SUSPENSION

Syllabus:

Definition, general formulation with example, suspending agents, preservatives, vehicles, stabilizers, colorants, flavoring agents and such other components, processing and equipment.

Questions:

1. Define and differentiate between solution and suspension. (98) 4
2. Give the importance of suspending agents in pharmaceutical dosage forms. (98) 4
3. Discuss the different methods of formation of suspensions. (96) 8
4. How do you evaluate the stability of a suspension? (96) 8
5. What are structured vehicles? How do they help in increasing the stability of a suspension? Mention any two materials which help in improving the stability of suspension with a brief explanation. (94) 12
6. Write an account of an ideal suspending agent and stabilizer used in suspension. (94) 16
7. Define suspensions. Describe the formulation of a suspension. (93) 8

DEFINITION

A suspension is a two phase system composed of a solid material dispersed in a liquid. The liquid can be oily or aqueous. However, most suspensions of pharmaceutical interest are aqueous.

ADVANTAGES

Suspensions offer distinct advantages _ they are as follows:

1. **Stability**: Some drugs are not stable in solution form. In such cases it is necessary to prepare an insoluble form of that drug. Therefore drugs are administered in the form of suspension. e.g. Procaine Penicillin G.
2. **Choice of solvent**: If the drug is not soluble in water and solvents other than water are not acceptable, suspension is the only choice. e.g. Parenteral corticosteroid.
3. **Mask the taste;** In some cases drugs are made insoluble and dispensed in the form of suspension to mask the objectionable taste. e.g. Chloramphenicol base is very bitter in taste, hence the insoluble chloramphenicol palmitate is used which does not have the bitter taste
4. **Prolonged action:** Suspension has a sustaining effect, because, before absorption the solid particles should be dissolved. This takes some time. e.g. Protamine Zinc Insulin and procaine penicillin G.
5. **Bioavailability:** Drugs in suspension exhibit a higher bioavailability compared to other dosage forms (except solution) due to its large surface area, higher dissolution rate. e.g. Antacid suspensions provides immediate relief from hyperacidity than its tablet chewable tablet form.

TYPES OF SUSPENSIONS

The pharmaceutical suspension preparations are differentiated into suspensions, mixtures, magmas, gels and lotions.

Suspensions

Simple suspension is the insoluble solid dispersed in a liquid. The stability considerations suggest that the manufacture of drugs in dry form is ideal. They are reconstituted as suspensions using a suitable vehicle before administration.

Few examples are:

i) Dispersible tablets of antibiotic, amoxycillin (e.g. PRESSMOX)
ii) Procaine penicillin G powder (E.G. PENIDURE)

Gels

Gels are semisolid systems consisting of small inorganic particles suspended in a liquid medium. It consists of a network of small discrete particles. It is a two-phase system. e.g. Aluminum hydroxide gel.

Lotions

Lotions are suspensions which are intended to be applied to the unbroken skin without friction. e.g. Calamine lotion, hydrocortisone lotion.

Magmas and Milks

Magmas and milk are aqueous suspensions of insoluble, inorganic drugs and differ from gels mainly in that the suspended particles are larger. when prepared they are thick and viscous and because of this, there is no need to add a suspending agent. e.g. Bentonite magma, milk of magnesia.

Mixtures

Mixtures are oral liquids containing one or more active ingredients, dissolved, suspended or dispersed in a suitable vehicle. Suspended solids may separate slowly on standing, but are easily redispersed on shaking. e.g. Kaolin mixture with pectin.

CLASSIFICATION OF SUSPENSIONS

Based on the proportion of solids, suspensions are empirically classified as dilute or concentrated systems.

i) **Dilute suspensions** : Solid content 2 - 10 % e.g. Cortisone acetate and prednisolone acetate suspension.
ii) **Concentrated suspensions**: Solid content 10 - 50 % e.g. Zinc oxide suspension for external use, Procaine penicillin G injection, Antacid suspension etc.

Depending on the nature and behavior of solids suspensions are classified as flocculated and deflocculated.

DEFLOCCULATED SUSPENSION

In this system, solids are present as individual particles.

FLOCCULATED SUSPENSION

In this system, particles aggregate themselves by physical bridging. These flocs are light, fluffy conglomerate which are held together by weak van der Waal's forces of attraction.

If the aggregate is an open network it is called **floccule**. They are fibrous, fluffy, open network of particles. It is loosely packed after sedimentation.

If the aggregate is a closed one - it is called **coagule**. They are tightly packed, produced by surface film bonding.

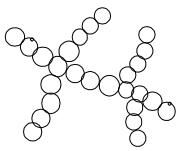


Fig. floccule

Fig. Coagule

TABLE: Comparison between Deflocculated and Flocculated System

Deflocculated System	Flocculated System
i) Pleasant appearance, because of uniform dispersion of particles.	i) Somewhat unsightly sediment.
ii) Supernatant remains cloudy.	ii) Supernatant is clear
iii) Particles exist as separate entities	iii) Particles form loose aggregates.
iv) Rate of sedimentation is slow, as the size of particles are small.	iv) Rate is high, as flocs are the collection of smaller particles having a larger size.
v) Particles settle independently and separately	v) Particles settle as flocs.
vi) The sedimentation is closely packed and form a hard cake.	vi) Sediment is a loosely packed network and hard cake cannot form.

vii) The hard cake cannot be redispersed. viii)Bioavailability is higher due to large specific surface area.	vii) The sediment is easy to redisperse. viii)Bioavailability is comparatively less due to small specific surface area.

FACTORS AFFECTING THE STABILITY OF A SUSPENSION

SETTLING IN SUSPENSIONS

Brownian movement

Brownian movement of particles prevents sedimentation. In general, particles are not in a state of Brownian motion in pharmaceutical suspensions, due to

i) larger particle size (Brownian movement is seen in particles having diameter of about 2 to 5 μm (depending on the density of the particles and the viscosity and the density of the suspending medium.
ii) and higher viscosity of the medium.

Sedimentation

The rate of sedimentation of particles can be expressed by the Stoke's law, using the following formula:

$$\text{Sedimentation rate} = \frac{d^2(\rho_s - \rho_l)g}{18\eta}$$

Where d is the particle diameter
ρ_s, ρ_l are densities of a particle and liquid respectively.
g is the acceleration of gravity.
η is the viscosity of the medium.

Stock's law is applicable if:

i) particles are spherical; but particles in the suspension are largely irregular.
ii) Particles settle freely and independently.

In suspensions containing 0.5 - 2 % (w/v) solid, the particles do not interfere with each other during sedimentation - hence free settling occurs.

Most pharmaceutical suspensions contain 5 - 10 % or higher percentages of solid. in this cases particles interfere with one another as they fall - hence hindered settling occurs and Stoke's law no longer applies.

Stoke's law is applicable to deflocculated systems, because particles settle independently. However, this law is useful in a qualitative manner in fixing factors which can be utilized in formulation of suspensions.

1. Particle size

Rate of sedimentation $\propto$ (diameter of particle)^2

So smaller the particle size more stable the suspension. The particle-particle interaction results in the formation of floccules or coagules where the sedimentation rate increases. The particles are made fine either by **dry milling** prior to suspension or **wet-milling** of the final suspension in a colloid mill or a homogenizer.

2. Viscosity of the medium

According to Stoke's law:

Rate of sedimentation $\propto$ 1 / (viscosity of the medium)

The viscosity of suspension should be optimum. Viscosity can be increased by adding suspending agents or thickening agents. selection of high viscosity have both advantages and disadvantages.

Advantages

i) Sedimentation rate is retarded, hence enhances the physical stability of the suspension.
ii) Inhibits crystal growth, because movement of particles is diminished.

iii) Prevents the transformation of metastable crystals to stable crystals.

Disadvantages

i) Redispersibility of the suspension on shaking is difficult.
ii) Pouring out of the suspension from the container may be difficult.
iii) Creates problems in the handling of materials during manufacture.
iv) May retard absorption of drugs from the suspension.

3. Density

Rate of sedimentation ∞ (density of solid – density of liquid medium)

Lesser the difference between the densities of solid particles and liquid medium slower is the rate of sedimentation. Since it is very difficult to change the absolute density of the solid particles so the density of the liquid medium can be manipulated by changing the composition of the medium. The addition of nonionic substances such as sorbitol, polyvinylpyrrolidone (PVP), glycerin, sugar, or one of the polyethyleneglycols or combination of these may be helpful in the manipulation.

If the density of the particles is greater than the continuous medium the particles will settle downwards, the phenomenon is known as sedimentation. If the density of particle is lesser than that of the liquid medium then the particles will move upward - the phenomenon is known as creaming.

FORMULATION OF SUSPENSIONS

The product must

1) Flow readily from the container
2) Possesses a uniform distribution of particles in each dose.

Two approaches are commonly employed to secure the two requirements,

(i) the use of structured vehicle t maintain deflocculated particles in suspension. Structured vehicles are pseudoplastic and plastic in nature; it is frequently desirable that thixotropy be associated with these two type of flow. Structured vehicles act by entrapping the particles so that, ideally no settling occurs. In reality some degree of sedimentation will usually take place. The *shear thinning* property of these vehicle does however facilitate the redispersion when shear is applied.
(ii) and the application of the principles of flocculation to produce flocs that, although, they settle rapidly are easily redispersed with a minimum of agitation.

WETTING OF PARTICLES

The initial dispersion of an insoluble powder in a vehicle is an important step in the manufacturing process. Powders sometimes are added to the vehicle, particularly in large scale operations, by dusting on the surface of the liquid. It is frequently difficult to disperse the powder owing to an adsorbed layer of air, minute quantity of grease and other contaminants.

Powders those are not easily wetted by water and accordingly show a large contact angle, such as sulfur, charcoal and magnesium stearate are said to be *hydrophobic*. Powders those are readily wetted by water when free of adsorbed contaminants are called *hydrophilic*. e.g. zinc oxide, talc, magnesium carbonate etc. belong to this category.

When a strong affinity exists between a liquid and a solid, the liquid easily forms a film over the surface of the solid. When this affinity is non-existent or weak, the liquid faces difficulty in displacing the air or other substances surrounding the solid.

Hydrophilic solids usually can be incorporated into suspensions without the use of a wetting agent, but hydrophobic materials are extremely difficult to disperse and frequently float on the surface of the fluid owing to poor wetting of the particles or the presence of tiny air pockets on the surface of the solid particles.

To reduce the **contact angle** between solid and liquid (i.e. increase the wettability) the following agents can be tried out:

1. **Surfactants** Solid-liquid interfacial tension is reduced by incorporating a surfactant with a HLB value between 7 to 9. These are employed to allow the displacement of air from hydrophobic material and permit the liquid, to surround the particles and provide a proper dispersion. The surfactant is mixed with the solid particles if required by shearing. The hydrocarbon chain is preferentially adsorbed to the hydrophobic surface, with the polar part of the surfactant being directed towards the aqueous phase.

2. **Hydrophilic polymers** such as sodium carboxymethyl cellulose, certain water-insoluble hydrophilic material such as bentonite, aluminum-magnesium silicates, and colloidal silica, either alone or in combination can be incorporated in desired concentration. These materials are also used as suspending agents and may produce a deflocculated system particularly if used at low concentration.
3. **Solvents** such as alcohol, glycerol and glycols which are water miscible will reduce the liquid / air interfacial tension. The solvent will penetrate the loose agglomerates of powder displacing the air from the pores of the individual particles thus enabling wetting by dispersion medium.

Method of selection of a suitable wetting agent

In order to select a suitable wetting agent Heistand has used a narrow trough, several inches long and made of a hydrophobic material, such as Teflon, or coated with paraffin wax. At one end of the trough is placed the powder and the other end the solution of the wetting agent. The rate of penetration of the wetting agent solution into the powder can then be observed directly. Greater the rate of penetration of the solution into the powder better is the wetting property of the solution.

RHEOLOGIC CONSIDERATIONS

Rheologic consideration are important in

(i) the viscosity of a suspension as it affects the settling of particles. As viscosity increases rate of sedimentation of the particles reduces.
(ii) the change in flow properties of the suspension when the container is shaken and when the product is poured out off the bottle.
(iii) the spreading quality of the lotion when applied to the affected area.
(iv) during the manufacture of the suspensions.

Importance of suspending agents

The particles in a suspensions are experiencing bombardment constantly with each other owing to the Brownian movement. During this type of inter-particular interaction the particles may circumvent the repulsive force between them and form larger particles which will then settle rapidly. Suspending agents reduce this movement of the particles by increasing the viscosity of the medium.

According to Stoke's law rate of sedimentation is inversely proportional to the viscosity of medium. So the settling of the particles , either in flocculated or deflocculated system, can be slowed down by increasing the drag force on the moving particles by increasing the viscosity of the medium.

Hydrophilic polymers such as sodium carboxymethyl cellulose, certain water-insoluble hydrophilic material such as bentonite, aluminum-magnesium silicates, and colloidal silica, either alone or in combination can be incorporated in low concentration as **wetting agent.**

Hydrophilic polymers also acts as **protective colloids** and particles coated in this manner are less prone to cake than are uncoated particles.

Cellulose polymers e.g. sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose.

Proteins e.g. gelatin.

Synthetic polymer e.g. Polyacrylic acid (Carbopol)

Clays essentially hydrated aluminum and/or magnesium silicates are also useful in suspension formulation.

Characteristics of ideal suspending agent

(i) An ideal suspending agent should have a high viscosity at negligible shear; i.e. during shelf storage; and it should have a low viscosity at high shear rates, i.e. it should be free flowing during agitation, pouring and spreading on the skin.
(ii) Suspending agents should coat the particles which will be less prone to caking than the uncoated particles.

Pseudoplastic substances e.g. tragacanth, sodium alginate and sodium carboxymethylcellulose show these desirable qualities. It is a shear thinning system, i.e. when this type of system is shaken or agitated the viscosity diminishes.

A suspending agent that is thixotropic as well as pseudoplastic should prove to be useful since it forms gel on standing and becomes fluid when disturbed. e.g. Bentonite - Carboxymethylcellulose has both pseudoplastic and thixotropic behavior.

Suspending agent	**Concentration in which generally used**
Sodiumcarbxymethylcellulose	0.5 – 2.5 %
Tragacanth	1.25 %
Guargum	0.5 %
Carbopol 934	0.3 %

CONTROLLED FLOCCULATION

Assuming that the powder is properly wetted and dispersed attention may now be given to the various means by which controlled flocculation may be produced so as to *prevent compact sediment which is difficult to redisperse*. Controlled flocculation can be described in terms of the materials used to produce flocculation I suspensions, namely, (i) electrolytes, (ii) surfactants, and (iii) polymers.

(i) Electrolytes act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta-potential and formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

Example: When bismuth subnitrate is suspended in water it has been found (by electrophoretic studies) that they possess a large positive charge, or zeta potential. Because of the strong forces of repulsion between adjacent particles, the system remains in deflocculated (peptized) state. The addition of monobasic potassium phosphate (KH_2PO_4) to the suspension causes the positive zeta-potential to decrease owing to the adsorption of the negatively charged phosphate anion. The particles then can come closer to form aggregates.

On further addition of KH_2PO_4 the zeta potential eventually falls to zero and then increases in a negative direction. Microscopic examination of the various suspensions shows that at a certain positive zeta potential, maximum flocculation occurs and will persist until the zeta potential has become sufficiently negative for deflocculation to occur once again. The onset of flocculation coincides with the maximum sedimentation volume determined. F remains reasonably constant while flocculation persists, and only when the zeta potential becomes sufficiently negative to effect deflocculation.

(ii) Surfactants both ionic and nonionic, have been used to bring about flocculation of suspended particles. The concentration necessary to achieve this effect would appear to be critical since these compounds may also act as wetting agents to achieve dispersion.

(iii) Polymers are long chain, high molecular weight compounds containing active groups spaced along their length. These agents act as flocculating agents because part of the chain is adsorbed on the particle surface, with the remaining parts projecting out into the dispersion medium. Bridging between these latter portions leads to the formation of flocs.

hydrophilic polymers also acts as protective colloids and particles coated in this manner are less prone to cake than are uncoated particles.

FLOCCULATION IN STRUCTURED VEHICLE

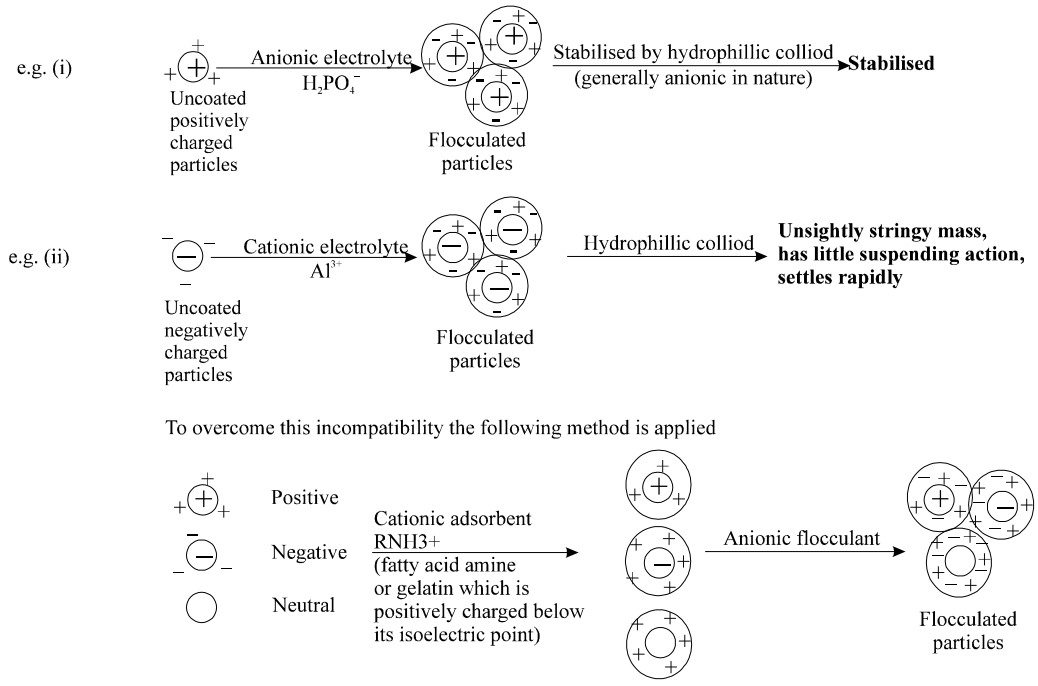
Although the controlled flocculation approach is capable of fulfilling the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if F, the sedimentation volume, is not close to or equal to 1. So a suspending agent is added to retard sedimentation of the flocs. Such agents as carboxymethylcellulose (CMC), Carbopol 934, Veegum, tragacanth or bentonite have been employed, either alone or in combination.

These may lead to incompatibilities, depending on

(i) the initial particle charge

(ii) the charge carried by flocculating agent and

(iii) the charge carried by suspending agent.



PREPARATION OF SUSPENSIONS

Method of preparations can be subdivided into two broad categories:

Precipitation method

There are three methods

1. organic solvent precipitation
2. precipitation effected by changing the pH of the medium and
3. double decomposition

(i) Organic solvent precipitation

Water insoluble drugs can be precipitated by dissolving them in water-miscible organic solvents (e.g. alcohol, acetone, propylene glycol and polyethylene glycol) and then adding the organic phase to distilled water under standard conditions produces a suspension having a particle size in the 1 to 5 μm range.

Example: Prednisolone is precipitated from a methanolic solution to produce a suspension in water.

Disadvantage: Harmful organic solvents may be difficult to remove.

Advantage: In case of parenteral or inhalation therapy very fine particles are required, which can be prepared by this method.

(ii) Precipitation effected by changing the pH of the medium

A drug may be readily soluble at a certain pH and precipitate at another pH. This type of drug is first dissolved in the favorable pH and then the solution is poured in another buffer system to change the pH of the medium and the drug will form a suspension in the medium of the second pH.

Example 1: Estradiol suspensions can be prepared by changing the pH of the of its aqueous solution; estradiol is readily soluble in alkali as potassium or sodium hydroxide solutions. If a concentrated solution of estradiol is thus prepared and added to a weakly acidic solution of hydrochloric, citric or acetic acids, under proper conditions of agitation, the estradiol is precipitated in a fine state of subdivision.

Example 2: Insulin suspension may also be prepared by pH change method. Insulin has an isoelectric point of approximately pH5. When it is mixed with a basic protein, such as protamine, it is readily precipitated when pH is between the isoelectric points of the two components, i.e. pH 6.9 to 7.3. Protamine-Zinc-Insulin (PZI) contains an excessive quantity of zinc to retard the rate of absorption. According to the British Pharmacopoeia phosphate buffer is added to an acidified solution of PZI so that the pH is between 6.9 to 7.3 to form the suspension.

(iii) Double decomposition method

In this method two water soluble reagent forms a water insoluble product.

Example: White Lotion NF is prepared by slowly adding zinc sulfate solution in a solution of sulphurated potash to form a precipitate of zinc polysulphide.

Dispersion method

In this cases the powder form of the drug is directly dispersed in the liquid medium. The liquid medium should have good power of wetting the powder.

1. Small scale preparation method

A suspension is prepared on the small scale by grinding or levigating the insoluble material in the mortar to a smooth paste with a vehicle containing the dispersion stabilizer and gradually adding the remainder of the liquid phase in which any soluble drugs may be dissolved. The slurry is transferred to a graduate, the mortar is rinsed with successive portions of the dispersion medium is finally brought to the final volume.

2. Large scale preparation method

On large scale dispersion method the solid particles are suspended using ball, pebble and colloid mills. Dough mixers, pony mixers and similar apparatus are also employed.

EVALUATION OF SUSPENSION STABILITY

Sedimentation volume

Since redispersibility is one of the major considerations in assessing the acceptability of a suspension, and since the sediment formed should be easily dispersed by moderate shaking to yield a homogeneous system, measurement of the sedimentation volume and its ease of redispersion are the two common evaluative procedures.

Definition: The sedimentation volume, F, is defined as the ratio of the final, or ultimate volume of the sediment (Vu), to the original volume of the suspension (Vo), before settling. Thus

$$F = Vu / Vo$$

The sedimentation volume can have values less than 1 to greater than 1. If the volume of sediment in a flocculated system equals the original volume of suspension, then F = 1. Such a product is said to be in 'flocculation equilibrium'.

Procedure: The suspension is taken in a measuring cylinder upto a certain height and left undisturbed. The particles will settle gradually. The value of F is determined from the ratio of the volume of the sediment at that instant of time (Vu) and the original volume of the suspension (Vo). The value of F is plotted against time (t). The plot will, will start at 1.0. at time zero. The curve will either run horizontally or gradually sloping downward to the right as time goes on.

One can compare different formulations and choose the best by observing the line, the better formulation obviously producing lines that are more horizontal and/or less steep.

If the suspension is highly concentrated then the suspension is diluted with the continuous medium (liquid phase) and then the sedimentation volume is determined.

Degree of flocculation

A more useful parameter is the degree of flocculation, β.

Definition: degree of flocculation is the ratio of ultimate sediment volume of *flocculated* suspension to that of *a deflocculated* suspension.

$$\beta = \frac{\text{sedimentation volume of } \textit{flocculated} \text{ suspension (F)}}{\text{sedimentation volume of } \textit{deflocculated} \text{ suspension (F}\infty\text{)}}$$

$F\infty = V\infty / Vo$ — $F\infty$ = sedimentation volume of *deflocculated* suspension; $V\infty$ = ultimate sediment volume of *deflocculated* suspension; Vo = original volume of suspension

$F = Vu / Vo$ — F = sedimentation volume of *flocculated* suspension; Vu = ultimate sediment volume of *flocculated* suspension

Therefore, $\beta = F / F\infty$

$= (V\infty / Vo) / (Vu / Vo)$

$$\beta = \frac{\text{ultimate sediment volume of } \textit{flocculated} \text{ suspension (Vu)}}{\text{ultimate sediment volume of } \textit{deflocculated} \text{ suspension (V}\infty\text{)}} = (V\infty / Vu)$$

Redispersibility

The evaluation of redispersibility is also important. To quantitate this parameter to some extent, a mechanical shaking device may be used. It simulates human arm motion during the shaking process and can give reproducible result when used under controlled conditions.

Rheologic methods

Rheologic behavior can also be used to help determine the settling behavior and the arrangement of the vehicle and particle structural features for purposes of comparison. The structure of the suspension changes during storage period. This structural changes can be evaluated by rheologic method.

A practical rheologic method involves the use of a Brookfield viscometer mounted on a helipath stand. The T-bar spindle is made to descend slowly into the suspension, and the dial reading on the viscometer is then a measure of the resistance the spindle meets at various level in the sediment. In this technique, the T-bar is continually changing position and measures undisturbed samples as it advances down in the suspension This technique also indicates in which level of the suspension the structure is greater, owing to the particle agglomeration, because the T-bar descends as it rotates, and the bar is continually entering new and essentially undisturbed material.

Thus using the T-bar spindle and the helipath, the dial reading can be plotted against the number of turns of the spindle. The result indicates how the particles are setting with time. In a screening study the better suspensions show a lesser rate of increase of dial reading with spindle turns, i.e. the curve is horizontal for a longer period.

Electrokinetic techniques

Instrument : Microelectrophoresis apparatus.

Such instrument permit measurement of the migration velocity of the particles with respect to the surface electric charge or the zeta potential. Zeta potential correlated well with the visually observed caking and certain zeta potential produced more stable suspensions because aggregation was controlled and optimized.

Particle Size Changes

During storage or transport the product may experience a fluctuation of temperature which may lead to crystal growth or physical incompatibilities. Normally it may take time to check the stability regarding crystal growth. So to accelerate this effect ***freeze-thaw cycling*** technique is particularly applicable. The product is put into refrigerator and again brought into room temperature — this type of temperature cycling promotes the growth of particle size. The growth of particle and size distribution are estimated by microscopic means.

Example(i) The crystal growth of sulfathiazole in suspensions is found to accelerate after temperature cycling

Example(ii) the preservative and protective colloid, may have a profound effect on the physical performance of a suspension under freeze-thaw conditions. Two low solid content steroid injectable preparations of following compositions underwent freeze-thaw condition the first preparation showed intense caking while the latter was unaffected.

Preparation	Protective colloid	Preservative	Result after freeze-thaw
I	sodium carboxy methylcellulose	benzyl alcohol	Caked badly
II	carboxy methyl cellulose	methyl paraben, propyl paraben	No caking

Example (iii) Gelatin solidifies at low temperature and methyl cellulose is precipitates in hot water.

CHAPTER – 1 **HISTORY OF PHARMACY IN INDIA**

In ancient India the sources of drugs were of vegetable, animal and mineral origin. They were prepared empirically by few experienced persons. Knowledge of that medical system was usually kept secret within a family.

There were no scientific methods of standardization of drugs.

Muslim rule in India

The Indian system of medicine declined during the Muslim rule while the Arabic or the Unani-Tibbi system flourished.

British rule in India

The western or the so-called Allopathic system came into India with the British traders who later become the rulers. Under British rule this system got state patronage. At that time it was meant for the ruling race only. Later it descended to the people and become popular by the close of 19th Century.

Before 1940

Initially all the drugs were imported from Europe. Later some drugs of this system began to be manufactured in this country.

1901: Establishment of the Bengal Chemical and Pharmaceutical Works, Calcutta by Acharya P.C. Ray.
1903: A small factory at Parel (Bombay) by Prof. T.K. Gujjar.
1907: Alembic Chemical Works at Baroda by Prof. T.K. Gujjar.

Drugs were mostly exported in crude form and imported in finished form. During World War-I (1914 – 1920) the imports of drugs were cut-off. Imports of drugs were resumed after the War. In absence of any restrictions on quality of drugs imoported, manufacturer abroad took advantage of the situation. The consequences were as follows:

(i) foreign manufacturers dumped inferior quality medicines and adulterated drugs.
(ii) Markets were full of all sorts of useless and deleterious drugs were sold by unqualified men.

Examples of maladies:

- Poisoning due to quinine.
- Putting of croton oil into eye instead of atropine solution.
- Selling of chalk powder tablets in place of quinine.
- Drug santonin was badly adulterated.
- Potent drugs like compounds of antimony and arsenic and preparations of digitalis were dispensed without any standard.

