing excess solvent

- exhaustive extraction is shown
- Loss of color of the extractive
- Loss of bitter taste characteristics of alkaloids
- Absence of the principles as determined by spot tests with specific reagents

Improving percolation

- the crude drug must be properly packed in the column to maintain uniform movement of the menstrum.
- To improve solvent penetration the crude drug is allowed to soak with the menstrum in the percolator for a period of time then open the orifice

Type of percolator

- **Long and narrow**
- Each particle of crude drug is exposed to nearly all of the solvent added to the column
- lowering the rate of solvent movement will ensure efficient extraction with minimum amount of solvent
- Used for extraction from leaves

- **Wide and short**
- Menstrum is of high viscosity
- Nature of crude drug slows the movement of menstrum
- Used for extraction from seeds

Maceration and percolation

- Crude drugs containing alkaloids are macerated in acidified hydroalcoholic solvent to convert to the more soluble amine salts then followed by percolation with a hydroalcoholic solvent
- Removal of fats with an organic solvent or tannins before the percolation step will aid solvent penetration

Decoctions

- Used for water soluble principles
- Brewing tea and coffee
  - Place the plant in water
  - Boil the water for 15 min
  - Express and strain the remaining marc

Digestion

- Maceration with continued heating
- Temperature range between 40-60°
- Used for water soluble principles

Infusion

- Maceration the crude drug in cold water followed by addition of boiling water in an amount equal to 90% of the desired volume
- Used for water soluble principles

Extractives

- Products of extraction, contain varying constituents depending on the crude used and the conditions of the extracting
- The most common official extractives are

1. Tinctures
2. Fluid extracts
3. Extracts

Tinctures

- Alcoholic or hydroalcoholic solutions of principles extracted from natural sources or of pure chemicals
- The amount of active ingredients in tinctures vary
- Tinctures of potent medication obtained by extraction are adjusted so that each 1ml of tincture contain 0.1g of active crude drug constituents or 10% activity
- Alcohol content range from 15-80%

Tinctures preparation Process M

- Process M maceration of the crude drug
- Used for substances containing a high proportions of soluble constituents
- Maceration for 3 days with alcohol or dilute alcohol and small amount of glycerin (prevent separation of tannins in Cpd Cardamom Tincture)
- Compound Benzoin Tinctures USP (topical protective)
- Sweet orange peel Tincture USP
- Lemon Tincture USP
- Compound Cardamom Tincture NF
- Tolu balsam Tincture NF

flavors

Process P

- Percolation for extraction of tinctures
- Belladonna Tincture USP (Anticholinergic)
- Vanilla Tincture NF (flavor)
- Iodine Tincture NF
- Thimerosal Tincture NF

} Disinfectant

- Green Soap Tincture NF (detergent)

Fluid extracts

- Liquid preparation of a vegetable drug prepared by percolation, containing alcohol as a solvent and as preservative or both so that each I ml contain the therapeutic constituents of 1 g of the standard drug
- Usually prepared by percolation for exhaustive extraction

Fluid extracts preparation NF

Process	Menstrum	Comments
A	Alcoholic Hydroalcoholic	
B	Alcoholic ,Hydroalcoholic Glycerin, or acid	More than one menstrum
C	Divide crude drug in 3 portions and percolate the larger portion use this percolate to percolate the other portion	Fractional technique
D	Boiling water	Similar to process A and B
E	Column length greater than its width	Similar to process C

Official fluidextracts

Fluid extract	Process	use
Eriodictyon NF	A	Flavor
Senna NF	A	Cathartic
Belladonna leaf NF	E	anticholinergic
Glycyrrhiza USP	D	Flavor
Cascara Sagrada USP	D	Flavor
Aromatic Cascara Sagrada USP	D	glycyrrhiza extract, anise oil, coriander oil, methyl salicylate, alcohol, water

Extracts

- Concentrated preparations of animal or vegetable drugs which first have been extracted by maceration and or percolation
- They are potent preparations, usually 2-6 times as potent on a weight basis as the crude drug
- After percolation, the volume is reduced by evaporation

Types of extracts

- Semi-liquid with syrupy consistency
- Pilular extracts with plastic consistency
- Powdered extracts   dry
- Adjustment of potency by addition of inert diluent
- Liquid glucose for pilular extracts
- Starch for powdered extracts

Official extracts

Extract	
Pure Glycyrrhiza extract USP	Pilular
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Resins

- Natural resins are solids or semisolid exudates from plants or from insects that feed on plants
- Oxidized terpenes of the volatile oils of the plants
- Prepared by percolation using alcohol as menstrum
- **Podophyllum Resin USP** percolation of the dried rhizome and roots of Podophyllum peltatum used as topical caustic
- Prepared as a dispersion in alcohol or in Compound benzoin Tincture.

Extracted products

Methods of extraction

Extraction

- Withdrawal of desired constituents from crude drugs through the use of selected solvents, in which the desired constituents are soluble
- Efficient extraction will obtain a potent palatable more conveniently administered dosage form

Crude drugs

- Are either plant or animal source which have collected , cleaned and dried to prevent fermentation
- Contain a number of constituents that may be soluble in a given solvent
- Plant materials are composed of heterogeneous mixture of constituents

1. Pharmacologically active e.g. alkaloids, glycosides ..etc
2. Pharmacologically inactive inert like tannins, gums, mucilage, pectin, fats

Efficient extraction

- Penetration of the solvent into the cellular material to dissolve the desired ingredients with minimum of undesired material
- Rate of penetration by diffusion of the solvent is enhanced by

1. increasing the surface area of exposure by comminution,
2. agitation and replacement the solvent will remove the saturated solution of the constituents that otherwise cause barrier to diffusion
3. Pre –soaking the dried cellular material will aid in the extraction which is also influenced by the surface tension of the liquid and it's wetting properties.
4. Increasing the time of exposure to the solvent

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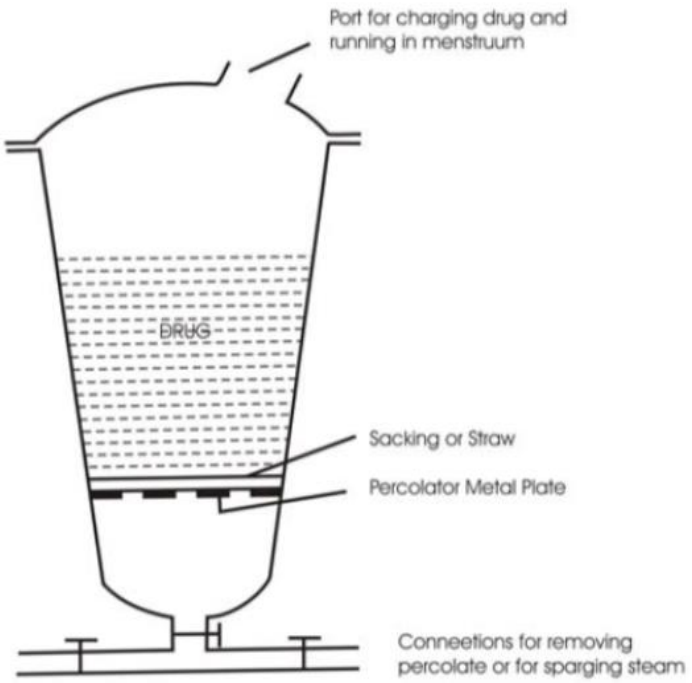

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Spirits

Solutions containing mixed solvent system

Spirits (essence)

- Spirits are solutions of volatile substances in alcoholic.
- The volatile substance is usually a volatile oil
- The content in spirits is more than in aromatic water.
- Spirits are alcoholic or hydro-alcoholic solutions of volatile substances prepared by simple solution or by admixture of ingredients.
- These are used as flavoring agents and may have medicinal value.

Preparation of spirits

- Volatile oil dissolved in alcohol
- Water is avoided during preparation because it will cause turbidity due to precipitation of the water insoluble volatile oil
- Graduates and other equipment should be dry. Filter paper should be moistened with alcohol

Peppermint Spirit NF

- Used as a carminative and flavor.
- Leaves macerated in water to remove the tannins and water soluble and then discard the water express the leaves and macerate in alcohol, the alcohol will dissolve the chlorophyll which is green in color . To this alcoholic solution 10% of volatile oil is added.

Compound orange spirit USP

- Used entirely as a flavoring agent
- It is a blend of several oils
- It is readily prepared by simple solution
- Important ingredient of aromatic elixir

Preparation. "—(U. S. P.).—"

- Oil of orange peel, (200 Cc.) [6 fl℥, 366℥];
- oil of lemon, (50 Cc.) [1 fl℥, 332℥];
- oil of coriander, (20 Cc.) [325℥];
- oil of anise, (5 Cc.) [81℥];

Deodorized alcohol, to(1000 Cc.) [33 fl℥, 391℥].

