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Introduction

- Liquid oral preparations are pharmaceutical preparations containing one or more active ingredient dissolved or dispersed in an aqueous or non-aqueous vehicle with or without additives.
- These dosage forms are available as ready-to-use liquids or powders for reconstitution that can be administered through oral, internal or into various body cavities such as nose, ear & eye etc.
- They are supplied as multi-dose or single dose preparations.
 - Solutions, Syrup, Elixir, Emulsion, Suspension, Dry powder for reconstitution

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Solutions

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Solutions

- Solutions are defined as homogenous liquids containing one or more soluble chemical substances dissolved usually in purified water intended for internal or external use.

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Method of Preparation

1. Solutions are prepared by any one of the four methods mentioned below.
 - Solutions are prepared by simple admixture of solute and solvent (solution method). E.g. Sodium chloride solution.
2. Solution prepared reaction, E.g. Iodine solution.
3. Solution prepared by simple solution with sterilization method. E.g. irrigating solutions, ophthalmic solutions.
4. Solutions prepared by extraction method. E.g. Tinctures of various crude drugs.

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Formulation Ingredients of Solution

1. **Solvents:** Solvents are also known as vehicles, because they form the medium which carries or holds the drug. E.g. Aqueous solvents and Non-aqueous solvents (Fixed oil, alcohol, Polyhydric alcohol, dimethyl – sulphoxide, ethyl ether, liquid paraffin etc.
2. **Buffers:** Agents which resist the change in pH. E.g. phosphate, tartrate, borates carbonates, citrates, gluconates, lactates, etc.
3. **Preservatives:** Agents which prevents the growth of microorganism. E.g. Benzalkonium chloride (0.002- 0.02%), Methyl and propyl parabens (0.1- 0.25%) etc.
4. **Organoleptic agents:** Agents which improve the organoleptic properties i.e., colour, odour and taste.
5. **Density Modifiers:** Agents which modify or change the density of the solutions. Especially used in preparation of spinal anaesthetic solution.

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Advantages of Solutions

1. They can be easily absorbed because the drug is in solution/liquid form.
2. Easy to swallow and more convenient to administer in comparison to solid dosage forms.
3. Suitable dosage form for pediatric preparation.
4. The irritation of drugs are reduced by administration in solution form.

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Disadvantages of Solutions

1. Inconvenient to transport and store because they are bulky and stored in glass container.
2. Stability of most drugs in solution form is lower.
3. Shelf life is shorter in solutions as compared to solid dosage forms.
4. Suitable media for the microbial contamination and may therefore require the addition of suitable preservative.

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Syrups

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Syrups

- Syrups are sweetened, viscous, concentrated or nearly saturated solutions of sucrose in purified water or other aqueous liquids.
- The concentration of sucrose in syrup is 85% w/v or 65% w/w.

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Classification of Syrups

Simple Syrup Only water is used as solvent.

Medicated Syrup Contains medicinal substances and used for therapeutic purposes.

Flavoured Syrup Contains various aromatic or pleasantly flavored substances but are non-medicated.

Inverted Syrup It is prepared by hydrolyzing sucrose with hydrochloric acid and neutralizing the solution with calcium or sodium carbonate.

Artificial Syrup It is prepared using artificial sweetening agent i.e., aspartame or saccharin and thickening agents methylcellulose, hydroxymethylcellulose

Dry Syrup The syrups that are manufactured in dry powder form, that require the addition of water at the time of dispensing.

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Method of Preparation

- Four methods are commonly used for preparation of syrup.
 - **Agitation without heat**
 - **Solution with heat**
 - **Addition of a medicated liquid**
 - **Percolation**

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1. Agitation without heat

- This method is used for the preparation of syrup containing volatile substances.
- In this process active substance is added in solution and agitated in a glass stoppered bottle.
- Closing of bottle is necessary to protect the syrup from contamination and loss of solution during the process.
- Cough syrups are commonly prepared by this process. E.g. Codeine syrup, Ephedrine sulphate syrup.