Few laws were there having indirect bearing on drugs, but were insufficient.

1878	Opium Act	Dealt with cultivation of poppy and the manufacture, transport, export, import and sale of opium.
1889	Indian Merchandise Act	Misbranding of goods in general
1894	Indian Tariff Act	Levy of customs duty on goods including foods, drinks, drugs, chemicals and medicines imported into India or exported there from.
1898	Sea Customs Act	Goods with ‘false trade description’ were prevented from importing under this act.
1919	Poisons Act	Regulated the import, possession and sale of poisons.
	Indian Penal Code	Some sections of IPC have mention of intentional adulterations as punishable offence.

Some state-level law had indirect references to drugs:

1884	Bengal Municipal Act	
1901	City of Bombay District Municipal Act	Concerned with food.
1909	Bengal Excise Act	
1911	Punjab Municipal Act	
1912	United Provinces (now Uttar Pradesh) Prevention of Adulteration Act	Refers to adulteration of foods and drugs.
1914	Pujab Excise Act	
1916	United Provinces Municipalities Act	Inspection of shops and seizure of adulterated substances.
1919	Bengal Food Adulteration Act	
1919	Bihar and Orissa Prevention of Adulteration Act	
1919	Madras Prevention of Adulteration Act	Chiefly concerned with food adulteration
1922	Bihar and Orissa Municipal Act	
1922	Central Provinces Municipalities Act	
1925	Bombay Prevention of Adulteration Act	
1929	Punjab Pure Food Act	

The laws were too superficial and had indirect link to drugs.

Drug enquiry committee

Government of India on 11th August 1930 , appointed a committee under the chairmanship of Late Col. R.N.Chopra to see into the problems of Pharmacy in India and recommend the measures to be taken. This committee published its report in 1931. It was reported that there was no recognized specialized profession of Pharmacy. A set of people known as compounders were filling the gap.

Just after the publication of the report Prof. M.L.Schroff (Prof. Mahadeva Lal Schroff) initiated pharmaceutical education at the university level in the Banaras Hindu University.

In 1935 United Province Pharmaceutical Association was established which later converted into Indian Pharmaceutical Association.

The Indian Journal of Pharmacy was started by Prof. M.L. Schroff in 1939. All India Pharmaceutical Congress Association was established in 1940. The Pharmaceutical Conference held its sessions at different places to publicize Pharmacy as a whole.

1937: Government of India brought 'Import of Drugs Bill'; later it was withdrawn.

1940: Govt. brought 'Drugs Bill'to regulate the imort, manufacture, sale and distribution of drugs in British India. This Bill was finally adopted as 'Drugs Act of 1940'.

1941: The first Drugs Technical Advisory Board (D.T.A.B.) under this act was constituted. Central Drugs Laboratory was established in Calcutta

1945: 'Drugs Rule under the Drugs Act of 1940' was established.

The Drugs Act has been modified from time to time and at present the provisions of the Act cover Cosmetics and Ayurvedic, Unani and Homeopathic medicines in some respects.

1945: Govt. brought the Pharmacy Bill to standardize the Pharmacy Education in India

1946: The Indian Pharmacopoeial List was published under the chairmanship of late Col.R.N. Chopra. It contains lists of drugs in use in India at that time which were not included in British Pharmacopoeia.

1948: Pharmacy Act 1948 published.

1948: Indian Pharmacopoeial Committee was constituted under the chairmanship of late Dr. B.N. Ghosh.

1949: Pharmacy Council of India (P.C.I.) was established under Pharmacy Act 1948.

1954: Education Regulation have come in force in some states but other states lagged behind.
1954: Drugs and Magic Remedies (Objectionable Advertisements) Act 1954 was passed to stop misleading advertisements (e.g. Cure all pills)
1955: Medicinal and Toilet Prepartions (Excise Duties) Act 1955 was introduced to enforce uniform duty for all states for alcohol products.
1955: First Edition of Indian Pharmacopoeia was published.
1985: Narcotic and Psychotropic Substances Act has been enacted to protect society from the dangers of addictive drugs.
Govt. of India controls the price of drugs in India by Drugs Price Order changed from time to time.

CODE OF ETHICS AS DRAFTED BY PHARMACY COUNCIL OF INDIA (P.C.I.)

Ethics is defined as 'code of moral principles'. It emphasizes on the determination of right or wrong while doing one's duty.

Code of Pharmaceutical Ethics as formulated by Pharmacy Council of India which are meant to guide the pharmacist as to how he should conduct himself (or herself), in relation to himself (or herself), his / her patrons (owner of the pharmacy), general public, co-professionals etc. and patients.

Introduction:

Profession of Pharmacy is a noble profession as it is indirectly healing the persons to get well with the help of medical practitioners and other co-professionals. Government has restricted the practice of Pharmacy to only Profession Pharmacists i.e registered Pharmacist under the Pharmacy Act 1948. PCI framed the following ethics for Indian Pharmacists, which may be categorised under the following headings:

1. Pharmacist in relation to his job.
2. Pharmacist in relation to his trade.
3. Pharmacist in relation to medical profession.
4. Pharmacist in relation to his profession.

<u>Pharmacist in relation to his job</u>

A pharmacist should keep the following things in relation to his job.

(i)*Pharmaceutical services*

Pharmacy premises (medicine shops) should b e registered. Emergency medicines and common medicines should be supplied to the patients without any delay.

(ii)*Conduct of the Pharmacy*

Error of accidental contamination in the preparation, dispensing and supply of medicines should be checked in a pharmacy.

(iii)*Handling of Prescription*

A pharmacist should receive a prescription without any comment on it that may cause anxiety to the patient. No part of the prescription should be changed without the consent of the prescriber. In case of changing the prescription should be referred back to the prescriber.

(iv)*Handling of drugs*

A prescription should always be dispensed correctly and carefully with standard quality drug or excipients. Drugs that have abusive potential should not be supplied to any one.

(v)*Apprentice Pharmacist*

Experienced pharmacists should provide all the facilities for practical training of the apprentice pharmacists. Until and unless the apprentice proves himself or herself certificate should not be granted to him / her.

Pharmacist in relation to his trade

Following are the provisions which pharmacist should keep in mind while dealing with his trade:

(i)*Price structure*

The prices charged should be fair keeping with the quality, quantity and labour or skill required.

(ii)*Fair trade practice*

Fair practice should be adopted by a pharmacist in the trade without any attempt to capture other pharmacist's business.

If a customer brings a prescription (by mistake) which should be genuinely by some other pharmacy the pharmacist should refuse to accept the prescription.

Imitation of copying of the labels, trade marks and other signs or symbols of other pharmacy should not be done.

(iii)*Purchase of drugs*

Pharmacists should buy drugs from genuine and reputable sources.

(iv)*Advertising and Displays*

The sale of medicines or medical appliances or display of materials in undignified style on the premises, in the press or elsewhere are prohibited.

Pharmacist in relation to medical profession.

Following are the code of ethics of a pharmacist in relation to medical profession:

(i)*Limitation of professional activity*

The professional activity of the medical practitioner as well as the pharmacists should be confined to their own field only.

Medical practitioners should not possess drugs stores and pharmacists should not diagnose diseases and prescribe remedies.

A pharmacist may, however, can deliver first aid to the victim incase of accident or emergency.

(ii)*Cladenstine arrangement*

A pharmacist should not enter into a secret arrangement or contract with a physician by offering him any commission or any advantages.

(iii)*Liasion with public.*

A pharmacist should always maintain proper link between physicians and people. He should advise the physicians on pharmaceutical matters and should educate the people regarding heath and hygiene. The pharmacist should be keep himself / herself up-to-date with pharmaceutical knowledge from various journals or publications.

Any information acquired by a pharmacist during his professional activities should not be disclosed to any third party until and unless required to do so by law.

Pharmacist in relation to his profession

Regarding to the profession the following code of ethics should be fulfilled.

(i)*Professional vigilance*

A pharmacist must abide by the pharmaceutical laws and he/she should see that other pharmacists are abiding it.

(ii)*Law-abiding citizens*

The pharmacists should have a fair knowledge of the laws of the country pertaining to food, drug, pharmacy, health, sanitation etc.

(iii)*Relationship with Professional Organizations*

A pharmacist should be actively involved in professional organization, should advance the cause of such organizations.

(iv)*Decorum and Propriety*

A phrmacist should not indulge in doing anything that goes against the decorum and propriety of Pharmacy Profession.

(v)*Pharmacists Oath*

A young prospective pharmacist should feel no hesitation in assuming the following pharmacist's oath:

- *"I promise to do all I can to protect and improve the physical and moral well-being of society, holding the health and safety of my community above other considerations. I shall uphold the laws and standards governing my profession, avoiding all forms of misinterpretation, and I shall safeguard the distribution of medical and potent substances.*
- *Knowledge gained about patients, I shall hold in confidence and never divulge unless compelled to do so by law.*
- *I shall strive to perfect and enlarge my knowledge to contribute to the advancements of pharmacy and the public health.*
- *I furthermore promise to maintain my honour in all transactions and by my conduct never bring discredit to myself or to my profession nor to do anything to diminish the trust reposed in my professional brethren.*
- *May I prosper and live long in favour as I keep and hold to this, my Oath, but if violated these sacred promises, may the reverse be my lot."*

SCOPE AND POTENTIAL OF PHARMACY

<u>Business</u>		<u>Service</u>
1. Drug Store		1. Hospital Pharmacy
2. Whole sale		2. Chemist in Drug Store / Whole sale store
3. Repacking		
4. Bulk drug distribution	D. PHARM	3. Medical representative
5. Cosmetic manufacturing		4. Packaging, store maintenance in Pharmaceutical Industry
		5. Secretary / PA to MD in Pharm. industry
<u>Business</u>		1. FDA job
1. Pharmaceutical industry		2. Teacher diploma courses
2. Bulk Drug Manufacturing	B.PHARM.	3. Production
3. Pharmacist job abraod	M. PHARM.	4. Marketing
4. Cultivation of medicinal plants		5. Teacher for Graduate level courses
5. Public testing laboratories	PhD	6. Research and development
6. Consultancy		

PHARMACEUTICAL LITERATURE

Syllabus: Development of Pharmacopoeias
History and development of Indian Pharmacopoeia.
Various official publications related to pharmacy profession in India.

PHARMACOPOEIA / FORMULARIES / COMPENDIA

The books containing the standards for drugs and other related substances are known as pharmacopoeia and formularies - collectively these books are known as the drug compendia.

The pharmacopoeias or formularies contain a list of drugs and other related substances regarding their source, descriptions, standards, tests, formulae for preparing the same, action and uses, doses, storage conditions etc.

These books are prepared under the authority of the Government of the respective countries. The word "pharmacopoeia" is derived from the Greek words '*pharmacon'* meaning 'drug' and '*poieo'* means 'make'. Literally it means that it is a list of medicinal substances, crude drugs and formulae for making preparations from them.

These books are revised from time to time so as to introduce the latest information available as early as possible after they become established. In order to keep the size of book within reasonable limit it becomes necessary to omit certain less frequently used drugs and pharmaceutical adjuvants from each new edition of the book. Therefore, in each new edition of these books certain new monographs are added while the older ones are deleted.

For the preparation of these books the expert opinion of medical practitioners, teachers and pharmaceutical manufacturers are obtained.

CLASSIFICATION

The drug-compendia are classified as:

(i) Official compendia
(ii) Non-official compendia

A. OFFICIAL COMPENDIA

Official compendia are the compilations of drugs and other related substances which are recognized as legal standards of purity, quality and strength by a government agency of respective countries of their origin.

e.g. British Pharmacopoeia (BP)
British Pharmaceutical Codex (BPC)
Indian Pharmacopoeia (IP)
United States Pharmacopoeia (USP)
National Formulary (NF)
The State Pharmacopoeia of USSR and
Pharmacopoeias of other countries

B. NON-OFFICIAL COMPENDIA

The book other than official drug compendia which are used as secondary reference sources for drugs and other related substances are known as non-official drug compendia. e.g. Merck Index
Extra Pharmacopoeia (Martindale)
United States Dispensatory etc.

INDIAN PHARMACOPOEIA

History

The historical developments of Pharmacopoeia in India traces back to 1563 and the credit goes to Garcia da Orta a Portugese physician-cum-teacher.

The idea of indigeneous Indian Pharmacopoeia was concieved in 1837 which bore fruits in 1841 in the shape of **Bengal Pharmacopoeia** and **Conspectus of Drugs**.

The hindustani version in Bengali and Hindi of **London Pharmacopoeia** was made available in India from 1901 onwards.

The **Indian Pharmacopoeial List**, published in 1946 formed the seeding for the true **Official Indian Pharmacopoeia** published in 1955.

The first edition of Indian Pharmacopoeia was published in 1955, but actually the process was started as early as 1944. In 1944 Government of India asked the Drugs Technical Advisory Board to prepare the list of drugs used, in India, having sufficient medicinal value to justify their inclusion in official pharmacopoeia.

The Indian Pharmacopoeial List, 1946.

The list of drugs both included and not included in the British Pharmacopoeia along with standards to secure their usefulness, tests for identity and purity was prepared by the committee and was published by the Government of India under the name '*The Indian Pharmacopoeial List 1946*'.

The committee constituted under the chairmanship of Col. Sir R.N.Chopra along with other nine members, prepared the list of drugs with the following details:

Substances included in the British Pharmacopoeia for crude drugs, chemicals and their preparations.

Substances not included in the British pharmacopoeia

a) Drugs of plant origin
b) Drugs of animal origin
c) Biological products
d) Insecticides
e) Colouring agents
f) Synthetics
g) Miscellaneous
h) Drugs for veterinary use.

The Indian Pharmacopoeial List 1946 was prepared by Department of Health, Govt. of India in 1946.

The history of development of Indian Pharmacopoeia:

Year	Events
1946	The Govt. of India published the *Indian Pharmacopoeial List*.
1948	The Govt. of India constituted a permanent Indian Pharmacopoeia Committee. This committee was assigned the task of preparing Indian Pharmacopoeia and to keep it up-to-date.
1955	The **first** edition of **Indian Pharmacopoeia** (IP) was published.
1960*	Supplement of IP 1955 was published. N.B. The work of revision of the Indian Pharmacopoeia as well as compilation of new edition was taken up simultaneously under the chairmanship of Dr. B.N.Ghosh, who died in 1958. After Dr. B.N.Ghosh, Dr. B.Mukherjee, the Director of Central Drug Research Institute was appointed as the chairman of Indian Pharmacopoeia committee.

1966*	The **second** edition of IP was published.
1975	A supplement of IP 1966 was published.
1978	The Indian Pharmacopoeia Committee was reconstituted by the Govt. of India, Ministry of Health and Family Welfare, under the chairmanship of Dr. Nitya Nand, Director, Central Drug Research Institute, Lucknow.
1985	The **third** edition of IP was published in two volumes, Volume-I and Volume-II by the Controller of Publications, on behalf of Govt. of India, Ministry of Health and Family Welfare. **Volume-I** contains: Legal Notices, Preface, Acknowledgments, Introduction, General Notices, and Monographs from A to P. **Volume-II** contains: Monographs from Q to Z, Appendices, Contents of Appendices and Index.
1989	Addendum (I) to IP 1985 was published.
1991	Addendum (II) to IP 1985 was published.
1996*	The **fourth** edition of IP was published.

For the preparation of Pharmacopoeia of India, the pharmacopoeias of other countries, like British, Europe, United States, USSR, Japan, the National Formulary (USA) and Merck Index were consulted. The persons working in pharmaceutical industry, drug control laboratories, research and teaching institutions also actively participated.

Under the Drugs and Cosmetics Act 1940, the Indian Pharmacopoeia is an official book which contains the standards for drugs and other related substances included in the pharmacopoeia. The drugs and other related substances prepared by pharmaceutical manufacturers must comply with these standards.

VARIOUS OFFICIAL PUBLICATIONS RELATED TO PHARMACY PROFESSION IN INDIA

1. NATIONAL FORMULARY OF INDIA

For the guidance of medical practitioners, medical students and pharmacists in hospitals and in sales departments National Formulary of India has been formulated.

1960 First edition was published by Govt. of India, Ministry of Health.
1966 Second edition was published.
1979 Third edition was published.

It contains information about drug interaction, resistance, cumulative effects, drug dependence, prescription writing etc.

2. THE INDIAN PHARMACOPOEIA

Under the Drugs and Cosmetics Act 1940, the Indian Pharmacopoeia is an official book which contains the standards for drugs and other related substances included in the Pharmacopoeia. The drugs and other related substances prepared by pharmaceutical manufacturers must comply with these standards.

1946 Indian Pharmacopoeial List was published by Govt. of India.
1955 First edition of Indian Pharmacopoeia was published.
1960 Supplement of IP 1955 was published.
1966 Second edition of IP was published.
1975 Supplement of IP 1966 was published.
1985 Third edition of IP was published.
1989 Addendum-I to IP 1985 was published.

1991 Addendum-II to IP 1985 was published.
1996 Fourth edition of IP was published.

Under each monograph chemical structures, molecular weight, physical description, solubility, identification tests, standards, assay method, storage etc. are given. Indian Pharmacopoeia is published by the Controller of Publications, Delhi on behalf of Govt. of India, Ministry of Health and Family Welfare.

3. THE BRITISH PHARMACOPOEIA (BP)

Under the Medical Act 1858 the General Council of Medical Education and Registration was empowered to alter, amend and republish the British Pharmacopoeia (BP) as often as necessary. The first BP was published in 1964.

1864 The **first** BP was published.
1926 Committee of Civil Research recommended that a Pharmacopoeia Commission be formed and it should be entrusted the work of new editions of BP and also recommended that BP be revised and reissued at an interval of ten years.
1932 New edition of BP was published according to the above recommendation.
1968 Medicines Act 1968 gave the responsibility of preparing the BP to the Medicines Commission. Medicines Commission reconstituted the British Pharmacopoeia Commission and gave the responsibility to British Pharmacopoeia Committee.
1980 The **thirteenth** edition of BP was [published.
1988 The 14th edition of BP was published.
1993 The 15th edition of BP was published.

BP 1988 contains two volumes with 2100 monographs:

Vol-I contains monographs on medicinal and pharmaceutical substances along with Infra-red (IR) reference spectra.
Vol-II contains formulated preparations, blood products, immunological products, radio-pharmaceutical preparations, surgical materials and appendices.

BP is the source of standards of drugs in United Kingdom and other parts of Common Wealth Countries.

4. BRITISH PHARMACEUTICAL CODEX (BPC)

It was in 1903 that the council of Pharmaceutical Society of Great Britain decided to prepare a reference book for the use of medical practitioners and dispensing pharmacists. The first edition of BPC was published in 1907.

On the request of British Pharmacopoeia Commission, the Council of the Pharmaceutical Society agreed in 1959 for the publication of Codex to coincide with that of the BP, so that BP and BPC should come into effect on the same date.

The BPC differs from BP in that :

a) It contains many more drugs and preparations some may be included in advance to the pharmacopoeia while other drugs may have been included in the former editions of pharmacopoeia but now they are retained in the Codex because they are still commonly used.
b) It provides information on the actions and uses of drugs, their undesirable effects, precautions and the treatment of poisoning.
c) It contains formulae, method of preparation, container and storage conditions of most of the preparations which are still extemporaneously prepared in the pharmacy.

5. THE UNITED STATES PHARMACOPOEIA (USP)

The USP was originally published in 1820 under the authority of United States Pharmacopoeial Convention. The National Formulary (NF) was published in 1888 under the guidance of American Pharmaceutical Association.

In 1974 the NF was purchased by the United States Pharmacopoeial Convention and from 1980 onwards only one official book of drug standards was published under the heading The United States Pharmacopoeia and The National Formulary (USP-NF).

6. EXTRA PHARMACOPOEIA

The Extra Pharmacopoeia was first produced in 1883 by William Martindale and is still known as '*Martindale*'. This is an authorized reference book on drugs and is used throughout the world. It provides all sorts of latest information on drugs and medicines. It is published by the direction of the Council of the Royal Pharmaceutical Society of Great Britain and prepared in the Society's Department of Pharmaceutical Sciences.

7. THE MERCK INDEX

It is an encyclopaedia of chemicals, drugs and biologicals. The first edition was published in 1989 and the eleventh edition was published in 1989 by Merck & Co., Inc. Rahway, New Jersy, USA.

8. THE INTERNATIONAL PHARMACOPOEIA

The International Pharmacopoeia is published by the World Health Organization and is particularly used in developing countries. The first edition was published in 1951 (Volume-I) and in 1955 (Volume-II).

The object of this was to provide a uniform list which would avoid the confusion caused by different national standards, strengths and names especially for the use of travelers who might need to use the same prescription in different countries.

QUESTIONS:

Q1. *What do you know about the IP. [91,94,95(2nd)]* *4*

Q2. *Short Note on Pharmacopoeia. [93,94]* *4*

Ans: See page 1; From Pharmacopoeia/Formularies/Compendia upto classification.

Q3. *Short note on Indian Pharmacopoeial List (IPL 1946) [94]* *5*

Ans:- page 2

Q4. *What is meant by National Pharmacopoeia? [91]* *4*

Ans:- Pharmacopoeias are generally prepared under the authority of the government of the respective countries - these pharmacopoeias are known as national pharmacopoeias.

Example of some national pharmacopoeias are as follows:-

Indian Pharmacopoeia, British Pharmacopoeia, united States Pharmacopoeia etc.

The drugs used may vary from nation to nation so, the respective pharmacopoeia includes those drugs or dosage forms which are frequently used in that very country at that time.

The national pharmacopoeia is recognized as the reference book by the legislative authority (by law) of the respective country, Whenever a conflict arises regarding drugs these books will be referred.

Q5. *What are the points discussed in the Monograph of an official drug? [94(2nd)] 6*
Ans:- The word '*Monograph*' means the written study of a subject. The pharmacopoeial monographs (for example in IP) give the following information about the drugs and pharmaceutical aids:-

1. Main title: The main name of the substance.
2. Synonym: The common name(s), if any, of the substance.
3. Chemical formula and Molecular Weight of the substance: If necessary , its I.U.P.A.C. chemical name and/or its chemical structure is also given.
4. Category: Indicates the use of the drug in medicine and pharmaceutical practices. e.g. Antibacterial, antimalarial, diuretic, emetic, expectorant etc.
5. Doses: Represents the average range of quantities suitable for adults.
6. Description: This includes the general physical properties, i.e. whether the substance is a solid or liquid, colourless or coloured, crystalline or amorphous, its taste etc.
7. Solubility: According to IP the solubilities of the substances are mentioned in terms of descriptive phrases as follows:

Descriptive phrase	Volume of solvent for dissolving 1 part of solute.
Very soluble	Less than 1 part
Freely soluble	1 to 10parts
Soluble	10 to 30 parts
\Sparingly soluble	30 to 100 parts
Slightly soluble	100 to 1000 parts
Very slightly soluble	1000 to 10,000 parts
Practically insoluble / insoluble	more than 10,000 parts

8.Standards: Prescribes the standards of purity and strength e.g. Sodium bicarbonate IP contains not less than 99.0 % and not more than 100.5 % of $NaHCO_3$.
9.Identification: This includes some specific and some non-specific tests for identity of substance.
10. Tests of purity: These tests include melting point, boiling point, weight per ml, limit tests for chloride, sulfates, iron, heavy metals, lead and arsenic, specific optical rotation, sulfated ash, loss on drying, pH of solution, etc. as may be applicable for the substance.
11.Method of Assay: The term 'Assay' is used in pharmacopoeias for quantitative determination of principal ingredients of the official substances and of their preparations.
12.Storage: Prescribes some conditions for the storage of some official substances which are likely to deteriorate if not properly stored.

Q6. *What are the various official publications related to pharmacy profession of India.? [95] 12*
Ans:- See page 3-5. Write in brief with following points for each pharmacopoeia.

a) Publishing authority
b) Year of 1st publication
c) Any special features
d) Other information

Q7. *Discuss briefly the importance of pharmacopoeia to drug industry and administration.* *[94]* *12*

Ans:- The importance of Pharmacopoeia can be discussed from the following three angles:

(i) Drug industry
(ii) Administration
(iii)Academic

From the point of view of drug industries

To market a new drug molecule stupendous amount of money is required for the research and development. Very few companies can bear this cost , especially the drug industries in developing countries (like India) are unable to bear the expenditure. In that case the drugs of products mentioned in the pharmacopoeias can be marketed without any further research on it, because only the tested, safe and efficacious drugs and pharmaceuticals are included in the pharmacopoeias.

Drugs and pharmaceuticals products are prepared from some raw materials, the standards of which should rigorously be met with that of pharmacopoeia. Though there are several other sources of information about the standard of drugs and pharmaceuticals, the pharmacopoeia is the most reliable one.

Assay methods and identifications of drug of pharmaceuticals are given very clearly in the pharmacopoeias so it becomes easy for the drug industry to design the tests and follow the methods confidently because the assay and identification methods are tested and approved by the authority.

2. From the point of view of drug-administration

In every country there are drug industries with varied intentions - among which the major one is ‘to make profit’. While making the profit some industries ignore the quality of the drugs and pharmaceuticals. Since drugs are related to the health of human beings and animals, this negligence is unpardonable. So every nation made their own Drugs and Acts and Rules. Whenever a conflict surfaces between a drug industry and Government the first reference book that is consulted, regarding the quality if the product, is the pharmacopoeia.

3.From the stand point of academicia

The pharmacopoeias are mines of information regarding drugs and pharmaceuticals. The researchers always consult it in first hand for developing an assay method of certain drug, for testing the quality of a dosage form. The microbiological and bioassays are given in details in the appendices with statistical quality controls. The usage of the drug, the adverse reaction, if any, and many more information are provided in the pharmacopoeias. The reason for the popularity of pharmacopoeias among the students, researchers, teachers is for the reliability of the information provided in it.

Extraction and Galenicals

Syllabus: Principles and Equipment used in the following extraction processes:- Infusion, Decoction, Expression, Maceration, Percolation.

Extraction:

extraction involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by using selective solvents in standard extraction procedures.

Discussion:

Belladonna extract is obtained from the leaves of the plant *Atropa belladonna*. The active ingredient is atropine. Besides atropine starch, lignin, pigments etc. are also present. So to extract the atropine from the leaves a selective solvent has to be used so that only atropine is soluble in it. Thus the active ingredient can be separated from the plant.

Source of drugs (active ingredients) may be plant or animal.

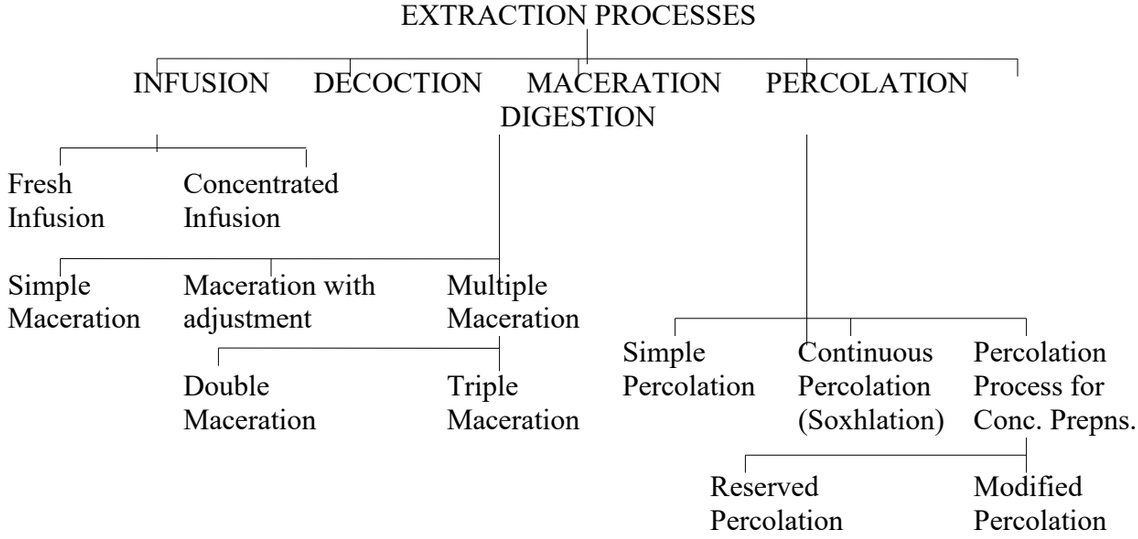
Plant source: Emetine from Ipecac root, reserpine from *Rauwolfia serpentina* root, atropine from Belladonna leaves.