- Mix them. Keep the product in completely filled, well-stoppered bottles, in a cool and dark place

Aromatic ammonia spirit NF

- It acts as a carminative due to volatile oils present
- And as antacid, and as a
- mild reflex circulatory stimulant due to liberation of ammonia from ammonium carbonate (used for fainting)
- Makes a milky preparation upon dilution with water due to oils present
- Cannot be used with alkaloids like codeine phosphate

Aromatic ammonia spirit NF

- solution of ammonia (1.7g -2.1g) and ammonium carbonate (3.5-4.5g) in alcohol and distilled water perfumed with the oils of lemon, lavender, and nutmeg.

Camphor spirit NF

- Simple solution of 10% camphor in alcohol
- Used externally
- Applied to cold sores

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Suspensions

Definition

- A pharmaceutical suspension is a coarse dispersion in which insoluble particles, generally greater than 1 /μm in diameter, are dispersed in a liquid medium, usually aqueous.
- Suspensions may be defined as preparations containing finely divided drug particles (the suspensoid) distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility.

(for)/ suspension

- Some suspensions are available in ready-to-use form, that is, already distributed through a liquid vehicle with or without stabilizers and other additives.
- Prepared suspensions not requiring reconstitution at the time of dispensing are simply designated as "**Suspension**."
- Other preparations are available as dry powders intended for suspension in liquid vehicles. Generally, this type of product is a powder mixture containing the drug and suitable suspending and dispersing agents to be diluted and agitated with a specified quantity of vehicle, most often purified water. Drugs that are unstable if maintained for extended periods in the presence of an aqueous vehicle (e.g., many antibiotic drugs) are most frequently supplied as dry powder mixtures for reconstitution at the time of dispensing. This type of preparation is designated in the USP by a title of the form "**for Suspension" or " to be reconstituted "**

Advantage (REASONS FOR SUSPENSIONS)

- An aqueous suspension is a useful formulation system for administering an **insoluble or poorly soluble drug.** The large surface area of dispersed drug ensures a high availability for dissolution and hence absorption.
- Certain drugs are chemically **unstable in solution** but stable when suspended. In this instance, the suspension ensures chemical stability while permitting liquid therapy
- The **disadvantage of a disagreeable taste** of certain drugs in solution form is overcome when the drug is administered as un-dissolved particles of an oral suspension. In fact, chemical forms of certain poor-tasting drugs have been specifically developed for their insolubility in a desired vehicle for the sole purpose of preparing a palatable liquid dosage form. 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, the result being Erythromycin Estolate Oral Suspension, USP

Uses

- Aqueous suspensions may also be used for parenteral and ophthalmic use(<10μm), rectal and provide a suitable form for the applications of dermatological materials to the skin.
- Suspensions are similarly used in veterinary practice, and a closely allied field is that of pest control.
- Pesticides are frequently presented as suspensions for use as fungicides, insecticides, and herbicides.

ORAL SUSPENSIONS BY CATEGORY

1-Antacid			
Magnesia and alumina	Maalox Suspension (Novartis Consumer Health)	Aluminum hydroxide 225 mg; magnesium hydroxide 200 mg/5 mL	Counteract gastric hyperacidity, relieve distress in the upper gastrointestinal tract
Aluminum hydroxide, magnesium carbonate	Gaviscon Liquid Antacid (GlaxoSmithKline	Aluminum hydroxide 95 mg; magnesium carbonate 358 mg/ 15 mL; sodium alginate	
2-Antiflatulent			
Simethicone		40 mg/0.6 mL	Symptomatic treatment of gastrointestinal distress due to gas. Reduces surface tension of gas bubbles, enabling them to coalesce and be released through belching or flatus

ORAL SUSPENSIONS BY CATEGORY

3- Anti-bacterials (Antibiotics)

Erythromycin Estolate		125, 200, 250 mg/5 mL	Broad-spectrum macrolide antibiotic; bacteriostatic activity
Sulfamethoxazole and trimethoprim	Bactrim Suspension (Roche), Septrin Suspension (GSK)	Trimethoprim 40 mg, sulfamethoxazole 200 mg/5 mL	For acute middle ear infection (otitis media) in children, urinary tract infections due to susceptible microorganisms

ORAL SUSPENSIONS BY CATEGORY

4-Anthelmintics			
Albendazole	Zental	200mg/20ml	
5-Antifungals			
Nystatin	Mycostatin Squibb	100,000 U/mL	Antibiotic with antifungal activity. Suspension is held in mouth as long as possible before swallowing in treatment of mouth infections caused by *Candida* (*Monilia*) *albicans,* other *Candida* spp

ORAL SUSPENSIONS BY CATEGORY

6- *Nonsteroidal Anti-inflammatory*			
Indomethacin	Indocin Oral Suspension (Merck & Co.)	25 mg/5 mL	Patent ductus arteriolis
Mefenamic acid	Ponstan Pfizer		Pain reliever Antiprytic
Ibuprofen	Brufen Abbott		

Rectal suspensions

Barium Sulfate for Suspension, USP,	**May be employed orally or rectally**	**Diagnostic visualization of the gastrointestinal tract.**
5-aminosalicylic acid suspension	Rowasa (Solvay)	for treatment of Crohn disease, distal ulcerative colitis, proctosigmoiditis, and proctitis

Specifications

- An acceptable suspension possesses certain desirable qualities, among which are the following:

1. The suspended material should not settle too rapidly; the particles that do settle to the bottom of the container must not form a hard mass but should be readily dispersed into a uniform mixture when the container is shaken;
2. The particle size of the suspensoid should remain fairly constant throughout long periods of undisturbed standing.
3. The suspension must not be too viscous to pour freely from the bottle or to flow through a syringe needle. (The suspension should pour readily and evenly from its container)

Ideal suspensions

- The physical stability of a pharmaceutical suspension may be defined as the condition in which the particles do not aggregate and in which they remain uniformly distributed throughout the dispersion.
- As this ideal situation is seldom realized it is appropriate to add that if the particles do settle they should be easily re-suspended by a moderate amount of agitation.

Difference between suspensions and colloids

- The major difference between a pharmaceutical suspension and a colloidal dispersion is one of size of the dispersed particles, with the relatively large particles of a suspension liable to sedimentation owing to gravitational forces.
- Apart from this, suspensions show most of the properties of colloidal systems.

SEDIMENTATION RATE OF THE PARTICLES OF A SUSPENSION

- The various factors involved in the rate of settling of the particles of a suspension are embodied in the equation of Stokes law,

- dx/dt is the rate of settling,
- d is the diameter of the particles,
- ρ_i is the density of the particle,
- ρ_e is the density of the medium,
- g is the gravitational constant, and
- η is the viscosity of the medium

$$\frac{dx}{dt} = \frac{d^2(\rho_i - \rho_e)g}{18\eta}$$

- Stokes' equation was derived for an ideal situation in which uniform, perfectly spherical particles in a very dilute suspension settle without producing turbulence, without colliding with other particles of the suspensoid, and without chemical or physical attraction or affinity for the dispersion medium.

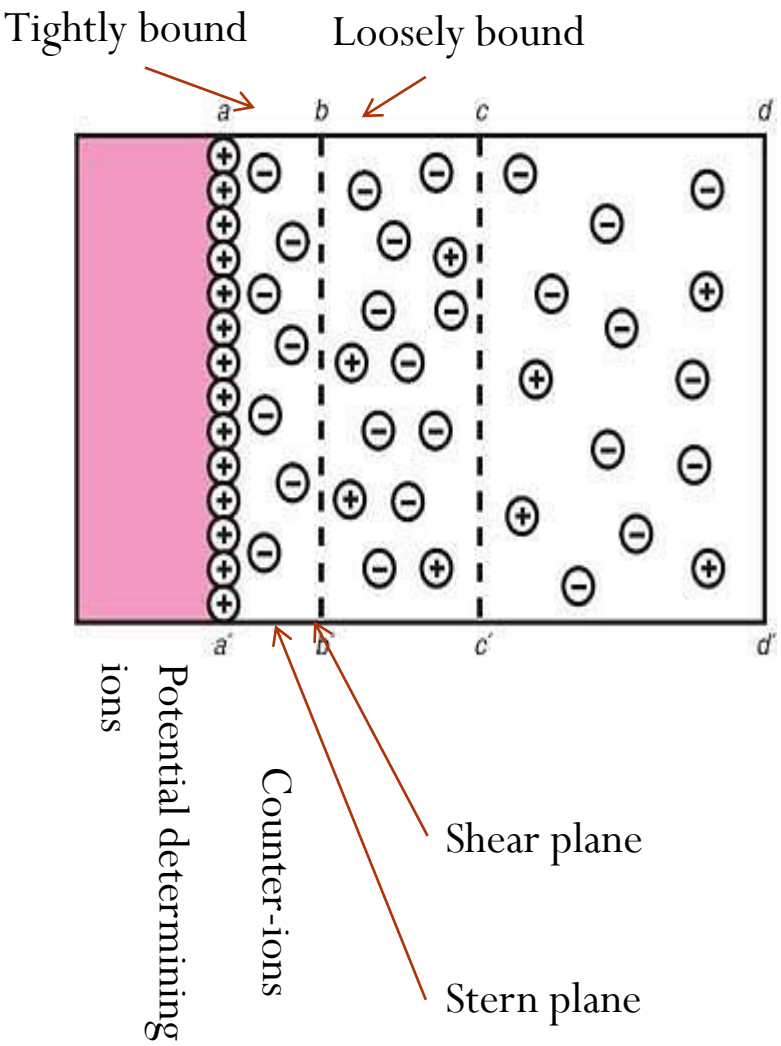
Factors affecting the rate of sedimentation