2. Solution with heat

- This process is generally prepared as it is simple, less time consuming method, particularly if the constituents are not affected by heat and non-volatile in nature.
- Sugar is generally added to the purified water and heat is applied until solution is formed.

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3. Addition of a medicated liquid

- This method to put to use in those cases in which tinctures, fluid extracts or other medicated substances in liquid forms are added to syrup to medicated.
- In this process some time precipitation takes place due to presence of resinous and oily substances.

4. Percolation

- In this method, either sucrose may be percolated to prepare the syrup, or the sucrose of the medicinal components may be percolated to form an extractive to which sucrose or syrup may be added.

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Formulation Ingredients in Syrup

1. Vehicle
2. Preservatives
3. Flavouring and Colouring agents
4. Stabilizers
5. Aromatic waters
6. Buffers
7. Viscosity Enhancers
8. Antioxidants

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Advantages of Syrups

1. They provide a pleasant means of administering a disagreeable tasting drug.
2. They are widely accepted by pediatric population.
3. Any water soluble drug which is stable in aqueous solution may be added to flavored syrup.
4. Syrup contains little or no alcohol.

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Disadvantages of Syrups

1. They are not suitable for patients who are on a restricted intake or those who are diabetic.
2. They may cause an increase in dental caries and gingivitis.
3. Pleasant taste may attract the children to consume extra doses than actually prescribed.
4. If sucrose concentration is not proper i.e. 66.7% w/w, it is prone to microbial growth, which requires addition of preservatives.

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Elixirs

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Elixirs

- Elixirs are clear, flavored, sweetened, hydro-alcoholic preparation containing potent or unpleasant tasting drugs, intended for oral administration.
- The alcoholic contents in elixirs vary from 5 to 40%.

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Types of Elixirs

Non-Medicated Elixir

- They are used purely as diluting agents or solvents for drugs containing approximately 23% alcohol.

Medicated Elixir

- Elixirs containing therapeutically active compounds are known as medicated elixirs.

Aromatic Elixir

- An aromatic elixir is a pharmaceutical preparation containing an volatile active ingredient.

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Method of Preparation

1. Simple dissolutions or mixtures of two or more liquids can be used to prepare elixirs after the ingredients have been dissolved in their respective solvents.
2. Those that are alcohol-soluble will dissolve in alcohol, and those that are water-soluble will dissolve in water
3. Aqueous solutions are added to alcoholic solutions to maintain the strength of the alcohol.
4. In this stage, some of the flavoring agents can separate from the product due to the reduction in alcohol strength.
5. Once the elixir is allowed to stand for a while, oil globules begin to precipitate
6. The filtrate is then added. The excess oils are absorbed by talc The resulting product is clear after filtration.

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Advantages of Elixirs

1. Drugs having poor water solubility can be formulated.
2. Hydroalcoholic preparation maintains both water soluble and alcohol soluble drugs in solutions. Hence they are the stable dosage forms compared to syrups.
3. Elixirs containing more than 10% alcohol usually acts as self-preserved and does not require additional preservatives.
4. Elixirs are less viscous than syrups and thus do not create difficulty in filtration.

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Disadvantages of Elixirs

1. Elixirs are less sweet and less viscous.
2. Elixirs are less effective in masking the bitter taste of drugs.
3. Elixirs having high percentage of alcohol require sweetening agent other than sucrose since sucrose is slightly soluble.
4. Elixirs are expensive than syrups.

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Difference between Syrup and Elixir

Sr. No.	Syrup	Elixir
1.	Syrups are sweetened, viscous, concentrated or nearly saturated solutions of sucrose in purified water or other aqueous liquids.	Elixirs are clear, flavored, sweetened, hydro-alcoholic preparation containing potent or unpleasant tasting drugs, intended for oral administration.
2.	Aqueous preparations.	Hydro-alcoholic preparations.
3.	Sweeter than elixirs.	Less sweet compared to syrup.
4.	More Viscous	Less Viscous

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Emulsions

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Emulsions

- Emulsion is a biphasic liquid preparation containing two immiscible liquids one of which is dispersed as globules (dispersed phase or internal Phase) in the other liquid (continuous phase or external phase) by using a suitable emulsifying agent.
- The diameter of the droplets varies from 0.1 -10 um.

