

Formulation

838806

Liquid dosage forms

Suspension

Dr. Upasana M. Patel

Associate Professor

M.Pharm, PhD



SU:



PHARMACEUTICAL SUSPENSIONS



SUSPENSIONS

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WHAT ARE SUSPENSIONS?

WHY WE ARE USING SUSPENSIONS?

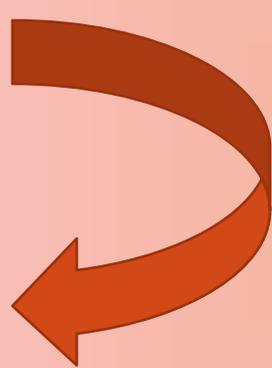


DISPERSE SYSTEM

- The term "**Disperse System**" refers to a system in which one substance (**The Dispersed Phase**) is distributed, in discrete units, throughout a second substance (**the continuous Phase**).
- Each phase can exist in **solid, liquid, or gaseous state** .
- *Suspensions are heterogenous system consisting of 2 phases.*

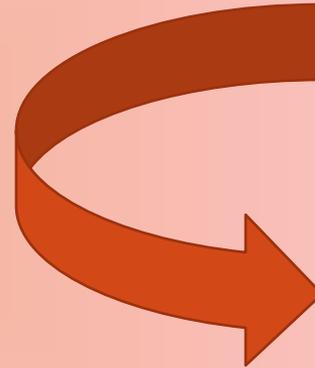
A solid in liquid dispersion in which the particles are of colloidal size.

DISPERSE SYSTEM



DISPERSED MEDIUM

○ **Aqueous oily liquid**



DISPERSED PHASE

○ **Insoluble solid**

Definition

➤ A Pharmaceutical suspension is a coarse dispersion in which internal phase (**therapeutically active ingredient**) is dispersed uniformly throughout the external phase.



- The **internal phase** consisting of insoluble solid particles having a range of size(**0.5 to 5 microns**) which is maintained uniformly through out the suspending vehicle with aid of **single or combination of suspending agent**.
- The external phase (**suspending medium**) is generally aqueous in some instance, may be an organic or oily liquid for non oral use.



The reasons for the formulation of a pharmaceutical suspension:

- when the drug is insoluble in the delivery vehicle.**
- To mask the bitter taste of the drug.**
- To increase drug stability.**
- To achieve controlled/sustained drug release.**

SOME PHARMACEUTICAL SUSPENSIONS

- 1. Antacid oral suspensions
- 2. Antibacterial oral suspension
- 3. Dry powders for oral suspension (antibiotic)
- 4. Analgesic oral suspension
- 5. Anthelmintic oral suspension
- 6. Anticonvulsant oral suspension
- 7. Antifungal oral suspension

Classification

Based On General Classes

- Oral suspension
eg: Paracetamol suspension
antacids, Tetracycline HCl.
- Externally applied suspension
eg :Calamine lotion.
- Parenteral suspension
eg: Procaine penicillin G
Insulin Zinc Suspension



Based on Proportion of Solid Particles

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

Eg: cortisone acetate, prednisolone acetate

- Concentrated suspension (50% w/v solid)

Eg: zinc oxide suspension



Based on Electrokinetic Nature of Solid Particles

- Flocculated suspension
- Deflocculated suspension



Based on Size of Solid Particles

➤ Colloidal suspensions (< 1 micron)

-Suspensions having particle sizes of suspended solid less than about 1micron in size are called as colloidal suspensions.

Coarse suspensions (>1 micron)

- Suspensions having particle sizes of greater than about 1micron in diameter are called as coarse suspensions.



Nano suspensions (10 ng)

- Suspensions are the biphasic colloidal dispersions of nanosized drug particles stabilized by surfactants.
- Size of the drug particles is less than 1mm.



Advantages And Disadvantages

Advantages

.Suspension can improve chemical stability of certain drug.
E.g. Procaine penicillin G.

➤ Drug in suspension exhibits higher rate of bioavailability than other dosage forms.

Solution > Suspension > Capsule > Compressed Tablet > Coated tablet

➤ Duration and onset of action can be controlled.
E.g. Protamine Zinc-Insulin suspension.

➤ Suspension can mask the unpleasant/ bitter taste of drug.
E.g. Chloramphenicol

Disadvantages

- Physical stability , sedimentation and compaction can causes problems.
- It is bulky sufficient care must be taken during **handling and transport.**
- **Uniform and accurate dose can not be achieved** unless suspension are **packed in unit dosage form.**

Applications

- Suspension is usually applicable for drug which **is insoluble (or) poorly soluble.**
E.g. Prednisolone suspension
- To prevent **degradation** of drug or to **improve stability of drug.**
E.g. Oxy tetracycline suspension
- To mask the taste **of bitter of unpleasant drug.**
E.g. Chloramphenicol palmitate suspension
- Suspension of drug can be formulated for **topical application**
e.g. Calamine lotion

- Suspension can be formulated for parenteral application in order to **control rate of drug absorption**. E.g. penicillin procaine
- **Vaccines as a immunizing agent** are often formulated as suspension. E.g. Cholera vaccine
- **X-ray contrast agent** are also formulated as suspension . eg: Barium sulphate for examination of alimentary tract.

Features Desired In Pharmaceutical Suspensions

- The suspended particles should not settle rapidly and sediment produced, must **be easily re-suspended** by the use of moderate amount of **shaking**.
- It should be easy to pour yet **not watery** and **no grittiness**.
- It should have **pleasing odour , colour and palatability**.
- Good **syringeability**.
- It should be **physically,chemically and microbiologically stable**.
- Parenteral /Ophthalmic suspension should be sterilizable.

THEORETIC CONSIDERATION OF SUSPENSIONS

A knowledge of the theoretic considerations pertaining to suspension s technology ultimately help formulator to select ingredients that are

- Appropriate for suspension preparation
- That available for milling
- Mixing equipment

▪ Some theoretic considerations are :

- **Particle size control.**
- **Wetting**
- **Sedimentation**
- **Brownian movement**
- **Electokinetic**
- **Aggregation**

Particle size control:

- Particle size of any **suspension is critical and must be reduced within the range .**
- Too large or too small particles should be avoided.

Larger particles will:

- settle faster at the bottom of the container
- particles $> 5 \text{ um}$ impart a gritty texture to the product and also cause irritation if injected or instilled to the eye
- particles $> 25 \text{ um}$ may block the needle

- Too fine particles will easily form hard cake at the bottom of the container.

Wetting of the particles

- Hydrophilic materials (talc, ZnO, Mg₂CO₃) are easily wetted by water while hydrophobic materials (sulphur , charcoal) are not due to the layer of adsorbed air on the surface.
- Thus, the particles, even high density, float on the surface of the liquid until the layer of air is displaced completely.
- The use of wetting agent allows removing this air from the surface and to easy penetration of the vehicle into the pores.
- However hydrophobic materials are easily wetted by non-polar liquids.

THEORY OF SEDIMENTATION

SEDIMENTATION:

Sedimentation means settling of particle (or) floccules occur under gravitational force in liquid dosage form.

Velocity of sedimentation expressed by Stoke's equation

Where,

d = Diameter of particle

$$V_{\text{sed.}} = \frac{d^2 (\rho_s - \rho_o) g}{18 \eta_o}$$

$$= \frac{2r^2 (\rho_s - \rho_o) g}{9 \eta_o}$$

r = radius of particle

$V_{\text{sed.}}$ = sedimentation velocity in cm / sec

ρ_s = density of disperse phase

ρ_o = density of disperse media

g = acceleration due to gravity

η_o = viscosity of disperse medium in poise

Limitation Of Stoke's Equation ·

Stoke's equation applies only to:

- Spherical particles in a **very dilute suspension** (0.5 to 2 gm per 100 ml)
- Particles which **freely settle without collision** .
- Particles with **no physical or chemical attraction**.

Sedimentation Parameters

Sedimentation volume (F) or height (H) for flocculated suspensions:

Definition:

Sedimentation volume is a ratio of the ultimate volume of sediment (V_u) to the original volume of sediment (V_O) before settling.

$$F = V_u / V_O$$

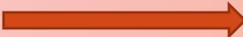
Where,

V_u = final or ultimate volume of sediment

V_O = original volume of suspension before settling

F has values ranging from less than one to greater than one.

When $F < 1$  $V_u < V_o$

When $F = 1$  $V_u = V_o$

The system is in flocculated equilibrium and show no clear supernatant on standing.

When $F > 1$  $V_u > V_o$

Sediment volume is greater than the original volume due to the network of flocs formed in the suspension and so loose and fluffy sediment

The sedimentation volume gives only a qualitative account of flocculation.