- From the equation it is apparent that the velocity of fall of a suspended particle is greater for larger particles than it is for smaller particles, all other factors remaining constant.
- **Reducing the particle size** of the dispersed phase produces a slower rate of descent of the particles.(in a range of 1-50μm)
- Also, the greater **the density** of the particles, the greater the rate of descent, provided the density of the vehicle is not altered. Because aqueous vehicles are used in pharmaceutical oral suspensions, the density of the particles is generally greater than that of the vehicle, a desirable feature.
- The rate of sedimentation may be appreciably reduced by increasing the **viscosity of the dispersion medium**, and within limits of practicality this may be done. However, a product having too high a viscosity is not generally desirable, because it pours with difficulty and it is equally difficult to redisperse the suspensoid. Therefore, if the viscosity of a suspension is increased, it is done so only to a modest extent to avoid these difficulties

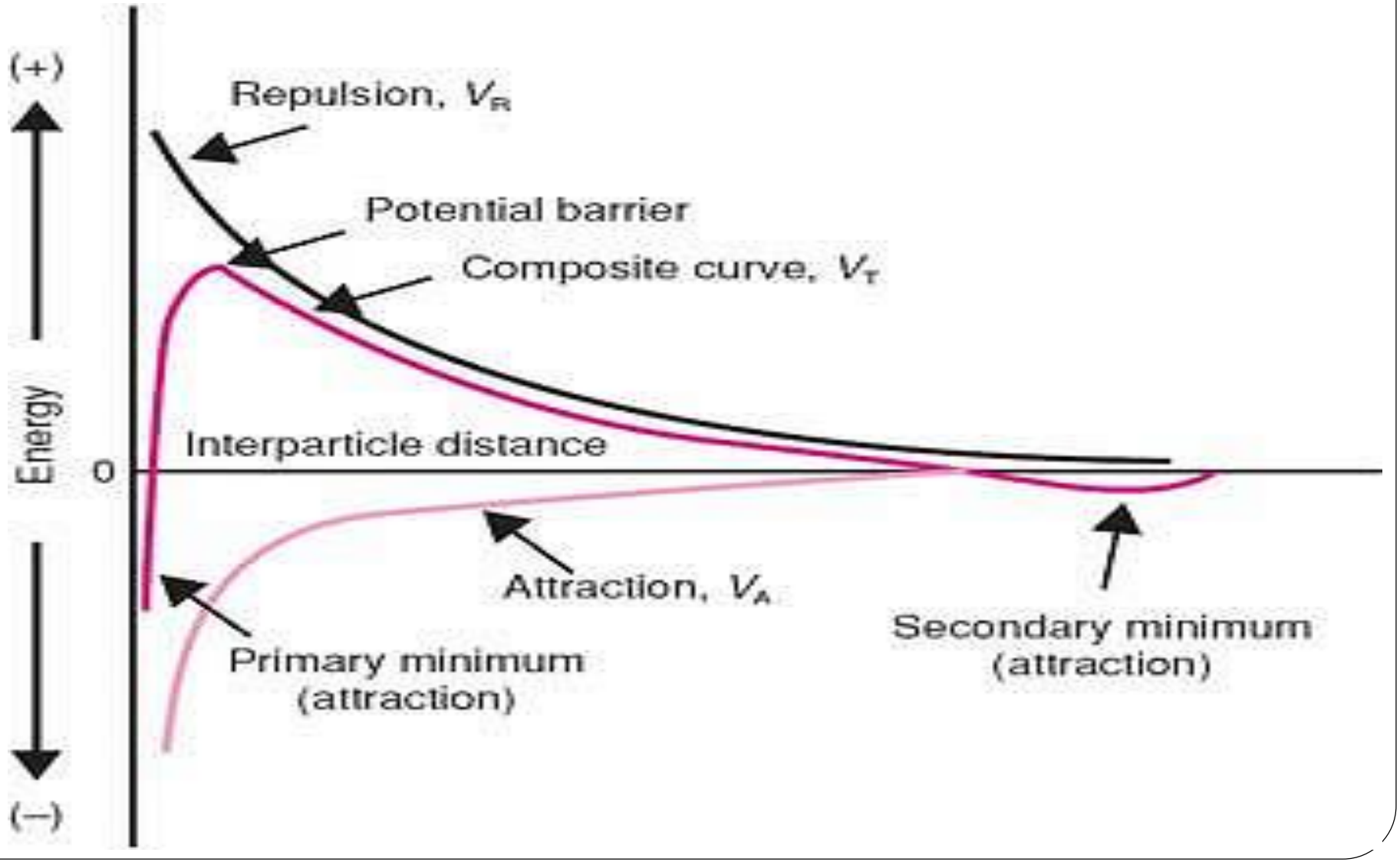
The electrical double layer

Electro-thermodynamic
(Nernst) potential

Electro-kinetic, or zeta potential



Verwey and Overbeek and Derjaguin and Landau DLVO theory



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1. Electrostatic repulsion. Repulsion potential V_R,
2. London-type van der Waals attraction. Attraction potential V_A,

When combined together forming the curve for the composite potential energy, V_T

- There is a deep potential "well" of attraction near the origin and a high potential barrier of repulsion at moderate distances.
- A shallow secondary trough of attraction (or minimum) is sometimes observed at longer distances of separation.
- The presence of a secondary minimum is significant in the controlled flocculation of coarse dispersions.
- Following this principle, one can determine somewhat quantitatively the amount of electrolyte of a particular valence type required to precipitate a colloid..

Suspension behavior

- A suspension in which all the particles remain discrete would, in terms of the DLVO theory, be considered to be stable.
- However, with pharmaceutical suspensions, in which the solid particles are very **much coarser**, such a system would sediment because of the size of the particles
- The electrical repulsive forces between the particles allow them to slip past one another to form a **close-packed arrangement** at the bottom of the container, with the small particles filling the voids between the larger ones.
- The **supernatant** liquid may remain cloudy after sedimentation owing to the presence of colloidal particles that remain dispersed.
- Those particles lowermost in the **sediment are gradually pressed together** by the weight of the ones above.
- The repulsive barrier is thus overcome, allowing the particles to **pack** closely together.

Coagulation –cake or clay formation

- Physical bonding, leading to 'cake' or 'clay' formation, may then occur owing to the formation of bridges between the particles resulting from crystal growth and hydration effects, forces greater than agitation usually being required to disperse the sediment.
- Coagulation in the primary minimum, resulting from a reduction in the zeta potential to a point where attractive forces predominate, thus produces coarse compact masses with a 'curdled' appearance, which may not be readily dispersed.

Deflocculated	Flocculated
Particles exist in suspension as separate entities	Particles form loose aggregates
Rate of sedimentation is slow, since each particle settles separately and the particle size is minimal	Rate of sedimentation is high , particles settle as flocs (collection of particles)
Sediment formed slowly	Sediment formed rapidly
Sediment pack into a cake difficult to redispose	Sediment is loosely packed
The sediment eventually becomes very closely packed, owing to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed which is difficult to redispose	The sediment is loosely packed Particles do not bond tightly to each other the sediment is easy to re-disperse
The suspension has a pleasing appearance since the suspended materials remains suspended for a relatively long time The supernatant remains cloudy even settling is apparent	Suspension is unsightly due to rapid sedimentation Clear supernatant , can be minimized if the volume of the sediment is made large

Sedimentation parameters

- Parameters used as quantitative measurement of flocculation in a suspension

1. Sedimentation volume F
2. The degree of sedimentation β

Sedimentation volume ratio, *F*,

- A convenient parameter for assessing a suspension is the sedimentation volume ratio, *F*, which is defined as the ratio of the final settled volume Vu to the original volume Vo.

$$F = Vu / Vo$$

- The ratio *F* gives a measure of the aggregated deflocculated state of a suspension and may usefully be plotted, together with the measured zeta potential, against concentration of additive, enabling an assessment of the state of the dispersion to be made in terms of the DLVO theory.
- The appearance of the supernatant liquid should be noted and the re-dispersibility of the suspension evaluated.