Animal source: Cochineal from insect *Coccus cacti*.

General procedures:

In this discussion we are concerned primarily with basic extraction procedures for crude drugs to obtain the therapeutically desirable portion and eliminate the inert crude material by treatment with a selective solvent, known as the menstruum.

Let us take some dried leaves (known as the **crude drug)** in a container, add water in it. The active ingredient will come out in the water. Here water, i.e. the solvent of extraction is called **menstruum.** Later the water is filtered. The filtrate is known as the **extract**. The damp crude drugs (damp leaves) are called **marc**. This marc can be expressed i.e., pressed in a chamber to get the residual liquid, which is mixed with the previous extract.



Extraction procedures:
There are several procedures for extraction: e.g maceration, percolation, digestion, infusion, decoction, digestion etc. Most pharmacopoeias generally refer to maceration and percolation for the extraction of active principles from crude drugs.

MACERATION
Principle:
In this process solid ingredients are placed in a stoppered container with the whole of the solvent and allowed to stand for a period of at least 3 days (3 - 7 days) with frequent agitation, until soluble matter is dissolved. The mixture is then strained (through sieves / nets), the marc pressed and the combined liquids clarified (cleaned by filtration) or by decantation, after standing.

N.B.
Stoppered container is generally taken to reduce the loss of solvents by evaporation. If the volume of solvent is reduced by evaporation then the extract may become concentrated, which may not be desired.
The drug is allowed to stand for few days
i) to help the solvent to penetrate the cells of the drugs,
ii) to provide the time for partitioning the active ingredient into the solvent and
iii) to transfer the drug out of the cells into the bulk of the solvent.
Frequent agitation is required to reduce the localized concentration around the cells and tissues.
As indicated in the pharmacopoeia the process consists of the following:

- Placing the solid materials with whole menstruum in the closed vessel and allowed to stand for 7 days shaking occasionally.
- Strained, pressed the marc and the liquid is obtained.
- Liquid (i.e the extract) is clarified by subsidence or filtration.

The process is normally used for the preparation of tinctures or extracts and menstruum is usually alcoholic, hydroalcoholic (in case of tinctures) or may be aqueous.

1. **Simple maceration** - a process for tinctures made from organized drugs e.g. roots, stems, leaves etc.
2. **Maceration with adjustment** - a process for tinctures made from unorganized drugs such as oleo-resins and gum resins.
3. **Multiple maceration** - a process to prepare concentrated extract. It includes 'Double maceration' and 'Triple maceration'.

SIMPLE MACERATION
Organized drugs having specific cell structures like roots, stems, leaves, flowers etc. are extracted by this procedure.

Apparatus
A wide mouthed bottle or any other container which can be well stoppered can be used for maceration process. A closed container is essential to prevent the

evaporation of menstruum which is mostly concentrated alcohol. Otherwise this may lead to variation in strength as no adjustment in volume is made.

Method

Water or alcohol is used as menstruum and the drug menstruum ratio is 1 : 10.

- The drug is placed with the whole of the menstruum in a closed vessel for seven days. During this period shaking is done occasionally.
- After 7 days the liquid is strained and marc is pressed.
- The expressed liquid is mixed with strained liquid.
- It is then filtered to make a clear liquid.
- The **final volume is not adjusted.**

Explanation

1. Shaking of the drug during maceration is essential in order to replace the saturated layers around the drug with fresh menstruum.

2. After straining, the marc is pressed in a filter press, hydraulic press or hand press etc. The marc can be squeezed out of a fine muslin piece, when the quantity of the drug is very small.

3. The pressed liquid is mixed with the strained liquid and then filtered. No final adjustment is made, since the volume of pressed liquid is likely to vary with the process of pressing the marc. If the final adjustment in volume is made, it will give variation in the concentration of active principle although the volume of the final preparation may be the same.

4. Filtration is necessary to remove insoluble cell contents obtained during the pressing of marc.

Examples: The tinctures made by simple maceration process are-

1. Tincture of Orange
2. Tincture of Lemon
3. Tincture of Squill

MACERATION WITH ADJUSTMENT

The process is used for **unorganized** drugs.

Apparatus: Same as simple maceration.

Method:

- In this process the unorganized drug is placed with 4/5 th of the menstruum in a closed vessel for a period of 2-7 days. During this period, shaking is done occasionally .
- After the stated period, the liquid is filtered and the volume is made up by passing the remaining 1 / 5 the of the menstruum through the filter.
- The marc is not pressed.

Explanation

1. The period of maceration is reduced from 7 to 2 days in some cases, because the unorganized drugs behave like simple chemicals that dissolve in the solvent very easily and quickly.
2. 4/5th of the menstruum is used to keep the drug in contact with it in order to take into account the increase in volume after dissolving the soluble matter of the drug. The volume is made up at the end with 1/5th of the menstruum remained.
3. The marc left is a compact gummy matter. It does not retain the menstruum and hence it is not necessary to press the marc.
4. The final volume is made up because all the active constituents of drug get dissolved in the menstruum. Marc is not pressed. hence, there is no change in the concentration of the preparation in case the final volume is made up.

Example

1. Tincture of tolu
2. Compound tincture of benzoin.

MULTIPLE MACERATION

Multiple maceration process is carried out in the same way as simple maceration process, but the menstruum used is divided into two parts in double maceration process and three parts in triple maceration process

Double maceration process:

In this process, the drug is macerated twice by using the menstruum which is divided into two parts in such a manner that the same volume is used for each maceration. The quantity of menstruum required for two macerations are calculated as follows:

Volume of menstruum required for first maceration

$$= \frac{\text{Total vol. of menstruum} - \text{Vol. to be retained by the drug}}{2} + \text{Vol. to be retained}$$

Volume of menstruum required for second maceration

= Total vol. of menstruum – Vol. of menstruum used in first maceration

The volume of menstruum to be retained by the drug is determined by experiment, in a test batch of drug by adding a known volume of menstruum to known weight of the drug. After maceration, straining and pressing of the marc, measured volume volume of liquid is obtained. Difference in the volume and the volume used represents the volume retained by the weighable quantity of the drug used.

- In double maceration process, the whole of the drug is macerated for 48 hours with the quantity of the menstruum required for first maceration.
- The liquid is strained and the marc is pressed.
- The marc is macerated again for 24 hours with the remaining menstruum required for second maceration.
- The liquid is strained and and the marc is pressed.
- First and the second liquid is mixed and allowed to stand for 14 days and then filter.

Examples:

The following concentrated infusions are prepared by double maceration process:

1. Concentrated infusion of orange.
2. Concentrated compound infusion of chirata.
3. Concentrated compound infusion of gentian.

Triple maceration process

In this maceration process, the drug is macerated thrice by using the menstruum which is divided into three parts in such a manner that the same volume for three parts in such a manner that the same volume is used for each maceratin.The quantity of menstruum required for three macerations is calculateas follows:

Volume of menstruum required for first maceration

$$= \frac{\text{Total vol. of menstruum} - \text{Vol. to be retained by the drug}}{3} + \text{Vol. to be retained by the drug}$$

Volume of menstruum required for 2nd and 3rd maceration

$$= \frac{\text{Total vol. of menstruum} - \text{Vol. of menstruum used in first maceration}}{2}$$

- The whole of the drug is macerated for one hour with part of menstruum required for first maceration and strained.

- The marc is macerated again for one hour with the part of the menstruum required for 2nd maceration and strained.
- The marc is macerated again for one hour with the part of the menstruum required for 3rd maceration and strained.
- The marc is pressed lightly.
- The liquid obtained from 2nd and 3rd maceration is pooled and evaporated to a specified concentration. This concentrated liquid is mixed with the liquid obtained from the 1st maceration.
- 90 % alcohol equal to 1/4th of the volume of the finished product is added.
- Volume adjusted with water and allowed to stand for 14 days and then filtered.

Examples

The following concentrated infusions are prepared by triple maceration process:

1. Concentrated Infusion of Quassia
2. Liquid Extract of Senna

PERCOLATION PROCESS

1. Simple percolation process
2. Percolation process for concentrated preparations
    (a) Reserved percolation
    (b) Modified percolation
3. Continuous hot percolation / Soxhlet Extraction / Soxhlation

SIMPLE PERCOLATION

Apparatus:

Three types of apparatus are generally used,

i) Conical percolator
ii) Cylindrical percolator
iii) Steam jacketed percolator [for higher temperature extraction]

Stages:

1. **Size reduction:**

The drug to be extracted is subjected to suitable degree of size reduction, usually from coarse powder to fine powder, to

i) increase the surface area of the drug exposed to the menstruum,
ii) for uniform packing of the percolator,
iii) to slow down the movement of the menstruum and
iv) to ensure complete exhaustion of the drug.

2. Imbibition:

During imbibition the powdered drug is moistened with a suitable amount of menstruum and allowed to stand for four hours in a well closed container. During this period the drug swells up as the menstruum penetrates the cell walls. The preliminary moistening of the drug is necessary because:

i) the dried tissue swells when it comes in contact with the menstruum but if packed in the dry condition subsequent swelling will reduce the porosity of the material and choke the percolator,
ii) the air present in the interstices is removed by menstruum, which will otherwise disturb the packing of the percolator due to which the menstruum will run through the channels results in inefficient extraction,
iii) it does not allow the fine particles to be washed out of the percolator during percolation.

3. Packing:

After imbibition the moistened drug is evenly packed into the percolator. Cotton wool or fibres of flax; previously moistened with menstruum is placed on the perforated plate of the percolator.

The packing should not be too tight, it will lead to slow extraction rate. Similarly, loose packing will allow the menstruum to pass through quickly resulting in incomplete contact with the drug.

The drug should occupy 2/3rd capacity of the percolator. After packing , a piece of filter paper is placed over top of the bed, on which small quantity of washed sand is placed to prevent disturbance of the packed material.

4. Maceration:

After packing sufficient menstruum is added to saturate the material. When the liquid begins to drip from the bottom of the percolator, the tap fitted at its bottom

is closed. More menstruum is added if required, so that a shallow layer of menstruum is maintained over the drug bed.
The percolator is allowed to stand for 24 hours to macerate the drug.

5. Percolation:

After 24 hours maceration, the lower tap is opened and liquid collected therein is allowed to drip slowly at a controlled rate until 3/4th volume of the finished product is obtained.
Sufficient amount of menstruum is simultaneously added over the drug because at no time packed material should be allowed to become dry. After collecting 3/4 th volume, the percolate is tested for complete exhaustion of the drug by various tests.
Tests to check complete exhaustion of the drug:

i) Take a few ml of the last percolate and evaporate to dryness, it no residue remains - it shows that the drug is completely exhausted.
ii) The specific gravity of last few ml of percolate is measured. If it is equal to the specific gravity of the fresh menstruum the exhaustion is taken to be complete.
iii) Specific chemical tests may be performed on the percolate for the drugs containing alkaloids, glycosides, tannins, resins or bitter constituents.

- The marc is then pressed and the expressed liquid is added to the already collected percolate.
- More menstruum is added to produce the required volume.
- The liquid is then allowed to stand to settle the suspended particles, decanted or clarified by filtration.

Examples:

i) Tincture of belladonna
ii) Compound tincture of cardamom
iii) Strong tincture of ginger etc.

2.(a) RESERVE PERCOLATION

- In this process, the first portion (about 3/4 th of the final product) of the percolate which contains the maximum amount of active constituents is reserved. Subsequently, percolation is completed as usual until the drug is exhausted but the last part (about 1/4th of the final product) is collected separately.
- The second dilute part is then evaporated to get a syrupy consistency which is then mixed with the reserved first portion of the percolate.
- Finally volume is adjusted by adding more menstruum.

Example:

Liquid extract of liquorice

Advantages:

i) The reserved part of the percolate which contains the maximum amount of dissolved active principles is not subjected to heat, only the dilute portion is evaporated. Hence, the major portion of the active constituents of the drug are saved from deterioration.
ii) The process is economical as the whole of the percolate is not evaporated.

2.(b) MODIFIED PERCOLATION

In percolation process for preparation of tinctures the drug/percolate (d/p) ratio is about 1:4. The d/p ratio is reduced to 1:3 by modifying the percolation process and hence, there is a lot of saving in heat, time and menstruum.

Percolation is a displacement process. The strong solution of active constituents of drug formed during maceration is displaced by the fresh menstruum when percolation process is started. It is proved that stationary menstruum (menstruum remaining in contact with the drug) dissolves more menstruum is required to exhaust the drug when simple percolation is used. But if continuous percolation stage has suitable breaks by short maceration stages, the d/p ratio can be reduced to 1:3.

Example:

In simple percolation process:

Drug (1000 g)	Imbibition (for 4 hrs)	Maceration (for 24 hrs)	Percolation and collect the percolate, i.e. 3/4 the of the volume of finished preparation

Drug : Percolate = 1000 g : 4000 ml = 1 : 4

In modified percolation process:

Drug collect (1000 g)	Imbibition (for 4 hrs)	Maceration (for 24 hrs)	Percolation and 1000 ml of percolate
		Maceration (for 12 hrs)	Percolation & collect 1000 ml of percolate
		Maceration (for 12 hrs)	Percolation & collect 1000 ml of percolate

Drug : Percolate = 1000 g : 3000 ml = 1 : 3

CONTINUOUS HOT PERCOLATION PROCESS / SOXHLET EXTRACTION / SOXHLATION

This process is used for those drugs

- where the penetration of the menstruum into the cellular tissues is very slow and
- the solute is not readily soluble into the solvent and
- the quantity of the menstruum is very less.

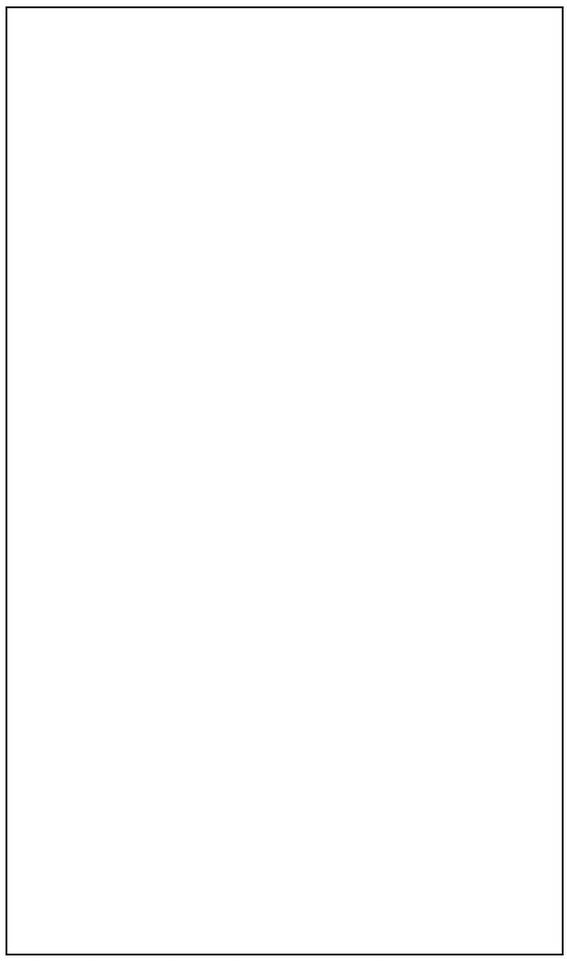
In such cases Soxhlet extractor is used where small volume of hot menstruum is passed over the drug time and again to dissolve out the active constituents until the drug is exhausted. The process is known as Soxhlation.

Apparatus:

i) A flask in which the menstruum is boiled,

ii) an extraction chamber in which drug is filled, is fitted with side tube and a siphon.

iii) a condenser.



The drug to be extracted , in suitably comminuted form is usually packed in a '**thimble**' made of filter paper which is then placed into the wider part of the extractor.

N.B. thimble is used to prevent choking of the lower part of the extractor.

Menstruum is placed in the flask and boiled. The vapor rises through the side tube to the condenser, where the vapor is condensed and fall on the packed drug, through which it percolates and extract out the active constituents.

As the volume of menstruum in the extractor increases, the level of liquid in the siphon also increases till it reaches the maximum point from where it is siphoned out into the flask.

On further heating the menstruum vaporizes while the dissolved active constituents remain behind in the flask. The alternate filling and emptying of the body of the extractor goes on continuously till the drug is exhausted. Thus the same quantity of menstruum is made to percolate repeatedly, about 14 to 15 times through the drug and the active constituents are collected in the flask.

Limitations of continuous hot percolation process:

1. Physical character of the drug: If the physical character of the drug is such that it would block the soxhlet apparatus then this method is not suitable. e.g opium, gum, resin, orange peel etc.
2. Solvent: Only pure solvents or constant boiling mixtures (like alcohol-water)can be used for this purpose.
3. Chemical constituents of the drug: The process is unsuitable for thermolabile active constituents, e.g. enzymes, alkaloids, anthraquinone derivatives, esters etc.

Examples:

Soxhlation process of extraction is used to

i) extract cantharidins from cantharides with benzene
ii) alkaloids from the seeds.

INFUSION

This method is used for those drugs

i) which are soft in nature so that water may penetrate easily to the tissues and
ii) the active constituents are water soluble.

Apparatus:

Coffee-pot or tea-pot is the simplest form of apparatus used for preparing infusion. Sometimes special pots known as **infusion pots** are used for the preparation of infusions. It consists of a loose perforated shelf resting on a projection near the top of the pot.

Method:

In coffee-pot or tea-pot:

i) The drug is placed at the bottom of the pot. Water is added and it is well stirred three or four times during the period of infusion.
ii) Infusion can also be prepared by enclosing the drug in a muslin bag and then suspending it just below the level of water in a beaker. Stirring is not required in this case because the water slowly circulates due to the increase in specific gravity of water near the drug.

In infusion pot:

The drug is placed on the perforated shelf. The pot is filled with water and the perforated shelf is adjusted below the surface of water.

* **Final volume is not adjusted.**

There are two types of infusions:

1. Fresh infusion, 2. Concentrated infusion

Fresh infusions:

A fresh infusion is an aqueous solution of active constituents of a vegetable drug prepared by the process of infusion e.g. Fresh infusion of Quassia.

Coarse powder of drug is used in the preparation of infusion. Water is used as menstruum.

Pharmacopoeia states that fresh infusion should be used within 12 hours after its preparation because it gets spoiled due to fungal or bacterial growth.

Concentrated infusions

Concentrated infusions differ from fresh infusions in that the concentrated infusions are prepared by maceration or percolation process and alcohol is used either as a menstruum or as a preservative.

An infusion containing 20 - 25 % alcohol can be stored for sufficiently long time.

e.g. Concentrated compound infusion of chirata and
Concentrated compound infusion of gentian.

DECOCTION

Decoction is the process in which the water soluble and heat stable constituents of hard and woody crude drugs are extracted out.

Water is used as menstruum and the drug, cut in small pieces, is boiled with the menstruum for 10 to 15 minutes.

After boiling, the liquid is cooled and filtered, more water is passed through the marc to produce the required volume.

Adjustment to final volume is necessary to get a uniform product.

A freshly prepared decoction should only be dispensed and the same must be consumed within 24 hours.

At present no decoction is official in IP or BP.

DIGESTION

This process is a modified form of maceration where the drug is extracted by heating at a particular pressure. This will increase the penetration power of the menstruum, so that there is complete extraction of the drug.

Apparatus:

The apparatus is known as 'Digestor' is a vessel made up of metal. The whole of the drug is placed in the body of the digestor; placed the cover over it and bolted it with the help of nuts.

The drug is treated with menstruum for a definite period under specified condition of temperature and pressure.

FACTORS AFFECTING SELECTION OF AN EXTRACTION PROCESS

1. Nature of the drug

The selection of an extraction process mainly depends on the physical nature of the drug.

Physical nature of the drug	Extraction procedure
• Hard and woody	• By percolation
• Soft drugs	• By maceration
• Unorganised drug	• By maceration and not by percolation because it may block the percolator.

2. Cost of the drug

Costly drugs are extracted by percolation whereas cheaper drugs may be extracted by maceration. Cost involve in size reduction (i.e. comminuting) of the drug should also be taken into consideration.

3. Stability of drugs

Continuous hot extraction process should not be used for those drugs containing thermolabile active constituents.

4. Therapeutic value of the drug

The drug containing flavoring agents or bitters etc. which does not have much therapeutic value may be extracted by maceration; but if the drug has considerable therapeutic value then percolation process should be used.

5. Nature of solvent

If the solvent is water maceration is generally adopted but, if the solvent is volatile then percolation process should be used.

6. Concentration of the product

Dilute preparations such as, tinctures may be prepared by maceration or by percolation but, concentrated preparations such as, liquid extracts or dry extracts should be prepared by percolation or reserved percolation process.

EXTRACTION METHODS	EXAMPLES
A. MACERATION	
i) Simple maceration	i) Tincture of Orange ii) Tincture of Lemon iii) Tincture of Squill.
ii) Maceration of unorganized drug / Maceration with adjustment	i) Tincture of Tolu Balsam ii) Compound Tincture of Benzoin
iii) Multiple Maceration a) Double maceration	i) Concentrated infusion of orange. ii) Concentrated infusion of chirata iii) Concentrated infusion of gentian
b) Triple maceration	i) Concentrated infusion of Quassia ii) Concentrated infusion of Senna
B. PERCOLATION i) Simple percolation	i) Tincture of Belladonna ii) Compound tincture of cardamom iii) Strong tincture of ginger etc. Liquid extract of Liquorice
ii) Reserved percolation iii) Continuous hot percolation / Soxhlation	i) Cantharidin from cantharides ii) Alkaloids from seeds
C. INFUSION i) Fresh infusion ii) Concentrated infusion	Fresh infusion of Quassia i) Concentrated compound infusion of chirata ii) Concentrated compound infusion of gentian No official preparations in IP or BP.
D. DECOCTION	

DIFFERENCE BETWEEN MACERATION AND DECOCTION

Maceration	Decoction
1. Menstruum may be water or hydroalcoholic solvents.	1. Menstruum is water.
2. The crude drug is macerated for 3-7 days.	2. Just 10 to 15 minutes is required to complete the process.
3. The drug is kept in contact with cold or warm menstruum.	3. Boiling water is passed through the crude drug.
4. After extraction the marc is expressed.	4. After extraction the marc is not expressed.
5. Extra menstruum is not added to make up the required volume.	5. Extra menstruum is passed through the extracted drug to make up the volume.
6. Alcohol acts as a preservative, hence it may be dispensed after 24 hours also.	6. A freshly prepared decoction should be taken within 24 hours because microorganisms may grow in aqueous medium.

Short note: EXTRACT

Extracts are concentrated preparations containing the active principles of vegetable or animal drugs. The drugs are extracted with suitable solvents and the product is concentrated to one of the three types of extract -

Liquid extract - of which 1 ml usually contains the active constituents from 1 g of the drug.

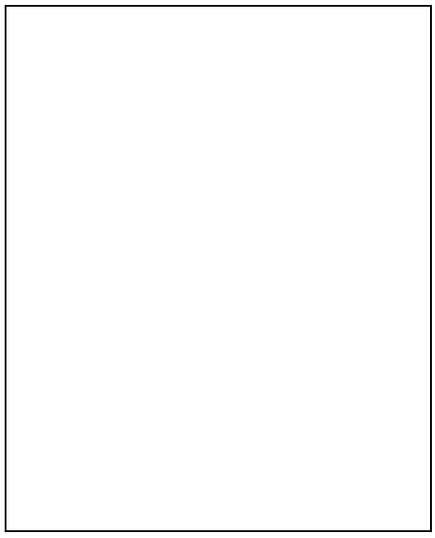
Dry extract - obtained by completely removing the solvent under reduced pressure.

Soft extract _ obtained by evaporation to a plastic mass.

Short note on EXPRESSION

The resudue of the drug after extraction (often known as the marc) is saturated with solvent. To recover the residual liquid pressure may be applied by a **hydraulic** press.

The marc is wrapped in cloth, is placed in the perforated inner vessel, which is enclosed in another vessel having an outlet for the expressed liquid. Application of hydraulic pressure to the ram presses the marc against the fixed head, expelling residual liquid.



Comparison between extraction method:

Extraction method	Time for extraction	Temperature	Characteristics of the active constituents
Maceration	3-7 days	Room temp	• Soluble in the menstruum • Heat stable / unstable
Percolation	24 hours	Room temp	• Soluble in the menstruum • Heat stable / unstable
Digestion	Few days	Moderately high	• Heat stable
Infusion	Short period	Cold or boiling water	• Readily soluble
Decoction	15 mins	Boiling water	• Water soluble • Heat stable

THEORY OF EXTRACTION OF DRUGS

Mass transfer

Consider a crystal of soluble material (e.g sugarcube) is immersedin asolvent in which it is dissolving. The crystal will be surrounded by a stationary boundary layer of the solvent, with the bulk of the fluid able to move.

The transport of molecules will take place in two stages:

1. The molecules will move through the boundary layer by **molecular diffusion**, with no mechanical mixing or movement.

2. Once material has passed through the boundary layer, mass transfer takes place by bulk movement of the solution, known as **eddy diffusion**.

Since there is no limit to the vigor of the movement of the bulk of the fluid, so the **rate controlling step** is the molecular diffusion.

Mass transfer by molecular diffusion can be represented by an equation, similar to conduction of heat transfer, in which

$$\frac{m}{t} = \frac{DA(C1 - C2)}{h}$$

where m = mass transferred in time t
D = diffusion coefficient of the solute
A = area of the solute exposed to the solvent
C1 = concentration of the solute at solid / liquid interface
C2 = conentration of solute in the bulk phase
h = thickness of the stagnant layer

Theory of extraction of drugs

Examination of the extraction processes will show that all have certain stages in common:

(i) Suitable size reduction of the drug
(ii) Penetration of the drug by the solvent
(iii) Solution of the soluble material within the cells.
(iv) Escape of the soluble material through the cell walls and through the solvent boundary layer surrounding the particles of the drug.
(v) Separation of the solution and the exhausted drug.

(I) Suitable size reduction of the drug:

From the mass transfer equation it is evident that m/t is proportional to A. If the area (A) is increased then rate of dissolution also increases. So if the size of the drug (plant or animal parts containing the active constituents) is reduced surface

area will increase, the consequence of which is the increase of the dissolution rate (m/t) of the active constituent. The **ideal size reduction** would be at cellular level but it poses the following disadvantages:

(i) It is difficult to reduce the size of a drug to its cellular dimension. It requires costly instruments which may not be cost effective.

(ii) Obviously it will take more time to reduce the size to such a level. Thus prolonged comminution (size reduction) will produce heat that may damage the heat labile constituents of the drug.

(iii) After extraction of such small particles they will make a suspension which will be difficult to filter.

(iv) While reducing the size to cellular level it is most probable that the cell walls will be broken and breakage of cell walls will release unwanted cellular materials like gums, starch, proteins etc. which may produce the filtrate cloudy by the release of **colloidal material**.

So the degree of size reduction to be used will depend, therefore, on the botanical structure of the drug.

Name of the drug	**Type of the drug**	**Degree of size reduction**
Gentian	Soft	Sliced and bruised
Cascara, Belladonna	Moderately hard	Coarse and moderately coarse powders
Ipecacuanha	Hard and woody	Moderately fine powder

(II) Penetration of the solvent into the drug:

Before drying the fresh drugs are surrounde by a thin film of water. After drying that water film evaporates and becomes porous due to shrinkage. The pores are then occupied by air. To penetrate the cell wall the solvent must have to displace the air first.

When the dry drug is moistened, the liquid film is again renerated and then the cells imbibe the solvent and swell.

Sometimes to facilitate the removal of air from the pores the solvent and the drug is first taken in a vessel, vacuum is applied - thus air is removed from the pores. Then, when the vacuum is released, pressure of the atmosphere forces the solvent into the drug and penetration is facilated considerably.