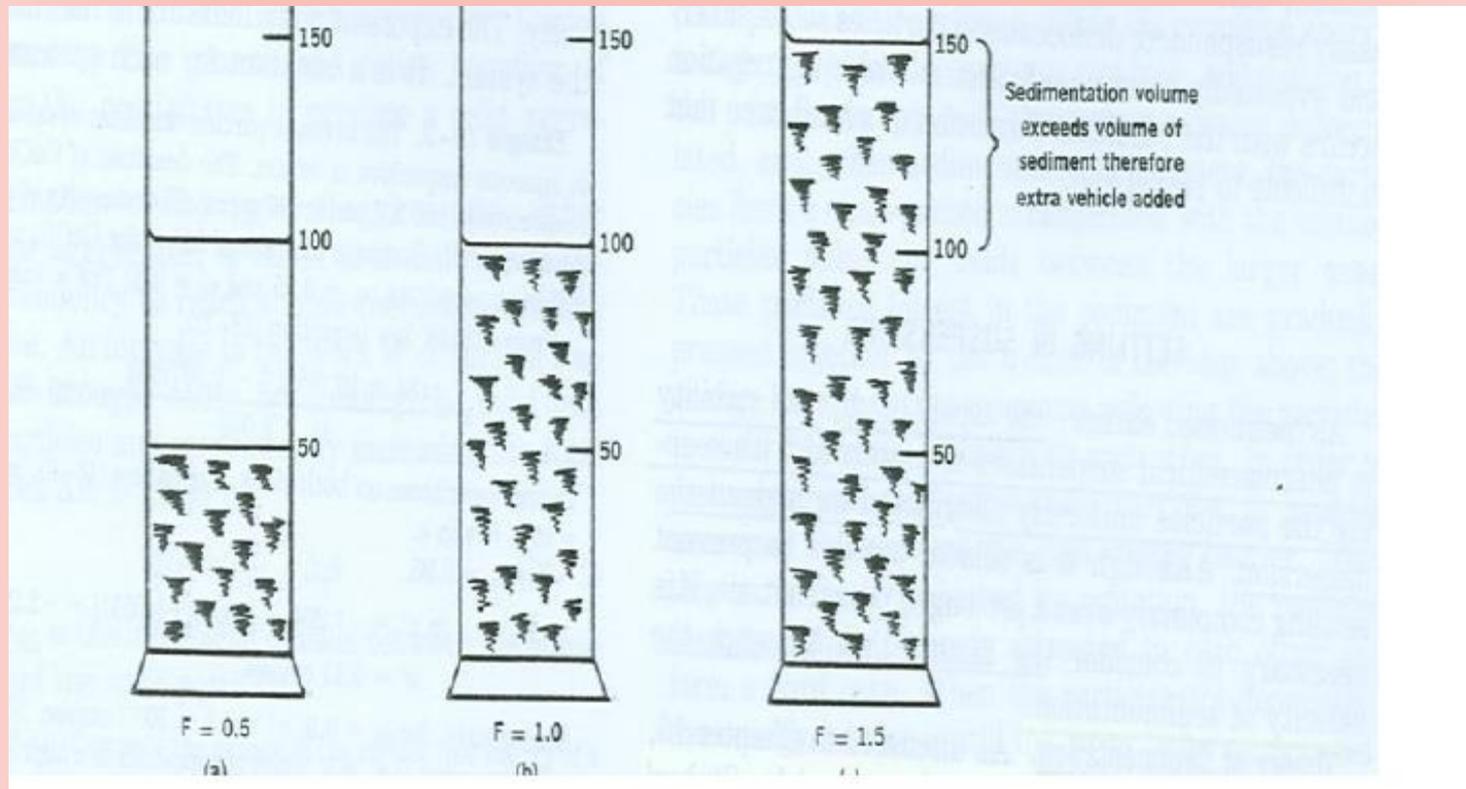


Fig : Suspensions quantified by sedimentation volume (f)

Degree of flocculation (β)

It is the ratio of the sedimentation volume of the flocculated suspension, F , to the sedimentation volume of the deflocculated suspension, F_{∞}

$$\beta = F / F_{\infty}$$

(V_u/V_o) flocculated

$$\beta = \frac{\text{-----}}{\text{-----}}$$

(V_u/V_o) deflocculated

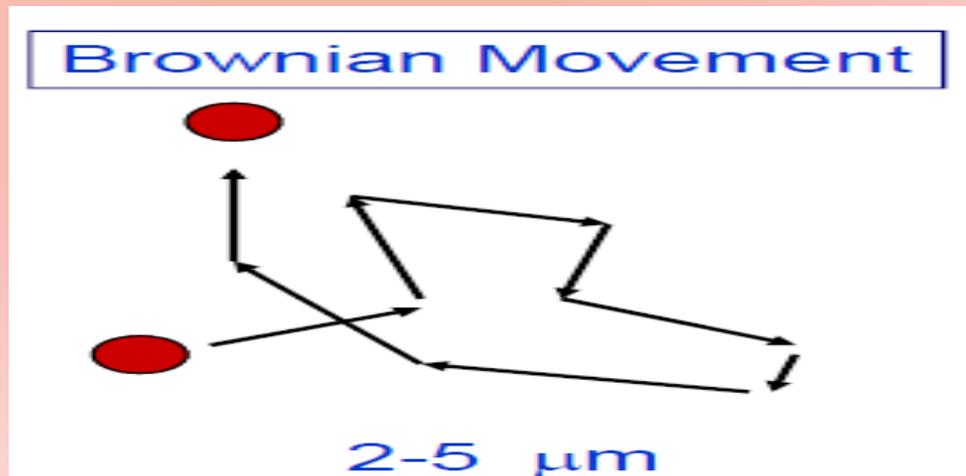
➤ **The minimum value of β is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.**

2. Brownian Movement (Drunken walk)

- Brownian movement of particle prevents sedimentation by keeping the dispersed material in random motion.
- Brownian movement depends on the **density of dispersed phase** and **the density and viscosity of the disperse medium**.
- The kinetic bombardment of the particles by the molecules of the suspending medium will keep the particles suspending, provided that their size is below critical radius (r).

➤ Brownian movement can be observed,

- If particle size is about 2 to 5 μ m,
- When the density of particle & viscosity of medium are favorable.



Brownian motion is given by equation:

$$D_i^2 = \frac{RTt}{N_3 \pi \eta r}$$

Where, R = gas constant

T = temp. in degree Kelvin

N = Avogadro's number

η = viscosity of medium

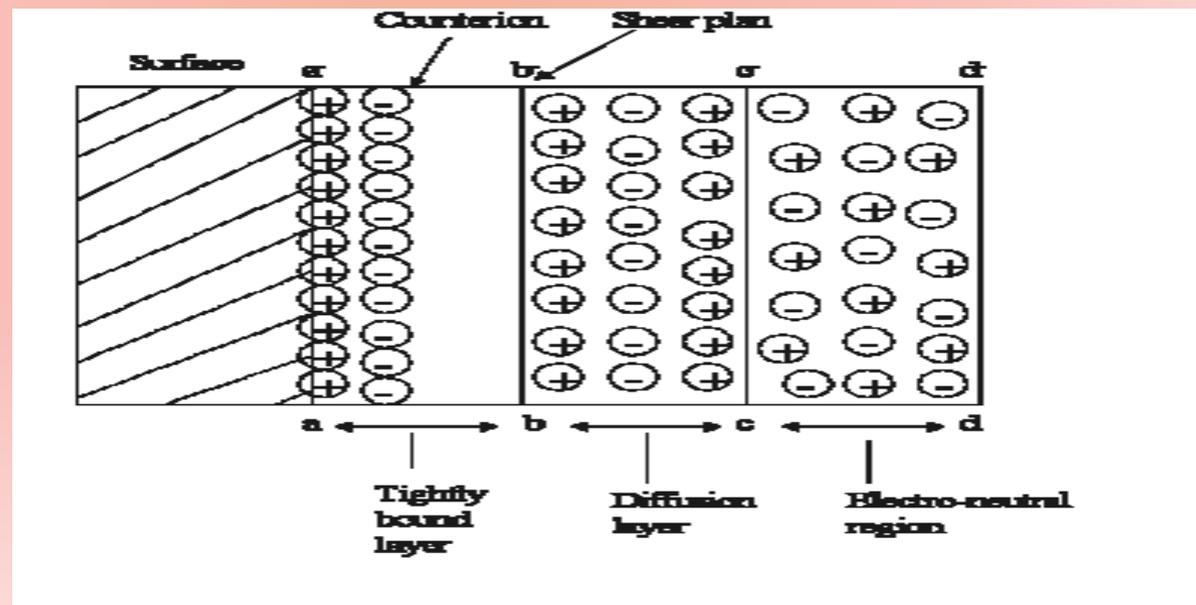
t = time

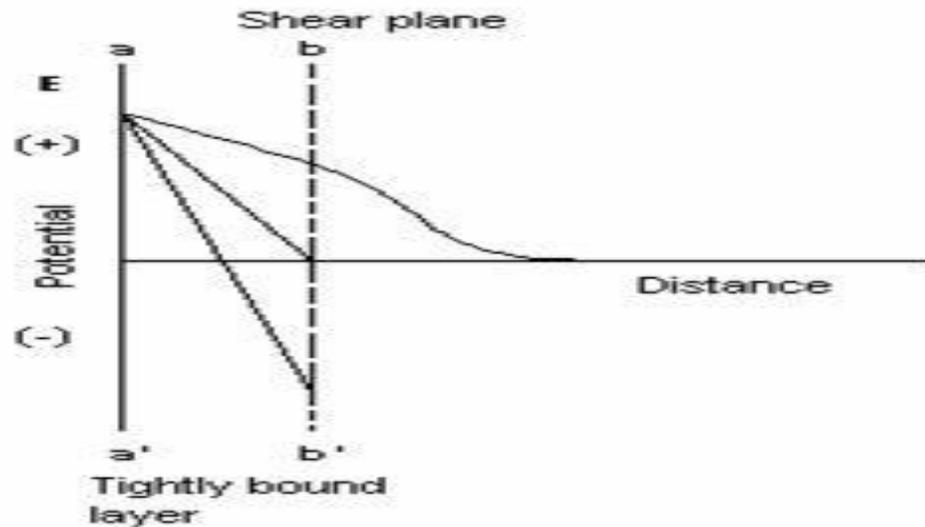
r = radius of the particle

3. Electro kinetic Properties

Zeta Potential

The zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and electro-neutral region of the solution.





- As the potential drops off rapidly at first, followed more gradual decrease as the distance from the surface increases.
- This is because the counter ions close to the surface acts as a screen that reduce the electrostatic attraction between the charged surface and those counter ions further away from the surface.

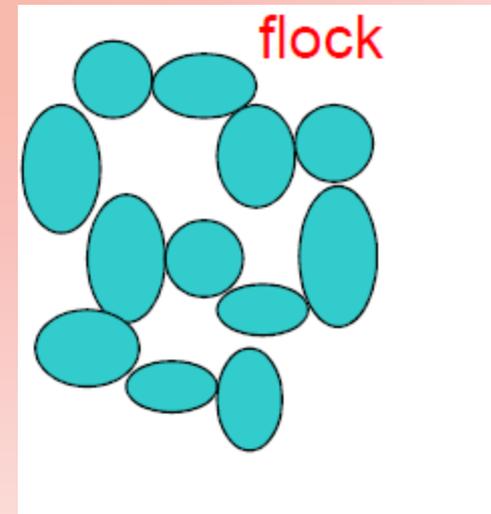
- Zeta potential has practical application in **stability of systems** containing dispersed particles .
- Since this potential, rather than the Nernst potential, governs the degree of repulsion between the adjacent, similarly charged, dispersed particles.
- If the zeta potential is reduced below a certain value , the attractive forces exceed the repulsive forces, and the particles come together.
- This phenomenon is known as flocculation.

- The flocculated suspension is one in which zeta potential of particle is -20 to +20 mV.
- **Thus the phenomenon of flocculation and de flocculation depends on zeta potential carried by particles.**

Deflocculation and flocculation

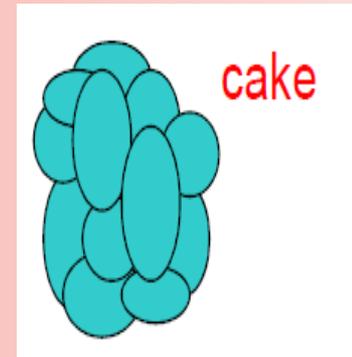
Flocculated Suspensions

- In flocculated suspension, **formed flocs (loose aggregates)** will cause increase in sedimentation rate due to increase in size of sedimenting particles.
- Hence, flocculated suspensions sediment more rapidly.
- Here, the sedimentation depends **not only on the size** of the flocs but also on the porosity of flocs.



Deflocculated suspensions

- In deflocculated suspension, individual particles are settling.
- Rate of sedimentation is slow , which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation.
- This phenomenon called ‘caking’ or ‘claying’.
- In deflocculated suspension larger particles settle fast and smaller remain in supernatant liquid so supernatant appears cloudy.



FORMULATION OF SUSPENSIONS

- The formulation of a suspension depends on whether the suspension is flocculated or deflocculated.

- Three approaches are commonly involved
 1. Use of structured vehicle
 2. Use of controlled flocculation
 3. Combination of both of the methods

Flow chart of formulation of suspension

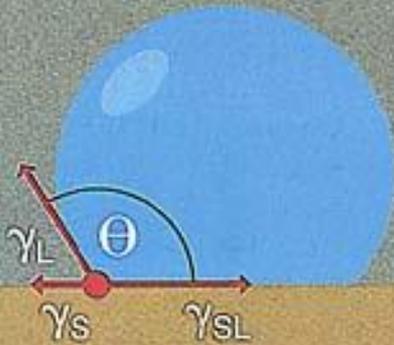


wetting agents

- Some **insoluble solids** may be easily wetted by water and will disperse readily throughout the aqueous phase with only minimal agitation.
- Most, however, will exhibit varying degrees of hydrophobicity and will not be easily wetted. Some particles will form large porous clumps within the liquid, whereas others remain on the surface and become attached to the upper part of the container.
- To ensure adequate wetting, the interfacial tension between the solid and the liquid must be reduced so that the adsorbed air is displaced from the solid surfaces by the liquid.

