

EMULSION

Syllabus:

Definitions, general formulation of an emulsion and the components used in the formulation of emulsions with examples: Emulsifying agents, oil phase ingredients, aqueous phase ingredients, preservatives, stabilizers, coloring and flavouring agents and such other components processing and equipments on industrial scale. An account of lotions, creams, collodions with the processing and equipment.

Questions:

- Q.1 What are emulsions and emulsifying agents? Give examples. [8]
Q.2. Give any one method of formulation of emulsion and production on large scale with different additives. (98) [8]
Q.3. Explain the different mechanical equipments those are at present available for emulsification. (96) [8]
Q.4. Discuss problems that may arise in production of emulsions. (96) [8]
Q.5. Write notes on auxiliary emulsifiers.

DEFINITION

An emulsion is a thermodynamically unstable dispersed system consisting of at least two immiscible liquid phase, one of which is dispersed as globules in the other liquid phase.

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

Emulsified systems range from lotions of relatively low viscosity to ointments and creams, which are semisolid in nature.

The particle diameter of the dispersed phase generally extends from about 0.1 to 10 μm and as 100 μm are not uncommon in some preparations.

TYPES OF EMULSIONS

(I) Ordinary emulsion systems / Primary emulsion systems / Simple emulsion systems

- (i) o/w type – oil dispersed in water
oil → dispersed phase
water → continuous phase
- (ii) w/o type – water dispersed in oil
water → dispersed phase
oil → continuous phase

(II) Special emulsion systems

- (i) Multiple emulsions → w/o/w – type
 o/w/o – type
- (ii) Micro emulsion

Simple emulsion type:

o/w- type of emulsion is a system in which the oil is dispersed as droplet throughout the aqueous phase. Most pharmaceutical emulsions designed for oral administration are of the o/w type; emulsified lotions and creams either of o/w or w/o type depending on their use.

Certain foods such as butter and some salad creams are w/o type emulsions.

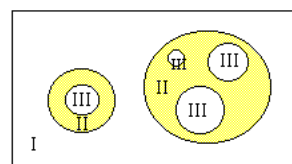
Multiple emulsion type

These multiple emulsions have been developed with a view to delay the release of an active ingredient. In this type of emulsions three phases are present, i.e. the emulsion has the form w/o/w or o/w/o. In these “emulsions within emulsions”, any drug present in the innermost phase now has to cross two phase-boundaries to reach the external continuous phase.

I : Continuous phase (External aqueous phase)

II: Middle oil phase

III: Inner aqueous phase



Photomicrograph of w/o/w emulsion system

Advantages of multiple emulsions

- (i) Prolongation of drug action
- (ii) Location of drug in the body.

Micro emulsions

Microemulsions are liquid dispersion of water and oil that are made homogeneous, transparent and stable by the addition of relatively large amount of a surfactant and a co-surfactant. They appear to represent a state intermediate between thermodynamically unstable emulsions and solubilised systems.

Unlike emulsions, they appear as clear transparent solution, but unlike solubilised systems microemulsions may not be thermodynamically stable.

Microemulsions containing droplets (w/o or o/w types) with the globule size 10 to 200nm and the volume fraction of the dispersed phase varies from 0.2 to 0.8.

DETERMINATION OF EMULSION TYPE

Several methods are commonly used to determine the type of emulsion. The types of emulsion determined by one method should always be confirmed by means of second method.

(1) Dye solubility test

A small amount of a water soluble dye (e.g. methylene blue or brilliant blue) may be dusted on the surface of the emulsion.

If water is the external phase (i.e. o/w type) then the dye will be dissolved uniformly throughout the media.

If the emulsion is of the w/o -type then particles of dye will lie in clumps on the surface.

(2) Dilution test

This method involves dilution of the emulsion with water. If the emulsion mixes freely with the water, it is of o/w -type. Generally, addition of disperse phase will crack an emulsion.

(3) Conductivity test

This test employs a pair of electrodes connected to an external electric source and immersed in the emulsion. If the external phase is water, a current will pass through the emulsion and can be made to deflect a volt-meter needle or cause a light in the circuit to glow. if the oil is the continuous phase then the emulsion will fail to carry the current.

Methods for determination of emulsion type:

Test	Observation	Comments
1. Dilution test	Emulsion can be diluted only with external phase.	Useful for liquid emulsions only.
2. Dye test	Water-soluble solid dye tints only o/w emulsion and reverse. Microscopic observation usually is helpful.	May fail if ionic emulsifiers are present.
3. Conductivity test	Electric current is conducted by o/w emulsions, owing to the presence of ionic species in water.	Fails in nonionic o/w emulsions.
4. Fluorescence test	Since oils fluoresce under UV-light, o/w emulsions exhibit dot pattern, w/o emulsions fluoresce throughout.	Not always applicable
5. CoCl ₂ / filter paper test	Filter paper impregnated with CoCl ₂ and dried (blue) changes to pink when (o/w) emulsion is added.	May fail if emulsion is unstable or breaks in presence of electrolyte.

FORMULATION OF EMULSION

In developing the formula of an emulsion the crucial decisions are related to the choice of the aqueous and oil phases and of the emulgents and their relative proportions. There can be no general guideline in this respect and the choice of phases and emulgents should be related to the qualities desired for the final product. Usually, ingredient selection is made on the basis of the experience and personal tastes of the formulator and by trial and error.

CHEMICAL PARAMETERS

Chemical stability

All the ingredients of an emulsion should be chemically compatible.

e.g. a soap cannot be used as an emulsifier in a system having a final pH of less than 5.

e.g. some lipids are subjected to chemical changes due to oxidation (rancidity); so in general it is simpler to avoid their use than to depend on antioxidants

Safety

All the ingredients should pass the toxicological tests. It is essential, therefore, for the formulator to depend heavily on toxicologic information from suppliers or in the scientific literature, and on regulatory activities by governmental agencies.