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Advantages of Emulsion

- Emulsions may commonly use to administer oils that may have a therapeutic effect.
- Medicines having an unpleasant taste and odor can be made more palatable for oral administration in the form of an emulsion.
- Emulsion provides protection against drugs which are prone to oxidation or hydrolysis.
- Emulsions can be given by intravenous, E.g. fats, carbohydrates, vitamins.

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Disadvantages of Emulsion

- Emulsions are thermodynamically unstable and therefore must be formulated to stabilize from separation of the two phases.
- Emulsions are difficult to manufacture.
- If not stored properly, stability will be affected.

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Ideal Properties of Emulsion

1. It should be physically stable.
2. The flow properties of the emulsion should enable
3. the formulation to be easily removed from the container.
4. The formulation should be easily spread over the affected area in case of topical or external application.
5. It should be aesthetically and texturally pleasing.
6. If the emulsion is designed for oral route, the flavor must be acceptable.

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Types of Emulsions

- Emulsions can be classified on the basis of the properties of the dispersed phase and dispersion medium.

Oil in Water (O/W)

- Oil is dispersed phase and water is dispersion medium

Water in Oil (W/O)

- Water is dispersed phase and Oil is dispersion medium

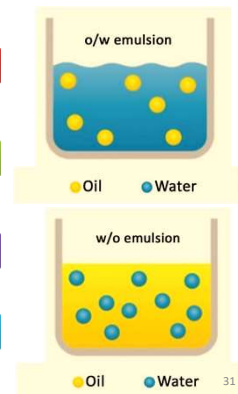
Multiple Emulsion

- O/W/O or W/O/W

Micro Emulsion

- Dispersed phase having diameter of 0.1 μm

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Classification of Emulsions

- Emulsions are classified on the basis of emulsifying agents used and mode of administration.

1. Classification of emulsions based on emulsifying agents used

1. Emulsions containing gum substitute. E.g. gum acacia, tragacanth.
2. Emulsions containing natural gum Eg. cellulose and its derivatives.
3. Emulsions containing various soaps.
4. Emulsions containing saponin.
5. Emulsions containing starch.
6. Emulsions containing natural waxes. E.g. wool fat, bees wax.
7. Emulsions containing synthetic waxes. Eg. emulsifying and macrogol wax.
8. Emulsions containing other emulsifying agents such as pectin, egg yolk, gelatin and lecithin's.

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2. Classification of emulsions based on mode of administration

1. **Emulsions for oral administration:** They are usually o/w type of emulsions used for administering oils having medicinal values. E.g. castor oil, cod-liver oil, almond oil.
2. **Emulsions for external use:** They can be o/w or w/o type of emulsions. E.g. Creams, lotions.
3. **Emulsions for parenteral use:** They can be o/w or w/o type of emulsions. o/w type of emulsions are administered through intramuscular route, whereas w/o type through subcutaneous route. E.g. fat soluble vitamins, oil soluble sex hormones.
4. **Emulsions for rectal use:** They are used in the form of enemas for the evacuation of bowels. E.g. enema.

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Emulsifying Agents

- An emulsifying agent must be employed in the preparation of stable emulsion. Its purpose is to prevent coalescence of droplets and maintain the stability of individual droplets of the continuous phase.
- Griffin devised a method for calculating balanced mixtures of emulsifying agents to provide a particular type of emulsion.
- It is called Hydrophilic Lipophilic Balance (HLB). Every emulsifying agent is given a number on HLB scale, which is divided into 18 units.