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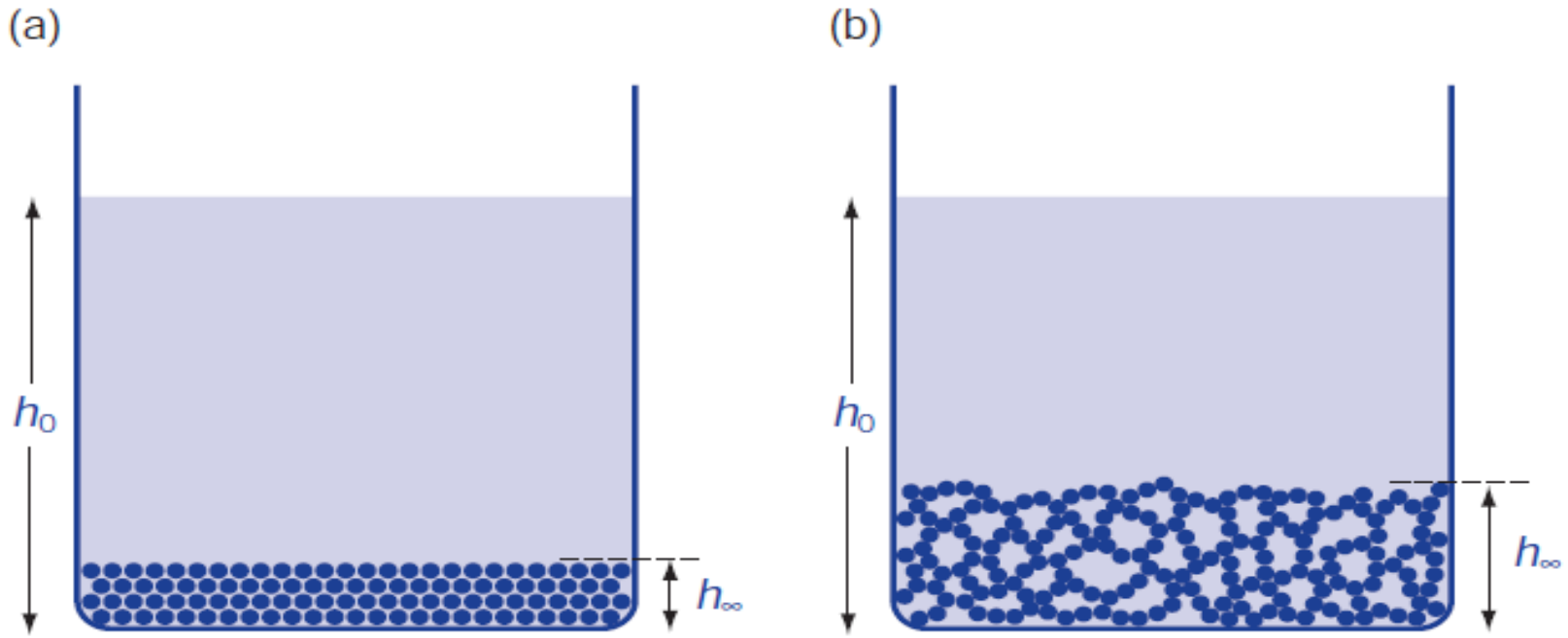


Sedimentation of (a) deflocculated and (b) flocculated suspensions.

Sedimentation volume

- F<1 ordinary case, sediment settles to some ultimate volume that is less than the original volume of the suspension
- F >1 particles form a loose fluffy network in the vehicle the final volume of the sediment may swell sufficiently to become greater than the total volume of the original suspension
- F=1 flocculation equilibrium acceptable suspension on standing show no sediment or clear supernatant

Degree of flocculation β

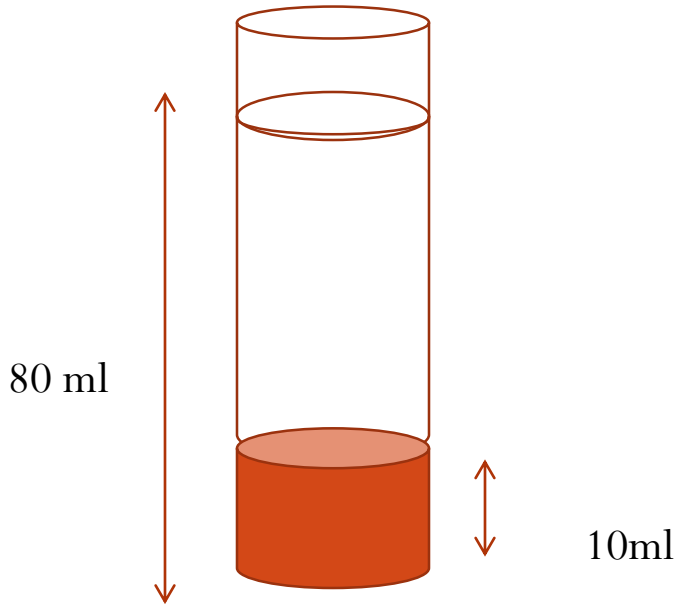
- Describes the relationship between the sedimentation volume of the flocculated suspension F to the sedimentation volume of the same suspension when deflocculated F∞
- $\beta = \frac{F}{F\infty}$
- $\beta = \frac{V_u/V_0}{V_\infty/V_0} = \frac{V_u}{V_\infty} =$

$$\frac{ultimate\ sediment\ volume\ of\ flocculated\ suspension}{ultimate\ sediment\ volume\ of\ deflocculated\ suspension}$$

Degree of flocculation

- β measure the degree of flocculation
- Large β suspension consists of floccules held loosely in an open scaffold like arrangement
- Small β value suspension condensed sediment
- Lower limit is 1 no flocculation in the system

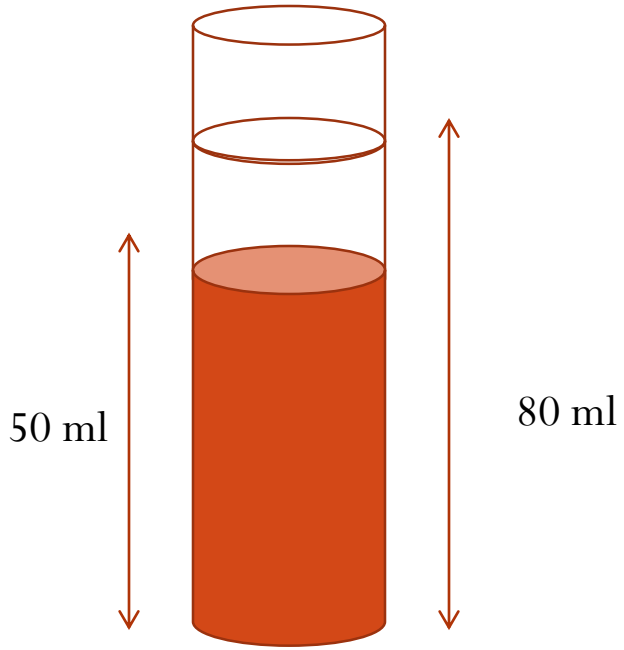
Deflocculated



$$F = \frac{10}{80} = 0.125$$

β=0.625/0.125 = 5

Flocculated



$$F = \frac{50}{80} = 0.625$$

Flocculation

- Particles flocculated in the secondary minimum form a loosely bonded structure, called a ***flocculate or floc.*** A suspension consisting of particles in this state is said to be flocculated.
- Although sedimentation of flocculated suspensions is fairly rapid, a loosely packed, high-volume sediment is obtained in which the flocs retain their structure and the particles are easily re-suspended. The supernatant liquid is clear because the colloidal particles are trapped within the floes and sediment with them. Secondary minimum flocculation is therefore a desirable state for a pharmaceutical suspension

Flocculation

1. **Particle size:** Particles greater than 1 /μm radius should, unless highly charged, show a sufficiently deep secondary minimum for flocculation to occur because the attractive force between particles, Va , depends on particle size.
2. **Particle shape:** Other factors contributing to secondary minimum flocculation are shape (asymmetric particles, especially those that are elongated, being more satisfactory than spherical ones)
3. **Concentration:** The rate of flocculation depends on the number of particles present, so that the greater the number of particles the more collisions there will be and the more flocculation is likely to occur