(III) Solution of constituents:

Once the solvent has penetrated into the cells solution of the constituents takes place and is governed by the solubility of the constituents in the solvent and again solubility depends on the temperature. So if the temperature is increased the solubility will also enhance.

(IV) Escape of the solution from the cells:

The solute molecules are transferred through the boundary layer or stagnant layer. Factors controlling mass transfer will show that the rate of extraction can be affected in the following ways:

(i) $m / t \propto 1 / h$ i.e. if the thickness of the boundary layer can be reduced rate will ne increased. h can be reduced by agitating the mixture occassionally which disperses local concentrations of the solution, thereby, increasing the concentration gradient.

(ii) By suspending the drug in a cloth bag or placing it on a perforated plate near to the surface of the liquid the escape of the solution can be hastened. As the constituents dissolve, the density of the solution increases, so that convection currents are established, leading to circulation of the solution followed by the reduction of local concentration surrounding the cloth.

(V) Separation of solution and exhausted drug:

After dissolution the solid materails has to be strained off. Since, the drug absorbs solvent and there is a residue of soluble constituents in that solvent, so the drug is subjected to pressure and sometimes under hydraulic pressure.

PROPERTIES OF SOLVENTS USED FOR EXTRACTING DRUGS

The ideal solvent would be:

1. It must be cheap.
2. Non-toxic
3. It should be stable chemically and physically.
   a) neutral to reaction
   b) not too volatile
   c) non-inflammable
4. Selective, i.e. it should remove the desired constituents with minimum amount of the inert materials.

N.B.

- Many extracts are intended for internal use. So the solvents should be selected cautiously.
- All the above properties of an ideal solvent render the majority of the organic solvents unsuitable.
- In special cases petroleum ether is required to remove the fat from a drug before extracting (e.g. some seeds containing fatty coating) the desired active constituents.

Water as a solvent for extraction:

Advantages:

(i) It is cheap.

(ii) It has a wide solvent action (e.g. protein, coloring maters, gums, antharaquinone derivatives, most alkaloidal salts, glycosides, sugars and tanins).

(iii)It is non-toxic and can be taken internally.

It is non-inflammable. In industry handling of large volume of volatile solvents may cause accident. Hence the inflammability of a solvent is very important from the point of view of industry.

Disadvantages:

(i) It is not selective. It dissolves a wide range of substances that may interfere with the extract's clarity e.g. gum, protein (coagulated).

(ii) Water is good medium for mold and bacterial growth. Generally most preparations are preserved with a small amount of glycerine, chloroform or by sterilization.

(iii)Water promotes hydrolysis of many substances and allows enzymatic actions to take place [e.g glycosides such as digitalis].

(iv)Concentration of aqueous solution requires more heat than for most other solvents due to its higher latent heat of evaporation (537 cal / gm).

Ethanol as solvent:

Advantages:

(i) Reasonably selective, e.g. in a drug containing gum, albuminous matter and a glycoside or an alkaloidal salt, ethanol in a suitable dilution with water would dissolve only the glycoside or the alkaloidal salt, whereas water would usually dissolve all of the constituents.

(ii) Molds cannot grow in solvent mixture containing more than 20 % ethanol.

(iii)Non-toxic in the quantities prescribed in the medicinal preparations.

(iv)It is neutral, hence compatible with other products .

(v) Latent heat of vaporization is less than water , so less heat will be consumed to make an extract concentrated.
(vi)Can be mixed in any combination with water.
Disadvantage:
Cost due increases due to the duty imposed by the Government on it

Questions
Ques. 1 *How will you make an infusion of Gentian? (1991) 8*
Ans:- See the method for **Fresh infusion.**
Ques. 2. Write the principle, method and equipment used in the following preparations:-(i) Tincture Belladonna (1992) 4
(ii)Tolu Balsam syrup. (1992) 4
Ans:- Tolu balsam is an unorganized drug. Tolu balsam is taken on a tared vessel and boiling purified water is added to it. The vessel is tightly closed and boiled gently for 30 minutes, stirring frequently. Purified water is added to adjust the specified weight. The preparation is cooled and filtered and then sucrose is added to it. It is heated again in water bath to dissolve the sucrose. Finally sufficient purified water is added to produce the required volume.
Tolu syrup has some aromatic odour and flavour and it is believed to have a mild expectorant action.
Ques. 3. Discuss what do you mean by extraction. How triple percolation is conducted? (1993) 4+12
Extraction may be defined as the process in which the animal or plant tissue are treated with specific solvents whereby the medicinally active constituents are dissolved out, cell tissues and most of inactive or inert components remain undissolved. The solvent used for extraction purpose is known as menstruum and residue left after extraction the desired constituents is known as marc.
The various processes used for extraction are: 1. Infusion, 2. Decoction, 3. Maceration, 4. Percolation, 5. Digestion.
The various preparations prepared by using one of the above methods are Infusions, Decoctions, Spirits, Elixirs, Extracts etc. All these preparations are commonly known as ‘Galenicals’.
Triple percolation:- Write Modified Percolation Process.
Ques.4. Describe the percolation process in details with a schematic diagram of a typical percolator. (1994, 1996) 12
Ans:- Simple percolation process.
Ques 5 What is reserved percolation? (1994) 4
Ans:- Reserved percolation process.
Ques.6. Short notes on Maceration and Decoction. (1994) 8
Ans:- Write the difference between Maceration and Decoction.
Ques. 7. Short note on Soxhlet extractor with diagram. (1994) 8
Ans:- Soxhlet apparatus with diagram.
Ques. 8. Factors affecting the choice of extraction process. (1994) 8
Ans:- Factors affecting the choice of extraction process.
Ques.9. How does the method of preparation vary for concentrated infusion and infusion. (1995)
Ans:- See ‘Infusion’.
Ques. 10. Difference between infusion and decoction? (1995) 2
Ans:- Write yourself.
Ques. 11. What do you by leaching? Name the methods used for the same mentioning their procedure. (1995) 4+12

Ans:- “Leaching” is same as “Extraction”.
Two main methods of leaching are maceration and percolation. Give the description briefly with diagram.

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MONOPHASIC LIQUID DOSAGE FORM

SYLLABUS

Definition and account of oral solutions, syrups and elixirs.
Their importance in the Medical field.
Components of the formulations with examples: Solvents, buffers, sweeteners, acidifiers, flavors, and preservatives.
Development of the formula.
Preparation , equipment in industrial scale.

QUESTION S

1. Short note on preservatives in pharmaceutical dosage forms. (98) 4
2. Short note on syrups. (98) 4
3. Give the importance of colorants, sweeteners, solvents, stabilizers, flavoring agents in pharmaceutical dosage forms. (98)
   4 x 4
4. Discuss the preformulatory and informulatory aspect of designing a multivitamin syrup. 16
5. What are syrups? Write about the preparation, properties and uses of at least two medicated syrups. (93) 10
6. Differentiate between solution and elixirs. (95) 8
7. Classify organoleptic compounds with examples. (93) 10

SOLUTION

In pharmaceutical terms, solutions are liquid preparations that contains one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents.

CLASSIFICATION OF SOLUTION

(i) According to the route of administration

a) *Oral solutions*—through oral route.
b) *Otic solutions*—instilled in the ears.
c) *Ophthalmic solution*—instilled in the eyes.
d) *Topical solutions*—applied over the skin surface.

(ii) According to composition and uses

a) *Syrup*—aqueous solution containing sugar.
b) *Elixir*—sweetened hydroalcoholic (combination of water and ethanol) solution.
c) *Spirit*—Solution of aromatic materials in alcohol.
d) *Aromatic Water*—Solution of aromatic material in water.
e) *Tincture / Fluid extract*—Solution prepared by extracting active constituents from crude drugs. e.g. Compound cardamom tincture. They may also be solutions of chemical substances dissolved in alcohol or in hydroalcoholic solvent. e.g. Tincture of Iodine.
f) *Injection*—Certain solution prepared to be sterile and pyrogen-free and intended for parenteral administration.

FORMULATION CONSIDERATION

1) **Solubility**
   a) pH
   b) Cosolvency
   c) Solubilization
   d) Complexation
   e) Hydrotrophy
   f) Chemical modification of the drug molecule
2) **Preservation**
3) **Organoleptic consideration**
   a) Sweetening agents
   b) Flavoring agents
   c) Coloring agents
   d) Viscosity control
   e) Overall appearance
4) **Stability**

a) Preservatives
b) Antioxidants
c) Reducing agents
d) Synergists

a) Chemical stability
b) Physical stability

SOLUBILITY

When a solid solute is dissolved in a liquid solvent two types of interactions are evident—one is the intra-molecular force between the solute molecules and the other is the intermolecular force between the solute and solvent molecules. When a solute dissolves, the substance's intra-molecular forces (cohesive force) must be overcome by the force of attraction between the solute and solvent molecules (adhesive force).This involves breaking the solute-solute forces and the solvent-solvent forces to achieve the solute-solvent forces attraction.

EXPRESSION OF SOLUBILITY

According to Indian Pharmacopoeia

Descriptive Phrase	Approximate quantities(ml) of solvent by volume for 1 part (1 gm) of solute by weight
Very soluble	less than 1 part
Freely soluble	from 1 to 10 parts
Soluble	from 10 to 30 parts
Sparingly soluble	from 30 to 100 parts
Slightly soluble	from 100 to 1000 parts
Very slightly soluble	from 1000 to 10,000 parts
Practically insoluble	more than 10,000 parts

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.

Determination of Equilibrium Solubility of a Drug

An excess of the drug (finely powdered to minimize the time required to attain the equilibrium) is placed in a vial along with a specific amount of the solvent. The tightly closed vial is then agitated at constant temperatures (preferably at temperature somewhat higher than room temperature e.g. 30^0C so that constant conditions can be maintained regardless of normal laboratory temperature variations), and the amount of drug in solution is determined periodically by assay (by some chemical method) of a filtered sample of the supernate. Equilibrium is not achieved until at least two successive samplings give the same result.

The *solubility* is generally expressed in mg of solute per ml of solvent at 25^0 C or per 100 ml etc.

Solubility of a drug depends on temperature, solvent, pH and the chemical nature of the molecule itself. By modifying these parameters the solubility of a drug can be manipulated according to the requirement of designing the dosage form.

PH

A large number of drugs are either weak acids or weak bases. The solubility of these agents can be markedly influenced by the pH of the environment. When a weakly acidic drug is dissolved in water it can remain in three states, namely undissolved, dissolved and ionized which can be expressed in the following reaction format:

$$\underset{\text{(Undissolved)}}{\text{DH (solid)}} \rightleftharpoons \underset{\text{(Undissociated)}}{\text{DH (solution)}} \rightleftharpoons \underset{\text{(Dissociated / ionized)}}{D^-} + \underset{\text{(Proton)}}{H^+}$$

The relationship between equilibrium solubility of a weakly acidic drug and the pH of the environment can be expressed by Henderson-Hasselbach equation:

$$pH = pKa + \log \frac{[D^-]}{[DH]}$$

where pKa = Dissociation constant of the acid

$[D^-]$ = Molar concentration of ionized drug
[DH] = Molar concentration of unionized drug
The same equation can be written in the following forms:

$$pH = pKa + \log \frac{[ionized]}{[unionized]}$$

$$pH = pKa + \log \frac{[base]}{[acid]}$$

where DH = Acid
D^- = Corresponding base of the acid (DH)

Weak Acid

$DH\ (solid) \rightleftharpoons DH\ (solution) \rightleftharpoons D^- + H^+$.
Dissolved
Unionised

$$pH = pKa + \log \frac{[D^-]}{[DH]}$$

$$pH = pKa + \log \frac{[ionised]}{[unionised]}$$

$$pH = pKa + \log \frac{[base]}{[acid]}$$

DH = acid
D^- = corresponding base of DH

Weak Base

$DOH\ (solid) \rightleftharpoons DOH\ (solution) \rightleftharpoons D^+ + OH^-$.
Dissolved
Unionised

$$pH = pKa + \log \frac{[DOH^-]}{[D^+]}$$

$$pH = pKa + \log \frac{[unionised]}{[ionised]}$$

$$pH = pKa + \log \frac{[base]}{[acid]}$$

DOH = base
D^+ = corresponding acid of the base DOH

To maintain the drug in soluble state the solution of a drug must be done in a suitable buffer solution. The buffer must have the following properties:

1. The buffer must have adequate capacity in the desired pH range.
2. The buffer must be biologically safe for the intended use.
3. The buffer (or its pH range) must have minimum interference on the stability of the final product.
4. The buffer should permit acceptable flavoring and coloring of the product.

e.g. Some commonly used buffer systems are ammonium chloride, diethanol amine, triethanolamine, boric acid, carbonic acid, phosphate buffer, glutamic acid, tartaric acid, citric acid buffer, acetic acid buffer etc.

COSOLVENCY

Weak electrolytes and nonpolar molecules frequently have poor water solubility. These types of solutes are more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as cosolvency; and the solvents that, in combination increases the solubility of the solute are called cosolvents.

To increase the water solubility of a drug another water miscible solvent in which the drug has good solubility is mixed.

Mechanism of action

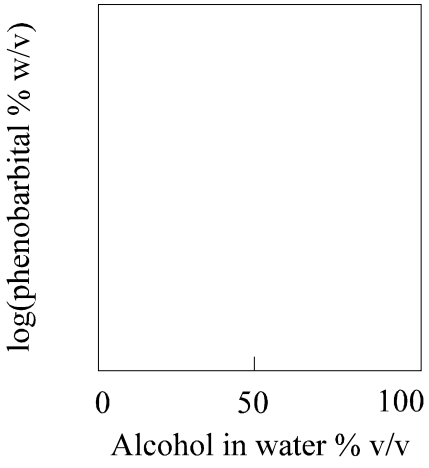
It has been proposed that a cosolvent system works by reducing the interfacial tension between the predominantly aqueous solutions and the hydrophobic solute.

Examples of commonly used cosolvents

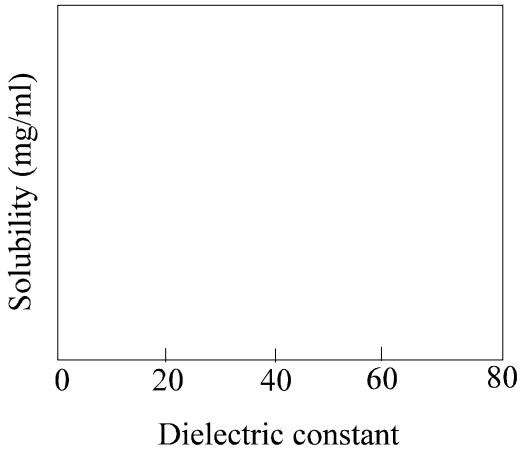
Ethanol, sorbitol, glycerin, propylene glycol and several members of the polyethylene glycol polymer (PEG200) series are the limited number of cosolvents (of water) those are used and are acceptable in oral preparation.

Use of cosolvents

Cosolvents are used to increase the solubility of weak electrolytes, non-polar molecules and volatile constituents used to impart a desirable flavor and odour to the product.



The solubility of phenobarbital in a mixture of alcohol & water



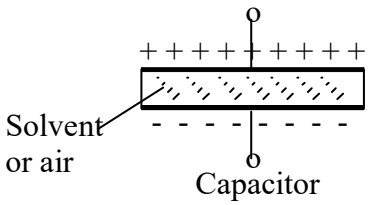
Caffeine in dioxane-water mixtures at solubility (mg/ml) plotted vs. dielectric constant of dioxane-water system.

DIELECTRIC CONSTANT

One property of a solvent system is its dielectric constant. The dielectric constant of a solvent can be defined as the ratio of the capacitances of a capacitor filled with the solvent and air respectively.

$$\text{Dielectric constant } (\varepsilon) = \frac{\text{C solvent}}{\text{C air}}$$

where, C is the capacitance of the condenser filled with respective medium (solvent or air)
e.g dielectric water is 78.5



Every solute shows a maximum solubility in any given solvent system, at one or more specific dielectric constants.

To determine the relationship between solubility of a solute with dielectric constant(s) at which maximum solubility is attained is noted.

Pharmaceutical formulations of comparable dielectric constant can thus be prepared, and the most appropriate solvent system can be selected on the basis of solubility, stability and organoleptic characteristics requirements.

SOLUBILIZATION

spontaneous increase of solubility of a poorly water-soluble solute molecules into an aqueous solution of surface active agents (or surfactants) in which a thermodynamically stable solution is formed.

Mechanism

When surfactants are added to water at low concentrations, they tend to orient at the air-liquid interface.

As additional surfactant is added, the interface becomes fully occupied, and the excess molecules are faced into the bulk of the liquid.

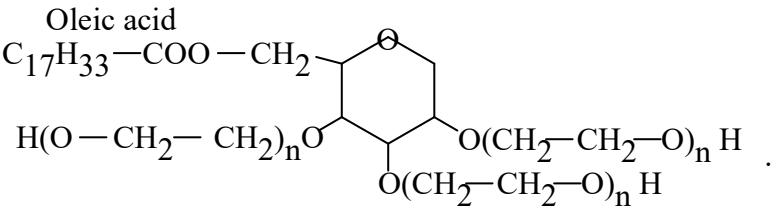
At still higher concentrations, the molecules of surfactant in the bulk of the liquid begin to form oriented aggregates or micelles, this change in orientation occurs abruptly (suddenly).

The concentration of surface active agent at which micelles occurs is called critical micelle concentration .

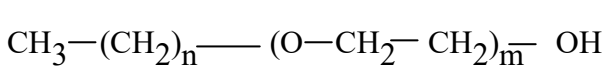
Solubilization is thought to occur by virtue of the solute dissolving in or being adsorbed onto the micelle. The water solubility of the solute increases with the concentration of the micelles.

Examples of some solubilizing agents:

Polyoxyethylene sorbitan fatty acid ester (Tween series)



Polyoxyethylene mono alkyl ether (BRIJ, MYRJ series)



n = 15 to 17 m = 20 to 24

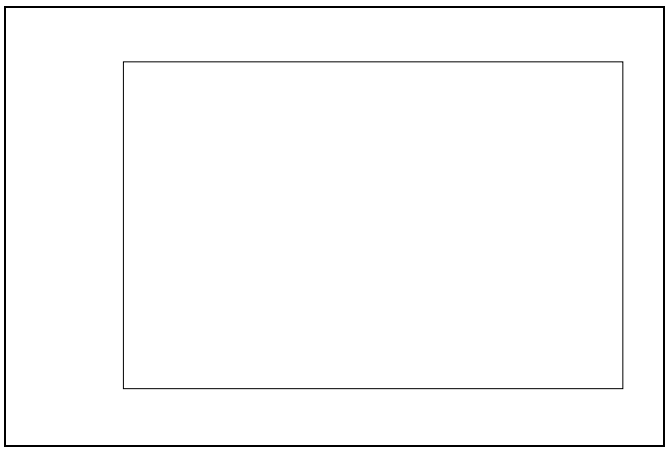
Other examples are Sucrose monoesters, Lanolin esters etc.

It has generally been found that surface-active-agents having HLB (Hydrophilic Lipophilic Balance) values higher than 15 acts better as solubilizing agents.

COMPLEXATION

Solubility of a compound may be increased by complexing with a complexing agent. e.g. solubility of para amino benzoic acid (PABA) may be increased by complexing with caffeine.

When an insoluble compound forms a complex which is more soluble in the solvent - the total solubility is equal to the inherent solubility of the uncomplexed drug plus the concentration of drug-complex in solution.



When a certain amount of drug is mixed in water some amount will get dissolved (A) and some amount will remain undissolved. If a complexing agent is added to it some drug will be complexed and become soluble in water. So the total solubility will be will be increased.

When more complexing agent is added total solubility will increase; at a certain concentration of complexing agent the solution will become saturated with respect to free drug and the complex (B). After this point if still complexing agent is used then remaining drug (undissolved) will form complex and the excess complex will be precipitated (C). When no drug is left for complexation, complexes of higher order may be formed.

e.g. I_2 is sparingly soluble in water. To dissolve it KI (potassium iodide) is added which makes a complex $KI.I_2$ (i.e. KI_3). After point C it forms $KI.2I_2$, $KI.3I_2$ etc.

HYDROTROPHY

The term hydrotrophy has been used to designate the increase in solubility in water of various substances due to the presence of large amounts of additives.

Mechanism of action

Not clear yet. Some workers have speculated that this phenomenon is more closely related to complexation involving a weak interaction between the hydrotrophic agent and the solute.

Another view is that the phenomenon must be due to change in solvent character because of the large amount of additive needed to bring about the increase in solubility.

Examples

Since a large concentration of hydrotrophic agent is required (in the range of 20 to 50%) to produce a modest increase in solubility, hence its pharmaceutical applications are very less in number.

Drug	**Hydrotrophic agent**

1. Benzoic acid	Sodium benzoate
2. Theophylline	Sodium acetate and sodium glycinate
3. Iodine	Polyvinyl pyrrolidone (PVP)
4. Adrenochrome mono semicarbazone	Sodium salicylate

SOLVENTS FOR ORAL PREPARATIONS

The solvents those are usually used in the oral liquid preparations are purified water, alcohol, glycerin and propylene glycol.

PURIFIED WATER (H_2O)

Naturally occurring water exerts its solvent effect on most substances. In oral preparations the water used is potable water or Purified Water USP.

Specifications of Purified Water USP

Method of preparations	:	By distillation or by ion-exchange.
Total solid	:	Less than 10 parts per million (ppm)
pH	:	Between 5 and 7.

ALCOHOL (ETHANOL)

Next to water, alcohol is the most useful solvent in pharmacy.

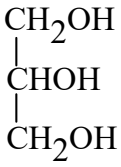
- It is used as a primary solvent for many organic compounds.
- With water it acts as a cosolvent and increases the solubility of drugs. Alcohol is often preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavorants, and antimicrobial preservatives.
- Alcohol is frequently used with other solvents, as glycols and glycerin, to reduce the amount of alcohol required.
- It also is used in liquid products as an antimicrobial preservative alone or as a co-preservative with parabens, benzoates, sorbates and other agents.

Disadvantages

It produces pharmacologic and potential toxic effects of alcohol when ingested in pharmaceutical products particularly by children. Hence, it should not be given to children below 6 years. For OTC (over the counter) oral product for children the recommended alcohol-content limit is 0.5 %.

Age of the patient	Permitted alcohol content
For children below 6 years	0.5 %
For children between 6-12 years	5.0 %
Children over 12 years and adults	10.0%

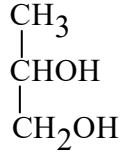
GLYCERIN (Glycerol)



- Glycerin is a clear syrupy liquid with a sweet taste.
- It is miscible both with water an alcohol.
- Glycerin has preservative qualities.

Disadvantages

As a solvent, it is comparable to alcohol, but because of its viscosity, solutes are slowly soluble in it unless it is rendered less viscous by heating.



PROPYLENE GLYCOL

It is a viscous liquid, is miscible with water and alcohol. It is useful solvent with a wide range of application and is frequently substituted for glycerin in pharmaceutical formulation.

BUFFERS

A buffer is a compound or mixture of compounds that, by its presence in solution, resists changes in pH upon addition of small quantities of acid or base.

Buffering agents are necessary to resist the change of pH upon dilution or addition of acid or alkali in the liquid preparation.

The usual buffering agents used in oral liquid preparations are *acetate buffer* and *phosphate buffer*.

Buffer	Mixture of	Buffering Range
Acetate buffer	Glacial acetic acid Potassium, sodium, ammonium salt of acetic acid	pH 2.8 to 6.0
Phosphate buffer	Potassium dihydrogen phosphate Di-sodium hydrogen phosphate	pH 2.0 to 8.0

Buffering is required to:

1. Keeping weakly acidic or basic drug in solution
2. Increase the stability of the drug
3. Resist the change of pH upon dilution or addition of acid or alkali (e.g. leaching or alkali from glass container).

SWEETENERS

Solutions come in immediate contact with the taste buds (on the tongue). Drugs and other adjuvants are generally not good to taste (i.e. not palatable). To enhance palatability and to mask the taste of the drugs etc. sweeteners are used.

Example: Sucrose (sugar), saccharin, aspartame, liquid glucose.

Sucrose

Source Commercially sucrose is obtained from sugarcane, beet root and shorgum.

Advantages

1. It is soluble in aqueous medium.
2. It is available in highly purified form at reasonable price.
3. It is chemically and physically stable in the pH range of 4.0 to 8.0.
4. It is frequently used in conjunction with sorbitol, glycerin and other polyols.
5. Above 66.7 % mold growth will not take place.

Disadvantages

Concentration of sucrose solution above 66.7% (w/w) the sucrose crystallize making the solution hazy (i.e. reducing the gloss of the solution).

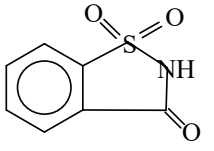
Caps of the containers are generally found to be locked due to this crystallization. Sorbitol, glycerin or other polyols are used to reduce the crystallization.

Liquid Glucose

Liquid glucose is an extremely viscid substance that imparts both body (i.e highly viscous) and sweetness to liquid formulations.

Preparation Partial hydrolysis of starch with strong acid produce liquid glucose. Its main component is dextrose and maltose.

Saccharin (Sodium and Calcium salts are soluble)



Advantages

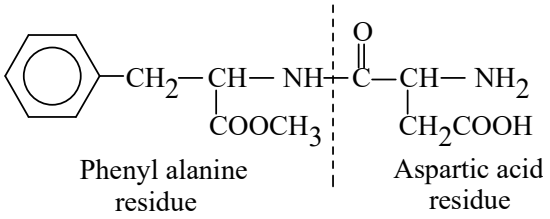
1. Saccharin is used to supplement sugars and polyols as sweeteners.
2. It is approximately 250 to 500 times as sweet as sugar.
3. It has no calorie value, hence can be given to obese patients and diabetic patients.

Disadvantages

It has a bitter after taste.

Aspartame

Aspartame is the methyl ester of aspartic acid and phenylalanine.



Advantages

1. It is approximately 200 times sweeter than sugar.
2. No bitter after taste.
3. Solubility in water is adequate for formulation purpose.

Disadvantage

Although it is very stable as dry powder, its stability in aqueous solutions is pH and temperature dependent. it is stable at pH between 3.4 and 5.0 and at refrigerated temperature.

COLORANTS

To enhance the appeal of the vehicle, a coloring agent is generally used which matches well with the flavour employed in the preparation e.g. green with mint, brown with chocolate flavor etc. The colorant used is generally water soluble, non-reactive with other components, and color-stable at the pH range and under the intensity of light that the liquid preparation is likely to be exposed during its shelf-life.

N.B. From the psychological point of view the scheme may be as follows:

Color Red → Orange → Yellow → Green → Blue → Violet

Psychological reactions → Exciting → Cheerful → Tranquilizing → Subduing →

Desirable properties of a coloring agent

1. Must be harmless, should have no physiological activity
2. It should be a definite compound because then its coloring power will be reliable, its assay practicable.
3. Its tinctorial (coloring) power should be high so that only small quantities are required.
4. It should be unaffected by light, temperature, micro-organisms, pH changes.
5. It should not interfere with other adjuvants.
6. I must be free from objectionable odour and taste.
7. it must by inexpensive.

Example

- Coal tar colors e.g. Amaranth
- The permitted colors do not always give satisfactory shades when used alone but most popular tints and shades can be obtained by blending

  e.g. Green S and Tartrazine Solution B.P.C. contains GreenS (greenish blue) and Tartrazine (Yellow green)

PRESERVATION

Specific organisms generally recognized as undesirable in oral liquids include *Salmonella* species, *Escherichia coli*, *Enterobacter* species, *Pseudomonas* species (commonly *Pseudomonas aeruginosa*), *Clostridium* and *Candida albicans*.

Source of contamination:

Raw materials, processing containers and equipment, the manufacturing environment, operators, packaging materials and the user.

Characteristics of an ideal preservative

1. It must be effective against a broad spectrum of microorganisms.
2. It must be physically, chemically and microbiologically stable for the life-time of the product.
3. It must be nontoxic, non-sensitizing, adequately soluble, compatible with other formulation components, and acceptable with respect to taste and odour at the concentrations used.