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Classification of Emulsifying Agents

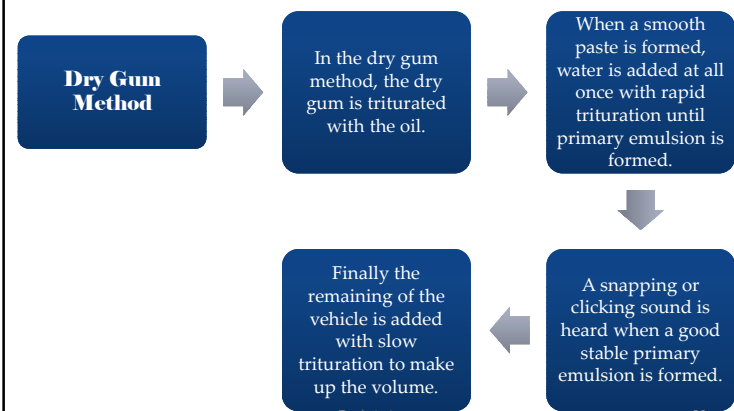
Table 7.5.1 : Classification of emulsifying agents

Emulsifying agents					
Natural		Semi-synthetic polysaccharides	Synthetic	Inorganic	Alcohols
Vegetable source	Animal source				
- Gum acacia	- Wool fat	- Methyl cellulose	- Anionic	- Milk of magnesia	- Carbowaxes
- Tragacanth	- Egg yolk	- Sodium carboxymethyl cellulose	- Cationic	- Magnesium oxide	- Lecithins
- Agar	- Gelatin		- Non-ionic	- Magnesium trisilicate	- Cholesterol
- Pectin				- bentonite	
- Starch					

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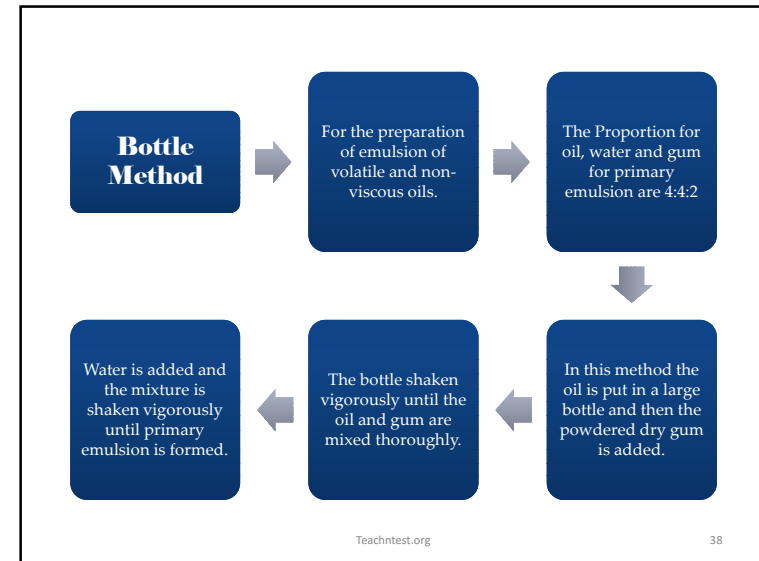
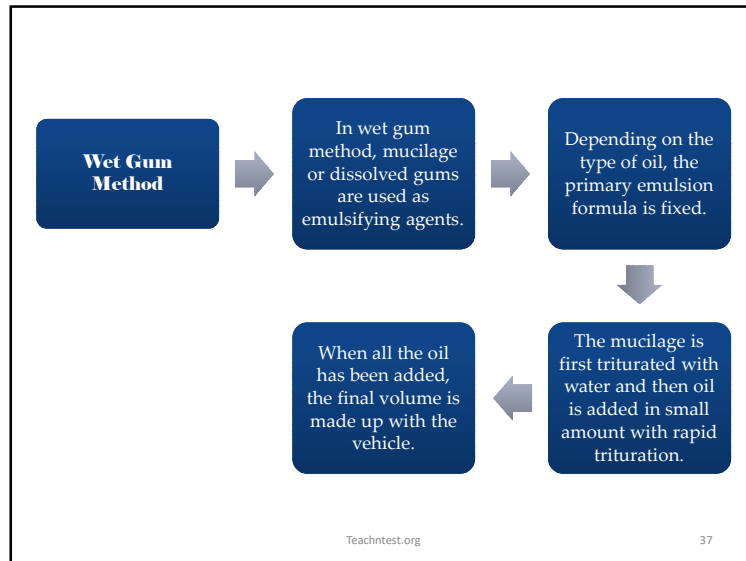
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Method of Preparation of Emulsions