Choice of lipid phase

The choice of lipid phase depends on the ultimate use of the product.

- (i) If the oily phase is the active-ingredient itself (e.g. liquid paraffin emulsion) the formulator has nothing to choose from.
- (ii) The drug in a pharmaceutical preparation should not be too soluble in lipid phase then it will reduce the rate of transfer of the drug molecule to other phases.
- (iii) Emulsions prepared for topical purpose (e.g. cosmetics and pharmaceutical emulsions) should possess a good "feel". Emulsions normally leave a residue of the oily components on the skin after the water has evaporated. Therefore, the tactile characteristics of the combined oil phase are of great importance in determining consumer acceptance of an emulsion

Phase - volume ratio

The ratio of the internal phase to the external phase is frequently determined by the **solubility** of the active ingredients, which must provide the required dose.

If this is not the primary criteria, the phase ratio is normally determined by the desired **consistency** of the product. For liquid emulsions the limits of internal phase vary from 40 to 60%, since with such amounts a stable and acceptable emulsion can be prepared. Lower amounts of internal phase (i.e. disperse phase) gives a product of low viscosity with pronounced degree of *creaming* while higher percentage may produce highly viscous emulsions with tendency of *phase inversion*.

TABLE 1: *Ingredients for oil-phase of emulsions*

Class	Identity	Consistency
Hydrocarbon	Mineral oils	Fluids of varying viscosity
Hydrocarbon	Petrolatum	Semisolid
Hydrocarbon	Polyethylene waxes	Solids
Hydrocarbon	Microcrystalline waxes	Solids
Ester	Vegetable oils	Fluids of varying viscosity
Ester	Animal fats	Fluids or solids
Ester	Lanolin	Semisolid
Ester	Synthetic (e.g. isopropyl myristate)	Fluids
Alcohols	Long chain (natural & synthetic)	Fluids or solids
Fatty acids	Long chain (natural & synthetic)	Fluids or solids
Ethers	Polyoxypropylenes	Fluids of varying viscosity
Silicones	Substituted silicones	Fluids of varying viscosity
Mixed	Plant waxes (e.g. Candellia)	Solid
Mixed	Animal waxes (e.g. Beeswax)	Solid

Choice of emulsifying agents / Emulsifiers / Emulgents

Emulsifying agents are broadly classified into three classes:

- (i) Synthetic emulsifying agent / Surface active agents (SAA) / Surfactants
- (ii) Hydrophilic colloid
- (iii) Finely divided solids

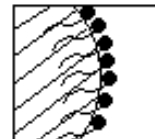
When an emulsifier is used alone to stabilize an emulsion – it is called *primary emulsifier*. Some times a second emulsifier is used to help the primary emulsifier in stabilizing the system – the second emulsifier is known as *auxiliary emulsifier*. Generally emulsifiers from (ii) and (iii) category are used both as primary and auxiliary emulsifier.

A successful emulsifier must possess some or all of the following characteristics:

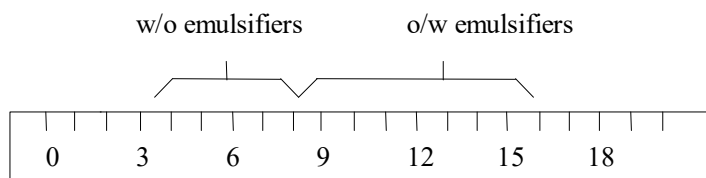
- (a) The surface tension should be reduced to a value less than 10 dynes/cm².
 (b) A complete and coherent film should be formed around the dispersed globules so as to prevent their coalescence.
 (c) Should assist in building up the zeta potential and viscosity since both of these phenomena contribute to the stability.

Choice of synthetic surface active agents / Surfactants:

Molecules and ions that are absorbed at interfaces are termed surface-active-agents or surfactants. An alternative expression is *amphiphile*, which suggests that the molecule or ion has a certain affinity for both polar and nonpolar solvents. Due to the amphiphilic nature of surfactants they absorb at the oil-water interface.



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



Griffin's HLB Scale

Mode of action of synthetic surfactants

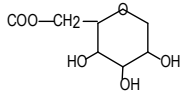
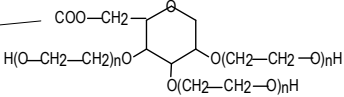
This group of emulsifiers form a flexible film on the oil-water interface. They lower interfacial tension markedly and this contribute to the stability of emulsion. In case of ionic surfactants surface charge is developed, increasing the zeta-potential, which will cause repulsion between two adjacent globules.

e.g. Sodium lauryl sulphate

Polyoxyethylene sorbitan mono oleate (Polysorbate 80).

Classification of synthetic Surface Active Agents

Class	Surface Active Agent	Chemical formula (in aqs. soln.)		
		Lipophilic group	Hydrophilic group	Surface inactive ion
1. <i>Anionic</i> (a) Alkali soap (b) Organic sulphates (c) Organic sulphonates	Potassium stearate	C ₁₇ H ₃₅	COO ⁻	K ⁺
	Sodium lauryl sulphate (Sod. dodecyl sulphate)	C ₁₂ H ₂₅	OSO ³⁻	Na ⁺
	Sodium cetyl sulphonate (Sod. hexadecane sulfonate)	C ₁₆ H ₃₃	SO ³⁻	Na ⁺
2. <i>Cationic</i> (a) Quaternary ammonium compounds (b) Pyridinium compounds	Cetyl trimethyl ammonium bromide (or cetrimide)	C ₁₆ H ₃₃	N ⁺ (CH ₃) ₃	Br ⁻
	Dodecyl pyridinium chloride	C ₁₂ H ₂₅	N ⁺ C ₅ H ₅	Cl ⁻
3. <i>Ampholytic</i> Amino acids	N-dodecyl alanine	C ₁₂ H ₂₅	In alkaline soln. – anionic NH – CH ₂ – CH ₂ – COO ⁻	Na ⁺
		C ₁₂ H ₂₅	In acid solution – cationic N ⁺ H ₂ – CH ₂ – CH ₂ – COOH	Cl ⁻
		C ₁₂ H ₂₅	At isoelectric point – zwitterion N ⁺ H ₂ – CH ₂ – CH ₂ – COO ⁻	none