Controlled flocculation

- Agents added to the suspension to counteract the electrtical double layer are called flocculation agents

1 Addition of charged molecule;

A-Electrolytes

B- Detergents

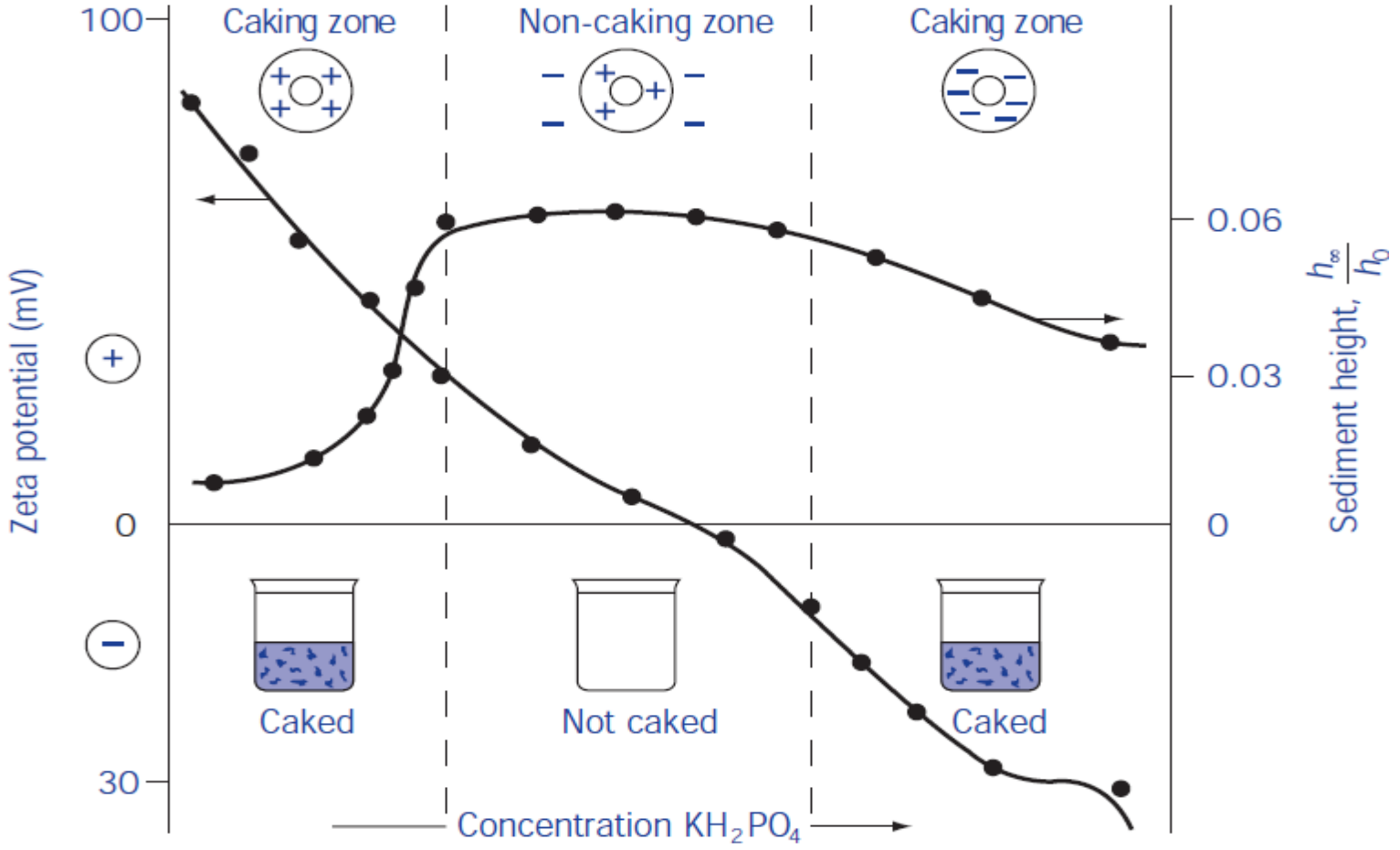
2- Polymers

Controlled flocculation

Addition of charged molecule

- The addition of electrolytes or ionic surface-active agents that reduce the zeta potential and hence Vr, resulting in the displacement of the whole of the DLVO plot to give a satisfactory secondary minimum, as with highly charged particles, to control the depth of the secondary minimum to induce a satisfactory flocculation state.
- The production of a satisfactory secondary minimum leading to floc formation in this manner is termed ***controlled flocculation*.**
- It is important to work at a constant, or narrow, pH range because the magnitude of the charge on the drug particle can vary greatly with pH.
- Other additives, such as flavoring agents, may also affect particle charge.

Controlled flocculation of bismuth sub-nitrate suspension using dibasic potassium phosphate as flocculating agent



Steric stabilization of suspensions

The use of non-ionic polymeric material - the concept of steric stabilization or protective colloid action.

This concept may be applied to pharmaceutical suspensions where naturally occurring gums such as Tragacanth, and synthetic materials such as non-ionic surfactants and cellulose polymers, may be used to produce satisfactory suspensions.

These materials may

- increase the viscosity of the aqueous vehicle and
- thus slow the rate of sedimentation of the particles,
- but they will also form adsorbed layers around the particles so that the approach of their surfaces and aggregation to the coagulated state is hindered ,the particles will not usually approach one another closer than twice the thickness of the adsorbed layer.

Polymer considerations

- However, an easily dispersed aggregated system is desirable.
- To produce this state a balance between attractive and repulsive forces is required. This is not achieved by all polymeric materials, and the equivalent of deflocculated and caked systems may be produced.
- The balance of forces appears to depend on both the **thickness** and the **concentration** of the polymer in the adsorbed layer. These parameters determine the Hamaker constant and hence the attractive force, which must be large enough to cause aggregation of the particles comparable to flocculation.
- The steric repulsive force, which depends on the concentration and degree of solvation of the polymer chains, must be of sufficient magnitude to prevent close approach of the uncoated particles, but low enough so that the attractive force is dominant, leading to aggregation at **about twice the adsorbed layer thickness**.

polymers

- Polysaccharide
- Acacia, tragacanth, alginate, starch, xanthan gum
- Water soluble cellulose
- Methylcellulose, *Hydroxyethylcellulose (Natrosol), Carmellose sodium (sodium carboxymethylcellulose), Microcrystalline cellulose*
- *Hydrated silicates*
- *Bentonite, Magnesium aluminium silicate (Veegum), Colloidal silicon dioxide (Aerosil)*
- *Carbomer*

Wettability

- One of the problems encountered in dispersing solid materials in water is that the powder may not be readily wetted This may be due to entrapped air or to the fact that the solid surface is hydrophobic.
- For a liquid to wet a powder completely there should be a decrease in the surface free energy as a result of the immersion process.
- Problems may arise because of the build-up of an adherent layer of suspension particles on the walls of the container just above the liquid line that occurs as the walls are repeatedly wetted by the suspension.
- This layer subsequently dries to form a hard, thick crust. Surfactants reduce this adsorption by coating both the glass and particle surfaces such that they repel each other.

Rheological properties of suspensions

- Flocculated suspensions tend to exhibit plastic or pseudoplastic flow, depending on concentration, whereas concentrated deflocculated dispersions tend to be dilatant.
- This means that the apparent viscosity of flocculated suspensions is relatively high when the applied shearing stress is low, but it decreases as the applied stress increases and the attractive forces producing the flocculation are overcome.
- Conversely, the apparent viscosity of a concentrated deflocculated suspension is low at low shearing stress, but increases as the applied stress increases. This effect is due to the electrical repulsion that occurs when the charged particles are forced close together, causing the particles to rebound and creating voids into which the liquid flows, leaving other parts of the dispersion dry.
- In addition to the rheological problems associated with particle charge, the sedimentation behavior is also of course influenced by the rheological properties of the liquid continuous phase.

Suspensions

Definition

- A pharmaceutical suspension is a coarse dispersion in which insoluble particles, generally greater than 1 /μm in diameter, are dispersed in a liquid medium, usually aqueous.
- Suspensions may be defined as preparations containing finely divided drug particles (the suspensoid) distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility.