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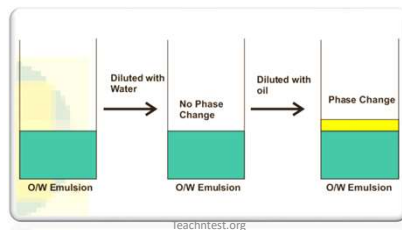
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Identification Tests for Different Types of Emulsions

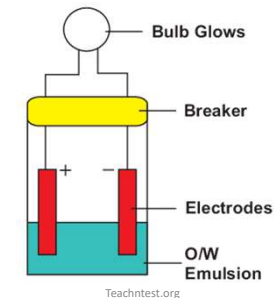
1. Dilution Test

- In this test the emulsion is diluted either with oil or water.
- If the emulsion is o/w type and it is diluted with water, it will remain stable as water is the dispersion medium but if it is diluted with oil, the emulsion will break as oil and water are not miscible with each other.



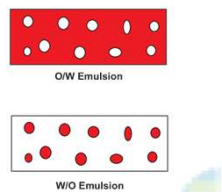
2. Electrical Conductivity Test

- The test is based on principle of conduction of electricity.
- An assembly is used, in which a pair of electrodes connected to an electric bulb is dipped into an emulsion.
- An o/w emulsion will conduct electricity as water conducts electricity, but a w/o will not conduct electricity.



3. Dye Solubility Test

- In this test an emulsion is mixed with a water soluble dye (amaranth) and observed under the microscope.
- If the continuous phase appears colored (red), it means that the emulsion is o/w type as water is in the external phase and the dye will dissolve in it to give color.
- If the scattered globules appear red and continuous phase colorless, then it is w/o type.



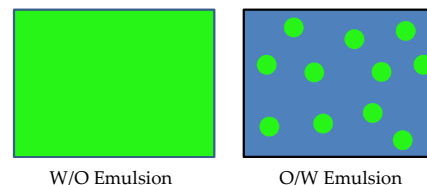
- Similarly if an oil soluble dye (Scarlet red C or Sudan III) is added to an emulsion and the continuous phase appears red, then it is w/o emulsion.

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4. Fluorescence Test

- If an emulsion on exposure to ultra-violet radiations shows-
- Continuous fluorescence under microscope, then it is w/o type and
- If it shows only spotty fluorescence, then it is o/w type.

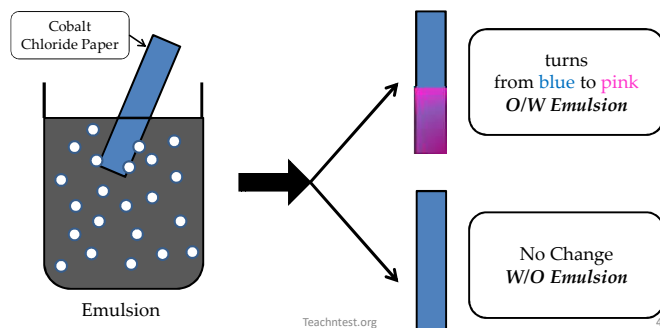


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5. Cobalt Chloride Test

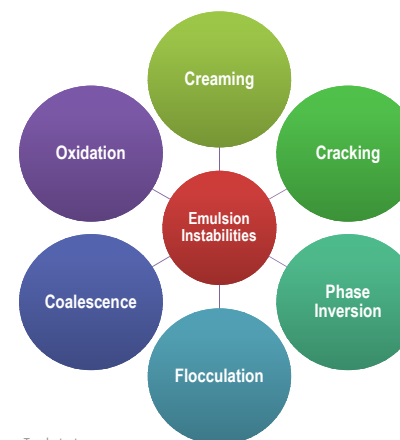
- When a filter paper soaked in cobalt chloride solution is dipped in to an emulsion and dried, it turns from blue to pink, indicating that the emulsion is o/w type.