Class	Surface Active Agent	Chemical formula (in aqs. soln.)		
		Lipophilic group	Hydrophilic group	Surface inactive ion
4. <i>Non-ionic</i> (a) Alcohol-polyethylene glycol ethers	Polyethylene glycol 1000 monocetyl ether (cetomacrogol 1000)	$\text{CH}_2-(\text{CH}_2)_n$ ($n = 15$ to 17)	$(\text{O}-\text{CH}_2-\text{CH}_2)_m-\text{COO}^-$ ($m = 20$ to 24)	none
(b) Fatty acid-polyethylene glycol ethers	Polyethylene glycol 40 monostearate	$\text{C}_{17}\text{H}_{33}$	$\text{CO}-(\text{O}-\text{CH}_2-\text{CH}_2)_{40}-\text{OH}$	none
(c) Fatty acid-polyhydric alcohol esters	Sorbitan mono-oleate (TWEEN)	$\text{C}_{17}\text{H}_{33}$		none
	Polyoxyethylene sorbitan mono-oleate	$\text{C}_{17}\text{H}_{33}$		none

The HLB number of surfactants may vary from 40 (sodium lauryl sulfate) to 1 (oleic acid). Emulsifying agents, sometimes used singly, are preferably a combination of two emulsifying agents, which will give a weighted HLB of 8 to 16 which is satisfactory for o/w emulsions and an HLB 3 to 8 for w/o emulsions.

NOTE: The HLB required for emulsifying a particular oil in water can be determined by trial and error method; i.e. by preparing appropriate emulsions with emulsifiers having a range of HLB values and then determining that HLB values that yields the "best emulsion". That HLB value is named as Required HLB or RHLB".

TABLE : Required HLB value for some oil phase ingredients

Oil	RHLB for o/w	RHLB for w/o
Cottonseed oil	6-7	—
Petrolatum	8	—
Beeswax	9-11	5
Paraffin wax	10	4
Mineral oil	10-12	5-6
Methyl silicone	11	—
Lanolin, anhydrous	12-14	8
Carnauba wax	12-14	—
Lauryl alcohol	14	—
Castor oil	14	—
Kerosene	12-14	—
Cetyl alcohol	13-16	—
Stearyl alcohol	15-16	—
Carbon tetrachloride	16	—
Lauric acid	16	—
Oleic acid	17	—
Stearic acid	17	—

Example: Formula of an emulsion is as follows:

Ingredient	Amount	RHLB (o/w)
1. Beeswax	15g	9
2. Lanolin	10g	12
3. Hard paraffin wax	20g	10
4. Cetyl alcohol	5g	15
5. Emulsifier	2g	
6. Preservative	0.2g	

7. Color	q.s.	
8. Water, purified q.s.	100g	

To calculate the overall RHLB of the emulsion the following calculation is carried out:

Oil Phase	Amount	(Amount/Total)xRHLB
1. Beeswax	15g	(15/50)x9 = 2.7
2. Lanolin	10g	(10/50)x12 = 2.4
3. Paraffin	20g	(20/50)x10 = 4.0
4. Cetyl alcohol	5g	(5/50)x15 = 1.5
Total	50g	10.6

Next, a blend of two emulsifiers is chosen, one with an HLB above 10.6 and the other below 10.6. Let these two surfactants be Tween80 (HLB = 15) and Span 80 (HLB = 4.3). These two surfactants should be mixed in such a ratio that the mixture will have a HLB of 10.6. By alligation method:

HLB of Tween80 → RHLB → Parts of Tween80 15 → 10.6 ← 6.3

HLB of Span80 → RHLB → Parts of Span80 4.3 → 10.6 ← 5.6

Required amount of Tween80 = $\{6.3/(6.3+5.6)\} \times \text{Total amount of emulsifier}$
 = 0.53x2 g
 = 1.06 g

Required amount of Span80 = $\{5.6/(6.3+5.6)\} \times \text{Total amount of emulsifier}$
 = 0.47x2 g
 = 0.94 g

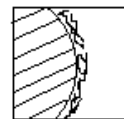
Therefore, using 1.06 g Tween80 and 0.94 g of Span 80 we can stabilize the above formula of an emulsion.

Choice of hydrophilic colloids

The naturally occurring gums and synthetic hydrophilic polymers are used as either primarily or (mainly) auxiliary emulsifiers.

Mode of action

- They do not reduce the surface tension but forms a rigid film on the oil droplets and form a stable o/w emulsion – thus inhibits coalescence of droplets.
- As an auxiliary emulsifier they increase the viscosity of the continuous phase so that movement of dispersed phase is reduced.



Examples:

- Plant origin: Acacia, tragacanth, alginates, chondrus and pectin.
- Animal source: Gelatin, egg yolk, casein, woolfat, cholesterol and lecithin.
- Synthetic: Methyl cellulose, Hydroxyethyl cellulose, Polyoxyethylene polymer and Carboxyvinyl polymer.

The natural gums exhibit some type of incompatibility or instability depending on the presence of various cations, on pH, or on a second hydrophilic polymer.

Choice of finely divided solid particles

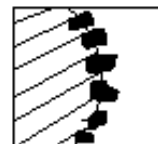
The compounds most frequently used in pharmacy are the colloidal clays: bentonite (aluminium silicate) and veegum (magnesium aluminium silicate). They act as good emulsifiers, especially in combination with surfactants or viscosity building agents.