poor wetting

$$\theta > 90^\circ$$



good wetting

$$90^\circ > \theta > 0^\circ$$



complete wetting

$$\theta \rightarrow 0^\circ$$



$$\gamma_L \times \cos \theta \quad j < 0$$

$$j > 0 \quad \gamma_L \times \cos \theta$$

$$\gamma_S > \gamma_{SL} + \gamma_L$$

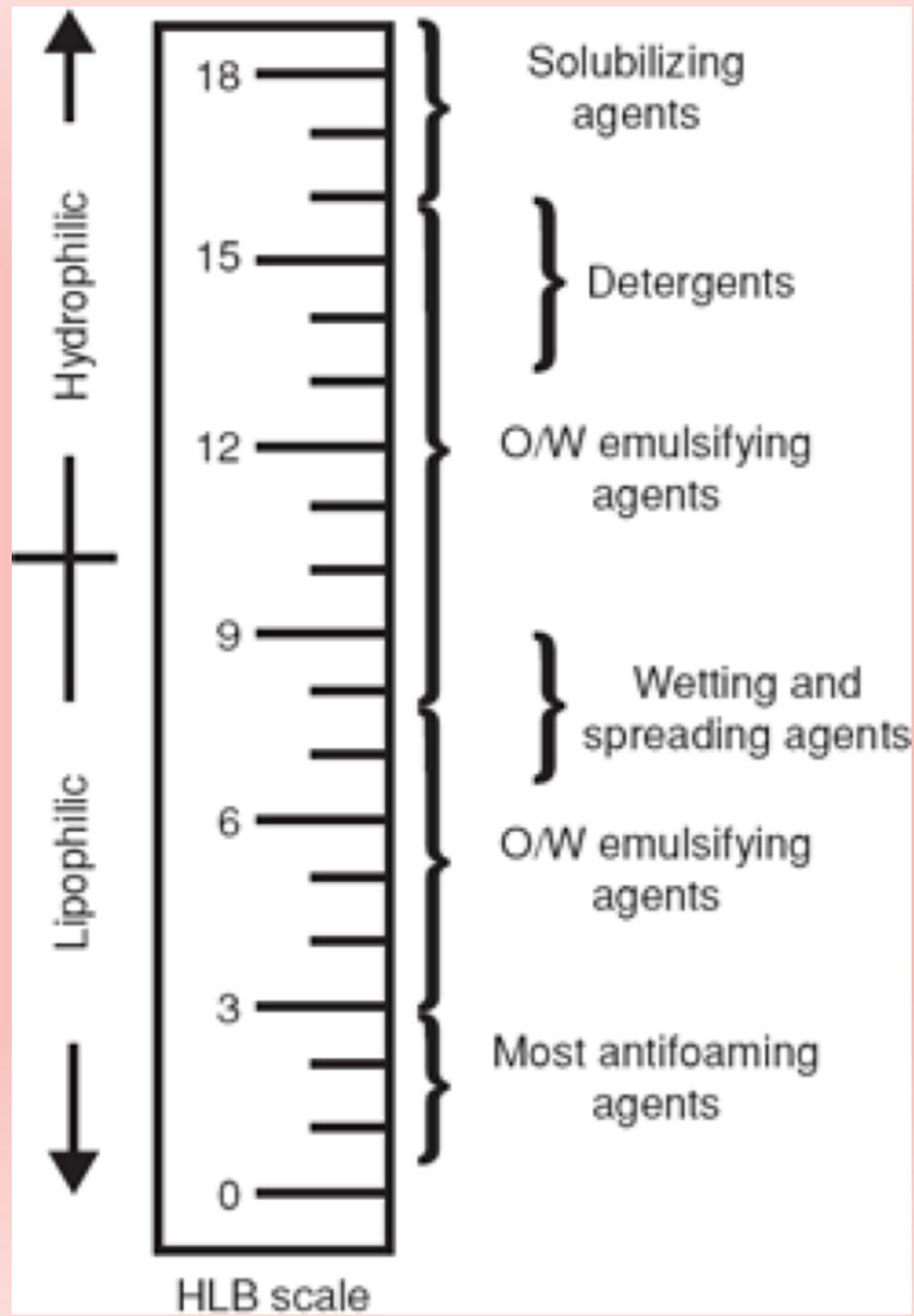
$\theta = \text{Theta}$

wetting agents

- 1. *Surface-active agents:*
- 2. *Hydrophilic colloids*
- 3. *Solvents*

1. *Surface-active agents:*

- surfactants possessing an HLB value between about 7 and 9 would be suitable for use as wetting agents.
- The hydrocarbon chains would be adsorbed by the hydrophobic particle surfaces, whereas the polar groups project into the aqueous medium and become hydrated.
- Wetting of the solid occurs as a result of a fall in interfacial tension between the solid and the liquid .



- Most surfactants are used at concentrations of up to about 0.1% as wetting agents and include:

1. for oral use, the polysorbates (Tweens) and sorbitan esters (Spans).

2. For external application, sodium lauryl sulphate, sodium dioctylsulphosuccinate and quillaia extract can also be used.

3. For parenteral use: polysorbates, some of the poloxamers (polyoxyethylene/polyoxypropylene copolymers) and lecithin.

- Disadvantages in the use of this type of wetting agent include excessive foaming and the possible formation of a deflocculated system, which may not be required.

2. Hydrophilic colloids

- These materials include acacia, bentonite, tragacanth, alginates, xanthan gum and cellulose derivatives, and will behave as **protective colloids by coating the solid hydrophobic particles** with a multimolecular layer.
- This will impart a hydrophilic character to the solid and so promote wetting.
- These materials are also used as suspending agents and may, like surfactants, produce a deflocculated system, particularly if used at low concentrations.

3. Solvents

- Materials 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, so enabling wetting to occur by the dispersion medium.
- Alcohol, glycerin, propylene glycol, and other hygroscopic liquids are employed as wetting agents when an aqueous vehicle is to be used as the dispersion phase.

Structured vehicle

- Structured vehicles called also **thickening or suspending agents**.
- They are aqueous solutions of natural and synthetic gums.
- These are used to increase the **viscosity of the suspension**.
- It is applicable only to deflocculated suspensions.
E.g. methyl cellulose, sodium carboxy methyl cellulose, acacia, gelatin and tragacanth.

- These structured vehicles entrapped the particle and reduces the sedimentation of particles.
- Thus, the use of deflocculated particles in a structure vehicle may form solid hard cake upon long storage.

➤ Too high viscosity is not desirable as:

a) It causes difficulty in pouring and administration.

b) It may affect drug absorption since they **adsorb on the surface of particle and suppress the dissolution rate.**

➤ Structured vehicle is not useful for **Parenteral suspension** because they may create problem in **syringeability** due to high viscosity.

Controlled flocculation

◦ Controlled flocculation of particles is obtained by adding flocculating agents, which are:

(1) electrolytes

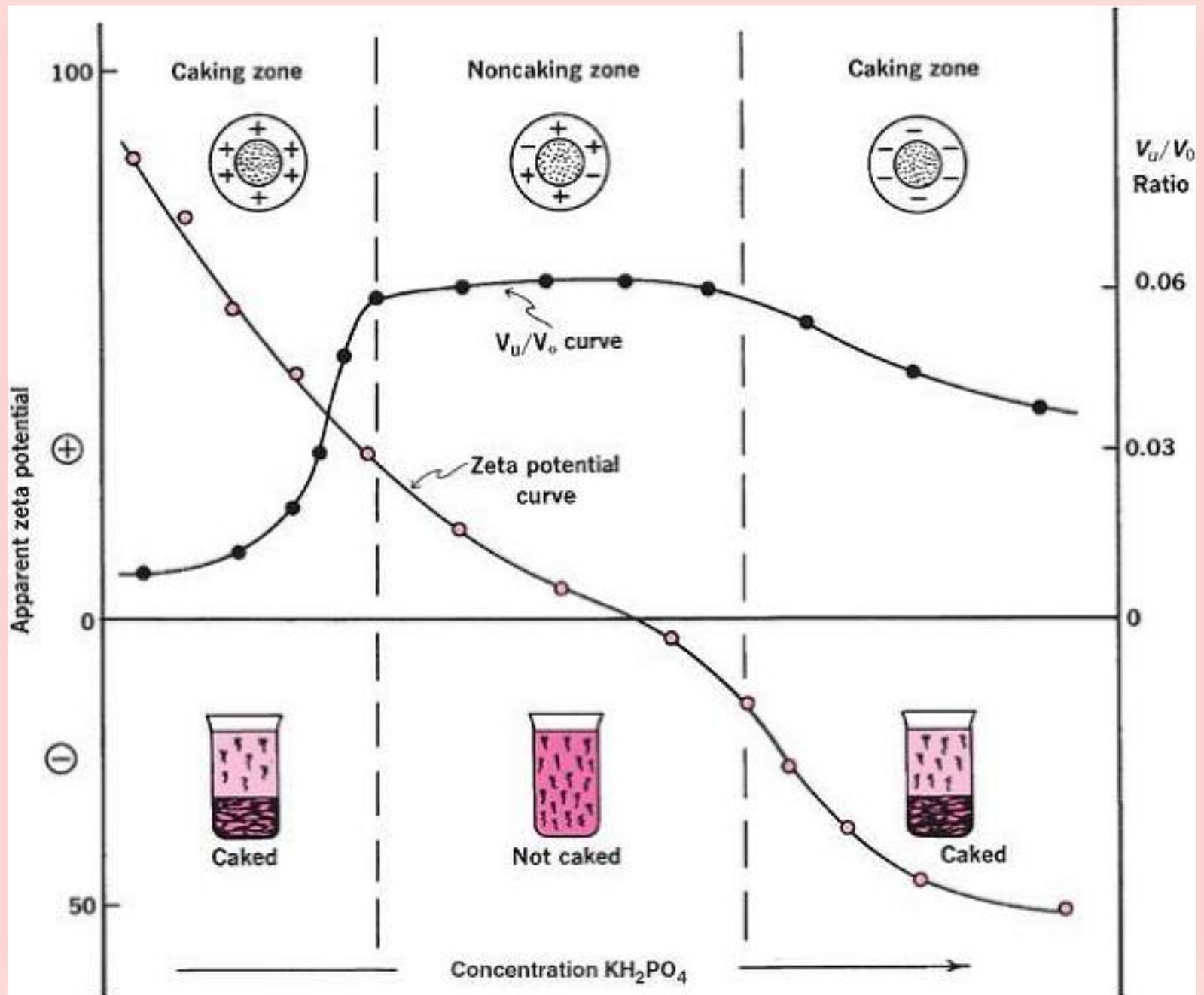
(2) surfactants

(3) polymers

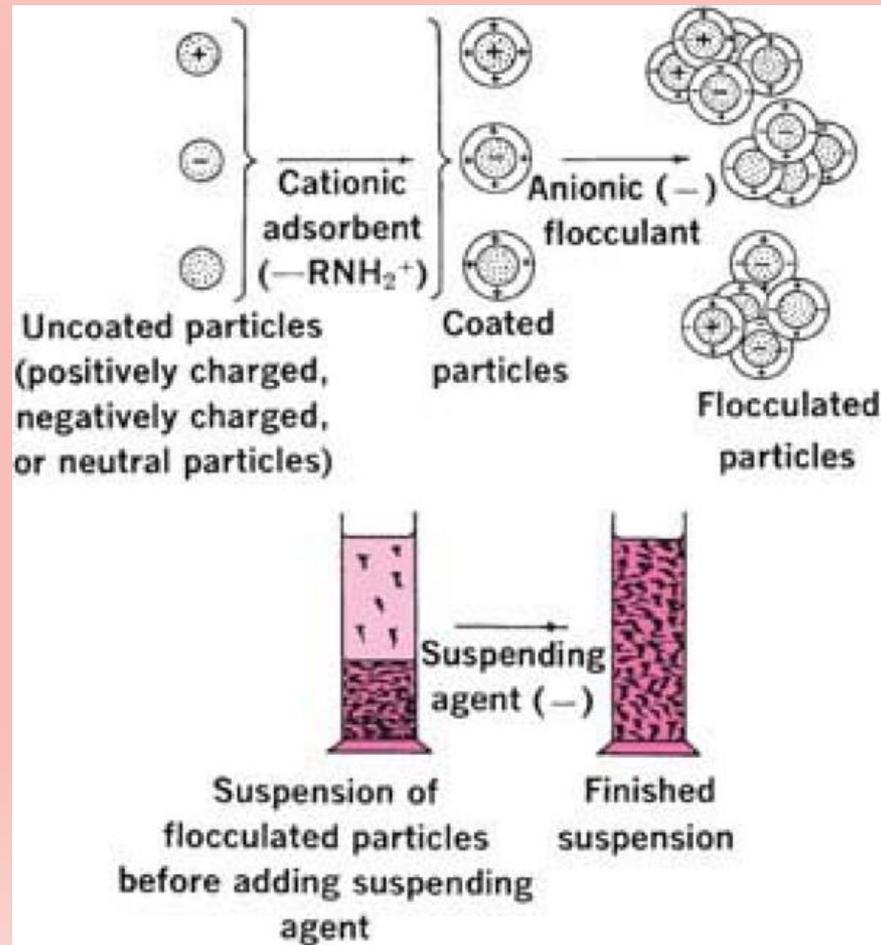
Controlled Flocculation

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

- If we disperse particles of bismuth subnitrate in water, we find that they possess a large positive charge, or zeta potential.
- Because of the strong forces of repulsion between adjacent particles, the system is deflocculated.
- The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease owing to the adsorption of the negatively charged phosphate anion.
- With the continued addition of the electrolyte, the zeta potential eventually falls to zero and then increases in the negative direction,
- 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 does the sedimentation volume start to fall.



The sequence of steps involved in the formation of a stable suspension



Flocculation in structured vehicles

- Sometimes suspending agents can be added to flocculated suspension to retard sedimentation
- Examples of these agents are:
 - Carboxymethylcellulose (CMC),
 - Carbopol 934,
 - Veegum, and bentonite

INGREDIENTS FOR
FORMULATION OF SUSPENSIONS

Wetting agents

They are added to disperse solids in continuous liquid phase.

Flocculating agents

They are added to floc the drug particles

Thickeners

They are added to increase the viscosity of suspension.

Buffers and pH adjusting agents

They are added to stabilize the suspension to a desired pH range.

Osmotic agents

They are added to adjust osmotic pressure comparable to biological fluid.

Coloring agents

They are added to impart desired color to suspension and improve elegance.

Preservatives

They are added to prevent microbial growth.

External liquid vehicle

They are added to construct structure of the final suspension.

Suspending agents

- Suspending agent are also known **as hydrophilic colloids** which form **colloidal dispersion with Water** and increase the viscosity of the continuous phase.
- Suspending agent form film around particle and decrease interparticle attraction.
- Most suspending agents perform two functions
i.e. besides **acting as a suspending agent**
they also **imparts viscosity to the solution.**

- Preferred suspending agents are those that give **thixotropy** to the media such as

**Xanthan gum,
Carageenan,
Na CMC/MC mixers,
Avicel RC 591
Avicel RC 581 and
Avicel CL 611.**



Stability pH range and concentrations of most commonly used suspending agents.

Suspending agents	Stability pH range	Concentrations used as suspending agent
Sodium alginate	4-10	1– 5 %
Methylcellulose	3-11	1– 2 %
Hydroxyethyl cellulose	2-12	1-2%
Hydroxypropyl cellulose	6-8	1-2%
Hydroxypropyl methylcellulose	3-11	1-2%
CMC	7-9	1-2%
Colloidal silicon dioxide	0-7.5	2- 4 %

List of Suspending Agents

Alginates

- Methylcellulose
- Hydroxyethylcellulose
- Carboxymethylcellulose
- Sodium Carboxymethylcellulose
- Microcrystalline cellulose
- Acacia
- Tragacanth
- Xanthan gum
- Bentonite
- Carbomer
- Carrageen
- Powdered cellulose
- Gelatin

Alginates

- Alginate salts have about same **suspending action to that of Tragacanth.**
- Alginate solution loses its viscosity when heated above 60°C. **due to polymerization.**

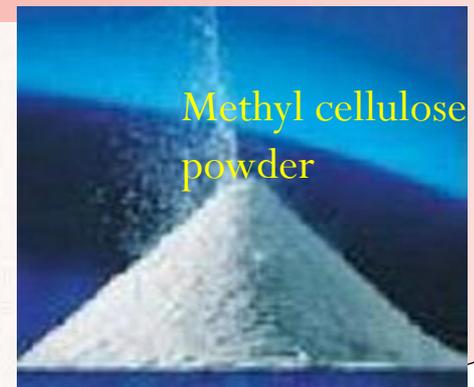
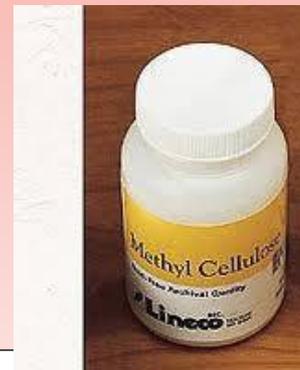


- Maximum viscosity is observed at a **pH range of 5-9** of alginate.
- Chemically alginates are polymers composed of **mannuronic acid** and **glucuronic acid monomers**.
- In practice, alginate is used at concentration **less than 10 % w/w, particularly at 5 % w/w**.

Methylcellulose

- Methylcellulose is available in **several viscosity grades**.
- The difference in viscosity is due to **difference in methylation and polymer chain length**.
- Methylcellulose is more soluble in cold water than hot water.
- Methylcellulose is stable at **pH range of 3-11**.

Methyl cellulose $\xrightarrow[\text{heating}]{\text{on}}$ Gel form $\xrightarrow[\text{cooling}]{\text{on}}$ Solution form



➤ Hydroxy ethylcellulose:

- Hydroxyethylcellulose (HEC) is another good suspending agent having somewhat similar characteristics to methylcellulose.
- In HEC **hydroxyethyl group is attached to cellulose chain.**
- Unlike methylcellulose, HEC is soluble in both hot and cold water and **do not form gel on heating.**



Carboxy methylcellulose (CMC)

- Carboxy methylcellulose is available at different viscosity grades.
- **Low, medium and high viscosity grades are commercially available.**
- In case of **HV-CMC**, the **viscosity** significantly decreases when temperature **rises to 40 °C from 25 °C**.
- Therefore, to improve viscosity and stability of suspension MV-CMC is widely accepted.

Microcrystalline Cellulose (MCC; Tradename-Avicel)

- It is **not soluble in water**, but it readily disperses in water to give thixotropic gels.
- It is used in combination with Na-CMC, MC or HPMC, because they facilitate dispersion of MCC.



The advantages of MCC:

- **Alginate complex compositions** are that they provide excellent **stability**.
- Formulation of dry powder suspensions with MCC;

Alginate complexes produce an excellent dry readily hydratable and dispersible formulation for reconstitution.

Wetting Agents

- Hydrophilic materials are easily wetted by water while hydrophobic materials are not.
- However hydrophobic materials are easily wetted by non-polar liquids.
- The extent of wetting by water is dependent on the hydrophilicity of the materials.
- If the material is more hydrophilic → less difficulty in wetting by water.
- The concentration used is less than 0.5 %.

Surfactants

- Surfactants decrease the interfacial tension between drug particles and liquid thus liquid is penetrated in the pores of drug particle displacing air from them and thus ensures wetting.
- Generally, we use **non-ionic surfactants** but ionic surfactants can also be used depending upon certain conditions.
- **Polysorbate 80** is most widely used due to its following advantages
 - It is non-ionic so no change in pH of medium
 - No toxicity. Safe for internal use.

Hydrophilic Colloids

- Hydrophilic colloids coat hydrophobic drug particles in one or more than one layer.
- This will provide hydrophilicity to drug particles **and facilitate wetting.**
- They cause deflocculation of suspension because force of attraction is declined. e.g. **acacia, tragacanth, alginates, guar gum.**



Solvents

- The most commonly used solvents used are alcohol, **glycerin, polyethylene glycol and polypropylene glycol.**



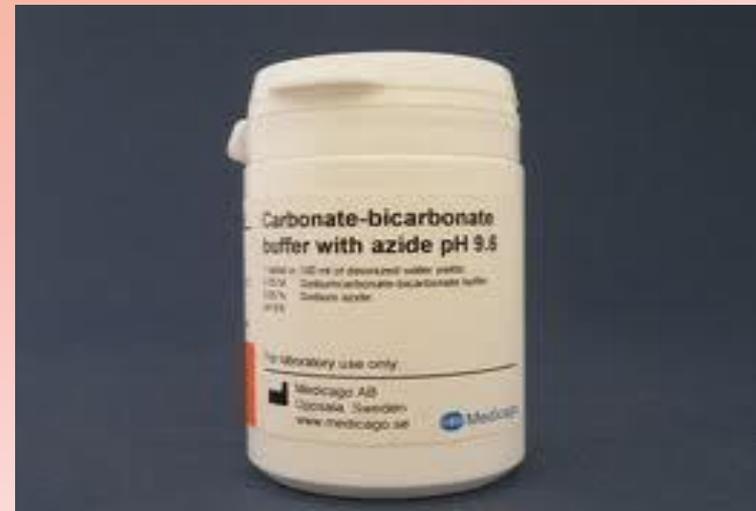
- The mechanism by which they provide wetting is that they are **miscible with water and reduce liquid air interfacial tension.**
- Liquid penetrates in individual particle and facilitates wetting.