(for)/ suspension

- Some suspensions are available in ready-to-use form, that is, already distributed through a liquid vehicle with or without stabilizers and other additives.
- Prepared suspensions not requiring reconstitution at the time of dispensing are simply designated as "**Suspension**."
- Other preparations are available as dry powders intended for suspension in liquid vehicles. Generally, this type of product is a powder mixture containing the drug and suitable suspending and dispersing agents to be diluted and agitated with a specified quantity of vehicle, most often purified water. Drugs that are unstable if maintained for extended periods in the presence of an aqueous vehicle (e.g., many antibiotic drugs) are most frequently supplied as dry powder mixtures for reconstitution at the time of dispensing. This type of preparation is designated in the USP by a title of the form "**for Suspension" or " to be reconstituted "**

Advantage (REASONS FOR SUSPENSIONS)

- An aqueous suspension is a useful formulation system for administering an **insoluble or poorly soluble drug.** The large surface area of dispersed drug ensures a high availability for dissolution and hence absorption.
- Certain drugs are chemically **unstable in solution** but stable when suspended. In this instance, the suspension ensures chemical stability while permitting liquid therapy
- The **disadvantage of a disagreeable taste** of certain drugs in solution form is overcome when the drug is administered as un-dissolved particles of an oral suspension. In fact, chemical forms of certain poor-tasting drugs have been specifically developed for their insolubility in a desired vehicle for the sole purpose of preparing a palatable liquid dosage form. 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, the result being Erythromycin Estolate Oral Suspension, USP

Uses

- Aqueous suspensions may also be used for parenteral and ophthalmic use(<10μm), rectal and provide a suitable form for the applications of dermatological materials to the skin.
- Suspensions are similarly used in veterinary practice, and a closely allied field is that of pest control.
- Pesticides are frequently presented as suspensions for use as fungicides, insecticides, and herbicides.

ORAL SUSPENSIONS BY CATEGORY

1-Antacid			
Magnesia and alumina	Maalox Suspension (Novartis Consumer Health)	Aluminum hydroxide 225 mg; magnesium hydroxide 200 mg/5 mL	Counteract gastric hyperacidity, relieve distress in the upper gastrointestinal tract
Aluminum hydroxide, magnesium carbonate	Gaviscon Liquid Antacid (GlaxoSmithKline	Aluminum hydroxide 95 mg; magnesium carbonate 358 mg/ 15 mL; sodium alginate	
2-Antiflatulent			
Simethicone		40 mg/0.6 mL	Symptomatic treatment of gastrointestinal distress due to gas. Reduces surface tension of gas bubbles, enabling them to coalesce and be released through belching or flatus

ORAL SUSPENSIONS BY CATEGORY

3- Anti-bacterials (Antibiotics)

Erythromycin Estolate		125, 200, 250 mg/5 mL	Broad-spectrum macrolide antibiotic; bacteriostatic activity
Sulfamethoxazole and trimethoprim	Bactrim Suspension (Roche), Septrin Suspension (GSK)	Trimethoprim 40 mg, sulfamethoxazole 200 mg/5 mL	For acute middle ear infection (otitis media) in children, urinary tract infections due to susceptible microorganisms

ORAL SUSPENSIONS BY CATEGORY

4-Anthelmintics			
Albendazole	Zental	200mg/20ml	
5-Antifungals			
Nystatin	Mycostatin Squibb	100,000 U/mL	Antibiotic with antifungal activity. Suspension is held in mouth as long as possible before swallowing in treatment of mouth infections caused by *Candida* (*Monilia*) *albicans,* other *Candida* spp

ORAL SUSPENSIONS BY CATEGORY

6- *Nonsteroidal Anti-inflammatory*			
Indomethacin	Indocin Oral Suspension (Merck & Co.)	25 mg/5 mL	Patent ductus arteriolis
Mefenamic acid	Ponstan Pfizer		Pain reliever Antiprytic
Ibuprofen	Brufen Abbott		

Rectal suspensions

Barium Sulfate for Suspension, USP,	**May be employed orally or rectally**	**Diagnostic visualization of the gastrointestinal tract.**
5-aminosalicylic acid suspension	Rowasa (Solvay)	for treatment of Crohn disease, distal ulcerative colitis, proctosigmoiditis, and proctitis

Specifications

- An acceptable suspension possesses certain desirable qualities, among which are the following:

1. The suspended material should not settle too rapidly; the particles that do settle to the bottom of the container must not form a hard mass but should be readily dispersed into a uniform mixture when the container is shaken;
2. The particle size of the suspensoid should remain fairly constant throughout long periods of undisturbed standing.
3. The suspension must not be too viscous to pour freely from the bottle or to flow through a syringe needle. (The suspension should pour readily and evenly from its container)

Ideal suspensions

- The physical stability of a pharmaceutical suspension may be defined as the condition in which the particles do not aggregate and in which they remain uniformly distributed throughout the dispersion.
- As this ideal situation is seldom realized it is appropriate to add that if the particles do settle they should be easily re-suspended by a moderate amount of agitation.

Difference between suspensions and colloids

- The major difference between a pharmaceutical suspension and a colloidal dispersion is one of size of the dispersed particles, with the relatively large particles of a suspension liable to sedimentation owing to gravitational forces.
- Apart from this, suspensions show most of the properties of colloidal systems.

SEDIMENTATION RATE OF THE PARTICLES OF A SUSPENSION

- The various factors involved in the rate of settling of the particles of a suspension are embodied in the equation of Stokes law,

- dx/dt is the rate of settling,
- d is the diameter of the particles,
- ρ_i is the density of the particle,
- ρ_e is the density of the medium,
- g is the gravitational constant, and
- η is the viscosity of the medium

$$\frac{dx}{dt} = \frac{d^2(\rho_i - \rho_e)g}{18\eta}$$

- Stokes' equation was derived for an ideal situation in which uniform, perfectly spherical particles in a very dilute suspension settle without producing turbulence, without colliding with other particles of the suspensoid, and without chemical or physical attraction or affinity for the dispersion medium.

Factors affecting the rate of sedimentation

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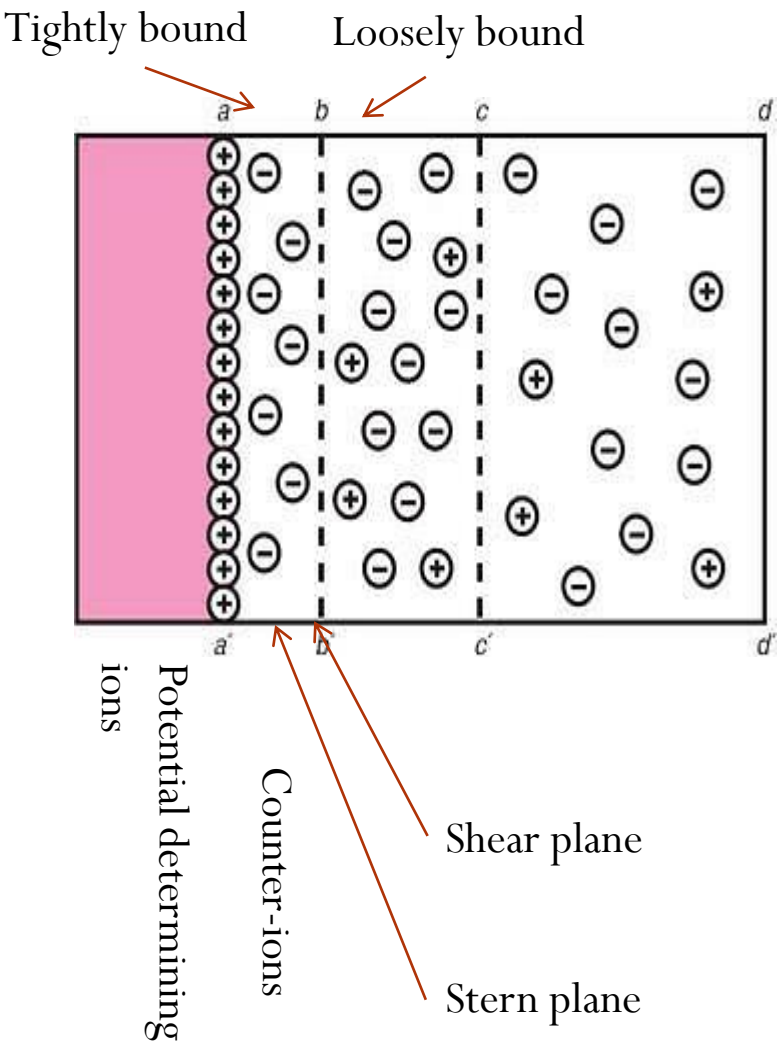