Mode of action

- They tend to absorb at the oil-water-interface and form thick impenetrable films.
- Sometimes increases the viscosity of water (as continuous phase).

Generally finely divided solids are used in conjunction with a surfactant to prepare o/w emulsions but both o/w and w/o preparations can be prepared by **adding the clay to the external phase first**.

They are used frequently for external purposes such as lotion or cream.



Specific formulation consideration: Consistency

Once the desired emulsion and emulsifiers have been chosen, a consistency that provides the desired stability and yet has the appropriate flow characteristics must be attained.

The sedimentation or creaming rate of suspended spherical particles is inversely proportional to the viscosity in accordance with Stoke's law.

Since emulsions should flow or spread easily and since higher viscosity favors stability – so thixotropy in an emulsion is desirable (thixotropy = phenomenon in which the viscosity of a preparation is reduced by agitation but increases after agitation has been stopped).

Viscosity of emulsions responds to the following changes:

1. When the viscosity of the continuous phase is increased the viscosity of emulsion is also increased.
 - o/w emulsion: Viscosity of water is increased by using gums, clays and viscosity building agents.
 - w/o emulsion: Viscosity of oil is increased by addition of polyvalent metal soaps or the use of high melting waxes and resins.
2. The greater the volume of internal phase, (i.e. greater phase volume ratio) the greater is the apparent viscosity.
3. The viscosity and stability of an emulsion is increased by reducing the size of droplets and by formation of floccules or clumps.
4. It is routinely observed that viscosity of emulsions increases upon aging. Hence, it is recommended that a newly formulated emulsion be allowed to rest undisturbed for 24 hours before checking its viscosity.

Choice of an antimicrobial preservative

Sources of contamination:

- (i) Contaminated raw materials
- (ii) Poor sanitation during preparation
- (iii) Contamination by the end users

Substrates of contamination:

- (i) Mainly the water phase is a good medium for microbial growth.
- (ii) Some ingredients, such as carbohydrates, pectin, proteins, sterols, and phosphates readily supports the growth of a variety of microorganisms.

Remedies:

- (i) Use of uncontaminated raw materials
- (ii) Careful and thorough cleaning of equipment with steam.
- (iii) Addition of preservatives

Preservatives commonly used:

Chlorocresol, chlorobutanol, mercurials [e.g. phenyl mercuric nitrate (PMN), phenyl mercuric acetate (PMA), esters of parahydroxy benzoate (methyl, propyl, butyl, benzyl paraben), sodium benzoate, sorbic acid etc.

[For more details see Lieberman & Lachman, *Industrial Pharmacy*, 3rd Edn. pp 521.]

Since microorganisms can reside in the water or the lipid phase or both, the preservative should be available at an effective level in both phases. So it is advisable to add an oil soluble and an water soluble preservative simultaneously.

A good example is methyl and propyl paraben. In this case methyl paraben is soluble in water while propyl and higher esters are almost water-insoluble.

Preservatives sometimes *interact* with some ingredients. e.g. phenolic preservatives are especially susceptible to interaction with compounds containing polyoxyethylene groups. Sometimes preservatives are solubilized by the surfactants. The bound or complexed or solubilized preservative can not act as preservative.

Choice of antioxidants

The inclusion of an antioxidant in an emulsion formulation may be necessary to protect, not only an active ingredient but also formulation components (e.g. unsaturated lipids) which are oxygen labile.

Oxidation occurs spontaneously under mild conditions generally involved some free radical reactions.

Kinetic measurements of fat oxidation in o/w emulsions indicate that the rate of oxidation is dependent on

- (i) the rate of oxygen diffusion in the system,
- (ii) oxygen pressure (i.e. oxygen content)

- (iii) trace element of metal such as Cu, Mn, or Fe or their ions may catalyze the oxidative reactions. Thus the use of chelating agents, in a formulation may markedly improve product stability.
- (iv) Some oxidative degradation is pH dependent. So the pH stability profile of the drug and of protective formulation should be established during product development.

List of selected antioxidants for emulsion system:

1. *Chelating agents* e.g. Citric acid
EDTA (Ethylene diamine tetraacetic acid)
Phenyl alanine
Phosphoric acid (H₃PO₄)
Tartaric acid
2. *Preferentially oxidized compounds (Reducing agents)*
e.g. Ascorbic acid
Sodium sulphite (Na₂SO₃)
Sodium bisulfite (NaHSO₃)
Sodium metabisulfite (Na₂S₂O₅)
3. *Chain terminators*
 - Water soluble compounds* e.g. Cystine hydrochloride
Thioglycerol
Thioglycollic acid
Thiosorbitol
 - Lipid soluble compounds* e.g. Alkyl gallates (octyl, propyl, dodecyl)
Butylated hydroxy toluene (BHT)
Butylated hydroxy anisole (BHA)
α-tocopherol (Vit-E)
Hydroquinone

Deaeration

The formulator may wish to deaerate the system by :

- (i) bubbling N₂ gas through the liquids to remove dissolved O₂.
- (ii) boiled before use
- (iii) exposure to vacuum during ultrasonic agitation
- (iv) the end space above the container can be flushed with N₂ just before sealing.

Reducing agents: e.g. Ascorbic acid (Vit-C)
Sulphites etc.

They preferentially get oxidized before the oxidation of oil takes place.

Uses:

- (i) BHA, BHT, Vit-E and the alkyl gallates are particularly popular in pharmaceuticals and cosmetics.
- (ii) BHA and BHT have a pronounced odour and should be added at low concentration.
- (iii) Alkyl gallates have a better taste.
- (iv) L-tocopherol (Vit-E) is well suited for edible or oral preparations, such as those containing Vitamin A.
- (v) Some trace metals like copper, iron, manganese ions catalyze the auto-oxidation reaction; therefore, a small amount of sequestering agents like citric acid, EDTA, tartaric or phosphoric acid reduce the reaction rate.