Some pharmaceutically useful preservative

Class	Preservative	Usual concentration (%)
Acidic	Phenol	0.2 - 0.5
	Chlorocresol	0.05 - 0.1
	o-Phenyl phenol	0.005 - 0.01
	Alkyl esters of parahydroxy benzoic acid (e.g. Methyl and Propyl Paraben)	0.001 - 0.2
	Benzoic acid and its salts	0.1 - .0.3
	Boric acid and its salts	0.5 - 1.0
	Sorbic acid and its salts	0.05 - 0.2
Neutral	Chlorbutanol	0.5
	Benzyl alcohol	1.0
	β-Phenyl ethyl alcohol	0.2 - 1.0
Mercurial	Thiomersal	0.001 - 0.1
	Phenyl mercuric acetate and nitrate (PMA & PMN)	0.002 - 0.005
	Nitromersol	0.001 - 0.1
Quarternary ammonium compounds	Benzalkonium chloride	0.004 - 0.02
	Cetylpyridinium chloride	0.01 - 0.02

Preservatives	Uses
Acidic	Have characteristic odor and unstable when exposed to oxygen, hence used rarely.
Phenol	
Alkyl esters of parahydroxy benzoic acid (e.g. Methyl and Propyl Paraben)	Mostly used Adequately soluble in water Have both antifungal and antibacterial activity Methyl & Propyl ester at a ratio of 10 to 1 produce a synergistic effect.
Sodium salt of benzoic acid Sodium salt of sorbic acid	Mostly used Have antibacterial action and antifungal action Water soluble
Neutral	
Chlorbutanol Benzyl alcohol β-phenyl ethyl alcohol	The are volatile alcohols, hence, have odor and loss of preservative action on aging. Not used in oral liquid preparations. Used in ophthalmic, nasal and parenteral products.
Mercurials	Not used in oral liquid preparations Used in ophthalmic, nasal and parenteral products. *Disadvantage*: Mercurials readily reduced to free mercury.
Quartenary ammonium compounds	Not used in oral preparations Used in ophthalmic, nasal and parenteral solutions. *Disadvantages*: They are inactivated by variety of anionic substances.

SYRUPS

Syrups containing approximately 85% sucrose resist bacterial growth by virtue of their exosmotic effect on micro-organisms. Syrups that contain less than 85% sucrose, a sufficient concentration of polyol (e.g. sorbitol, glycerin, propylene glycol or polyethylene glycol) should be added to have the required osmotic pressure.

It is possible, however, for surface dilution to take place in a closed container as a result of solvent evaporation followed by condensation, with the condensate flowing back onto the liquid surface. The resulting diluted medium for bacterial and fungal growth. A sufficient concentration of preservative or 5 to 10% ethanol should be added to arrest the growth of microorganisms.

FLAVORS

An objectionable taste may lead to nausea, vomiting and refusal to take the preparation regularly or at all. On the other hand, an attractive flavour will encourage continuation of treatment.

The four basic taste sensations are salty, bitter, sweet and sour. A combination of flavoring agents is usually required to mask these taste sensations effectively.

Flavor selection

Taste sensation	Recommended flavor
Salty	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint combinations, anise etc.
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, liquorice, root beer, raspberry

Flavor adjuncts

Menthol, chloroform and various salts frequently are used as flavor adjuncts.

Menthol and chloroform are sometimes referred to as *desensitizing agents*. They impart a flavor and odor of their own to the product and have a mild anaesthetic effect on the sensory receptor organs associated with taste.

MANUFACTURING CONSIDERATION

Raw materials

1. Incoming raw materials should be tested against some *specifications* regarding identity, purity, uniformity and freedom from excessive microbial contamination.
2. *Additional processing* may be required e.g. size-reduction or sterilization before manufacturing. It is usually much easier to begin with low microbial counts in the raw materials than to try to reduce these counts substantially during processing.
3. In oral liquid preparations *water* is the main vehicle. It should meet the USP requirements for **Purified water**. It may be obtained by distillation or ion-exchange treatment. To reduce the microbial burden water is passed through UV-rays and constant circulation in piping systems that have “dead ends” where micro-organisms can thrive.

EQUIPMENTS

The following types of equipments may be used in the manufacture of oral liquid solutions:-

1. Mixing tanks (SS 316 Stainless Steel) equipped with an agitator.
2. Measuring devices for large and small amount of solids and liquids.
3. A filtration system for the final polishing - e.g. Sparkler filter.

Cleaning of equipments

All equipments must be thoroughly cleaned and sanitized before use.

Disinfectants used: Dilute solutions of H_2O_2, phenol derivatives and paracetic acid.

Sterilized by: Alcohol, boiling water, autoclaving, steam or dry heat.

Material of construction

- *Tanks* are usually constructed of polished stainless steel and are usually jacketed to allow for heating or cooling of the contents.
- Tanks are covered and equipped with see-through charging ports and illumination for easy observation of the contents. If the tanks are used for compounding of the bulk liquid, they have a built in agitation system.
- The compounded liquid may then be transported to the filling line, either manually by filling into portable transport tanks (fitted with wheels) or by pumping (or gravity flow) through a liquid delivery conduit.
- All the equipments and pipe lines should be easy to disassemble, clean and sanitise.

COMPOUNDING PROCEDURE

Objective Complete solution should usually be confirmed at every stage in the manufacture of a homogeneous liquid.

Formula

1. Active constituent / Drug
2. Vehicle (Water / Alcohol / Glycerol)
   Sweetening agents (viscosity building agents) Syrup, Sorbitol, Glycerol
3. Preservatives
4. Flavors
5. Colors (Dyes)

Steps of preparation

1. Purified water is heated to approximately 50^0C to facilitate the dissolution of the solid solutes. Solid solutes are added to the warm water and stirred to dissolve (e.g. sugar, drug).
2. If any additive is required in small amount then it should be dissolved separately and then mixed with the bulk mixture.
3. Any large volume liquids (e.g. glycerol, sorbitol solution) are added and mixed until homogeneous.
4. Before adding flavors the temperature should be reduced to 30^0C (since most of the flavors are volatile). The flavor should be dissolved in small amount of alcohol (since flavors are generally insoluble in aqueous medium) and then it is mixed with the bulk mixture.
5. Dye should be dissolved n small amount of water. Then transferred to the bulk mixture.
6. Finally volume is made up to the required volume. The total mixture is agitated thoroughly until homogeneity is obtained.
7. Finally the batch is filtered to obtain a polished, clear solution.

ORAL SOLUTIONS

Liquid system where all the solutes remain in dissolved state is known as *solution*. Solutions intended to be taken orally is called *oral solutions*.

Advantages

1. Absorption is instant from the gastro-intestinal tract.
2. Uniform dosage is certain.
3. They provide a safe means of administering substances like potassium iodide that cause gastric pain if taken dry, e.g. as powders or tablets.
4. The attractive appearance of a solution in a well polished bottle has a beneficial psychological effect.

PREFORMULATION

Oral solutions contain

1. Active constituents (Water soluble)
2. Preservative
3. Flavorant
4. Colorant
5. Chemical stabilizers (Antioxidant, reducing agent, synergists)

Dose

Liquid pharmaceuticals for oral administration are usually formulated such that the patient receives the usual dose of the medication in a conveniently administered volume, as 5 ml (one teaspoonful), 10 ml or 15 ml (one table-spoonful).

On the other hand many solutions used in paediatric patients are given by drop, utilizing a calibrated dropper usually furnished by the manufacturer in the product package.

Calculation

The strengths of pharmaceutical preparations are usually expressed in terms of % strength (w/w, w/v, v/v).

Formulation

Some chemical agents may be slowly soluble. In this case rate of dissolution may be enhanced by

1. application of heat: the temperature should not destroy other ingredients.
2. decrease the particle size to increase the specific surface area.
3. by agitation: but dissolution is delayed compared to heat application.

Chemical interaction

Chemical interactions which may occur between the various components of a solution which may result in a alteration in the preparation's stability and / or potency. For example, it has been demonstrated that esters of p-hydroxy benzoic acid (methyl-, ethyl-, propyl- and butyl- parabens) frequently used preservatives in oral preparations, have a tendency to partition into certain flavoring oils.

SYRUPS

- *Syrups* are concentrated, aqueous preparations of a sugar or sugar-substitute with or without added flavoring agents and medicinal substances.
- Syrups containing flavoring agents but not medicinal substances are called *flavored vehicles* (syrups).e..g Cherry Syrup, Cocoa Syrup, Orange syrup, Raspberry Syrup.
- Syrups containing medicinal agents are called *medicated syrups*. e.g. Chlorpheniramine maleate syrup, Ipecac syrup, Chloral hydrate syrup etc.

Components of syrups

Most syrups contain the following components in addition to the purified water and any medicinal agents present:

1. the sugar, usually sucrose, or sugar substitutes used to provide sweetness and viscosity,
2. antimicrobial preservatives,
3. flavorants, and
4. colorants.

Sucrose and non-sucrose based syrup

Sucrose is most frequently employed in syrups. In special circumstances it may be replaced by sugars, such as, *dextrose*, or non-sugars as *sorbitol, glycerin* and *propylene glycol*.

Methyl cellulose or hydroxyethyl cellulose –these two materials are not hydrolyzed and absorbed into the blood stream, and their use results in an excellent syrup-like vehicle.

Taste masking by syrup

The syrup imparts a characteristics "body" (viscosity) and together with the sweetness and the flavorants results in a type of pharmaceutical preparation that is quite effective in making the taste of added medicinal agents. When the syrup is swallowed, only a portion of dissolved drug actually makes contact with the taste buds, the remainder of the drug being carried past them and down the throat in the containment of the viscous syrup.

In the case of antitussive syrups (e.g. linctus) the thick sweet syrup has a soothing effect on the irritated tissues of the throat as it passes over them.

Preservative action of syrup

Simple syrup NF contains 85% w/v sucrose. At this concentration the syrup is resistant to microbial growth, due to unavailability of the water required for the growth of micro-organisms.

85% w/v syrup has a specific gravity of 1.313

i.e. 100 ml syrup contains 85 gm sucrose

Weight of 100 ml syrup = 100 x 1.313 = 131.3 gm

∴ Weight of water present in 100 ml syrup = (131.3 – 85) gm
= 46.3 gm

Volume of water present in 100 ml syrup =46.3 ml

∴ Volume of sucrose present in 100 ml syrup = (100 – 46.3) ml
= 53.7 ml

∴ 100 ml 85% syrup contains

	Weight	Volume
Sugar	85.0 g	53.7 ml
Water	46.3 g	46.3 ml
Syrup (total)	131.3 g	100.0 ml

The solubility of sucrose in water is 1 g in 0.5 ml

∴ to dissolve 85 g sugar required will be = 85 x 0.5 ml
= 42.5 ml

Thus, only a very slight excess of water (46.3 – 42.5 = 3.8 ml per 100 ml of syrup) is employed in the preparation of syrup. The sight excess of water permits the syrup to remain physically stable under conditions of varying temperature.

If the syrup were completely saturated with sucrose, under cool storage conditions some sucrose might crystallize from solution and, by acting as nuclei, initiate a type of chain reaction that would result in the separation of an amount of sucrose disproportionate to its solubility at the storage temperature. The syrup would then be very much unsaturated and probably suitable for microbial growth. However, the syrup NF is stable and resistant to crystallization as well as to microbial growth.

Preparation of Syrups

Syrups are frequently prepared by one of four general methods; depending upon the physical and chemical characteristics of the ingredients.

1. Solution of the ingredients with the aid of heat
2. Solution of the ingredients by agitation without the use of heat
3. Addition of sucrose to a prepared medicated liquid or to a flavored liquid and
4. by percolation of either the source of the medicating substance or of the sucrose.

Solution with the aid of heat

The sugar is generally added to the purified water, and heat is applied until solution is effected. Then other required heat-stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by the addition of Purified Water.

The use of heat facilitates the rapid solution of the sugar as well as certain other components of syrups. If excessive heating occurs then sucrose may be hydrolyzed into dextrose (D-glucose), and fructose (levulose). This hydrolytic reaction is referred to as *inversion*, and the combination of the two monosaccharides is *invert sugar*. When heat is applied in the preparation of a sucrose syrup, some inversion of the sucrose is almost certain. The speed of inversion is greatly increased by the presence of acids, the hydrogen ion acting as a catalyst to reaction.

Invert sugar is more sweeter than sucrose, and normally colorless. Syrup darkens due to the effect of heat on the fructose. When the syrup is greatly overheated, it becomes amber colored due to the caramelization of the sucrose. Syrups so decomposed are more susceptible to fermentation and microbial growth.

Because of the prospect of decomposition by heat, syrups cannot be sterilized by autoclaving.

Solution by agitation without heat

Sucrose and other formulation agents may be dissolved in purified water by placing the ingredients in a vessel of greater capacity than the volume of syrup to be prepared, thus permitting the thorough agitation of the mixture.

Addition of sucrose to a medicated liquid or to a flavored liquid

Medicated liquid such as tincture or fluid extract is employed as the active ingredient in the preparation of syrup.

If the extract contains alcohol soluble ingredients and the alcohol amount is high then sucrose is added directly and stirred.

If alcohol content is low and all the ingredients are water soluble then the liquid extract is directly mixed with a prepared syrup.

Preparation of syrup by percolation

In this method purified water or an aqueous solutionis passed slowly through a bed of crystalline sucrose, thus dissolving it and forming the syrup. If required a poriton of the percolate is recycled.

Preparation of a multivitamin syrup

Formula: Each 15 ml contains

Active ingredients	Vitamin B1	4.5 mg
	Vitamin B2	2.5 mg
	Vitamin B6	1.5 mg
	Niacinamide	30 mg
	D-Pantothenol	5 mg
Sweeteners	Sorbitol	1 gm
	Glycerin	0.5 gm
	Sugar	7 gm
Preservative	Sodium benzoate	0.016 % (w/v)
	Methyl paraben sodium	0.015 % (w/v)
	Propyl paraben sodium	0.0015%(w/v)
Stabilizer	Disodium edetate	0.008%
Taste enhancer	Citric acid	0.008% (w/v)
	Flavours	q.s.
Colours	Caramel	q.s.
Vehicle	Purified water	15 ml

Procedure

1. Primary Syrup is prepared as usual, filtered and cooled to room temperature. The material is transferred to the mixing tank and stirring is started.
2. Vitamin B1 is dissolved in small volume of water and added to the syrup.
3. Vitamin B2 is slightly soluble in water, hence, it is dissolved with the aid of 10% sodium hydroxide. Vitamin B6 is also added to dissolve. The mixture is transferred to the mixing tank.
4. Niacinamide is dissolved in small amount of water and added to the mixing tank.
5. D-pantothenol is dissolved in hot water, cooled and transferred to the syrup.
6. Sorbitol and glycerin are added.
7. All the preservatives are dissolved in small volume of water and added to the syrup.
8. Citric acid and disodium edetate is dissolved separately in water and then mixed to the syrup.
9. Flavors and color are added and the final volume is made up with water.
10. Mixed for 2 hours and filtered.

CHAPTER 5: PHARMACEUTICAL DOSAGE FORMS

Syllabus: Introduction and classification of various pharmaceutical dosage forms. Critical study of the following:- Infusions, tinctures, extracts, aromatic waters, spirits, solutions, syrups, elixirs, mucilages, glycerites, collodions, gels, linctus, magmas.

Ques:

1. *How will you make simple syrup as per IP specifications. (91)* *[4]*
2. *How will you prepare collodion? Give the use of collodion. (91)* *[4+2]*
3. *What are solution dosage forms? How will you make liquor ammonium acetate fortes? How will you test the purity of the above product?(91, 92)* *[4+2]*
4. *What are pharmaceutical formulations?(91)* *[4]*
5. *Give a systematic classification of dosage forms.(91,95)* *[4]*
6. *Give the methods of preparation of aromatic waters.(91)* *[4]*
7. *What is the difference between:*
   - *a) Elixir & Syrup(92,93,94)* *[4]*
   - *b) Solution & aromatic waters (92,94,95)* *[4]*
   - *c) Tinctures & extracts (92)* *[4]*
   - *d) Tinctures & Spirits (93,94,95)* *[4]*
   - *e) Sol & Gel (93)* *[4]*
   - *f) Lotion & Liniment (94,95)* *[4]*
   - *g) Dose & Dosageforms (94)* *[4]*
   - *h) Linctuses & Glycerites (94)* *[2]*
   - *i) Elixir & Linctus (94)* *[2]*
   - *j) Mixture & Lotions (94)* *[2]*
9. *Discuss the preparation and uses:*
   - *a) Lysol (92)* *[4]*
   - *b) Flexible collodion (92)* *[4]*
   - *c) Milk of magnesia (92)* *[4]*
   - *d) Syrup of Ferrous Iodide (92)* *[4]*
10. *What is the principle, method and equipment used in aromatic ammonia spirit. (92)* *[4]*
11. *What is the difference between dose and dosage (93,94)* *[4]*
12. *Name and define different parenteral liquid dosage forms. (93,94)* *[12]*
13. *How does the method of preparation vary for:*
    - *a) Camphor water & Dill water (93)*
    - *b) Simple syrup & Invert syrup (93)*
    - *c) Syrup (96)* *[8]*
    - *d) Tinctures, Spirits, Gels, Elixir. (96)* *[4+4]*
14. *What are collodions? what are the constituents of such type of preparations? Differentiate between medicated and nonmedicated collodions. (99)* *[6]*
15. *Define creams. What are the type of creams available? Give the advantages and disadvantages. (99)* *[6]*
16. *what do you mean by draughts? What are the essential characteristics of such type of preparations? Give your answer with suitable illustrations. (91)* *[4]*

DEFINITION OF DRUG

A drug may be defined as an agent, intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in man or in animals.

DOSAGE FORM

Drugs are rarely administered in their original pure state. They are converted into suitable formulation which are called **dosage forms**. Every dosage form is a combination of the drug and other non-drug components.

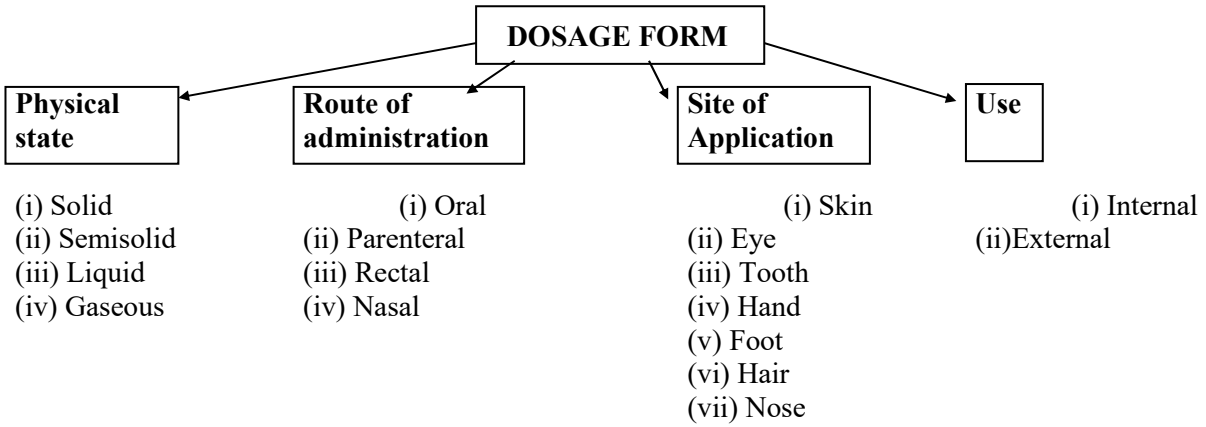
The non-dug components are known as "**additives**". The additives are used to give a particular shape to the formulation, to increase its stability and also to increase its palatability as well as to give more elegance to the preparation.

Ques. Why the drug should be converted into dosage forms ?

Ans. Transformation of drug into different dosage forms is done for the following reasons:

1. To protect the drug from oxidation (e.g. Vitamin C, Ferrous sulfate), hydrolysis (aspirin) and reduction. e.g. coated tablets, sealed ampoules.
2. To protect the drug from destructive effect of gastric juice (HCl) of the stomach after oral administration e.g. enteric coated tablets.
3. To provide a safe and convenient delivery of accurate dosage.
4. to conceal the bitter (e.g. chloramphenicol), salty or obnoxious taste or odour of a drug substance e.g. capsules, coated tablets and flavoured syrups etc.
5. To provide for the optimum drug action through inhalation therapy. e.g. inhalation aerosols and inhalants.
6. To provide for the drug into one of the body-cavities e.g. rectal suppositories.
7. To provide for the maximum drug action from topical administration sites. e.g. creams, ointments, ophthalmic preparations and E.N>T. (ear, nose and throat) preparation.
8. To provide sustained release action through controlled release mechanism. e.g sustained release tablets, capsules and suspensions.
9. To provide liquid dosage form of the drugs soluble in a suitable vehicle e.g. solutions.

CLASSIFICATION OF DOSAGE FORMS



Route of administration	Dosage forms
Oral	Powders, tablets, capsules, solutions, emulsions, syrups, elixirs, magmas, gels, cachets, pills.
Parenteral	Solutions, suspensions, emulsions.
Transdermal	Ointments, creams, powders, pastes, lotions, plaster
Rectal	Suppositories, tablets, ointments, creams, douches, foams.
Urethral	suppositories
Sublingual	Lozenges, tablets
Intranasal	Solutions, sprays, inhalations.
Conjunctival	Ointments
Intra-ocular	Solutions
Intra-respiratory	Aerosols

Classification according to physical state:

DOSAGE FORM

SOLID	SEMISOLID	LIQUID	GAS	MISCELLANEOUS
Cachets	Creams	Applications	Aerosols inhalation	Transdermal drug delivery systems
Capsules	Jellies	Aromatic water		
Powders	Ointments	Collodion		
Insufflations	Pastes	Draught		Sustained release drug delivery system
Dentrifices	Ophthalmic ointments	Ear drops		
Effervescent granules		eye drops		
Lozenges		Nasal drops		Ophthalmic drug delivery systems.
Pessaries		Elixirs		
Tablets		Mixtures		
Suppositories		Emulsions		Implants
		Suspensions		
		Enemas		
		Gargles		
		Gels		
		injections		
		Irrigations		
		Linctuses		
		Liniments		
		Lotions		
		Mouthwashes		
		Spirits		
		Sprays		
		Syrups		
		Tinctures		
		Paints		

CACHETS

Cachets consists of a dry powder enclosed in a shell. The shell is prepared from a mixture of rice flour and water by moulding into suitable shape and then dried.

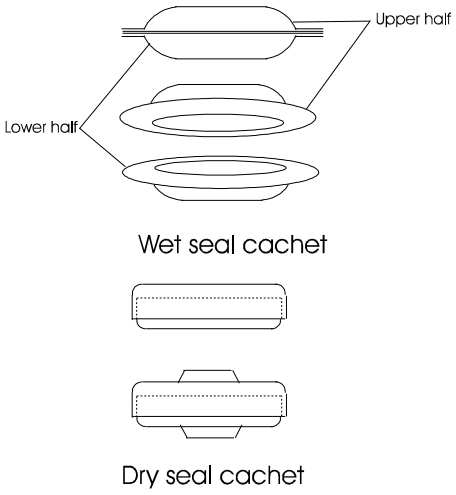
Two types of cachets are there:

(i) **Wet seal cachets:**

lower half of the cachet is filled with powdered drug. Then the flange of the empty upper half of the cachet is moistened with water, and pressed over the lower half. The cachet is dried for 15 minutes.

(ii)**Dry seal cachets:**

Drug powder is filled in the lower half and the upper half is pressed over it just like a capsule.



Use:

They are used for administering the drug with unpleasant taste and a large dose. Before administration, a cachet should be immersed in water for few seconds and then placed on the tongue and swallowed with water.

e.g. Sodium aminosalicylate cachets
Sodium aminosalicylate and isoniazid cachtets.

CAPSULES

Capsule are the solid unit dosage form of medicament in which the drug or drugs are enclosed in a practically tasteless, hard or soft soluble container of shell made up of gelatin.

Hard gelatin capsules are made up of two cylindrical halves, one slightly larger in diameter but shorter in length known as cap and the other slightly shorter in diameter but longer in length known as base.

Soft gelatin capsules are flexible in nature. They may be spherical, ovoid cylindrical or tubes. The small spherical capsules are also known as 'pearls'. soft gelatin capsules are used to enclose solids, semisolids or liquids.

for oral administration the capsule is placed on the tongue and swallowed with a drink of water.

Examples of hard gelatin capsules: Ampicillin capsules, multivitamin capsules.

Examples of soft gelatin capsules: chloramphenicol soft gelatin capsules.

DUSTING POWDER

These are meant for external application on to the skin and are generally applied in a very fine state of subdivision to avoid local irritation.

Dusting powders are of two types:

(i) Medical

(ii) Surgical

Medical dusting powders are mainly used for superficial skin conditions and for antiseptics, anti-pruritic, astringent, anti-perspirant, absorbent, protective and lubricant purposes.

e.g. dicophane dusting powder
zinc and salicylic acid dusting powder
zinc, starch and talc dusting powder.

Surgical dusting powders are used in body cavities, and also on major wounds as a result of burns and umbilical cords of infants. Surgical dusting powders must be sterilised before their use.

Dusting powders are generally prepared by mixing two or more ingredients on of which must be either starch, kaolin or talc as one of the ingredients of the formulations. Talc and kaolin are commonly used because they are chemically inert. however, since these materials are usually contaminated with pathogenic bacteria, these must be sterilised.

e.g. Neosporin powder.

INSUFFLATIONS

These are finely divided powders meant for introduction into the body cavities such as ears, nose, tooth sockets and vagina with the help of an apparatus known as 'insufflator', without which it will be difficult to apply the powders directly.

Insufflator sprays the powder into stream of finely divided particles all over the site of application. The following difficulties are generally faced while using the insufflators:

(i) It is difficult to obtain a measured quantity of the drug as a uniform dose.

(ii) It gets blocked when it is slightly wet or the powder used is wet.

Use: The insufflations are used to produce a local effect, as in the treatment of ear, nose and throat infection with antibiotics or to produce a systemic effect from a drug that is destroyed in the gastrointestinal tract.

DENTRIFICES (Tooth Powders)

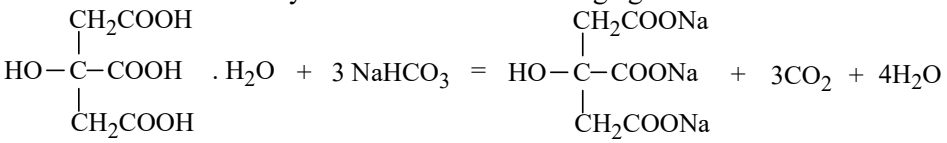
Dentrifices are preparations which are generally used with the help of tooth brush for cleansing the surfaces of the teeth. They are available in the form of fine powders and pastes.

They contain

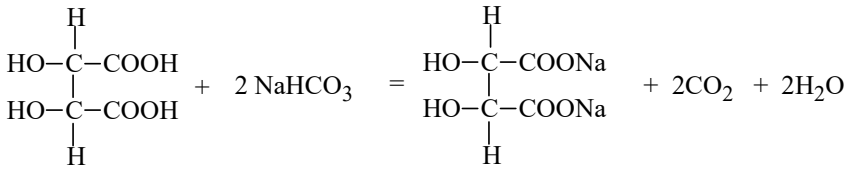
1. a suitable detergent or soap
2. some abrasive substance like calcium sulfate, magnesium carbonate, sodium carbonate in fine powder.
3. sweetening agent e.g. saccharin sodium
4. a suitable flavour e.g. peppermint oil, clove oil.

EFFERVESCENT GRANULES

The effervescent granules are specially prepared solid dosage form of medicament, meant for oral intake. they contain a medicament mixed with citric acid, tartaric acid and sodium bicarbonate. Sometimes saccharin or sucrose may be added as a sweetening agent.



Citric acid (monohydrate) Ttrisodium citrate



Tartaric acid Disodium tartarate

Ingredients used;

(i) Sodium bicarbonate: It reacts with the acids when the preparation is added to water. The evolved carbondioxide produces effervescence.