Buffers

Buffers are the materials which when dissolved in a solvent will **resist any change in pH when an acid or base is added.**

- To encounter stability problems all liquid formulation should be formulated to an optimum pH.
- Rheology, viscosity and other property are also dependent on the pH of the system.

- . Generally pH of suspension preferably at **7.4-8.4**.
- Most commonly used buffers are salts of weak acids such as **carbonates, citrates, gluconates, phosphate and tartrates.**



Osmotic Agents

- They are added to produce **osmotic pressure comparable to biological fluids** when suspension is to be intended for ophthalmic or injectable preparation.
- Most commonly used osmotic agents are
 - dextrose,
 - mannitol
 - sorbitol.
 - sodium chloride,
 - sodium sulfate
 - glycerol.



Preservatives

- Naturally occurring suspending agents such as tragacanth, acacia, xanthan gum are susceptible to microbial contamination.
- This leads to:
 - loss in suspending activity of suspending agents,
 - loss of color, flavor and odor,
 - change in elegance etc.

Name of preservatives

Concentration range

Propylene glycol

5-10%

Disodium EDTA

0.1%

Benzalkonium chloride

0.01-0.02%

Benzoic acid

0.1%

Butyl paraben

0.006-0.05% oral
suspension

0.02-0.4% topical
formulation



Flavoring And Coloring Agents

- They are added to increase patient acceptance.
- Only **sweetening agent** are not capable of complete taste masking of unpleasant drugs therefore, a **flavoring agents are incorporated.**

Eg:

Acacia

Ginger

Sarsaparilla
syrup

Anise oil

Glucose

Spearmint oil

Benzaldehyde

Glycerin

Thyme oil



Coloring agents

- Colors are obtained from natural or synthetic sources.
- Plant colors are most widely used for oral suspension.
- The **synthetic dyes should be used within range of(0.0005 % to 0.001%)**
 - **Color aids in identification of the product.**
 - **The color used should be acceptable by the particular country.**

Most widely used colors are as follows.

- Titanium dioxide (white)
- Brilliant blue (blue)
- Indigo carmine (blue)
- Amaranth (red)
- Tartarazine (yellow)
- Annatto seeds (yellow to orange)



Sweetening Agents

They are used for taste masking of bitter drug particles.

Bulk sweeteners

- Sugars such as **xylose, ribose, glucose, mannose.**
- Sugar alcohols such as **sorbitol, xylitol, mannitol**

A bulk sweeteners is used at **concentration of 15-70 %**

Artificial sweetening agents

- Sodium cyclamate
- Sodium saccharin
- Aspartame



Humectants

➤ Humectants absorb moisture and prevent degradation of API by moisture.

➤ Examples of humectants most commonly used in suspensions are

➤ propylene glycol

➤ glycerol.



➤ Total quantity of humectants should be **between 0-10 % w/w.**

Antioxidant

- Ascorbic acid derivatives such as **ascorbic acid, erythorbic acid,**
- Thiol derivatives such as **thio glycerol, cytosine, acetylcysteine,**
- Tocopherols
- Butylated hydroxy anisole(BHA)
- Butylated hydroxytoluene (BHT)
- Sodium bi sulfite,
- Sodium sulfateacetone



PREPARATION OF SUSPENSIONS

Following consideration are important for manufacturing pharmacist

- **Selection of right material that go into the manufacture.**
- **The step involved and their sequence in the manufacture.**
- **Preservation and storage of the product.**

Small scale preparation of suspensions:

Step 1:

Suspensions are prepared by grinding (or) levigating the insoluble materials in the mortar to a smooth paste with a vehicle containing the wetting agent.



Step 2:

- All soluble ingredients are dissolved in same portion of the vehicle and added to the smooth paste to step1 to get slurry.



Step 3:

The slurry is transferred to a graduated cylinder, the mortar is rinsed with successive portions of the vehicle.



Step 4:

Decide whether the solids are

- Suspended in a structured vehicle
- Flocculated
- Flocculated and then suspended

Add the vehicle containing the suspending agent (or) flocculating agent

Step-5

Make up the dispersion to the final volume .

Thus suspension is prepared.

Packaging of Suspensions

Introduction

- Pharmaceutical suspensions for oral use are generally packed in **wide mouth container** having adequate space above the **liquid to ensure proper mixing.**
- Parenteral suspensions are packed in either glass ampoules or vials.

Ideal Requirements of Packaging Material

- **It should be inert.**
- **It should effectively preserve the product from light, air, and other contamination through shelf life.**
- **It should be cheap.**
- **It should effectively deliver the product without any difficulty.**

Materials Used For Packaging

Generally **glass** and various grades of **plastics** are used in packaging of suspension.

Glass

Generally **soda lime** and **borosilicate glass** are used in preparation of non sterile suspensions.



SUSPENSIONS



- Amber glass doesn't allow U.V light to pass through.
- Amber characteristics can be developed in the glass by addition of various types of additives.

Type of glass

Additive giving amber color

Soda lime

FeO + sulfur (in presence of reducing agent)

Borosilicate

FeO+TiO₂

Disadvantages of Glass Materials:

- They are **fragile**.
- They are **very heavy as compared to plastic so handling and transport is difficult**.
- Most important disadvantage of glass that **glass constituents get extracted into the product**.

Plastic

Due to the negative aspects of glass, plastic material significantly use of plastic as packaging material for sterile as well as non-sterile pharmaceutical suspension increased.



Advantages Of Plastic Material:

- Non breakability.
- Light weight.
- Flexibility.

Materials used: -

Polyethylene, PVC, polystyrene, polycarbonate etc

Closure And Liners

With an exception of ampoules all containers required elastomeric closure.



Factors affecting in selecting closure:

- **Compatibility with product.**
- **Seal integrity.**
- **It should be stable throughout the shelf life.**

Factors affecting in selecting liner:

- **Chemical resistance.**
- **Appearance**
- **Gas and vapor transmission.**
- **Removal torque.**
- **Heat resistance.**
- **Shelf life.**
- **Economical factors**

STORAGE REQUIREMENTS & LABELLING

Labelling:

- **Shake well before use**
- **Do not freeze**
- **Protect from direct light(for light sensitive drugs)**
- **In case of dry suspensions powder the specified amount of vehicle to be mixed may indicated clearly on label.**

Label:

LB-065504-04 Rev. 10/03

Usual Dosage:
See full prescribing information on bottom of tray.
See enclosed patient instructions for use of fitment and syringe.
Store at controlled room temperature 20°-25°C (68°-77°F).

Produced under license from
JFC Technologies
Bound Brook, NJ, U.S.A.
U.S. Patents 5,599,846; 5,663,415

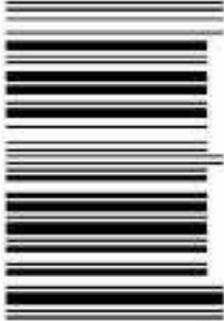
NDC 0037-0655-04
4 fl oz (118 mL)
RYNA-12 S[®]
SUSPENSION

Each 5 mL (one teaspoonful)
contains:
Phenylephrine Tannate 5 mg
Pyrilamine Tannate 30 mg
U.S. Patent 6,287,597

R_x Only

SHAKE WELL

medpointe
pharmaceuticals
Multi-Order Manufacturer Inc.
Scramset, New Jersey 08873