PREPARATION

- After the purpose of the emulsions has been determined, i.e oral or topical use,
 - and the type of emulsions, o/w or w/o,
 - and appropriate ingredients selected
 - and the theory of emulsification considered
- experimental formulations may be prepared by a method suggested by Griffin.

Experimental method

1. Group the ingredients on the basis of their solubilities in the aqueous and nonaqueous phase.

2. Determine the type of emulsion required and calculate an approximate HLB value
3. Blend a low HLB emulsifier and a high HLB emulsifier to the calculated value
[N.B. For experimental formulations, use a higher concentration of emulsifier (e.g. 10 to 30% of the oil phase) than that required to produce a satisfactory product.]
4. Dissolve the oil-soluble ingredients and the emulsifiers in the oil. Heat, if necessary, to approximately 5 to 10°C over the melting point of the highest melting ingredient of to a maximum temperature of 70 to 80°C.
5. Dissolve the water-soluble ingredients (except acids and salts) in a sufficient quantity of water. Heat the aqueous phase to a temperature which is 3 to 5°C higher than that of the oil phase.
6. Add the aqueous phase to the oily phase with suitable agitation.
7. If acids or salts are employed, dissolve them in water and add the solution to the cold emulsion.
8. Examine the emulsion and make adjustments in the formulation if the product is unstable.

Large scale industrial method

The preparation of an emulsion requires work to reduce the internal phase into small droplets and disperse them throughout the external phase. This can be accomplished by a mortar and pestle or a high speed emulsifier. The addition of emulsifying agents not only reduces this work but also stabilizes the final emulsion. Emulsions may be prepared by four principle methods:

1. Addition of internal phase to external phase

Let us take a model of o/w emulsion.

- (i) The water soluble substances are dissolved in water and the oil soluble substances are dissolved in oil.
- (ii) The oil mixture is added in portions to the aqueous preparation with agitation (in a colloid mill or homogenizer).

N.B. Sometimes, in order to give a better shearing action during the preparation, all of the water is not mixed with the emulsifying agent until the primary emulsion with oil is formed; subsequently, the remainder of the water is added.

e.g. *Emulsion using Gelatin-type A as the emulsifier.*

Gelatin (Type A)	8g
Tartaric acid	0.6g
Flavour as desired	
Alcohol	60ml
Oil	500ml
Purified water, to make	1000ml

Procedure

- (i) The gelatin & tartaric acid are added to approximately 300ml water, allowed to stand for few minutes, heated until gelatin is dissolve, then temperature is raised to 98°C and this temperature is maintained for about 20 minutes. Cooled to 50°C, flavor and alcohol are added and more water was added to make 500 ml.
- (ii) The oil is added to the aqueous phase (i.e. external phase), and the mixture is agitated thoroughly and passed it through a homogenizer or colloid mill.

2. Addition of the external phase to the internal phase

Let us take a model of o/w emulsion.

In this method water (external phase) is first added slowly to the oil (internal phase) to promote the formation of a more w/o emulsion due to the presence of more oil than water. After further addition of water phase inversion to an o/w emulsion should take place.

This method is especially successful when hydrophilic agents such as acacia, tragacanth or methyl cellulose are first mixed with oil, effecting dispersion without wetting. Water is added and, eventually, an o/w emulsion is formed.

e.g. *Mineral oil emulsion*

Mineral oil	500ml
Acacia, in very fine water	125g
Syrup	100ml
Vanillin	40mg
Alcohol	60ml
Purified water, upto	1000ml

- (i) The mineral oil and acacia are mixed in a dry mortar. Purified water, 250 ml (Phase volume ratio o/w = 2: 1) is added and the mixture triturated vigorously until an emulsion is formed.

- (ii) A mixture of the syrup, 50 ml of purified water and the vanillin dissolved in alcohol are added in divided portions with trituration
- (iii) Sufficient purified water is then added to the proper volume, the mixture well and homogenized.

3. Mixing both phases after warming each

This method is use when waxes or other substances which require melting are used. The oil-soluble emulsifying agents, oils and waxes are melted and mixed thoroughly. The water-soluble ingredients dissolved in the water and warmed to a temperature slightly higher than the oil phase.

The oil phases are then mixed and stirred until cold. For convenience, but not necessity, the aqueous solution is added to the oil mixture.

This method frequently is used in the preparation of ointments and creams.

e.g. *An oral emulsion (o/w) containing an insoluble drug*

- | | |
|--|-------|
| 1. Cotton seed oil | 460g |
| 2. Sulphadiazine | 200g |
| 3. Sorbitan monostearate | 84g |
| 4. Polyoxyethylene 20 sorbitan mono stearate | 36g |
| 5. Sodium benzoate | 2g |
| 6. Sweetener | q.s. |
| 7. Purified water | 1000g |
| 8. Flavor oil | q.s. |

Procedure

- (i) Heat the first three ingredients to 50⁰C and pass through colloid mill.
- (ii) Add the next four ingredients at 50⁰C to the first three ingredients at 65⁰C and stirred while cooling to 45⁰C.
- (iii) Add the flavor oil and continue stirring until room temperature is reached.

4. Alternate addition of the two phases to the emulsifying agent

Model: Let us prepare an o/w type of emulsion.

- (i) A portion of the oil is added to all of the oil-soluble emulsifying agents with mixing.
- (ii) Equal quantity of water is added to all of the water-soluble emulsifying agents with mixing.
- (iii) Aqueous solution is mixed with oil phase stirred until the emulsion is formed.
- (iv) Further portions of water and oil are added alternately until the final product is formed.

N.B. The high concentration of the emulsifying agent in the original emulsions makes the initial emulsification more likely and the high viscosity provides effective shearing action leading to small droplets in the emulsion.

This method is often used successfully with soaps.