(ii) Citric acid and tartaric acid: The quantity of these is slightly more than is necessary to neutralise the sodium bicarbonate because effervescent preparations are more palatable if slightly acidic.

Tartaric acid is anhydrous but citric acid has one molecule of water of crystallization. heating liberates this water and the moist condition thus produced allows partial interaction between the acids and bicarbonates, during which more water is formed -

The water of crystallization of the citric acid and the water from the reactions makes the material coherent.

(iii) Medicaments: often inorganic salts containing water of crystallisation are incorporated. e.g. magnesium and sodium sulphates, sodium phosphate and lithium citrate.

Methods of preparation

There are two methods of preparation : 1. Hot method and 2. Wet method

Hot method: A large evaporating dish is heated on water bath. All the powders are taken in that hot dish to ensure rapid evaporation of water liberated from citric acid. Thus a coherent damp mass is prepared.
The water required for granulation is provided from two sources:
1. From one molecule of water of crystallisation of citric acid which is liberated during heating.
2. The water produced from the reactions of citric acid and tartaric acid with sodium bicarbonate.

Wet method: in this method the mixed ingredients are moistened with non-aqueous liquid (e.g. Alcohol) to prepare a coherent mass.
The coherent damp mass from both the methods is then passed through a No. 8 sieve and dried in an oven at a temperature not exceeding 60^0C. The dried granules are again passed through the sieve to break the lumps which may be formed during drying. The dried granules are packed in an air tight container.

Use: Before administration, the desired quantity is dissolved in water, the acid and bicarbonate react together producing effervescence.
The carbonated water produced from the release of carbondioxide serves to mask the bitter and saline taste of drugs.
More over carbondioxide stimulates the flow of gastric juice and helps absorption of medicament.

LOZENGES
Lozenges are solid dosage form of medicaments which are meant for slow dissolution in the mouth. Along with medicament they contain a sweetening agent, flavouring agent and a strong binding agent.
They may be prepared either by moulding or by compression.
Examples are compound bismuth lozenges, liquorice lozenges.

PESSARIES
Pessaries are solid unit dosage form of medicament meant for introduction into vagina. The bases used for the manufacture of pessaries are such that at room temperature they retain the original shape but when inserted into the body cavity either it melts or dissolve in the cavity fluids to release the medicament.
They may be prepared either by moulding or by compression.
e.g. lactic acid pessaries, nystatin pessaries.

POWDERS
Powders are solid dosage form of medicament meant for internal and external use. The powders meant for internal use are known as oral powders whereas those meant for external use are known as dusting powders.
The powders may be simple or compound.
When the powders are dispensed in large quantities in a container and the patient is asked to measure a specified quantity as a dose then these powders are known as bulk powders.
e.g.
1. Bulk powder for internal use;
   e.g. Compound sodium chloride and dextrose oral powder.
   Compound rhubarb oral powder
2. Bulk powder for external use;
   e.g. Snuffs
   Talc dusting powders
   Tooth powder.

TABLETS

Tablets are unit solid dosage form of medicament or medicament with or without suitable diluents. They are prepared usually by compression.

Tablets are generally meant for oral administration but may be used by other routes of administration.

e.g. aminophylline tablets
paracetamol tablets
antacid tablets.

SUPPOSITORIES

Suppositories are special shaped solid dosage form of medicament for insertion into body cavities other than mouth. These products are so formulated that after insertion, they will either melt of dissolve in the cavity fluids to release the medicament.

Suppositories vary in shapes, sizes and weights. General suppositories from 1 to 2 gm are prepared with either cocoa-butter or glecero- gelatin base.

e.g. aminophylline suppositories
glycerol suppositories.

SEMISOLID DOSAGE FORMS

CREAMS

Creams are viscous liquid or semisolid emulsions intended for application to the skin i.e. for external use.

Creams are of two types, aqueous creams and oily creams. In case of aqueous creams the emulsions are oil-in-water type and in case of oily creams emulsions are of water-in-oil type.

Due to the presence of water soluble bases they can be easily removed from the skin.

The aqueous creams have a tendency to grow bacterial and mold growth, therefore a preservative must be added in their formulation.

e.g. cetomacrogol cream, cetrimide cream, hydrocortisone cream, zinc cream BPC.

Advantages of creams:

1. Creams are more acceptable to the patients because they are less greasy and are easier to apply.
2. They interfere less with skin functions.
3. o/w type of creams (superior to w/o type) can be rub onto the skin more readily and are easily removed by washing. w/o can be spread more evenly.
4. o/w type of cream are less likely to soil clothes.
5. Evaporation of water from o/w type of cream causes cooling sensation.
6. o/w creams absorbs the discharges from the wound (liquid exudate) very quickly.
7. w/o creams (e.g. cold creams) restricts evaporation from the skin, it can be used on non-weeping surfaces to prevent dehydration (in dry season), restore suppleness (softness) - this property is said to be 'emollient'.

Disadvantages:

1. Since it is a semisolid preparation and containing oil in large amount, some of which are inedible, hence creams are not used for internal use. Basically creams are meant for application onto the skin.
2. the aqueous phase is prone to the growth of molds and bacteria hence preservatives should be used.
3. Sometimes rancidification of oils take place.

JELLIES

Jellies are transparent or non-greasy semisolid preparations meant for external application to the skin or mucous membrane. They are used for medication or lubrication purposes.

e.g. contraceptive jellies (spermicidal action)
ichthammol jelly etc.

they are used for lubricating catheters, surgical gloves and rectal thermometers.

The gelling agents may be gelatin, or a carbohydrate such as starch, tragacanth, sodium alginate or cellulose derivative.

OINTMENTS

Ointments are the soft semisolid, greasy preparations meant for external application onto the skin or mucous membrane (rectum and nasal mucosa).
They usually contain a medicament dissolved, suspended or emulsified in the base.
Ointments are used for their emollient and protective action to the skin.
e.g. compound benzoic acid ointment, cetrimide emulsifying ointment

PASTES

Pastes are semisolid preparations meant for external application to the skin. they generally contain large amount of finely powdered solids such as starch, zinc oxide, calcium carbonate etc.
They provide a protective coating over the areas to which they are applied.
The base may be anhydrous (liquid or soft paraffin) or water-soluble (glycerol or a mucilage). Their stiffness make them useful as protective coatings.
e.g. magnesium sulfate paste.,
zinc and coal tar paste

OPHTHALMIC OINTMENTS

Ophthalmic ointments are meant for application to the eye. They should be sterile and free from irritation. They should be packed in sterile containers which should keep the preparation sterile until whole of it is used up.
e.g. atropine eye ointment
chloromycetin eye ointments

Difference between paste and ointments;

Paste	Ointment
1. Contains a large amount of (50%) of finely powdered solids. As a result they are often very stiff.	1. Ointments contain very less amount of powdered solids. They are soft.
2. When applied on the skin the paste adhere well and remain confined in the area of application.	2. Ointments are less viscous, hence spread beyond the area of application.
3. They are porous so the perspiration (sweat)can escape through it.	3. Non-porous - hence perspiration cannot escape through it.
4. They are less greasy than ointments.	4. More greasy than pastes.

LIQUIDS

APPLICATIONS:

Applications are liquid or viscous preparations intended for application to the skin. usually, they are suspensions or emulsions.
Most of the official preparations contain paraciticides and are intended for only a limited number of applications.
They should be dispensed in coloured fluted bottles in order to distinguish them from preparations meant for internal use. The container should be labeled “FOR EXTERNAL USE ONLY”.
Examples of applications are calamine application compound B.P.C.
dicophane application B.P.C.

MONOPHASIC LIQUID DOSAGE FORMS

Monophasic liquid dosage forms are represented by true or colloidal solutions.

The components of the solution which is present in a larger quantity is known as "solvent", whereas the component present in a smaller quantity is termed as "solute".

Classification

1. Liquid for internal use e.g. syrups, elixirs, linctus, drops and draughts.
2. Liquids for external use which are of two types:
   (a) Liquids to be applied to the skin e.g. liniments and lotions etc.
   (b) Liquids meant for body cavities e.g. gargles, throat paints, mouth washes, eye drops, eye lotions, ear drops, nasal drops, sprays and inhalation.

1. AROMATIC WATERS

Aromatic waters are also known as medicated waters. They are dilute , usually saturated, aqueous solutions of volatile oils (e.g. peppermint oil, cinnamon oil) or volatile substances (e.g. camphor).

Uses:

(i) Some of them have a mild therapeutic action but
(ii) mainly they are used as flavouring agents in preparations meant for internal use.

Name	**Concentrated preparation**	**Dilution (by volume)**		**Use**
		Concentrated	**Water**	
Anise water	Conc. Anise Water	1	39	Flavour Carminative Mild expectorant
Camphor water	Conc Camphor Water	1	39	Flavour Carminative Mild expectorant
Caraway Water	Conc. Caraway Water	1	39	Flavour Carminative
Chloroform Water	Double Strength Chloroform Water	1	1	Preservative Flavor
Dill Water	Conc. Dill Water	1	39	Flavor Carminative (in gripe water)
Peppermint Water	Conc. Peppermint Water	1	39	Carminative Weak preservative

Aromatic waters are prepared by two IP methods:

(1) *Solution*

* Essential oil is shaken with 500 times its volume of Purified Water.

The shaking is repeated several times during a period of 30 minutes. The mixture set aside for 12 hrs or overnight and then filtered.

* Alternatively, the oil may be triturated with a sufficient quantity of powdered talc or of Keiselghur, or of pulped filter paper and 500 times its volume of purified water and filtered.

(2) *Dilution from concentrated waters*:

One part (by volume) of concentrated water is diluted with 39 parts of Purified Water.

e.g. Preparation of Camphor Water

Formula:

Camphor	1gm
Alcohol 90%	2 ml
Purified Water q.s.	1000 ml

Camphor is dissolved in Alcohol (90%) and then the solution is added drop by drop to the purified water.

After each addition the mixture is shaken well until the camphor is dissolved. . If required the excess camphor was filtered out.

e.g. Preparation of Cinnamon Water Concentrated B.P.C.
Cinnamon oil is dissolved in the alcohol and then sufficient purified water was added in successive small portions, to produce 1000 ml. The mixture was shaken vigorously after each addition. Small amount of purified talc was suspended in water and a filter bed is prepared on the filter paper. The filter bed was dried and then the solution was filtered through it.

SYRUPS
Syrups are liquid oral preparations in which the vehicle is a concentrated aqueous solution of sucrose or other sugar.
N.B. Syrups generally are not issued directly to the patients when it is issued to the patients:
(i) if it is clear it is called elixir and
(ii) if it is suspension it is called mixtures.

- *Simple syrup IP* is a saturated solution of sucrose in purified water. The concentration of sucrose is 66.7 % w/w.
- Syrup containing medicinal substances are called *medicated syrups* and those containing aromatic or flavoured substances are known as *flavoured Syrup*.

Advantages of syrups
1. Syrups retards oxidation because it is partly hydrolyzed into reducing sugar such as dextrose and levulose.
2. It prevents decomposition of many vegetable substances. Syrups have high osmotic pressure which prevents the growth of bacteria, fungi and molds which are the chief causes of decomposition in solutions of vegetable matter.
3. They are palatable. Due to the sweetness of sugar it is a valuable vehicle for the administration of unpalatable substances.

The syrups may be divided into two categories:
(a) Syrups prepared by simple solution or admixture
e.g. *Simple Syrup IP* Sucrose 667 g
Purified water q.s. 1000
Method: Sucrose is added to water and dissolved by heating. The solution is cooled and the required volume is made up with the required amount of water.
e.g. *Ginger Syrup IP*
Strong Ginger Tincture 50 ml
Syrup, sufficient to produce 1000 ml
Both are mixed thoroughly.
(b) Syrups made by a process of extraction
e.g. *Tolu Syrup IP*
Tolu balsam 12.5 g
Sucrose 660 g
Purified Water q.s. 1000 g
Procedure: Boiling purified water is added to Tolu balsam contained in a tared vessel. The vessel is covered lightly and the contents are boiled gently for half an hour.
Purified water is added to adjust the specified weight.
The mixture is cooled, filtered and sucrose is added. Heated on a water bath to dissolve the sucrose. Finally sufficient purified water is added to produce the required weight.

ELIXIRS

Definition: Elixirs are clear, liquid, oral preparations of potent or nauseous drugs. They are pleasantly flavoured and usually attractively coloured and are very stable.

- Elixirs usually contains *potent drugs*, such as antibiotics, antihistamines and sedatives.
- *Vehicles* used in elixirs are alcohol, glycerol and propylene glycol.
  They are used
  (i) for the production of clear solution. Essential oils from flavoring agents may produce faint opalescence, hence alcohol 10 – 20% is useful for keeping oils in solution.
  (ii) When potent medicaments of low solubility is required to be dispensed, a mixture of solvents that will give complete solution is used.
  e.g. Phenobarbitone is virtually insoluble in water but a clear product can be made by dissolving it in alcohol and then diluting with glycerol and water.
  e.g. One part of paracetamol is soluble in 70 parts of water, 7 parts of alcohol, 9 parts of propylene glycol or 40 parts of glycerol. In paracetamol elixir a mixture of alcohol, propylene glycol and glycerol is used as vehicle.

Other adjuncts used are:

(i) *Chemical stabilizers*

e.g. Neomycin Elixir B.P.C. is adjusted to pH 4 to 5 with citric acid to minimize the darkening that occurs on storage.

e.g. Disodium edetate should be incorporated to sequester heavy metals that catalyse decomposition of antibiotic.

(ii) *Colouring agents*

e.g. Amaranth	Magenta red
Tartrazine	Saffron
Green S	Green

(iii) *Sweetening agents*

e.g. Sucrose syrups, glycerol, sorbitol solution, invert syrup and saccharin sodium are used.

(iv) *Flavours*

e.g. Blackcurrant Syrup in Chloral Elixir
Concentrated Raspberry Juice with invert syrup
Lemon spirit with syrup and invert syrup.
Compound Orange Syrup

(v) *Preservatives*

- 20% alcohol, propylene glycol or glycerol are preservative
- Syrup is self-preservative due to high osmotic pressure
- The most common additional preservative in chloroform; it is used in the form of double strength water.
- Some times the preparations contain benzoic acid and methyl parahydroxy benzoate.

LINCTUSES

Linctuses are viscous, liquid, oral preparations that are usually prescribed for the relief of cough.

- They contain medicaments which have demulcent (which soothes the inflammed mucous membrane preventing contact with air in the surroundings), sedative or expectorant action. The viscous vehicle soothes the *sore* membrane of the throat.
- The usual dose is 5 ml. Linctuses should be taken in small doses, sipped and swallowed slowly without diluting it with water in order to have the maximum and prolonged effect of medicaments.
- Simple Syrup is generally used as a vehicle. For diabetic patients Sorbitol solution is used instead of Simple Syrup.

GLYCERIN OR GLYCERITES

Glycerites are the viscous preparations in which the drug is dissolved in glycerin with or without heating. They are generally used as antiseptic or anti-inflammatory preparations.

e.g. icthammol glycerin
tannic acid glycerin
phenol glycerin

COLLODION

Collodions are liquid preparations meant for external application to the skin. They are convenient for application on small cuts and abrasions and are also used when a prolonged contact between the skin and the medicament is required.

- The vehicle is volatile and evaporates on application to the skin, leaving a flexible, protective film covering the site.
- *Preparations*
  Volatile solvents used are ether and alcohol.
  Film producing ingredient is pyroxylin (nitrocellulose)
  Plasticizer giving the flexibility is castor oil.

Preparation

The solution is made by shaking the ingredients in a closed container, allowing to stand for few days while impurities settle and then decanting the supernatant liquid, because the solution is too volatile for filtration.

Storage

Collodions are stored in small light-resistant, well closed containers.

LINIMENT

Liniments are liquid, semi-liquid or occasionally semi-solid preparations intended for application on the skin.

They may be alcoholic or oily solutions or emulsions.

Most are massaged onto the skin e.g. counter-irritant type.

Some are applied on warm dressing or with a brush. e.g. analgesic and soothing type.

Liniments must not be applied to broken skin because they would be very irritating.

e.g. Soap Liniment BPC
Camphor Liniment BP
Methyl salicylate liniment BPC

Alcohol is the main *vehicle*. In increases the penetration of counter-irritant molecules through skin.

LOTIONS

Lotions are liquid preparations for external application without friction.

They are either dabbed on the skin or applied on a suitable dressing and covered with water proof material to reduce evaporation.

e.g. Copper and zinc sulfate lotion is used for impetigo
Zinc sulfate and salicylic acid for ulcer
Salicylic acid lotion for dandruff
Salicylic acid and mercuric chloride lotion for follicular infection

N.B. Copper and Zinc sulfate have astringent action.
Salicylic acid has keratolytic action.

GELS

Gels are aqueous colloidal suspensions of the hydrated forms of insoluble medicaments e.g. aluminium hydroxide gel, used as antacid.

EXTRACTS

Extracts are concentrated preparations containing the active principles of vegetable or animal drugs. The drugs are extracted with suitable solvents and the product is concentrated o one of three types of extract –

Liquid Extract of which 1 ml usually contains the active constituents from 1 g of drug.
Dry Extract obtained by completely removing the solvent under, reduced pressure.
Soft Extract obtained by evaporation to a plastic mass.

TINCTURES

These are alcoholic preparations containing the active principles of vegetable drugs.
They are weaker than extracts.
They are usually prepared by maceration and percolation, or may be prepared by dissolving the corresponding liquid extract of chemical substances (e.g. iodine) in alcohol or hydroalcohol solvent.

e.g. Belladonna tincture
Aromatic cardamom tincture
Iodine tincture

SPIRITS

Spirits are alcoholic or hydroalcoholic solutions of *volatile* substances.
Most are used as *flavouring* agents but a few have medicinal value.
e.g. Chloroform Spirit, Lemon Spirit, Compound Orange Spirit.

INFUSIONS

(i) *Fresh Infusions* are made by extracting vegetable drugs for a short time with cold or boiling water (cf. making of tea). They quickly deteriorate as a result of microbial contamination and therefore must be used within 12 hours.
(ii) *Concentrated infusions* are made by cold extraction with 25 % alcohol. The alcohol preserves the product for an indefinite period.
Dilution of 1 part of concentrated infusions with 10 parts of water gives a preparation corresponding fresh infusion.

e.g. Concentrated Compound Gentian Infusion
concentrated Senega Infusion.

SURGICAL AIDS

Syllabus:
Surgical dressings, sutures and ligatures and their standards.

Question:

Q.1 How will you sterilize surgical gauge and bandages ? [1991]	[4]
Q.2. What is the difference between sutures and catguts?(1991)	[4]
Q.3. What are the various steps in the manufacturing of catguts?(1991)	[4]
Q.4. How will you test the sterility of surgical dressings? (1991)	[4]
Q.5. Write notes on standards of sutures and ligatures. (92-93)	[4]
Q.6. What is sutures and ligatures ?(1993)	[2]
Q.7. What is the differences between sutures and ligatures ? (1994)	[2]
Q.8. Name the different materials used for this purpose mentioning their merits and demerits. (1994)	[14]
Q.9. What do you mean by surgical aids ? (1994)	[3]
Q.10. What is catgut? (1994)	[3]
Q.11 What are the standards that a good catgut must possess ? (1994)	[10]
Q.12 Note on: Surgical dressing. (1993)	[4]
Q.13 Boilable and non-boilable catgut. (1993)	[4]
Q.14 Synthetic absorbable catgut. (1993)	[4]
Q.15 Metals used as surgical aids. (1993)	[4]

SURGICAL AIDS

These are referred to a wide range of materials used for dressing of wounds or injured or diseased tissues (Surgical dressings); some are used to hold wound edges closely during healing (sutures and ligatures). All these materials are collectively called surgical aids.

SURGICAL DRESSINGS

Definition Surgical dressing is a term applied to a wide range of materials used for the dressing of wounds or injured or diseased tissues.

Dressings may serve to :

i) Provide an environment for moist wound healing.

[N.B. Drying of the wound is a major factor in retarding wound healing and increasing scarring. Dressings which prevent drying (or desiccation) provide an optimal environment for autolysis, cell migration, granulation and re-epithelialization.]

ii) Prevent maceration by permitting evaporation or absorption.

[N.B. In highly exudative wounds, excessive moisture and autolytic enzymes will damage repairing tissue, and will provide a perfect culture medium for microbes.]

iii) Promote haemostasis (i.e. stops bleeding)

iv) Protect the wound from further damage [e.g. mechanical damage, microbial invasion, dehydration, maceration, chemical damage, alteration in pH.]

v) Reduce heat loss.

vi) Control microbial growth by incorporation of antimicrobial drugs.

vii) Promote healing.

viii)Provide compression, promoting haemostasis and reducing oedema.

ix) Reduce pain, increase patient comfort and improve functional use for wound site.

x) Reduce odour.

xi) Improve appearance of the wound site.

xii) Reduce overall costs associated with wound treatment.

Features of an ideal dressing

i) The dressing should be porous to water vapour; otherwise sweat from the surrounding skin, water evaporated from the epidermis, and tissue fluid exuded from the wound will accumulate and delay the healing process.
ii) It must be capable of absorbing excess secretions.
iii) Free from substances that cause tissue reactions , allergy or a hypersensitivity response.

[N.B. Fluorescent agents (optical whiteners), used to improve the appearance of bleached materials, delay healing.]

iv) It must be impervious to micro-organisms.
v) It must be impervious to fluid from outside.
vi) Capable of following joint contours during movement.
vii) It should have tensile strength to withstand stretching during movement.
viii)It must be non-inflammable.
ix) It must be sterilizable by conventional means.
x) Capable of preventing excessive movement of wound.
xi) Inexpensive.

It is obvious that not a single dressing has all of the above qualities.

Classification of surgical dressings:

Functionally surgical dressings can be divided into primary, and secondary dressing.

A **primary** dressing directly come in contact with the wound. It may provide absorptive capacity and may prevent desiccation, infection and adhesion of the secondary dressing to the wound.

A **secondary** dressing is placed over the primary dressing for further protection, absorptive capacity, compression or occlusion. Although some dressings are solely primary or secondary in nature, others have the characteristics of both. The following classification can be made:

i) primary wound dressings
ii) primary/secondary wound dressings
iii) secondary dressings (a) Absorbents
(b) Bandages
(c) Adhesive tapes
iv) Protectives

PRIMARY WOUND DRESSINGS

Plain gauze

This is a soft cotton cloth of plain weave, open texture and filmsy appearance.

Use: Because the cotton is in the form of spun threads and not loose fibres (contrast cotton wool) gauze can be applied directly to the wounds. It absorbs water readily but unless many folds thickness are used, it is not bulky enough to cope with the exudate or give adequate protection to a large wound. Hence, it is usually covered with more absorptive and protective dressing.

Wicks of gauze are used, after surgery, for draining exudate from large wounds.

Impregnate gauze

Cotton, rayon or cellulose acetate gauze has been impregnate with a variety of substances such as petroleum or paraffin, vaseline or petrolatum emulsion.

They are used to reduce its adherence to wounds.

Oiled silk: This is a silk fabric of plain weave, evenly water proof by treatment with drying oils. Oiled silk is used

i) to cover wet dressings, such as poultices and compress to keep them moist.
ii) to protect clothing from dressing.

Paraffin gauze dressing: This is a sterile dressing consisting of pieces of cotton, rayon or cotton and rayon gauze impregnated with yellow soft paraffin or it for use in warm countries, soft and hard paraffin.

Paraffin gauze dressings are used in skin grafting and for paraffin prevents adherence to the tissues and the open nature of the gauze allows air to reach the wound and exudate to drain away into secondary absorbent dressing.

Film dressing: are films of polyurethane with acrylic or polyether adhesives.

i) In lightly exuding wounds they permit enough evaporation to promote moist wound healing and prevent maceration.
ii) Film dressings exclude bacteria from wounds and permit bathing and observation of the wound.
iii) They will adhere well to intact skin and have a low adherence for wound tissues.

PRIMARY / SECONDARY WOUND DRESSINGS

Composite dressings: consists of lightly absorbent rayon or cotton pads sandwiched between porous polyethylene films.

Hydrogels are cross-linked polymer such as poly-vinyl-pyrrolidone (PVP), cross-linked polyethylene oxide gel or polyacrylamide in which the wound exudate may be trapped.

Uses: Hydrogels are non adherent dressings, which through semipermeable film allow a high rate of evaporation (and cooling) without compromising wound hydration. This makes them useful in burn treatment. Hydrogels are very useful in hairy areas where entrapment of hair into the dressing would not be traumatic.

Calcium alginate dressings:

Alginic acid is naturally occurring polysaccharide derived from a type of seaweed. The calcium salt is a fibrous non-woven dressings which are highly absorbent.

Use: They are used on moderate to highly exuding wounds.
They may be held in place with gauze tape or a film dressing.

SECONDARY WOUND DRESSINGS

ABSORBENTS

Surgical cotton

The raw cotton fibre, mechanically cleaned of dirt and processed to remove the natural waxes on the cotton fibres. The fibres are defatted with alkali, bleached, washed and dried. It is available as rolls or small balls.

Use:

i) It absorbs water readily hence used for absorbing wound exudates. However, as its fibres are loose (i.e. not in the form of a thread, they irritate and adhere to raw tissues, hence cotton should be separated from wounds by a woven fabric dressing.
ii) it can be used for cleaning, swabbing and medicating wounds and for applying bactericidal solutions to the skin before surgery.

Surgical gauzes:

The function of surgical gauze is to provide an absorbent material of sufficient tensile strength for surgical dressings.

Processing: Raw cotton fibre is cleaned and spun or twisted into thread, and the threads are woven into an open-mesh cloth. It is then bleached white and defatted to increase the absorbency.

Use: Various forms of pads, compressed and dressings are made from surgical gauze, alone or with absorbent cotton, tissue paper and other materials.

Other forms of secondary dressings are:

i) sanitary napkins
ii) eyepads
iii) disposable under pads
iv) cotton-tipped appliances etc.

BANDAGES

The function of bandages is to hold dressings in place by providing pressure or support. They may be inelastic, elastic or become rigid after shaping for immobilization.

common Gauze Roller Bandages: Each bandage is in one continuos piece, tightly rolled and substantially free from loose threads. It may be of various widths and lengths for various purposes.

Muslin Bandage Rolls: This bleached cotton cloth of plain but closely weaved. They are very strong and are used wherever gauze bandages do not provide sufficient strength or support. They are frequently used to hold splints or bulky compression dressing in place.

Elastic bandages:
(1) **Cotton and Rubber Elastic Bandages:** This bandages has a cotton weft but the warp contains rubber threads.
(2) **Crepe bandage** is elastic but contains no rubber. The warp threads are of cotton and wool and the weft threads are cotton. The wool content is not less than 33(1/3)%
The arrangement of the warp threads:
1 two-fold cotton thread with an S twist
2 wool threads
1 x two-fold cotton thread with Z twist
2 wool threads
The opposite twists of the alternate cotton threads gives the bandage its considerable elasticity.
Use: Crepe bandage conforms well to body contours allowing limited movement and stretching if swelling takes place. Hence it is very useful –
i) for giving light support to sprains and strains
ii) for correctional purposes and
iii) as a compression bandage.
(3) **Cotton Conforming Bandage**
If cotton gauze is mercerized under very carefully controlled conditions the fibres become bent (crimped) and this imparts elasticity to both warp and weft. The sides of the fabric are folded into the centre to avoid rough edges and produce a thicker, more absorbent layer.
Uses: Cotton conforming bandages are used to protect and secure dressings.
There is no need to reverse turn it during application. The overlapping parts do not slip because the crimped fibres tend to interlock.

ADHESIVE TAPES
When some adhesives are spread over a backing membrane it is called an adhesive tape.
This tapes are used
(i) to secure dressings and appliances firmly in place.
(ii) for support and compression e.g. for fractured ribs and clavicles, sprains and leg ulcers etc.
The adhesive tapes differ with the type of backing membrane (e.g. pain cloth, elastic cloth, plastic film).
Depending on the adhesive the tapes may be subdivided into two categories:
(i) rubber based adhesive and
(ii) acrylate adhesive.
Rubber based adhesive tapes:
These are cloth-backed rubber adhesives. these are used principally where heavy support and a high level of adhesion are required.
Acrylate adhesive tapes
In this case non-woven or fabric backing are spread with acrylate adhesives.
Acrylate adhesives are hypoallergenic i.e. they do not produce any allergic reaction.
Rubber adhesives generally contains a large number of components of which few may cause the allergy.
Because acrylate adhesives are basically a unipolymeric system, they eliminate the possibility of allergy.