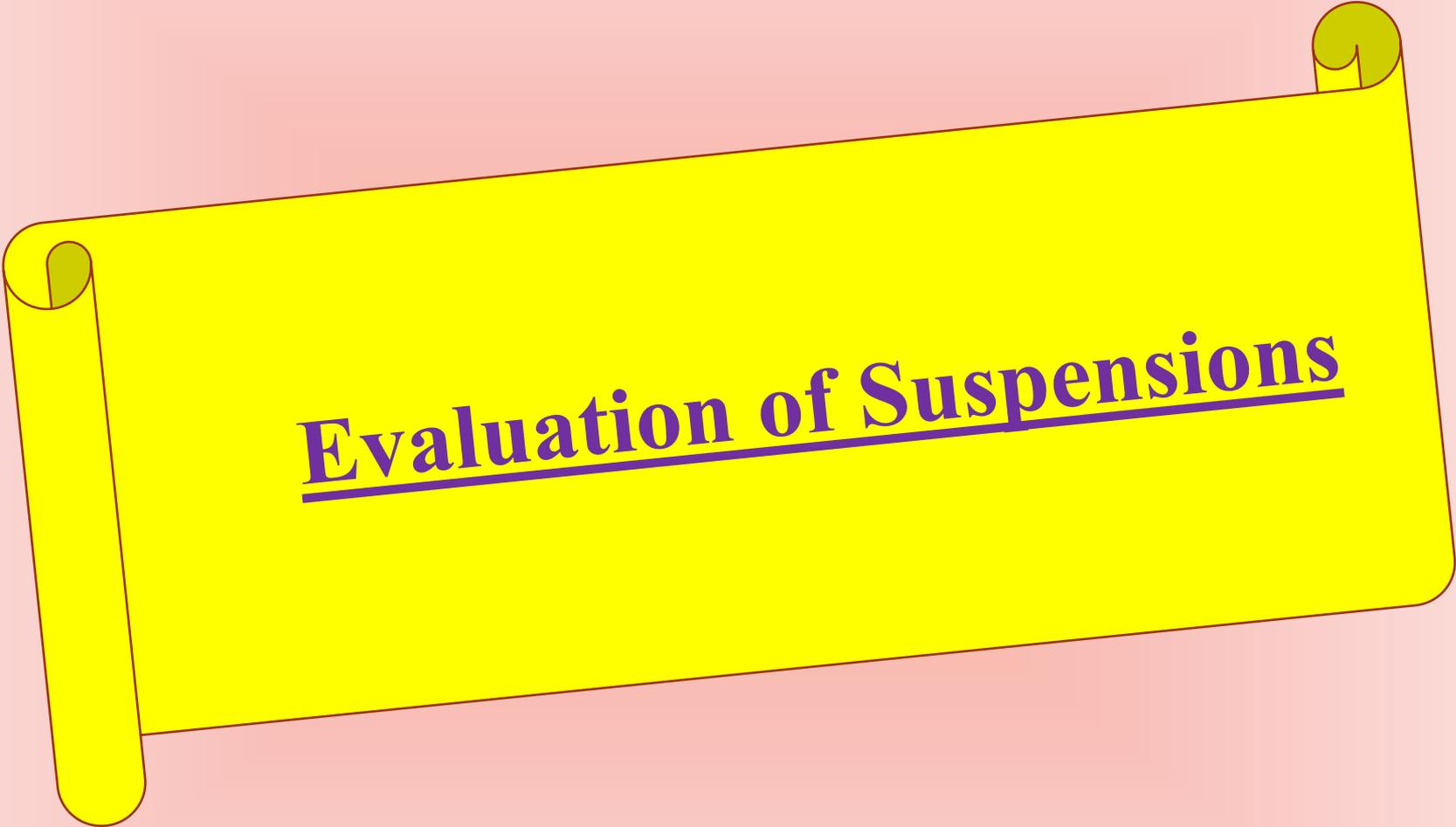
N 3 0037-0655-04 7



STORAGE :

- Suspensions should be stored in cool place **but should not be kept in a refrigerator**
- Freezing at very low temperatures should be avoided which may lead to aggregation Of suspended particles

Stored at controlled temperature from **20-25⁰c**



Evaluation of Suspensions

Evaluation of Suspensions

- Sedimentation method
- Rheological method
- Electro kinetic method
- Micromeritic method

Sedimentation method :

Two parameters are studied for determination of sedimentation.

1. Sedimentation volume,
2. Degree of flocculation.

,

Sedimentation volume

- The suspension formulation (50 mL) was poured separately into 100 mL measuring cylinders and sedimentation volume was read after 1, 2, 3 and 7 days, and thereafter at weekly intervals for 12 weeks.
- Triplicate results were obtained for each formulation.
- Sedimentation volume was calculated according to the equation:

$$F = V_u / V_o$$

- Where, F = sedimentation volume, V_u = ultimate height of sediment and V_o = initial height of total suspension

➤ Rheological method

- It provide information about **Settling behaviour** .
- The **arrangement of the vehicle** and **the particle structural features**.
- Brookfield viscometer is used to study the viscosity of the suspension .
- It is mounted on heli path stand and using T-bar spindle.
- 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.

- This technique also indicates at **which level of the suspension the structure is greater owing to particle agglomeration.**
- The dial reading is plotted against the number of turns of the spindle.
- The better suspension show a lesser rate of increase of dial reading with spindle turns, i.e. the curve is horizontal for long period.



Electro kinetic method

- Measurement of Zeta-potential using Micro electrophoresis apparatus & ZetaPlus (Brookhaven Instruments Corporation, USA)
- It shows the stability of a disperse system.



Zeta potential

- The zeta potential of the formulated suspensions was determined using a ZetaPlus (Brookhaven Instruments Corporation, USA).
 - Approximately 1 mL of suspension was transferred into a plastic cuvette using a pipette and diluted with distilled water.
- 
- The Brookhaven zeta potential software was used for the measurement .
 - Parameters set to a temperature of 25⁰C and refractive index (1.33)
 - The zeta potential of the formulations was determined on day 0, 7, 14, 21 and day 28 post formulation.

Micromeritic method :

- The stability of suspension depends on the **particle size of the dispersed phase.**
- Change in the particle size with reference to time will provide useful information regarding the stability of a suspension.
- A change in particle size distribution and crystal habit studied by
 - microscopy
 - coulter counter method

PHOTOMICROSCOPIC TECHNIQUE

- The microscope can be used estimate and detect changes in **particle size distribution** and **crystal form**.
- Rapid processing of photo micrographs is enhanced by attaching Polaroid camera to the piece of monomolecular microscope
- By using this photo micrographs we can determine the changes in **physical properties** and **stability of suspensions**.



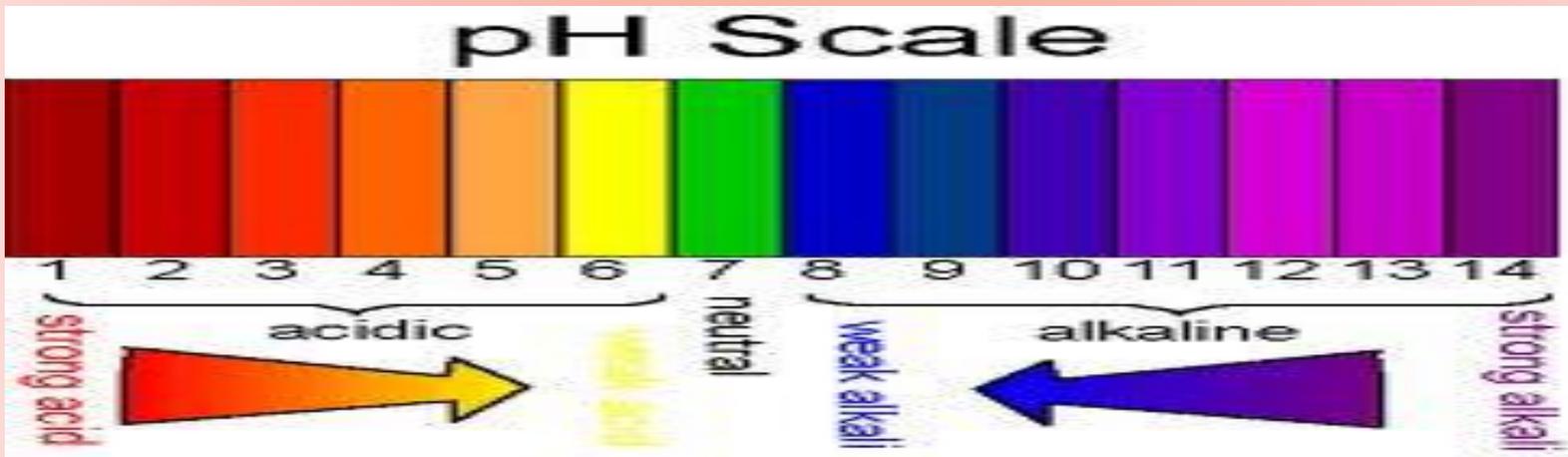
FREEZE- THAW TEST

- Freeze-Thaw test conducted by placing the sample in a freezer for **18 hours** followed by thawing at **room temperature for 4 to 6 hours**.
- Repeat the Freeze-Thaw cycle **for up to 10 times**.
- This test is conducted to determine the tendency to crystallize or cloud



pH MEASUREMENT

- The measurement and maintenance pH is also very important step in the Quality control testing .
- Generally there are 2 different types of methods used in the measurement of pH.