EQUIPMENTS

- The preparation of emulsion requires certain amount of energy to form the interface between the two phases, and additional work must be done to stir the system to overcome the resistance to flow.
- In addition, heat often is supplied to the system to melt waxy solids and /or reduce the viscosity of the oil phase.

Because of the variety of oils used, emulsifying agents, phase-volume ratio and the desired physical properties of the product, a wide selection of equipment is available for preparing emulsions.

1. Mortar and pestle

It consists of a glass or porcelain mortar and a pestle.

Advantages:

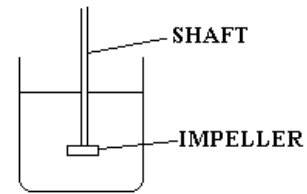
- (i) Small quantity emulsions can be prepared in the laboratory.
- (ii) Low cost
- (iii) Simplest operation among all other instruments.

Disadvantages

- (i) Generally, the final particle size is considerable larger than in other equipments.
- (ii) It is necessary for the ingredients to have a certain viscosity prior to trituration in order to achieve a satisfactory shear.

2. Agitators / Mechanical stirrers

An emulsion may be stirred by means of various impellers (propellers: produce axial movements; turbines produce radial and tangential movements) mounted on shafts, which are placed directly into the system to be emulsified. For low viscosity emulsions propeller type can be used but for higher viscosity turbine type is used.



The degree of agitation is controlled by the rotational speed of impeller, by the patterns of the liquid flow and the resultant efficiency of mixing are controlled by the type of impeller, its position in the container, the presence of baffles, and the general shape of the container.

Advantages:

- (i) Agitators are used particularly for the emulsification of easily dispersed, low-viscosity oils.
- (ii) Can be used for small-scale production and laboratory purpose.

Disadvantages:

Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium, in this way, impairs the ease of emulsification.

3. Colloid mill

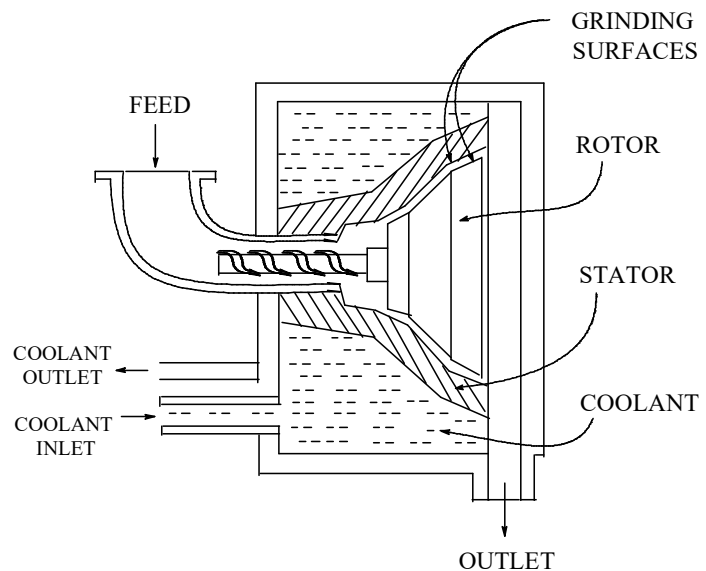
The principle of operation of the colloid mill is the passage of the mixed phases of an emulsion formula between a stator and a high speed rotor revolving at speeds of 2000 to 18,000 rpm.

The clearance between the rotor and the stator is adjustable, usually from 0.001 inch upward. The emulsion mixture, while passing between the rotor and the stator, is subjected to a tremendous shearing action which effects a fine dispersion of uniform size.

The shearing forces applied in the colloid mill usually raises the temperature within the emulsion. Hence, a coolant is used to absorb the excess heat.

Advantage

- (i) Very high shearing force can be generated.
- (ii) Very fine particles can be prepared.
- (iii) Particularly useful in preparing suspensions containing poorly wetted solids.
- (iv) Useful for the preparation of relatively viscous emulsions.



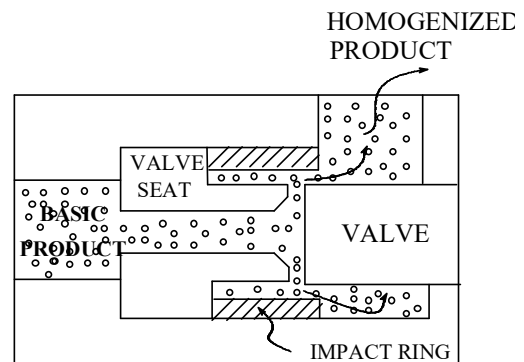
4. Homogenizers

Impeller type of equipment frequently produce a satisfactory emulsion; however, for further reduction in particle size, homogenizers may be employed.

Homogenizers may be used in one of two ways:

- (i) The ingredients in the emulsion are mixed and then passed through the homogenizer to produce the final product.
- (ii) A coarse emulsion is prepared in some other way and then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.

The coarse emulsion (basic product) enters the valve seat at high pressure (1000 to 5000 psi), flows through the region between the valve and the seat at high velocity with a rapid pressure drop, causing cavitation; subsequently the mixture hits the impact ring causing further disruption and then is discharged as a homogenized product. It is postulated that circulation and turbulence are responsible mainly for the homogenization that takes place.



Sometimes a single homogenization may produce an emulsion which, although its particle size is small, has a tendency to clump or form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high pressure (e.g. 3000 to 5000 psi) and then through the second stage at a greatly reduced pressure (e.g. 1000 psi). This breaks down any clusters formed in the first step (it is a two stage homogenizer).

5. Ultrasonic devices

The preparation of emulsions by the use of ultrasonic vibrations also is possible. An oscillator of high frequency (100 to 500 kHz) is connected to two electrodes between which placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the emulsion ingredients into this oil bath.

Advantages

Can be used for low viscosity and extremely low particle size.