STERILIZATION OF SURGICAL DRESSINGS
Surgical dressings are packed in drums made of steel and sterilized by moist heat sterilization; the outline of the process is as follows:
By horizontal automatically controlled autoclave:
i) Suitably packed dressings are correctly loaded into the chamber (autoclave).
ii) The door is closed and steam is admitted to the jacket.
iii) Air is partially or almost completely removed by vacuum.
iv) Dry saturated steam is admitted and if, necessary may be used to displace the rest of the air.
v) Heating up and exposure are carried out; air (drained from the dressings) and condensate are automatically discharged meanwhile. Either 115^0C is maintained for 30 mins or 121^0C is maintained for 15 mins.
vi) After the stipulated period the supply steam is cutoff and the chamber is vented.
vii) The dressings are dried either by drawing a high vacuum or by using a partial vacuum to suck warm sterile air through them.

viii)When high vacuum drying has been used the vacuum is broken by admitting sterile air.

STERILITY TEST OF SURGICAL DRESSINGS

Cotton wool, gauze, lint and adhesive plasters are examples of dressings that may require sterile. Before sterilization cotton wool may be heavily contaminated with microorganisms. As an example, gauze may carry about 15 organisms/ cm^2 . Since surgical dressings are used in direct or close contact with wounds or, in the case gauze, within the operation field during surgery the method of confirming sterility must be reliable.

Sampling:

Samples are of about 1 g or 10 cm^2 are taken from woven of non-woven fabric respectively. These are chosen from different places, including regions, such as the centre (contamination is minimum) and the outside (where the probability of contamination is maximum). A test and if required (and possible) two more repeat samples are taken.

Controls:

To check the tester's technique and the bacteriological condition of the atmosphere, a control is performed at the same time as the test. items that have been recently sterilized by a process known to ensure sterility are used for this purpose. They should be equal in number to the test items and preferably identical in structure. No growth should occur in any container.

Elimination of inhibitory action:

Some surgical dressing are impregnate with antimicrobial agents which may interfere with the growth of microorganisms in the culture medium. The action of antimicrobial agents in medicated dressings is eliminated either by including a suitable inactivator in the culture medium or preferably by membrane filtration.

Procedure:

1. The test is performed in an asepsis room or a screen provided with laminar flow of sterile air.
2. The dressings are generally wrapped in double wrapping. The area through which the outer wrapper is to be opened is first painted by Weak Iodine Solution B.P. and left for 5 mins. The outer wrapper is cut along the painted sterile line with a sharp scalpel or blade. The dressing is pulled out off the outer wrapping. The dressing is also drawn out of the inner wrap by a similar method.
3. If the dressing is a bigger one then 1 g or 10cm^2 samples are cut by a pair of sharp scissors from different area of the fabric.
4. Each portion of the dressing are inoculated into separate wide mouthed container containing 50, 100 or 150 ml of a suitable culture medium (e.g. fluid thioglycolate medium U.S.P.). It is then incubate at 32 ± 2^0C for at least 10 days.
5. *Interpretation:*

i) If there is no growth in any of container the batch passes.
ii) If growth occurs in only one container the test is repeated and, if the same result is obtained again. a second repeat is allowed.
iii) The product fails if there is growth in all three tests of the same organism is found in two.

SUTURES AND LIGATURES

- A surgical suture is a strand or fiber used to hold wound edges in application during healing.
- A ligature is a thread or string without a needle which is used to tie blood vessels and other tissues together.

CLASSIFICATION OF SUTURES

(i) Absorbable and (ii) Non-absorbable

ABSORBABLE SUTURES

Surgical gut / Catgut

Catgut is prepared from the intestine of the sheep.

N.B. The name is said to be derived from the word "kit-gut" (a 'kit' being a small violin used in olden times)

(i) Raw material; When sheep are slaughtered the intestines are roughly washed and placed in cold brine for transport.
(ii) Washing: The intestines are washed thoroughly with water.
(iii) Splitting: The intestinal tube is fitted over the end of a flat curved peg and then splitted longitudinally with a knife into "smooth" ribbons.

(iv) Mechanical processing: Mechanical processing remove the innermost mucosa and the outer muscularis and serosal layers, essentially leaving only the submucosa. This appears as a thin, strong network consisting chiefly of collagen.

(v) Chemical processing: At this stage the ribbons may be tanned or hardened by soaking in solution of chromic salts. This causes delay in the absorption depending on the strength of solutions used. Such products formerly were designed as 10, 20, or 40 days catgut, on the assumption that these sutures would remain for such periods in normal tissues. The variations in catgut depends on the variations in patients and on the sites of implantation. Two varieties of catgut, as distinguished by their resistance to absorptive action by tissue enzymes are described in the USP as Type - plain or untreated and
Type C - medium treatment.

In other terms they may be called as 'plain', 'chromic' or 'extra chromic'.

(vii) Spinning: The ribbons are next tied at the ends in groups of two, three or more, depending on the gauge of thread to be prepared, pulled to an even tension and spun. Hardening and chromicising may be done at this stage, but here it produces a case-hardened effect, the center of the string being unaffected by he chromic solution.

(viii) Drying: This is done in an atmosphere conditioned with regard to temperature and humidity, the strings being kept under a suitable tension.

(ix) Finishing: The dried strings are 'polished' by mechanical means. This is really a smoothing process, in which the strings are rubbed against an abrasive surface to produce a smooth, uniform string of circular section.

(x) Sterilization: The sheep intestine is normally infected with bacteria and is likely to contain pathogenic organisms such as the sporing anaerobic bacteria responsible for tetanus and gas gangrene.

The gut may be sterilized by chemicals, heat or ionizing radiations.

Chemical process: In this process the guts are sterilized by immersing them in iodine solution for a prolonged period. The disadvantage with this method is the variable increase in absorption time in the body.

The heat process:

Tubing: Suitable lengths of gut are coiled on a heat-resistant fibre card and placed in glass tubes along with a label of heat-resisting material, printed with heat-resistant ink.

Drying: The tubes are placed in baskets and dried in a drying oven in which the temperature is raised slowly to avoid damaging the gut. When thoroughly dried it is ready for the sterilization process which may be done in one of two ways.

1. The baskets of tubes are placed in an autoclave containing an anhydrous fluid such as toluene or xylol. A temperature of 160^0 C is maintained for several hours. [N.B. The catgut consists of collagen, which is converted into gelatin if heated in presence of moisture hence the anhydrous solvents are used.]
2. Alternatively, the heating may be done in a non-pressure vessel using an anhydrous liquid of high boiling point so that a temperature of 160^0 C can be readily maintained.

The tubes are then filled with sterile tubing fluid and sealed by fusion of the glass. This part of the process must be done under stringent aseptic conditions.

Ionizing radiation process: In this process the prepared gut is packed in aluminum foil envelopes containing 90 percent isopropyl alcohol as a preservative The packets are then passed through a gamma irradiation area on a conveyor system. Thus catgut is sterilised when sealed in final container and the process is a rapid one. Each suture receives a minimum dose of 2.5 megarads (unit of radiation).

BOILABLE AND NON-BOILABLE CATGUT

If the tubing fluid is anhydrous the tubes may be boiled before opening it for use; this type of catgut is called "boilable catgut".

If the tubing fluid contains water the tubes of the catguts are labeled 'Non-boilable'. This is a warning to avoid the use of heat in sterilizing the outside of the tube prior to opening it for use.

Non-boilable guts are more popular because the water in the tube keeps it pliable and immediately ready for use. The non-boilable tubes are filled with alcohol containing a small quantity of water.

SYNTHETIC ABSORBABLE SUTURES

Polymers derived from

i) condensing the cyclic derivative of glycolic acid (glycolide),
ii) mixtures of glycolide and lactide (derived by cyclizing lactic acid)

iii) dioxanone and glycolide with tetramethylene carbonate
have shown to possess high tensile strength and absorbability.
The first two polyesters mentioned are melt-extruded into multifilament yarns which then are braided into various sizes of sutures.
The second two polyesters are provided as pliable monofilaments.
Sterilization: They are packaged without fluid and sterilized with ethylene oxide to avoid degradation.
Synthetic absorbable sutures do not undergo the enzymatically mediated absorption process that is well-known for catgut. Rather, the suture is broken down completely by simple hydrolysis as it resides in the tissue. Tissue reaction is minimum since scavenger leukocytes are not involved significantly in the absorption process.

Standards:

The following tests are given in the *British Pharmaceutical Codex*.
Sterility tests: The tests for sterility are intended for detecting the presence of viable forms of microorganisms on the surgical suture materials.
Method 1: The suture materials are washed with a sterile fluid, the fluid is then passed through a filter membrane (for filtering bacteria), the filter membrane is then incubated in sterile medium and observed for minimum of 7 day. If any viable form of microorganisms were present in the suture material they will grow.
Method-II: The suture materials are incubated in culture medium for not less than 14 days. If microorganisms are present they will render the medium turbid.
Gauge: This is measured by means of a dial reading micrometer at several points along the strand.
Tensile strength: This is done by means of a machine in which the load necessary to rupture the gut is measured, the tests being performed on 'straight' and 'knotted' samples.

NON-ABSORBABLE SUTURES

This group of sutures are relatively resistant to attack by normal tissue fluids.
When non-absorbable sutures are used for skin closure, they usually are removed after the wound has healed to the point where suture support is no longer necessary.
Generally silk, linen, cotton, metallic wire, nylon and dacron are given in USP.

Silk:

Degummed commercial silk fibres consists chiefly of the protein fibroin as extruded by the silk-worm. Many such fibers are twisted into a single strand of various diameters as specified in USP, and sold in the natural colour or after dyeing.
Silk sutures are handled easily, and tolerated well by body tissue, although they may cause significant tissue reaction. The microorganisms can remain concealed in the interstices of silk strand and may protect them from antimicrobial agents. So chronic wound may not heal unless the suture is removed.
Silk occasionally migrates from the site of implantation and comes to the surface.
In certain sites the knots may produce irritation and may remain encapsulated in the tissue.

Dermal Silk

These sutures consists of natural twisted silk encased in an insoluble coating of tanned gelatin of other protein. This coating must withstand autoclaving without stripping.
Its purpose is to prevent the in-growth of tissue cells which would interfere with its removal after use as a skin or dermal suture.

Cotton and Linen

Sutures derived from cellulose, they are twisted from fiber staple, have moderately high tensile strength and are stable to heat sterilization.

Synthetic non-absorbable sutures:

Nylon is a polyamide obtained from the condensation of adipic acid and hexamethylenediamine or from the polymerization of caprolactum.

It is strong, water-resistant and can be used for all suturing and ligating.

Polyester fibres are multifilament synthetic fibres. They are prepared by melt-extruding polyethylene terephthalate into fine filaments which are then braided into various sizes.

The polyester sutures do not lose strength in contact with water or body fluids, for this reason they are used for permanent reinforcement as, for example, in installation of artificial heart valves.

They have the advantage of excellent knot holding characteristics and are available in the natural colour or dyed to enhance visibility in the surgical field.

Polyoelfin fibres : Examples are polyethylene and polypropylene.

Polypropylene sutures compared to monofilament nylon, tie more secure knots and have a very low order of tissue reactivity. Because of the smoothness, they slip through tissue in-growth, they may be removed easily when necessary. They are widely used in cardiovascular and other surgical specialties.

Metallic sutures:

Silver: Among the older materials which are still used to some extent are silver wire, foil and other forms. Silver though has some antiseptic action but in some tissues it produce irritation.

Stainless steel is a ferrous alloy is resistant to chemical attack has been used widely in the form of wire sutures, fixation plates, screws and other items.

Stainless steel sutures are available both as twisted and monofilament strands and presents the strongest available material. However, they are relatively difficult to use and are employed most commonly in areas where great strength is required, such as in the repair of the sternum after chest surgery.

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SUPPOSITORIES **CHAPTER 7(c)**

Syllabus:
Factors affecting drug absorption from rectal suppositories, suppository bases, preparation of suppository, packing and storage.

Questions:
1. Define suppositories and displacement value. (98) [4]
2. Discuss different suppository bases. (98) [4]
3. Write in brief, the preparation , packaing and storage of suppositories (98) [4]
4. Give the ideal properties of suppository bases.
5. Discuss the problems encountered in manufacturing of suppositories such as hygroscopicity, incompatibilities, viscosity etc. (96) [8]
6. Short note on packing of suppositories. (95) [4]
7. Short notes on suppository bases. (93) [4]
8. Factors affecting drug absorption from rectal suppositories. (93) [4]

DEFINITION

Definition:

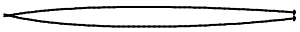
- Suppositories are specially shaped solid dosage form of medicament for insertion into body cavities other than mouth.
- They may be inserted into rectum, vagina or the urethra.
- These products are so formulated that after insertion, they will either melt or dissolve in the cavity fluids to release the medicament.

TYPES OF SUPPOSITORIES

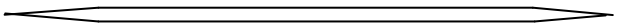
1. Rectal suppositories: These are meant for introduction into the rectum for local and systemic effect.

2. Pessaries: These are meant for introduction into vagina for local action. These are larger than rectal suppositories (3 – 6 gm).

3. Urethral bougies: These are meant for introduction into urethra.
Weight: 2 – 4 gm Length: 2 – 5 inches.



4. Nasal bougies: These are meant for introduction into nasal cavities.
Weight: 1gm Length: 9 – 10 cm



Advantages of rectal suppositories:

(i) *Mechanical action:* The rectal suppositories are extensively used as a mechanical aid to bowel evacuation which produce its action by either irritating the mucous membrane of the rectum (e.g. glycerol and bisacodyl) or by lubricating action or by mechanical lubrication.

(ii) *Local action:* The rectal suppositories may be used for soothing, antiseptic, local anaesthetic action or for astringent effect. Therefore, they may contain

soothing	e.g. zinc oxide
local anaesthetic-	e.g. cinchocaine, benzocaine
astringents	e.g. bismuth subgallate, hamamelis extract and tannic acid
antiinflammatory	e.g. hydrocortisone and its acetate.

(iii) *To provide systemic action*: Suppositories are convenient mode of administration of drugs which irritate the gastrointestinal tract, cause vomiting, are destroyed by the hepatic circulation, or are destroyed in the stomach by pH changes, enzymes etc.

Partial bypass: The lower portion of the rectum affords a large absorption surface area from which the soluble substances can absorb and reach the systemic circulation.

e.g.	*aminophylline*	used in asthmatic and chronic bronchitis.
	morphine	a powerful analgesic
	ergotamine tartarate	used to treat migraine
	indomethacin and phenyl butazone	analgesic and anti-inflammatory actions.

Systemic treatment by the rectal route is of particular value for
(a) treating patients who are unconscious, mentally disturbed or unable to tolerate oral medication because of vomiting or pathological conditions of the alimentary tract.
(b) administering drugs, such as aminophylline, that cause gastric irritation, and
(c) treating infants.

PROPERTIES OF IDEAL SUPPOSITORY BASE
1. It should melt at rectal temperature (36^0) or dissolve or disperse in body fluid. For eutectic mixtures and in tropical climate the melting range of the base should be higher.
2. Release medicaments easily.
3. Shape should remain intact while handling.
4. Non-toxic and non-irritant to sensitive and inflammed mucous membrane.
5. It should be stable on storage i.e. it does not change color, odor, or drug release pattern.
6. Compatible with broad variety of drug and adjuvants.
7. It should shrink so that it comes out easily from the mould without the use of any lubricants.

For fatty bases the following additional specifications are required:
8. "Acid value" is below 0.2
9. "Saponification value" ranges from 200 to 245
10. "Iodine value" is less than 7
11. The interval point and solidification point is small.

SUPPOSITORY BASES

Classification of suppository bases
1. *Fatty bases* – they melt at body temperature.
2. *Water-soluble or water miscible base* – they dissolve or disperse in rectal secretions.
3. *Emulsifying bases* – they emulsifies small amount of aqueous solution of drug.

FATTY BASES

Example: Theobroma oil (Cocoa butter), Synthetic fats.

Theobroma oil (Cocoa butter)
- It is a yellowish-white solid having chocolate flavor.
- It is a mixture of glyceryl esters of stearic, palmitic, oleic and other fatty acids.

Advantages:
(a) A melting point range of 30 to 36 ^{0}C; hence it is solid at normal room temperatures but melts in the body.
(b) Ready liquefaction on warming and rapid setting on cooling.
(c) Miscibility with many ingredients.
(d) Blandness i.e. does not produce irritation.

Disadvantages:
(a) Polymorphism

Cocoa butter has three polymorphs α-crystals (unstable, m.p. 20^0C), β-crystals (stable, m.p. 36^0C) and γ-crystals (unstable, 15^0C).

When melted and cooled it solidifies in different crystalline forms, depending on the temperature of melting, rate of cooling and size of the mass. If melted below 36^0C and slowly cooled it forms stable β-crystals with normal melting point, but if over-heated it may produce, on cooling, unstable γ-crystals, which melt at about 15^0C, or α-crystals, melting at about 20^0C. These unstable forms eventually return to the stable condition but this may take several days and meanwhile, the suppositories may not set at room temperature or, if set by cooling, may remelt in the warmth of the patient's home.

This lowering of the solidification point can also lead to sedimentation of suspended solids. Consequently, great care must be taken to avoid over-heating the base when making theobroma oil suppositories.

(b) Adherence to mould

Because theobroma oil does not contract enough on cooling to loosen the suppositories in the mould, sticking may occur, particularly if the mould is worn. This is prevented by lubricating the mould before use.

(c) Softening point too low for hot climates

To raise the softening point, whit beeswax may be added to theobroma oil suppositories intended for use in tropical and subtropical countries.

(d) Melting point reduced by soluble ingredients

Substances, such as chloral hydrate, that dissolve in theobroma oil, may lower its melting point to such an extent that the suppositories are too soft for use. To restore the melting point, a controlled amount of white beeswax may be added.

(e) Slow deterioration during storage

This is due to oxidation of the unsaturated glycerides.
(f) Poor water absorbing capacity
This fault can be improved by the addition of emulsifying agents.
(g) Leakage from the body
Sometimes melted base escapes from the rectum or vagina. This is most troublesome with pessaries because of their larger size, and therefore, these are rarely made with theobroma oil.
(h) Relatively high cost

Synthetic fats
As a substitute of theobroma oil a number of hydrogenated oils, e.g. hydrogenated edible oil, arachis oil, coconut oil, palm kernel oil, stearic and a mixture of oleic and stearic acids are recommended.

> [N.B. Synthetic suppositories bases are by hydrogenation and subsequent heat treatment of vegetable oils such as palm oil and arachis oil. The oils are generally esters of unsaturated fatty acids. Hydrogenation saturates the unsaturated fatty acids and heat treatment splits some of the triglycerides into fatty acids and partial esters (mono- and di-glycerides).]

Advantages of these synthetic fats over theobroma oil:
1. Their solidifying points are unaffected by overheating.
2. They have good resistance to oxidation because their unsaturated fatty acids have been reduced.
3. Their emulsifying and water absorbing capacities are good. [They usually contain a proportion of partial glycerides some of which, e.g. glyceryl monostearate, are w/o emulsifying agents and, therefore, their emulsifying and water absorbing capacity are good.
4. No mould lubricant is required because they contract significantly on cooling.
5. They produce colorless, odourless and elegant suppositories.

Disadvantages:
1. They should not be cooled in refrigerator because they become brittle if cooled quickly. Certain additives e.g. 0.05 % polysorbate80, help to correct this fault.
2. They are more fluid than theobroma oil when melted and at this stage sedimentation rate is greater. Thickeners such as magnesium stearate , bentonite and colloidal silicon dioxide, may be added to reduce this.

WATER SOLUBLE AND WATER MISCIBLE BASES
Glycero-Gelatin base
- This is a mixture of glycerol and water made into a stiff jelly by adding gelatin.
- It is used for the preparation of jellies, suppositories and pessaries. The stiffness of the mass depends upon the proportion of gelatin used which is adjusted according to its use.
- The base being hydrophilic in nature, slowly dissolves in the aqueous secretions and provide a slow continuous release of medicament. Glycerogelatin base is well suited for suppositories containing belladonna extract, boric acid, chloral hydrate, bromides, iodides, iodoform, opium, etc.
- Depending upon the compatibility of the drugs used a suitable type of gelatin is selected for the purpose. Two types of gelatins are used as suppository base

(i) *Type-A* or Pharmagel-A which is made by acid hydrolysis (has isoelectric point between 7 to 9 and on the acid side of the range behaves as a cationic agent, being most effective at pH 7 to 8.) is used for acidic drugs.
(ii) *Type-B* or Pharmagel-B which is prepared by alkaline hydrolysis (having an isoelectric point between 4.7 to 5 and on the alkaline side of the range behaves as an anionic agent, being most effective at pH 7 to 8) is used for alkaline drugs

Disadvantages:
Glycerogelain base suppositories are less commonly used than the fatty base suppositories because:
(i) Glycerol has laxative action.
(ii) They are more difficult to prepare and handle.
(iii) Their solution time depends on the content and quality of the gelatin and the age of the base.
(iv) They are hygroscope, hence must be carefully stored.
(v) Gelatin is incompatible with drugs those precipitate with the protein e.g. tannic acid, ferric chloride, gallic acid, etc.

Soap-Glycerin Suppositories
- In this case gelatin and curd soap or sodium stearate which makes the glycerin sufficiently hard for suppositories and a large quantity of glycerin up to 95% of the mass can be incorporated.
- Further the soap helps in the evacuation of glycerin.
- The soap glycerin suppositories have the disadvantage that they are very hygroscopic, therefore they must be protected from atmosphere and wrapped in waxed paper or tin foil.

Polyethylene glycol bases / Macrogol bases (Carbowaxes)
Depending on their molecular weight they are available in different physical forms.
Examples of Macrogol bases:

	I	II	III	IV
Macrogol 400	-	-	20	-
Macrogol 1000	-	-	-	75
Macrogol 1540	-	33	33	-
Macrogol 4000	33	-	-	25
Macrogol 6000	47	47	47	-
Water	20	20	-	-

By choosing a suitable combination a suppository base with the desired characteristics can be prepared.
Advantages:

1. The mixtures generally have a melting point above 42^0C, hence, does not require cool storage and they are satisfactory for use in hot climate.
2. Because of the high melting point they do not melt in the body cavity, rather they gradually dissolve and disperse, releasing the drug slowly.
3. They do not stick to the wall of the mould since they contract significantly on cooling.

EMULSIFYING BASES
These are synthetic bases and a number of proprietary bases of very good quality are available, few of which are described below:
Witepsol
They consist of triglycerides of saturated vegetable acids (chain length C12 to C18) with varying proportions of partial esters.
Massa Esterium
This is another range of bases, consisting of a mixture of di-, tri- and mono- glycerides of saturated fatty acids with chain lengths of C11 to C17.
Massuppol
It consists of glyceryl esters mainly of lauric acid, to which a small amount of glyceryl monostearate has been added to improve its water absorbing capacity.

Advantages of these bases over cocoa butter:

1. Over heating does not alter the physical characteristics.
2. They do not stick to the mould. They do not require previous lubrication of the mould
3. They solidify rapidly.
4. They are less liable to get rancid.
5. They can absorb fairly large amount of aqueous liquids.

FACTORS AFFECTING-ABSORPTION FROM RECTAL SUPPOSITORIES
A. Physiologic factors
The lower hemorrhoidal veins surrounding the colon and rectum directly goes to heart and the upper hemorrhoidal vein connects to liver via portal vein. So more than 50 to 70% of the drug administered rectally were found to directly passing to systemic circulation (i.e. bypassing the liver).
<u>pH of rectal secretion</u>
The principal method of drug absorption from the rectum is by passive diffusion. So a drug that remains mostly in unionized state will be absorbed more readily. Generally weakly basic and weakly acidic drugs remains in unionized state in the pH of rectum (6.8) and hence, absorbed readily than the stronger base or acids.

B. Physicochemical characteristics of the drug
The sequence of events that takes place before absorption n the anorectal area is as follows:

Drug in vehicle $\rightarrow$ Drug in colon fluids $\rightarrow$Absorption through the rectal mucosa

- *Partition coefficient*: Drugs with a high fat to water (Ko/w) partition coefficient are liberated very slowly from the fatty bases. So water soluble salt forms of drugs are more readily absorbed from anorectal area.
- *Rectal fluid volume*: Rectal fluid volumes also vary in different time and in different individuals. This influences the release rate and absorption of drug from suppository bases.
- *Physical state of medicament*: When a drug remains in suspension state in a suppository the drug particles should be very fine, so that the effective surface area is very high and thus dissolution rate is very high.
  Solution from a suppository will be faster when it melts quickly into a fluid of low viscosity that spreads into thin film over a large area in the rectum.

Generally, for *local action* fatty base is suitable and for *systemic action* water-soluble base is better for providing the quick release desirable for systemically active drugs.

- *Presence of surfactants*: Surfactants can both increase or decrease the absorption rate of a drug from anorectal region. Surfactants can reduce the surface tension of the colon fluid → help in washing the rectal mucosa, → new pores for absorption will be opened → absorption is accelerated.

C. Physicochemical characteristics of the base and adjuvants.

- Lower m.p. fatty base + sodium phenobarbitone → absorption rate is faster than higher m.p. fatty base + sod.phenobarbitone.
- High molecular weight PEG bases produces faster absorption than low molecular weight PEG base.
- Fatty bases may be hardened several months after molding, these increase in melting range decrease the drug release.
- Adjuvants in the base changes the rheologic characteristics of the base or may affect the dissolution of the drug.
  e.g. addition of colloidal silicon oxide to fatty base dramatically changes the rheologic characteristics of the base.
  e.g. Salicylates were found to improve the rectal absorption of water-soluble antibiotics in lipophilic bases.
- Emulsifying agents such as wool fat, wool alcohols, macrogols, stearates and polysorbates, may be included in the suppository bases to facilitate the incorporation of aqueous solutions. They may cause unpredictable release and absorption of a medicament.
- Large amount of emulsifying agents may cause excessive foaming.
- Strong surface active agent may produce increased absorption of drug and may produce toxic effects.

MANUFACTURING OF SUPPOSITORIES

Moulds

The suppository and pessary moulds are made of metals and have four, six or twelve cavities. By removing a screw, they can be opened longitudinally for lubrication, extraction of the suppositories and cleaning.
[N.B. The interior of the mould should never be scrapped or rubbed with abrasive. For cleaning they are immersed in hot water containing detergent, wiped gently with soft cloth and rinsed thoroughly.]

Capacity of moulds: The nominal capacities of the common moulds are 1g, 2g, 4g and 8g.

Calibration

The nominal capacity of a mould varies with the base selected. Each mould should be calibrated before use by preparing a set of suppositories or pessaries using the base alone, weighing the products and taking the mean weight as the true capacity. This procedure is repeated for each base.

Displacement value

The volume of a suppository from a particular mould is uniform but its weight will differ with the density of the base.

Definition

It is the quantity of the drug that displaces one part of the base. e.g. Zinc oxide, D = 5.

Calculation of displacement value

Formula for calculation of the amount of base required in each mould

$$\text{Amount of base required for each suppository (gm)} = \text{Capacity of each mould (gm)} - \frac{\text{Dose of drug (gm)}}{\text{Displacement value of the drug}}$$

Lubrication of mould

If the cavities are imperfect, i.e. poorly polished or scratched, it may be difficult to remove the suppositories without damaging their surfaces. So lubrication of the moulds is necessary.
In case of greasy or oily base water soluble lubricants are required.
e.g. For cocoa butter the following lubricant solution formula may be used:

Soft soap	10g
Glycerol	10ml
Alcohol(90%)	50ml

For water soluble /miscible bases oily lubricant may be used. e.g. For glycero-gelatin base liquid paraffin or arachis oil may be used as lubricant.