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Instabilities of Emulsions



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1. Creaming

– Separation of dispersed phase into two regions, one containing more of the dispersed phase.

2. Cracking

– The globules of the dispersed phase coalesce and there is separation of dispersed phase into a separate layer.

3. Phase Inversion

– Change of one type of emulsion into other type i.e. O/W into W/O and vice-versa.

4. Flocculation

– The ability of emulsion droplets to flocculate.

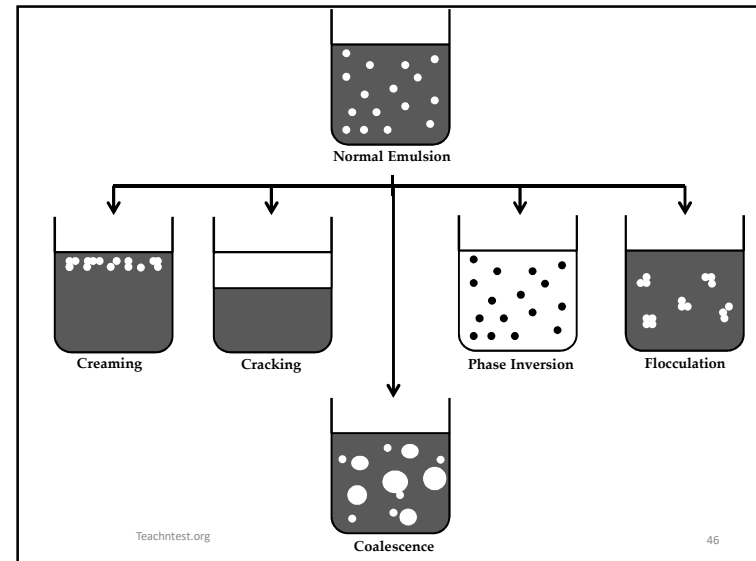
5. Coalescence or Ostwald's Ripening

– Coalescence, where the dispersed phase droplets merge to form large droplets, takes place in two distinct stages. Drainage of liquid films of continuous phase between the oil droplets. As they approach to one another, they end with the rupture of the film when a critical thickness is reached.

6. Oxidation

– Many of the oils and fats used in emulsion formulation are of animal or vegetable origin and can be Susceptible to oxidation by atmospheric oxygen or by the action of microorganisms.

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Evaluation of Emulsions

1. Tests to identify the type of emulsion.
2. Particle size or globule size analysis by microscopic method.
3. Rate of phase separation by centrifugation.
4. Viscosity by viscometer.
5. Electrophoretic properties.
6. Measurement of dielectric constant.
7. Organoleptic properties.

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Suspensions

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Suspension

- A Pharmaceutical suspension is a biphasic liquid dosage form in which the therapeutic agent is dispersed or suspended in the external phase.
- The particle size of the dispersed solid is usually greater than 0.5 μm . E.g. Magnesium hydroxide mixture, calamine lotion, etc.

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Type of Suspension

Sr. No.	Flocculated suspension	Deflocculated suspension
1.	Particles form loose aggregates and form network like structure known as 'flocs'	Particles exist as separate entities
2.	Rate of Sedimentation is high	Rate of Sedimentation is low
3.	Sediment is formed rapidly	Sediment is formed slowly
4.	Sediment is loosely packed and does not hard cake	Sediment is closely packed and forms a hard cake
5.	Re-disperse easily by shaking	Difficult to re-disperse by shaking

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Classification of Suspensions

1. Based on route of administration

- Oral
- Parenteral
- Topical

2. Based on proportion of solid particles

- Dilute (2 to 10% w/v solid)
- Concentrated (50% w/v solid)

3. Based on electro-kinetic nature of solid particles

- Flocculated
- Deflocculated

4. Based on size of solid particles

- Colloidal (< 1 micron)
- Coarse (> 1 micron)

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Preparation of Suspensions

These are generally two types :

1. Those in which the insoluble substances are added to the vehicle or the vehicle is added to the insoluble substances.
2. Those in which the insoluble material is formed in the liquid due to the interaction of two or more ingredients.