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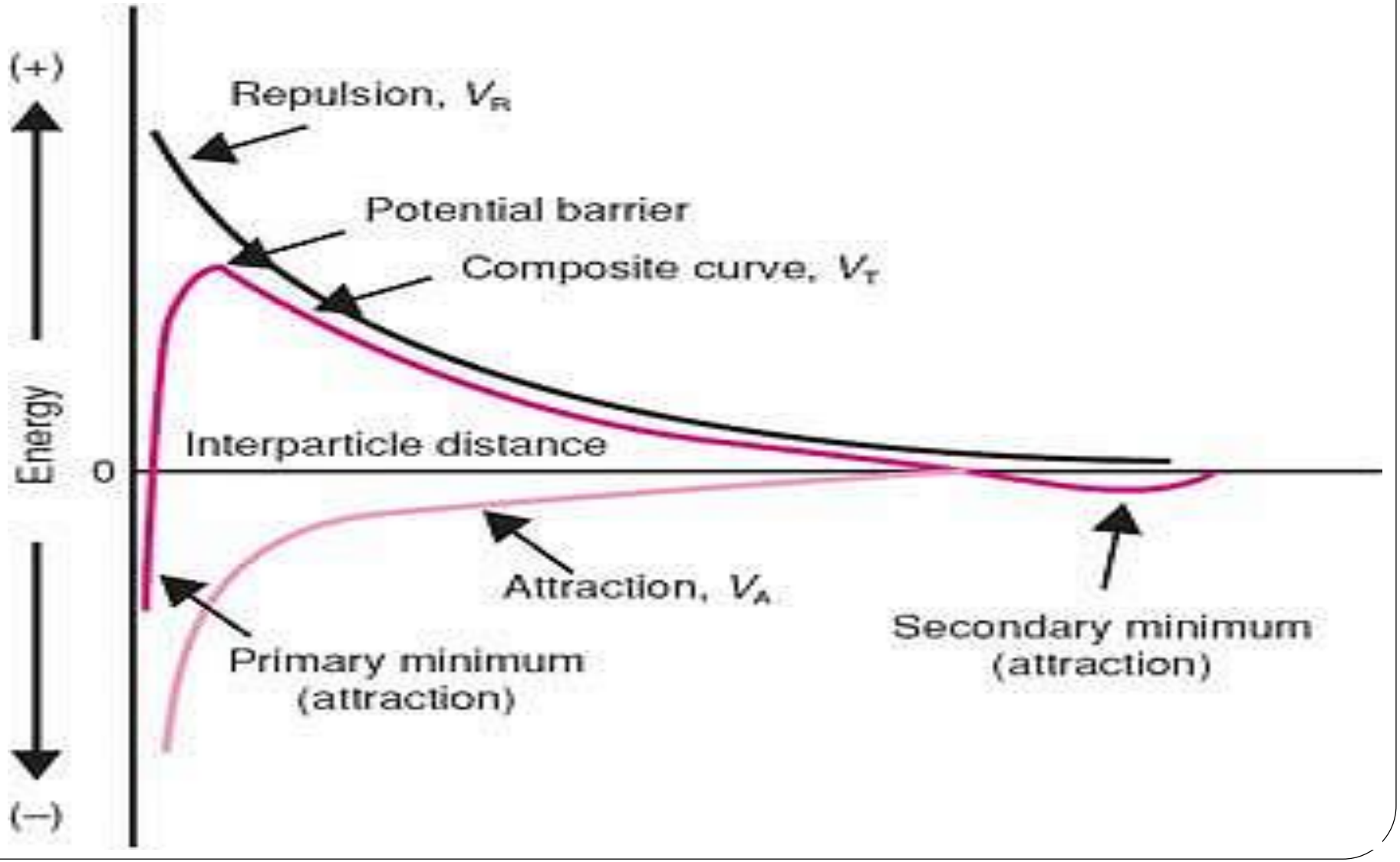

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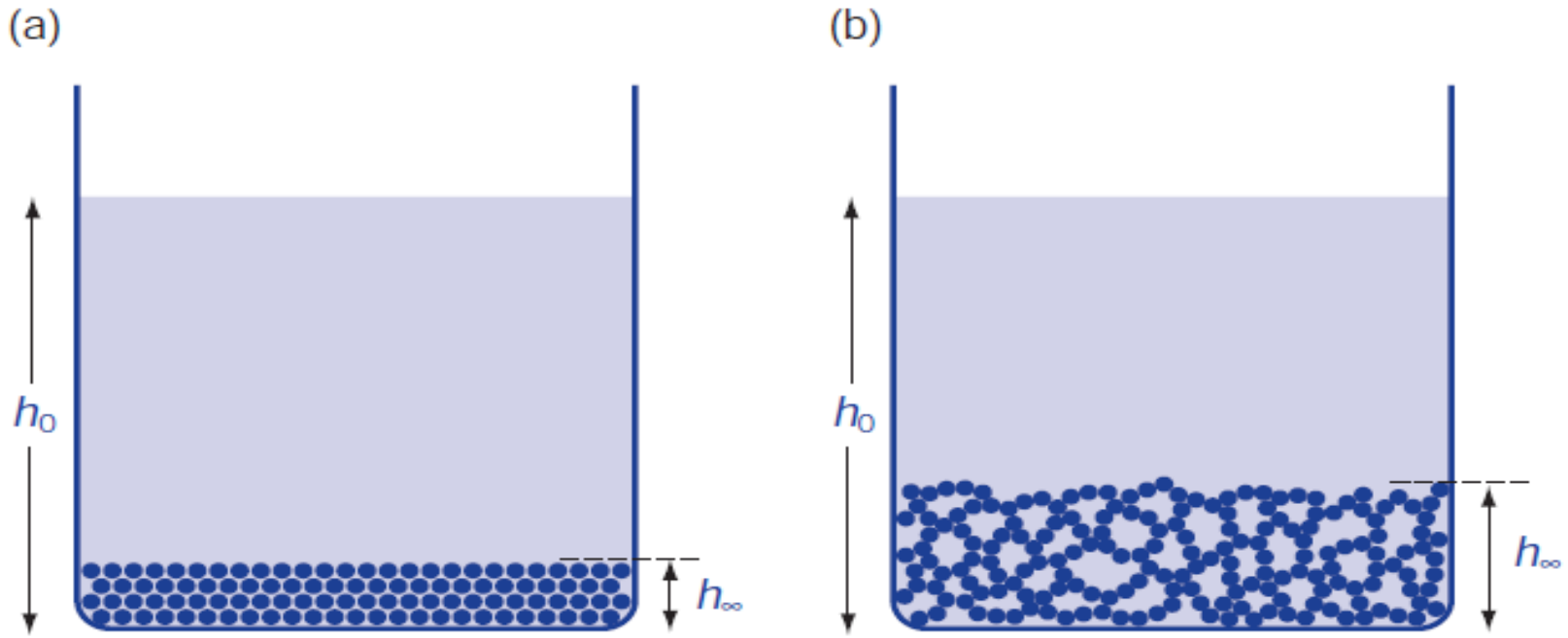

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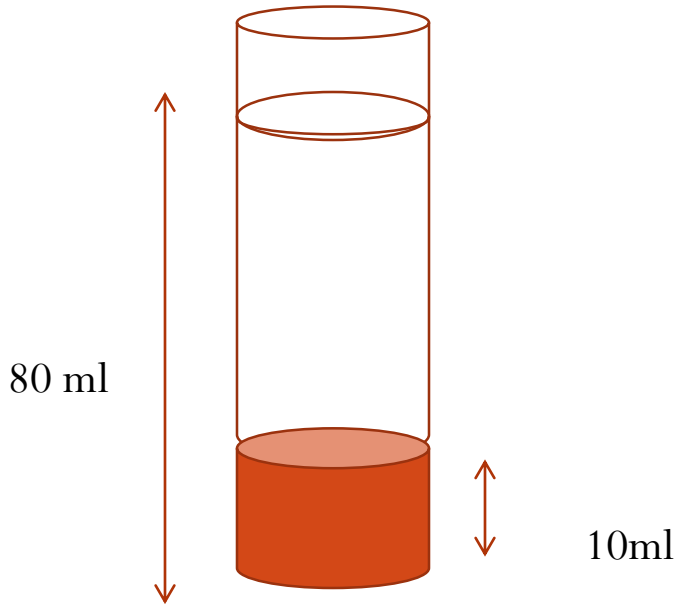