Four methods are used in preparing suppositories:

1. Hand molding [Cold Hand Shaping]

1. Drug is triturated in a mortar into fine powder.
2. Cocoa butter is grated into small particles.
3. Drug is mixed with small portion of cocoa butter in a mortar.
4. One drop fixed vegetable oil is added to give plasticity to the mass.

5. Remainder of the cocoa butter is added by geometric dilution (i.e. by adding the same amount of base as is already in the mortar), triturated wit pressure. Heat generated by trituration results in a plastic mass, which is cohesive and ready to roll.
6. The mass is scrapped from the mortar with a spatula and rolled into a ball.
7. An ointment tile is taken, dusted lightly with starch powder, ball is placed on it, rolled with a flat faced spatula to form a cylinder. The cylinder is cut into desired number of pieces with a sharp blade.
8. One end of a suppository is held firmly with a finger and the other end is tapered with the spatula to give the shape of suppository.

2. Compression molding

In this case an instrument known as *compression mould* is used.

1. Drug is powdered and mixed with grated cocoa butter.
2. The mixture is filled into a chilled cylinder. The mixture is pressed within the cylinder by a piston until a pressure is felt.
3. Then the suppositories are expelled from the cylinder.

3. Pour molding (Fusion method)

This is the main method of preparing suppositories.

1. Drug is powdered in a mortar.
2. Carefully grated cocoa butter is taken into a beaker and heated in a water bath. When $2/3^{rd}$ portion is melted the beaker is taken out of the heat source. The rest of the mass is melted by stirring with a glass rod. [If cocoa butter is heated to clear liquid then unstable α, and γ - crystals will form and the suppositories will remain in melted state at room temperature.]
3. Drug is added into the beaker and stirred thoroughly to mix with the "creamy" base.
4. The "creamy" melted base is then poured into previously lubricated mould.
5. The mould is allowed to congeal, then placed in the refrigerator for 30 minutes to harden (forms stable β-crystal after 24 hours of refrigeration).
6. Mould is taken out from the refrigerator and surface is trimmed off. The mould is opened and the suppositories are expelled out of the mould by gentle pressure with the finger.

4. Automatic molding machine

Two types of molding machines are available: (a) rotary molding machine and (b) straight-line molding machine

Manufacturing cycles in rotary molding machine:

1. Prepared mass is filled in a into a filling hopper where it is continuously mixed and maintained at constant temperature.
2. The suppository molds are lubricated by brushing or spraying lubricant solution.
3. The molten mass is filled in the molds to a slight excess.
4. The mass is *cooled* to solidify and the excess material is *scrapped off* and collected for re-use.
5. In the ejecting section the mold is opened and the suppositories are pushed out by steel rods.
6. The mold is closed, and then moved to the first step of the cycle.

The output of a typical rotary machine ranges from 3500 to 6000 suppositories an hour.

Manufacturing cycles in straight-line molding machine:

Here the cycle is similar to rotary molding machine but the individual molds are carried on a track through a cooling tunnel, where scrape-off and ejection occur.

PACKAGING OF MOLDED SUPPOSITORIES

Objective: The suppositories should be over-wrapped, or they must be placed in a container in such a way that they do not touch each other.

Why packing is required?

Suppositories in contact with one another may fuse with one another or with the container at room temperature.

Packing materials: Suppositories are usually over-wrapped in aluminium foils, paper strip or plastic strips.

Packaging machines

1. *Machine-I*: The chilled-hardened suppositories are placed in a notched turntable and then fed to the packing station, where the foil is unwounded from a roll, cut to size, and finally rolled around each suppository.
2. *Machine*-II*:* The suppositories are enclosed in cellophane or heal-sealed aluminium foils. Plastic may be thermoformed into two packaging halves. Suppository is mechanically placed in one half and the second half of plastic is sealed by heat.

Bulk storage

The individually wrapped suppositories are packaged in slide, folding, or set-up boxes.

Suppositories containing hygroscopic or volatile material are packed in glass or plastic containers.

Many suppositories are not individually over-wrapped. They are placed in sectioned card-board boxes or plastic containers to hold 6 or 12 suppositories.

In-package molding

In this automatic method individual suppository is molded in their wrapping material. Either plastic or aluminium foil/propylene/lacquer laminate are used.

Advantage: If the suppository melts at higher storage temperature their shapes are retained which can be used just by chilling again.

In *plastic* wrapping the plastic is thermoformed into the shape of mould. The molten mass is injected through the top end and tops is cooled and sealed.

In *aluminium foil* method two aluminium foils are embossed and sealed to give the shape of a mold and then the mass is injected at the top and then the top is cooled and sealed.

SPECIFIC PROBLESM IN FORMULATING SUPPOSITORIES

1. Water in suppositories

Water is used as a solvent to incorporate a water-soluble substance in the suppository base. Incorporating water should be avoided for the following reasons.

(a) Water accelerates the oxidation of fats.
(b) If the water evaporates the dissolved substances crystallize out.
(c) In presence of water reactions between various ingredients of suppositories may occur.
(d) The water may be contaminated with bacteria or fungus.

3. Hygroscopicity

Glycerinated gelatin suppositories lose moisture in dry climates and absorbs moisture in high humidity.

Polyethylene glycol bases are also hygroscopic.

4. Incompatibilities

Poyethylene glycol bases are incompatible with silver salts, tannic acid, aminopyrine, quinine, ichthammol, aspirin, benzocaine, iodochlorohydroxyquin, and sulfonamides.

Many chemicals have a tendency to crystallize out of PEG e.g. sodium barbital, salicylic acid and camphor.

5. Viscosity

Viscosity of melted base is low in cocoa butter and high in PEG and glycerinated gelatin. Low viscosity base when melted the suspended particles may sediment very quickly producing nonuniform distribution of drugs.

Remedies:

(a) The base should be melted at the minimum temperature required to maintain the fluidity of the base.
(b) The base is constantly stirred in such a way that the particles cannot settle and no air is entrapped in the suppository..
(c) A base with a narrow melting range closer to rectal temperature is used.
(d) Inclusion of approximately 2% aluminium monostearate increase the viscosity of the fatty base and also helps in homogeneous suspension of particles.
(e) Cetyl, stearyl, myristyl alcohol or stearic acid are added to improve the consistency of suppositories.

6. Brittleness

Cocoa butter base is not brittle but synthetic fat bases with high degree of hydrogenetation and high stearate containing bases are brittle. Brittle suppositories produce trouble during manufacture, handling, packaging and during use.

Causes: Rapid chilling (shock cooling) of the melted bases in an extremely cold mold.

Remedies:

(a) The temperature difference between the melted base and mold should be as small as possible.
(b) Addition of small amount of Tween80, castor oil, glycerin or propylene glycol imparts plasticity to a fat and make it less brittle.

7. Volume contraction

When the bases are cooled in the mould volume of some bases may contract. Volume contraction produces

(a) good mold release facilitating the ejecting from mold.
(b) contraction hole formation at the top: This imperfection can be solved by adding slight excess base over the suppositories and after cooled the excess is scrapped off.

8. Lubricants

Cocoa butter adheres to suppository molds because of very low volume of contraction. Aqueous lubricant may be used to remove the suppositories easily from the molds. They are applied by wiping, brushing or spraying. The mold surfaces may be coated with teflon to reduce the adhesion of base to mold wall.

9. Rancidity & oxidation

Due to auto oxidation of unsaturated fatty acids present in the base, saturated and unsaturated aldehydes, ketones and acids may formed, which have very strong unpleasant odor – this phenomenon is called rancidification. To prevent this suitable antioxidants like hydroquinione, β-naphthoquinone, α- and β-tocopherols, *gossypol* (present in cotton seed oil), *sesamol* (present in sesame oil) propyl gallate, gallic acid, tannins and tannic acids, ascorbic acid (Vit C.), butylated hydroxyanisole (BHA) and butylated hydroxyanisole (BHA).

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:

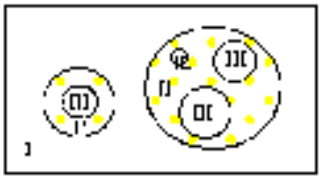
o/w- type of emulsion is a system in which the oil is dispersed as droplet throughout the aqueous phase. Most pharmaceutical emulsions designed for oral administration are of the o/w type; emulsified lotions and creams either of o/w or w/o type depending on their use.

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 solubolised systems.

Unlike emulsions, they appear as clear transparent solution, but unlike solubilised systems micro-emulsions 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 chose 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

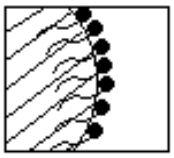
When an emulsifier is used alone to stabilize an emulsion – it is called *primary emulsifier.* Some times a second emulsifier is used to help the primary emulsifier in stabilizing the system – the second emulsifier is known as *auxiliary emulsifier*. Generally emulsifiers from (ii) and (iii) category 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/cm^2.

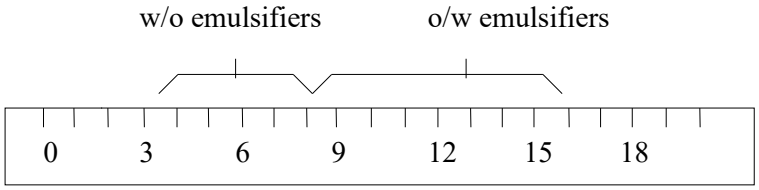
(b) A complete and coherent film should be formed around the dispersed globules so as to prevent their coalescence.
(c) Should assist in building up the zeta potential and viscosity since both of these phenomena contribute to the stability.

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.



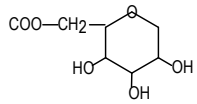
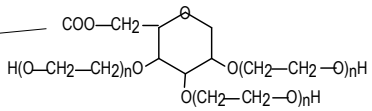
Griffin's HLB Scale

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. *Anionic*				
(a) Alkali soap	Potassium stearate	$C_{17}H_{35}$	COO^-	K^+
(b) Organic sulphates	Sodium lauryl sulphate (Sod. dodecyl sulphate)	$C_{12}H_{25}$	OSO^{3-}	Na^+
(c) Organic sulphonates	Sodium cetyl sulphonate (Sod. hexadecane sulfonate)	$C_{16}H_{33}$	SO^{3-}	Na^+
2. *Cationic*				
(a) Quaternary ammonium compounds	Cetyl trimethyl ammonium bromide (or cetrimide)	$C_{16}H_{33}$	$N^+(CH_3)_3$	Br^-
(b) Pyridinium compounds	Dodecyl pyridinium chloride	$C_{12}H_{25}$	$N^+C_5H_5$	Cl^-
3. *Ampholytic*				
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. *Non-ionic*				
(a) Alcohol-polyethylene glycol ethers	Polyethylene glycol 1000 monocetyl ether (cetomacrogol 1000)	$CH_2–(CH_2)n$ (n= 15 to 17)	$(O–CH_2–CH_2)m–COO^-$ (m = 20 to 24)	none
(b) Fatty acid-polyethylene glycol ethers	Polyethylene glycol 40 monostearate	$C_{17}H_{33}$	$CO–(O–CH_2–CH_2)_{40}–OH$	none
(c) Fatty acid-polyhydric alcohol esters	Sorbitan mono-oleate (TWEEN)	$C_{17}H_{33}$		none
	Polyoxyethylene sorbitan mono-oleate	$C_{17}H_{33}$		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 aligation method:

HLB of Tween80 → Parts of Tween80 → 15 → 6.3

RHLB → 10.6

HLB of Span80 → Parts of Span80 → 4.3 → 5.6

Required amount of Tween80 = {6.3/(6.3+5.6)}x Total amount of emulsifier
= 0.53x2 g
= 1.06 g

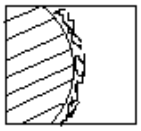
Required amount of Span80 = {5.6/(6.3+5.6)}x Total amount of emulsifier
= 0.47x2 g
= 0.94 g

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



(i) 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.
(ii) As an auxiliary emulsifier they increase the viscosity of the continuous phase so that movement of dispersed phase is reduced.

Examples:

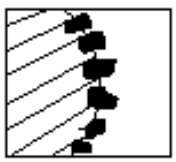
(i) Plant origin: Acacia, tragacanth, alginates, chondrus and pectin.
(ii) Animal source: Gelatin, egg yolk, casein, woolfat, cholesterol and lecithin.
(iii) Synthetic: Methyl cellulose, Hydroxyethyl cellulose, Polyoxyethylene polymer and Carboxyvinyl polymer.

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



(i) They tend to absorb at the oil-water-interface and form thick impenetrable films.
(ii) 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 thixotrophy in an emulsion is desirable (thixotrophy = 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 through 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 (H_3PO_4)
   Tartaric acid
2. *Preferentially oxidized compounds (Reducing agents)*
   e.g. Ascorbic acid
   Sodium sulphite (Na_2SO_3)
   Sodium bisulfite ($NaHSO_3$)
   Sodium metabisulfite ($Na_2S_2O_5$)
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 N_2 gas through the liquids to remove dissolved O_2.
(ii) boiled before use
(iii) exposure to vacuum during ultrasonic agitation
(iv) the end space above the container can be flushed with N_2 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 10^0C over the melting point of the highest melting ingredient of to a maximum temperature of 70 to 80^0C.
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 5^0C 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-typeA 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 98^0C and this temperature is maintained for about 20 minutes. Cooled to 50^0C, 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 50^0C and pass through colloid mill.
(ii) Add the next four ingredients at 50^0C to the first three ingredients at 65^0C and stirred while cooling to 45^0C.
(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 actin 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.

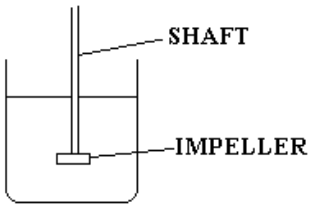
Advantages:

(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 then 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:

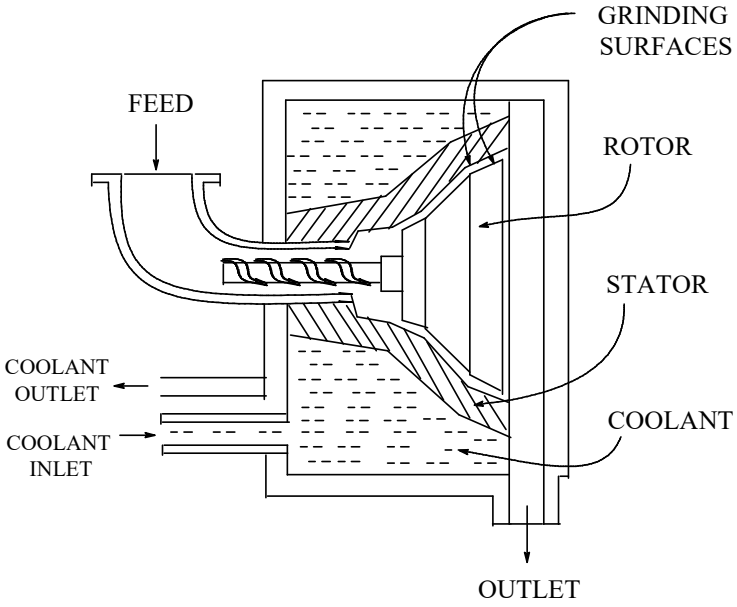
Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium, in this way, impairs the ease of emulsification.

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

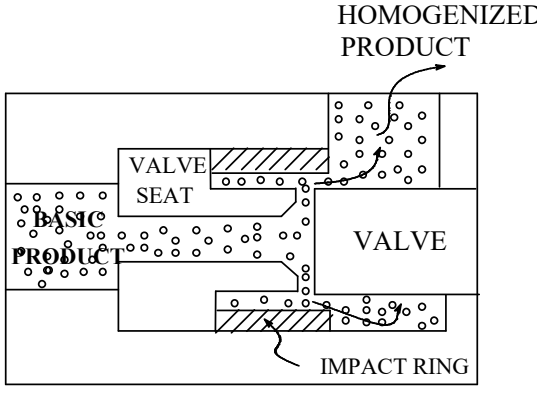
(i) Very high shearing force can be generated.
(ii) Very fine particles can be prepared.
(iii) Particularly useful in preparing suspensions containing poorly wetted solids.
(iv) Useful for the preparation of relatively viscous emulsions.

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 of 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.

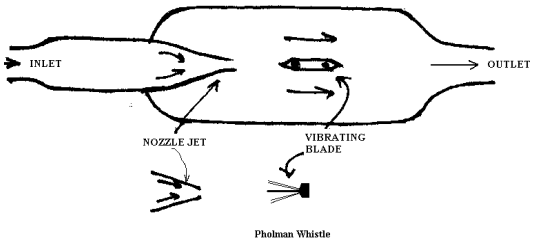
Disadvantages

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.



Pholman Whistle

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:

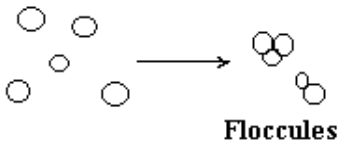
(i) reduction of droplet size
(ii) a decrease in the density difference between the two phases
(iii) increase in the viscosity of the continuous phase

- *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.



Flocculation

In the floccules the droplets remain aggregated but intact. The droplets can remain intact when the mechanical or electrical barrier is sfficient 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:

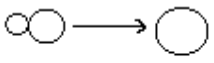
(i) the chemical nature of the emulsifier,
(ii) the phase-volume ratio, and
(iii) the concentration of dissolved substances, especially electrolytes.

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.


Coalescence

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 70^0C 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 4^0 and 45^0C.

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 thixotrophic 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 samples 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 co-axial 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

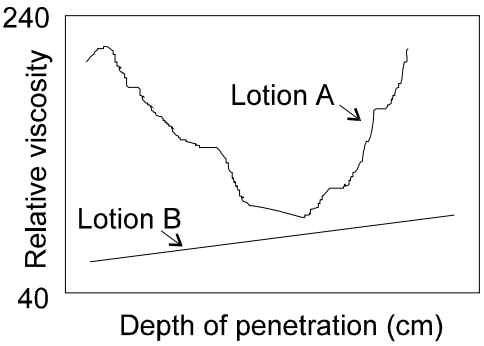
N.B. The Brookfield viscometer determines the resistance encountered by rotating spindle or cylinder immersed in a viscous material. The Helipath attachment slowly lowers the rotating spindle into the medium so that the resistance measured is always that of previously undisturbed test substances.

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 pr 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 some what 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 50^0C,

(ii) 5 to 6 months at 37^0C and

(iii) 12 to 18 months at room temperature.

(iv) After 1 month storage at 4^0C

(v) After 2 to 3 freeze-thaw cycles between –20 and $+25^0$C.

(vi) After 6 to 8 freeze-thaw cycles between 4 and 45^0C 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 45^0C.

INCOMPATIBILITIES IN PRESCRIPTIONS

Definition

When two or more ingredients of a prescription are mixed together the undesired change that may take place in the physical, chemical or therapeutic properties of the medicament is termed as *incompatibility*.

Classification

Incompatibilities are of three types:

1. Therapeutic incompatibility
2. Physical incompatibility
3. Chemical incompatibility

THERAPEUTIC INCOMPATIBILITY

Usually this incompatibility arises when one or more drugs produces response or intensity different from that intended in the patients.

Classification

A) Over doses
B) Under doses
C) Improper consumption by the patient
D) Contra-indicated drugs

A) Over doses: This can be subgrouped as follows:

Excessive single dose

Sometimes a single dose may become overdose depending on the health of the patient e.g. a normal dose (taking body weight as 70 kg for an adult male) may be overdose for a lowly built person. However it should not be more than 2 to 3 normal dose.

Remedy: The pharmacist should consult the physician and clarify the dose.

e.g. 1 Rx

Atropine sulphate	6 mg
Phenobarbital	360 mg

Make capsules.

Label: One capsule to be taken three times a day before meals.

Comments: In this prescription the doses of both atropine sulphate and phenobarbital are 12 times the normal doses. The physician intended for 12 capsules to be dispensed but he has mistaken or may be it is an incomplete prescription. Hence, before dispensing the pharmacist should consult the physician again.

Correct prescription

Rx

Atropine sulphate	6 mg
Phenobarbital	360 mg

Make capsules. Supply 12 capsules.

Label: One capsule to be taken three times a day before meals.

e.g. 2 Rx

Strychnine sulphate	20 mg
Iron and ammonium citrate	500 mg

Prepare capsules. Supply 12 capsules.
Label: One capsule to be taken three times a day after meals.
Comment: 10 times overdose of strychnine hydrochloride than that of normal. The pharmacist should consult the physician and obtain the permission to change the dose.
Corrected prescription

Strychnine sulphate	2 mg
Iron and ammonium citrate	500 mg

Prepare capsules. Supply 12 capsules.
Label: One capsule to be taken three times a day after meals.

Excessive daily dose

In this case the daily dose of drug is exceeded .

e.g.1 Rx

Codeine phosphate	15 mg
Ammonium chloride	500 mg

Prepare capsules and supply 24 capsules.
Label: Two capsules to be taken every hour for cough.
Comment: The U.S.P. recommends that the prescribed dose should be taken after every four hours and not every hour. Hence the physician should be consulted.

Additive and synergistic combinations:

There are certain drugs possessing similar pharmacological activity. If these drugs are combined together, they may produce additive or synergistic action. In such case advice of the physician is necessary.

e.g. Rx

Amphetamine sulphate	20 mg
Ephedrine sulphate	50 mg
Syrup q.s.	100 ml

Let a mixture be made
Label: Take 25 ml every four hours.
Comment: Both of the drugs are sympathetic stimulants and they are prescribed in their full dose. The formulation will produce additive overdose effect. Hence, The dose of individual drug should be reduced.

(B) Under dose In this type of incompatibility, effect of one drug is lessen or antagonised by the presence of another drug. This can be exemplified by combination of following types of drugs:

1. **Stimulants** like nux-vomica, strychnine sulphate, caffeine etc. with **sedatives** like barbiturates, paraldehyde etc.
2. **Sympathomimetic** or **adrenergic** like ephedrine, nor-adrenaline with **sympatholytic** drugs like ergotamine.
3. **Sympathetic stimulants** like methamphetamine with **parasympathetic stimulants** like pilocarpine.
4. **Purgatives** like castor oil, liquid paraffin etc with **antidiarrheal** agents like bismuth carbonates.
5. **Acidifiers** like dilute hydrochloric acid and **alkalisers** like sodium bicarbonate, magnesium carbonate.

e.g. Rx

Aspirin	300 mg
Probenecid	500 mg

Prepare capsules.
Label: One capsule a day for gout.
Aspirin is an NSAID given to reduce the pain and swelling in case of gout attack. Probenecid blocks the active reabsorption of uric acid from the lumen of nephron, but salicylates (aspirin) blocks this action of probenecid. Hence, both of the drugs are antagonistic to each other, so its combination is therapeutically useless.

(C) Improper consumption by the patient:
In certain prescription some special directions should be written. If the patients are nor advised the drugs may not produce the desired action due to low bioavailability.
e.g. Rx

Tetracycline hydrochloride 250 mg

Prepare capsules. Supply 10 capsules.
Label: Take one capsule every six hourly.
Comments: Calcium present in milk inactivates the tetracycline, hence a patient may not get any therapeutic effect if he/she takes the capsule with milk.
Remedy: The pharmacist should advise the patient to take the capsule with water and not with milk. The patient should not take antacid containing calcium salts.

(D) Contra-indicated drugs

Certain drugs should not be given in particular disease condition
e.g.
(i) corticosteroids are contraindicated in patients with peptic ulcer.
(ii) Vasoconstrictors are contraindicated in hypertensive patients
(iii)Some drugs should not be given in asthmatic patients e.g. barbiturates, morphine etc.
(iv)If a person is allergic to a drug (e.g. penicillin injection) then it should not be given to the patient.
(v) Certain combination of drugs are contraindicate:

Rx

Sulphadiazine	0.25 g
Sulphamerazine	0.25 g
Ammonium chloride	0.50 g

Prepare capsules
Label: Take two capsules six hourly for cough.
Comment: In this prescription ammonium chloride is a urinary acidifier and it could cause deposition of sulphonamide crystals in the kidney.

PHYSICAL INCOMPATIBILITY
Usually, this is due to immiscibility or insolubility. It can cause unsightly, non-uniform products from which removal of an accurate dose is very difficult.
Classification:
(A) Immiscibility
(B) Insolubility
(C)Liquefaction

(A) Immiscibility

1) Oils are immiscible with water and hence combination of oily drugs with water produces a product possessing two separate layers.
Remedy: This problem can be overcome by emulsification or solubilization.
2) Care must be taken when concentrated hydroalcoholic solutions of volatile oils such as *spirits and concentrated waters,* are used as adjuncts (e.g. as flavouring agents) in aqueous preparations. Large globules of oils may be separated.
Remedy: To prevent the formation of large globules, the hydroalcoholic solution should either be gradually diluted with the vehicle before admixture with the remaining ingredients or poured into the vehicle with constant stirring.
3) Addition of high concentrations of electrolytes to mixture in which the vehicle is a saturated aqueous solution of a volatile oil causes the oil to separate and collect as a surface layer.
e.g. This happens in *Potassium Citrate Mixture B.P.C.* in which large quantity of soluble solids salts out the lemon oil.
Remedy: To disperse the droplets evenly, quillaia tincture is added as a wetting agent.

(B) Insolubility

1) Liquid preparations containing indiffusible solids such as chalk, aromatic chalk powder, succinyl sulfathiazole and sulphadimidine (in mixtures) and calamine and zinc oxide (in lotions) - a thickening agent is necessary to obtain a uniform product from which uniform doses can be removed.
2) Some insoluble powders such as sulphur and certain corticosteroids (*hydrocortisone acetate*) and antibiotics are difficult to wet with water.
Remedy: Wetting agents
e.g. *saponins* for sulphur containing lotions
and *polysorbates* in parenteral suspensions of corticosteroids and antibiotics are used to distribute the powder and prevent formation of a slowly dispersing, solid stabilised foam on shaking.
3) When a resinous tincture is added to water the water insoluble resin agglomerate forming indiffusible clots.
Remedy: This is prevented by slowly adding the undiluted dispersion of protective colloid (*Tragacanth mucilage*).
e.g. Lobelia & Stramonium tincture which should be mixed with tragacanth mucilage and stirred constantly. This will produce a stable preparation.
4) high concentrations of electrolytes cause cracking of soap emulsions (ionic) by salting out the emulsifiers.

C) Liquefaction

When certain low melting point solids are powdered together a liquid or soft mass is produced due to lowering of the melting point of the mixture to below room temperature. Thus an **eutectic mixture** is formed

Any two of the following exhibits this type of behaviour, camphor, menthol, phenol, thymol and chloral hydrate, also sodium salicylate with phenazone.

e.g. Rx

Thymol	250 mg
Camphor	2 mg
Menthol	2 mg

Make powder.

Comments: If these ingredients are triturated together, they will form an eutectic mixture.

Method-I:

All the ingredients are triturated.

An eutectic mixture (liquid) will be formed. The liquid is triturated with enough absorbent powder e.g. light kaolin or light magnesium carbonate, to give a free flowing powder.

Method-II:

Each ingredient is triturated separately with small amount of adsorbent or diluent and then these powders are lightly mixed by tumbling action) and packed.

The diluent largely prevents contact between the ingredients and adsorbs any liquid that may be produced.

e.g. Rx

Chloral hydrate	250 mg

Prepare capsules. Supply 10 capsules.

Label: Take the capsules at night time.

Comment: Chloral hydrate is hygroscopic in nature. It will absorb moisture and soften the hard gelatin capsule shells and the shape of the capsule may change physically.

Remedy: An equal quantity of light magneisum oxide should be mixed with chloral hydrate.

Other adsorbents those may be used are kaolin, talc, starch etc.

e.g. Rx

Aminopyrine	0.3 g
Acetyl salicylic acid	0.2 g
Codeine sulphate	0.015 g
Belladonna extract	0.010 g

Prepare capsules.

Comment: In this prescription aminopyrine and acetyl salicylic acid form eutectic mixture and wetting of belladonna extract give green colour.

Remedy: Light magnesium oxide (approximately 65 mg) may be added. The half quantity of magnesium oxide is mixed with aminopyrine and the other half with acetyl salicylic acid separately. The two are mixed gently and then other ingredients are added and mixed gently.