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1. Suspensions Containing Diffusible Solids

- Diffusible solids are those substances which do not dissolve in water, but on shaking they can be mixed with it and remain evenly distributed throughout the liquid for sufficiently long time allowing uniform distribution of the drug in each dose.

2. Suspensions Containing Indiffusible Solids

- Indiffusible solids are those substances which do not dissolve in water and do not remain evenly distributed in the vehicle for sufficiently long time to ensure uniformity of the measured dose.

3. Suspensions Produced By Chemical Reactions

- The highly diluted solutions of the reacting substances are mixed together so as to form very finely divided precipitates that can be easily distributed throughout the liquid by shaking.

4. Suspensions Containing Precipitate-forming Liquids

- Precipitate-forming liquids are not only insoluble in water but they form indiffusible precipitates particularly when salts are present. They contain resinous matter and when mixed with water lead to precipitation of the resin and may stick to the sides of the bottle which will be difficult to re-disperse by shaking.

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Formulation Ingredients of Suspensions

1. Suspending agents
2. Flocculating agents
3. Thickeners/Protective Colloids
4. Wetting agents
5. Preservatives
6. Antioxidants
7. Chelating agents
8. Buffering agents
9. Sweetners
10. Flavors

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Ideal Properties of Suspension

1. The sediment formed should be easily re-suspended by the use of moderate shaking.
2. It should be easy to pour.
3. It should have pleasant odor, color and palatability.
4. It should have good syringeability.
5. It should be physically, chemically microbiologically stable.
6. Parenteral ophthalmic suspension should be sterile.

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Advantages of Suspensions

1. Certain drugs which are unstable in solution form are stable when suspended and dispensed as suspensions.
2. The disagreeable taste of certain drugs in solution form is negligible when they are given in their suspension form.
3. Mostly oral suspensions have aqueous vehicles which might be flavored or sweetened to impart patient compliance.
4. They may be formulated to provide controlled drug delivery.

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Disadvantages of Suspensions

1. These are fundamentally unstable and therefore require formulation skill to ensure that the physical stability of the formulation is retained over the period of the shelf-life.
2. The formulation of stable suspension formulation is difficult.
3. Suspension being the liquid dosage form is susceptible for physical, chemical and microbial contamination.
4. Rheological properties of suspension are often difficult to maintain in suspension with high concentration of indiffusible solids.

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Evaluation of Suspensions

1. Sedimentation volume "F"
2. Redispersability
3. Rheological Characteristics
4. Electro kinetic method
5. Micromeritic method

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Dry Powder for Reconstitution

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Dry Powder for Reconstitution

- These medicament in powder that form and are dosage forms contain the should be reconstituted by dissolving or suspending in water before administration. They are also known as powder for suspension and dry syrups.
- **Types of Dry Powder for Reconstitution**
 - Dry powder for Oral Solutions
 - Dry powder for Oral Suspensions and Syrups
 - Dry powders for Oral Drops
- **Method of Preparation**
 - Direct Mixing
 - Dry or Wet Granulation

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Advantages of Dry Powder

1. Accurate dosing is possible as the dose is packed in single dose sachets.
2. Drug dose remains unaffected of any physical factors like temperature, sedimentation rate and liquid flow properties.
3. Packaging of the powder mixture is done in sachets (single dose) making the formulation to carry.
4. Stable on storage and when reconstituted with an ingestible for administration, the corresponding liquid suspension is stable for the duration for which the therapy is required.

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Disadvantages of Dry Powder

1. Particle size and Powder flow affect the homogeneity of the preparation.
2. Loss of the active ingredient during mixing, the loss is significant if the drug is potent.

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