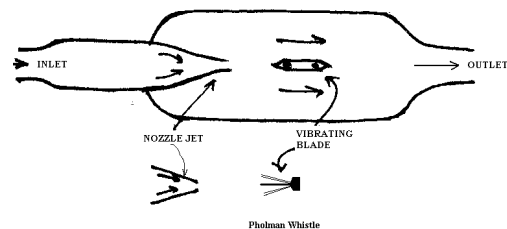
Disadvantages

Only in laboratory scale it is possible. Large scale production is not possible.

Example: Pohlman Whistle

Commercial products may be prepared using ultrasonics based upon the device known as the Pohlman whistle. In this apparatus, the premixed liquids are forced through a thin orifice and are allowed to impinge upon the free end of a knife-edge bar which is made to vibrate.

Ultrasonic waves are produced and areas of compression and rarefaction are formed. Shock waves are produced by the collapse of bubbles which produced a shear effect, thereby producing fine particle sizes.



STABILITY OF EMULSION

The stability of an emulsion must be considered in terms of physical stability of emulsion system and the physical and chemical stability of the emulsion component including pharmacologically active ingredients, if any.

Definition: A physically stable emulsion component may be defined as a system in which the globules retain their initial character and remain uniformly distributed throughout the continuous phase.

Symptoms of instability

As soon as an emulsion has been prepared, time and temperature dependent processes occur to effect its separation. During storage, an emulsion's stability is evidenced by (i) creaming, (ii) flocculation and / or (iii) coalescence.

CREAMING

Creaming is the upward or downward movement of dispersed droplets related to the continuous phase due to the difference of density between two phases.

N.B. The downward creaming is also called sedimentation. Generally the term "sedimentation" is associated with the downward movement of solid particles in suspension.

Creaming is undesirable in a pharmaceutical product where homogeneity is essential for the administration of correct and uniform dose. It may still be pharmaceutically acceptable as long as it can be reconstituted by a modest amount of shaking. However, in case of cosmetic products creaming is usually unacceptable because it makes the product inelegant.

Creaming or sedimentation brings the particle closer together and may facilitate a serious problem of coalescence. The rate at which a spherical droplet or particle sediments in a liquid is governed by Stoke's equation.

$$v = \frac{d^2(\rho_1 - \rho_2)g}{18\eta}$$

where v = velocity of creaming
 d = diameter of globule
 ρ_1, ρ_2 = densities of dispersed phase and continuous phase respectively
 η = viscosity of the continuous medium

A consideration of this equation shows that the rate of creaming will be decreased by:

- (i) reduction of droplet size
 - (ii) a decrease in the density difference between the two phases
 - (iii) increase in the viscosity of the continuous phase
- *Reduction in droplet size* is done by using an efficient homogeniser or colloid mill. There are, however, technical difficulties in reducing the diameter of droplets to below about 0.1 μm .
 - Stoke's equation predicts that no creaming is possible if the specific gravities of the two phases are equal. A few successful attempts have been made to equalize the densities of the oil and aqueous phase. This method is of little use in pharmaceutical practice because, it usually involves the addition of substances those are unacceptable in pharmaceutical preparations.
 - The most frequently used approach is to raise the viscosity of the continuous phase although this can be done to the extent that the emulsion still can be removed readily from its container and spread on the body surface conveniently.

FLOCCULATION

Flocculation of the dispersed phase may take place before, during or after creaming.

Flocculation is reversible aggregation of droplets of the internal phase in the form of three-dimensional clusters.

In the floccules the droplets remain aggregated but intact. The droplets can remain intact when the mechanical or electrical barrier is sufficient to prevent droplet coalescence.

e.g. if an insufficient amount of emulsifier is present, emulsion droplets aggregate and coalesce.

The reversibility of this type of aggregation depends on the strength of the interaction between particles, as determined by:

- (i) the chemical nature of the emulsifier,
- (ii) the phase-volume ratio, and
- (iii) the concentration of dissolved substances, especially electrolytes.

The viscosity of an emulsion depends to a large extent on flocculation, which restricts the movement of particles and can produce a fairly rigid network. Agitation of an emulsion breaks the particle-particle interactions with a resulting drop of viscosity; i.e. shear thinning.

COALESCENCE

Coalescence is a growth process during which the emulsified particles join to form larger particles.

Any evidence for the formation of larger droplets by merger of smaller droplets suggests that the emulsion will eventually separate completely.

The major factor which prevents coalescence in flocculated and deflocculated emulsions is the mechanical strength of the interfacial barrier. Thus macromolecules and particulate solids forms thick interfacial film – and hence natural gums and proteins are useful as auxiliary emulsifiers when used at low level, but can even be used as primary emulsifiers at higher concentrations.

Any agent that will destroy the interfacial film will crack the emulsion. Some factors are:

- (i) the *addition of a chemical* that is incompatible with the emulsifying agent. Examples include surfactants of opposite ionic charges, addition of large ions of opposite charge, addition of electrolytes such as Ca and Mg salts to emulsions stabilized with anionic surfactants.
- (ii) *Bacterial growth*: Protein materials and non-ionic surfactants are excellent media for bacterial growth.
- (iii) *Temperature change*: Protein emulsifying agent may be denatured and the solubility characteristics of non-ionic emulsifying agents change with a rise in temperature. Heating above 70°C destroys almost all emulsions. Freezing will crack an emulsion; this may be due to the ice-crystals disrupting the interfacial film around the droplet.

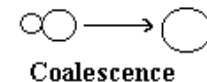
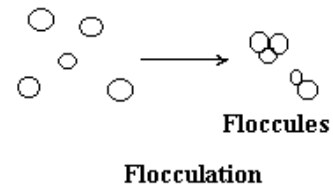
EVALUATION OF EMULSION

SHELF LIFE

The final acceptance of an emulsion depends on stability, appearance, and functionality of the packaged product. There is no quick and sensitive methods for determining potential instability in an emulsion are available to the formulator. To speed up the stability test program the emulsion is subjected to various stress conditions.