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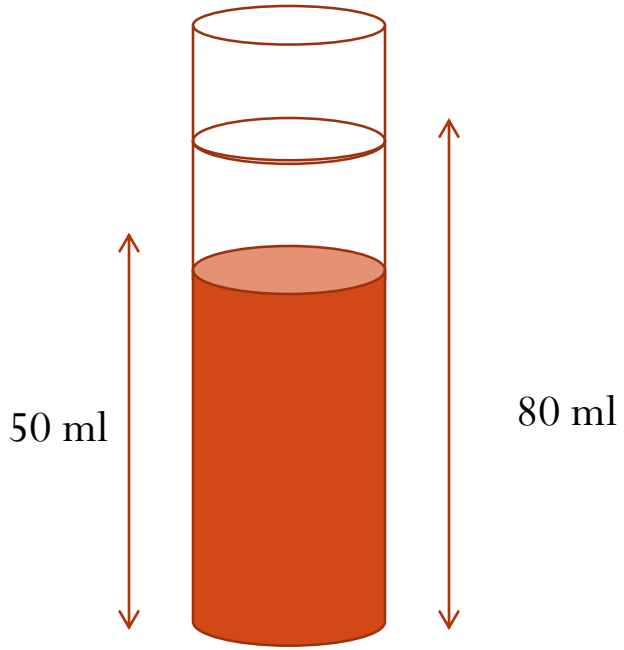

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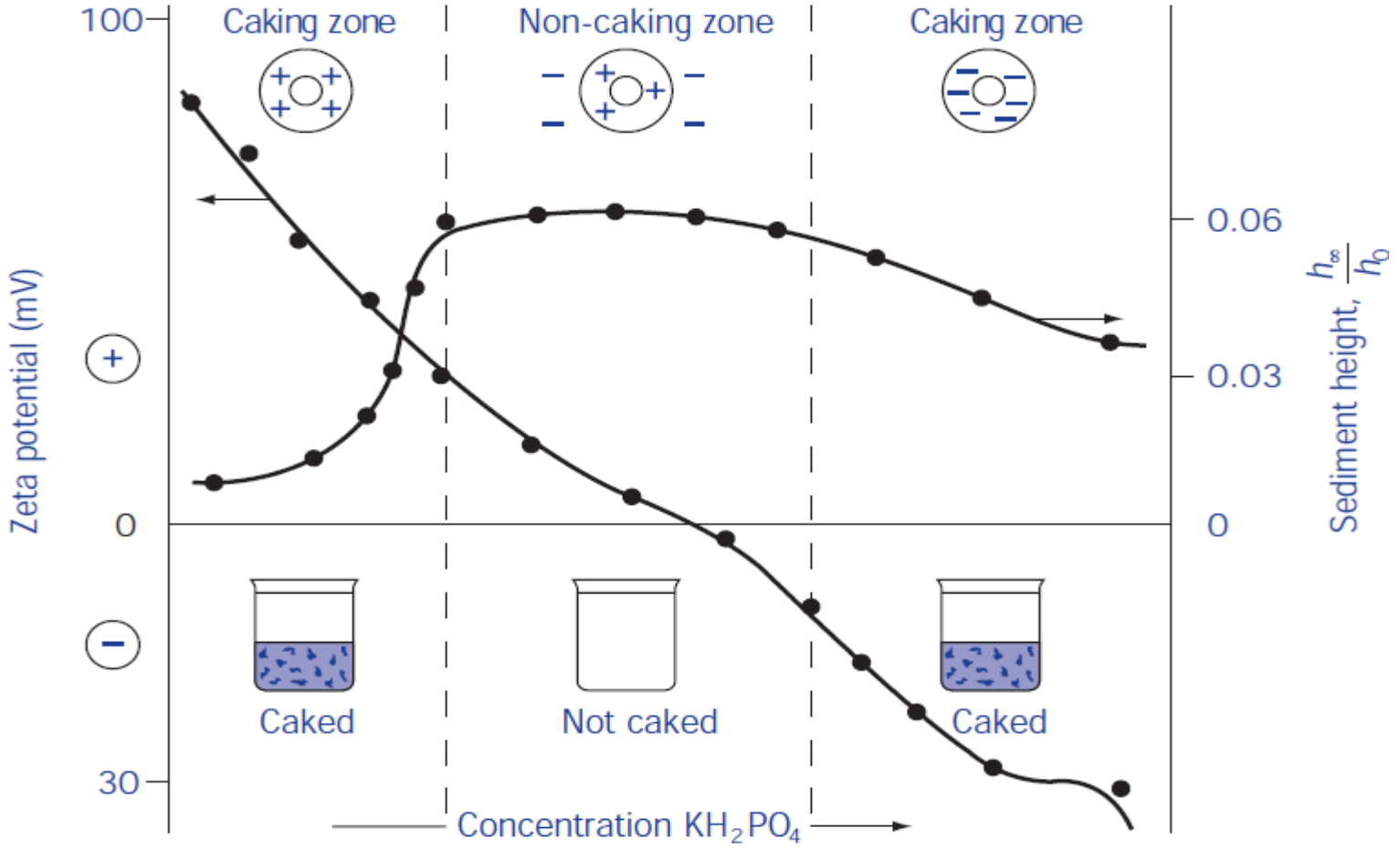
Addition of charged molecule

- The addition of electrolytes or ionic surface-active agents that reduce the zeta potential and hence Vr, resulting in the displacement of the whole of the DLVO plot to give a satisfactory secondary minimum, as with highly charged particles, to control the depth of the secondary minimum to induce a satisfactory flocculation state.
- The production of a satisfactory secondary minimum leading to floc formation in this manner is termed ***controlled flocculation*.**
- It is important to work at a constant, or narrow, pH range because the magnitude of the charge on the drug particle can vary greatly with pH.
- Other additives, such as flavoring agents, may also affect particle charge.

Controlled flocculation of bismuth sub-nitrate suspension using dibasic potassium phosphate as flocculating agent



Steric stabilization of suspensions

The use of non-ionic polymeric material - the concept of steric stabilization or protective colloid action.

This concept may be applied to pharmaceutical suspensions where naturally occurring gums such as Tragacanth, and synthetic materials such as non-ionic surfactants and cellulose polymers, may be used to produce satisfactory suspensions.

These materials may

- increase the viscosity of the aqueous vehicle and
- thus slow the rate of sedimentation of the particles,
- but they will also form adsorbed layers around the particles so that the approach of their surfaces and aggregation to the coagulated state is hindered ,the particles will not usually approach one another closer than twice the thickness of the adsorbed layer.

Polymer considerations

- However, an easily dispersed aggregated system is desirable.
- To produce this state a balance between attractive and repulsive forces is required. This is not achieved by all polymeric materials, and the equivalent of deflocculated and caked systems may be produced.
- The balance of forces appears to depend on both the **thickness** and the **concentration** of the polymer in the adsorbed layer. These parameters determine the Hamaker constant and hence the attractive force, which must be large enough to cause aggregation of the particles comparable to flocculation.
- The steric repulsive force, which depends on the concentration and degree of solvation of the polymer chains, must be of sufficient magnitude to prevent close approach of the uncoated particles, but low enough so that the attractive force is dominant, leading to aggregation at **about twice the adsorbed layer thickness**.

polymers

- Polysaccharide
- Acacia, tragacanth, alginate, starch, xanthan gum
- Water soluble cellulose
- Methylcellulose, *Hydroxyethylcellulose (Natrosol), Carmellose sodium (sodium carboxymethylcellulose), Microcrystalline cellulose*
- *Hydrated silicates*
- *Bentonite, Magnesium aluminium silicate (Veegum), Colloidal silicon dioxide (Aerosil)*
- *Carbomer*

Wettability

- One of the problems encountered in dispersing solid materials in water is that the powder may not be readily wetted This may be due to entrapped air or to the fact that the solid surface is hydrophobic.
- For a liquid to wet a powder completely there should be a decrease in the surface free energy as a result of the immersion process.
- Problems may arise because of the build-up of an adherent layer of suspension particles on the walls of the container just above the liquid line that occurs as the walls are repeatedly wetted by the suspension.
- This layer subsequently dries to form a hard, thick crust. Surfactants reduce this adsorption by coating both the glass and particle surfaces such that they repel each other.

Rheological properties of suspensions

- Flocculated suspensions tend to exhibit plastic or pseudoplastic flow, depending on concentration, whereas concentrated deflocculated dispersions tend to be dilatant.
- This means that the apparent viscosity of flocculated suspensions is relatively high when the applied shearing stress is low, but it decreases as the applied stress increases and the attractive forces producing the flocculation are overcome.
- Conversely, the apparent viscosity of a concentrated deflocculated suspension is low at low shearing stress, but increases as the applied stress increases. This effect is due to the electrical repulsion that occurs when the charged particles are forced close together, causing the particles to rebound and creating voids into which the liquid flows, leaving other parts of the dispersion dry.
- In addition to the rheological problems associated with particle charge, the sedimentation behavior is also of course influenced by the rheological properties of the liquid continuous phase.