METHODS FOR pH MEASUREMENT:

- The simplest and cheapest is to dip a piece of pH paper into the sample.
- The paper is impregnated with chemicals that change color and the color may be compared to a chart supplied with the paper to give the pH of the sample.



- If greater accuracy is required a pH meter should be used.
- A typical pH meter consists of a special measuring glass electrode connected to an electronic meter that measures and displays the pH reading.



VISUAL INSPECTION:

- With visual inspection, the ingredients and the final products are carefully examined **for purity and for appearance** .
- Physical appearance of products for patient adherence and compliance is critical so it should be:
 - Good looking
 - Elegance in appearance .

DISSOLUTION STUDY OF SUSPENSIONS

Introduction:

The drug release from suspensions is mainly through dissolution.

- Suspensions share many physico-chemical characteristics of tablet & capsules with respect to the process of dissolution.
- As tablets & capsules disintegrate into powder and form suspensions in the biological fluids.
- So dissolution is carried as follows

Dissolution Testing

Official Method (Conventional Method):

- It is known as paddle method.



- The apparatus consists of a cylindrical **1000- ml round bottom** flask in a multiple – spindle dissolution drive apparatus and immersed in a controlled **temp bath maintained**

- Dissolution profile of the 500 mg sample suspension is
 - **determined at 37°C in 900 ml of**
 - **pH 7.2 phosphate buffer using**
 - **the FDA paddle method at 25 RPM.**

- The paddle should position to extend to **exactly 2.5 cm** above the flask bottom.
- The suspension is to be introduced carefully into the flask at the bottom using a **10- ml glass syringe** with an attachment **19-cm needle**.
- Withdraw **5 ml of dissolution medium** (and replace with an equal volume of drug –free buffer) in a 5 ml glass syringe.
- Immediately filter through **a 0.2 μm membrane** and analyze.

INNOVATIONS OF SUSPENSIONS

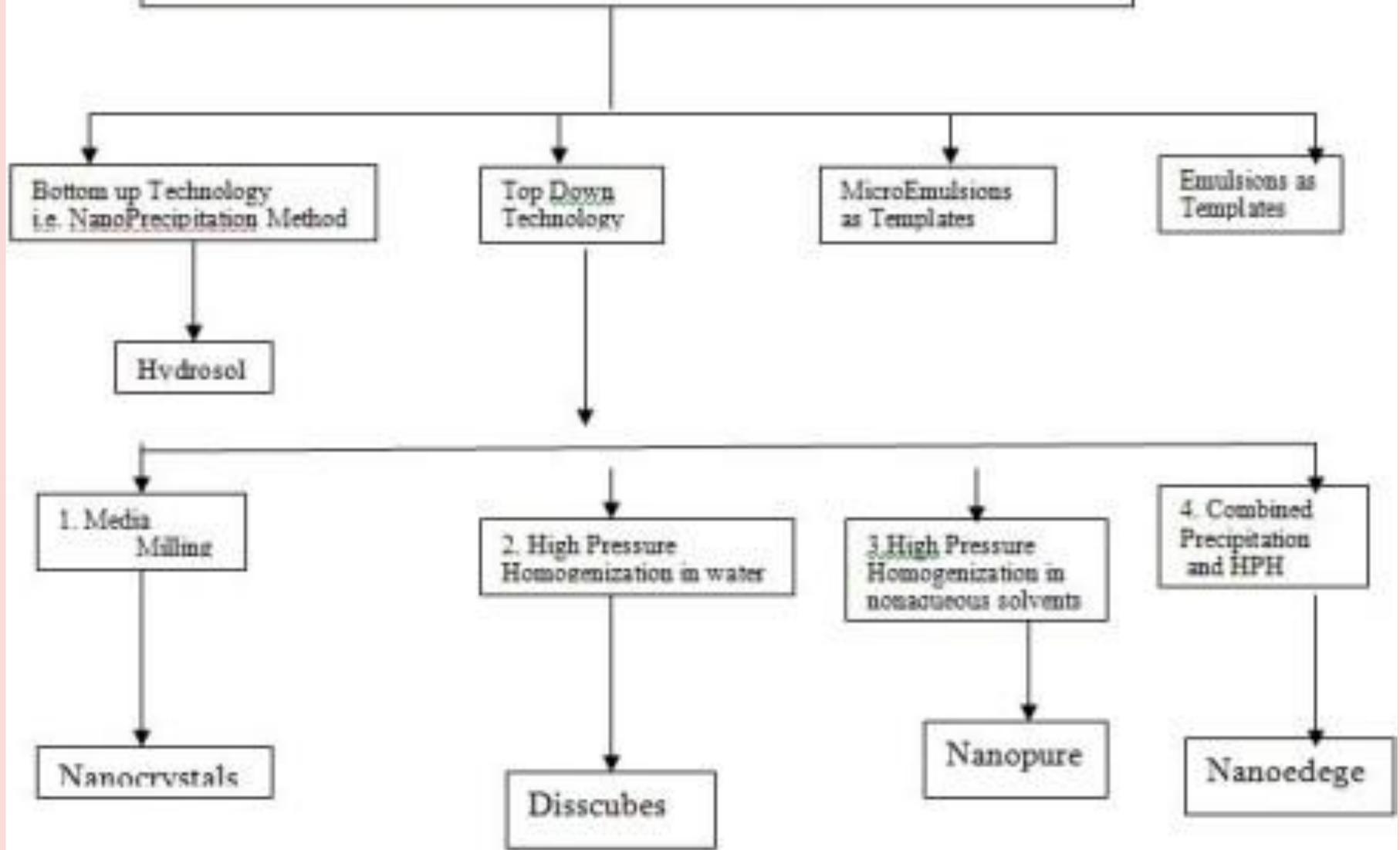
INNOVATIONS OF SUSPENSIONS

1. Nano suspensions
2. Taste masked pharmaceutical suspensions
3. Sustained release suspensions

1. Nano suspensions:

- Nano suspensions are the **biphasic colloidal dispersions of nano sized drug particles stabilised by surfactants without the matrix materials.**
- They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is **less than 1 μm in size.**

Methods of Preparation of Nanosuspensions



2. Taste Masked Pharmaceutical Suspensions

- Un-palatability due to bad taste is a major concern in most of the dosage forms containing bitter drugs.
- In case of suspensions also taste masking is being applied to mask bitterness of drugs formulated.

The taste masking approaches for suspensions are:

- a. **Polymer coating of drugs.**
- b. **Encapsulation with basic drugs.**
- c. **Polymer coating with basic substances.**
- d. **Coating and pH control.**

a. Polymer Coating of Drugs

The polymer coat allows the **time for all of the particles to be swallowed before the threshold concentration** is reached in the mouth and the taste is perceived.

The polymers used for coating are

- Ethyl cellulose
- Eudragit RS 100
- Eudragit RL 100
- Eudragit RS 30 D
- Eudragit RL 30 D

b. Encapsulation with a Basic Substance

- Here a basic substance is mixed with a bitter tasting drug which is insoluble at high pH.
- The mixer is then encapsulated with a polymer (cellulose derivative, vinyl derivative or an acid soluble polymer
Eg: **copolymer of dimethyl ammonium methyl methacrylate**).
- The drug after encapsulation are suspended, **dispersed or emulsified in suspending medium to give the final dosage form.**

c. Coating and pH Control

- Those drugs which are soluble at high pH are preferably be maintained in a suspension at a low pH where the drug exhibit maximum insolubility.
- Similarly drugs which are soluble at low pH are preferably maintained in suspension at a high pH where the drug is insoluble.
- Also applying polymeric coating to the drug substance avoids solubilization of drug when administered providing taste masking.

Some Examples of Taste Masked Suspensions

<u>Sr.No</u>	<u>Name of the drug</u>	<u>Taste masking approach</u>
1	RISPERIDONE	pH control and polymer coating (with Eudragit RS)
2	DICLOFENAC	Polymer coating with Eudragit RS 100
3	LEVOFLOXACIN	Polymer coating (Eudragit & cellulose acetate,)

Sustained Release Suspensions

- Sustained release is a method to **increase only the duration of action of drug being formulated without affecting onset of action.**
- In suspension sustained release affected by coating the drug to be formulated as suspension by **insoluble polymer coating.**
- The polymer coating **provides sustained release** and also masks the **taste of the bitter drug.**

- The polymer used for sustained release in suspension is as follows as
 - Ethyl cellulose,
 - Eudragit,
 - Cellulose acetate, etc.

- The main advantage of sustained release suspension is **decrease in dosing frequency.**

Approaches used in formulation of sustained release oral suspensions

1. Ion exchange resin.
2. Microencapsulation technique
3. Saturated drug suspension as a suspending medium.
4. Using non aqueous vehicle.
5. Reconstitution.
6. Protective coating.

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