The stress conditions normally employed include:

- (i) aging and temperature



(ii) centrifugation, and

(iii) agitation

Aging and temperature

It is routine to determine the shelf life of all types of preparations by storing them for varying periods of time at temperatures that are higher than those normally encountered. A particularly useful means of evaluating shelf life is cycling between two temperatures preferably between 4^o and 45^oC.

The normal effect of aging an emulsion at elevated temperature is acceleration of the rate of coalescence or creaming, and this is usually coupled with changes in viscosity.

Centrifugation

Stoke's law shows that creaming is a function of gravity (g), and an increase in gravity therefore accelerates separation. Centrifugation at 3750 rpm in a 10-cm radius centrifuge for a period of 5 hours is equivalent to the effect of gravity for about one year. Thus shelf-life under normal storage conditions can be predicted rapidly by observing the separation of the dispersed phase due to either creaming or coalescence when the emulsion is exposed to centrifugation.

Agitation

Droplets in an emulsion exhibit Brownian movement. Coalescence takes place when droplets impinge upon each other. Simple mechanical agitation contributes to the energy with which two droplets impinge upon each other.

Thus agitation can also break emulsion. A typical case is the manufacture of butter from milk.

Conventional emulsions may deteriorate from gentle rocking on a reciprocating shaker. This works in two ways:

- (i) increases the rate of impingement of droplets, and
- (ii) reduction of viscosity of a normally thixotropic system.

PHYSICAL PARAMETERS

The most useful parameters commonly are measured to assess the effect of stress conditions on emulsions include

1. phase separation,
2. viscosity,
3. electrophoretic properties, and
4. particle size analysis and particle count.

Phase separation

The rate and extent of phase separation after aging of an emulsion may be observed visually or by measuring the volume of separated phase.

A simple means of determining phase separation due to creaming or coalescence involves withdrawing a sample of the emulsion from the top and the bottom of the preparation after some period of storage and comparing the composition of the two samples by appropriate analysis of water content, oil content, or any suitable constituent.

Viscosity

The viscosity of an emulsion for the use of shelf studies is not concerned with absolute values of viscosity, but with changes in viscosity during aging. Since emulsions are generally non-Newtonian systems and the viscosity is measured by viscometer of the cone-plate type are particularly useful for emulsions, but instruments utilizing coaxial cylinders (e.g. cup and bob viscometer) are the easiest to use. The use of a penetrometer is often helpful in detecting changes of viscosity with age.

In case of w/o emulsions flocculation is quite rapid. After flocculation viscosity drops quickly and continues to drop for some time (5 to 15 days at room temperature).

In case of o/w emulsions globule flocculation causes an immediate increase in viscosity. After this initial change, almost all emulsions show changes in viscosity with time which follow a linear relationship when plotted on a log-log scale.

A practical approach for the detection of creaming or sedimentation, before it becomes visibly apparent, utilizes the Helipath attachment of the Brookfield viscometer

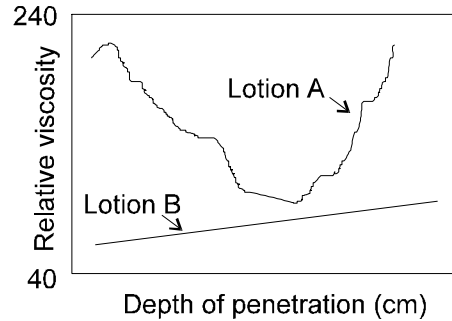
N.B. The Brookfield viscometer determines the resistance encountered by rotating spindle or cylinder immersed in a viscous material. The Helipath attachment slowly lowers the rotating spindle into the medium so that the resistance measured is always that of previously undisturbed test substances.

As a result of emulsion separation, the descending rotating spindle meet varying resistance at different levels and registers fluctuations in viscosity.

Example

Lotion A in the figure contains solids suspended in an emulsion, and the high viscosity near the top is due to non-wetted solid and creamed emulsion; the high viscosity at the lower level is due to sedimented particles.

The addition of polyoxyethylene monooleate (SAA) and methyl cellulose (viscosity enhancer) in lotion B yields a much more uniform viscosity pattern after eight weeks storage.

**Electrophoretic properties**

If the instability of the emulsion is due to flocculation only (and not due to coalescence) then the zeta potential will have to be measured.

Zeta potential can be determined with

- (i) the aid of the moving boundary method or
- (ii) more quickly and directly, by observing the movement of particles under the influence of electric current.

The zeta potential is especially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

The measurement of electrical conductivity has been claimed to be a powerful tool for the evaluation of emulsion shortly after preparation.

Particle size number analysis

Changes of the average particle size or of the size distribution of droplets are important parameters for evaluating emulsions.

Particle size determination can be carried out by microscopic method or by electronic counting machines. (e.g. Coulter counter). Light scattering and related reflectance relationships have been used for particle size determination.

The utility of particle size for predicting or interpreting emulsion shelf-life is somewhat doubtful.

Practical recommendation for shelf-life prediction in temperate (hot and humid) zone

A typical test program for an "acceptable" emulsion (in temperate zone) may be as follows:

The emulsion should be stable with no visible signs of separation for at least:

- (i) 60 to 90 days at 45 or 50°C,
- (ii) 5 to 6 months at 37°C and
- (iii) 12 to 18 months at room temperature.
- (iv) After 1 month storage at 4°C
- (v) After 2 to 3 freeze-thaw cycles between -20 and +25°C.
- (vi) After 6 to 8 freeze-thaw cycles between 4 and 45°C with storage at each temperature for not less than 48 hours.
- (vii) No deterioration by centrifuging at 2000 to 3000 rpm at room temperature.
- (viii) No deterioration by agitation for 24 to 48 hours on a reciprocating shaker (≈ 60 cycles per minute) at room temperature and at 45°C.