MODULE 2: Suspensions

Lecture 8

DISCLAIMER

All the content material provided here is only for teaching purpose

SUSPENSION

DEFINITION

- A pharmaceutical suspension is a coarse dispersion of insoluble solid particles in a liquid medium.

- The particle diameter in a suspension is usually ranges from 0.5-5 µm.

- The **advantages** of suspension dosage forms include effective dispensing of hydrophobic drugs; masking of unpleasant taste of certain ingredients; offering resistance to degradation of drugs due to hydrolysis, oxidation or microbial activity; easy swallowing for young or elderly patients; and efficient intramuscular depot therapy.

- In addition, when compared to solution dosage forms, relatively higher concentration of drugs can be incorporated into suspension products.

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 or dispersed medium).

- Each phase can exist in solid, liquid, or gaseous state .

- Suspensions are heterogenous system consisting of 2 phases.

DISPERSE SYSTEM

DISPERSED MEDIUM

- Aqueous oily liquid

DISPERSED PHASE

- Insoluble solid

Types of insoluble solids

- There are two types of insoluble solids which constitute the internal or dispersed phase.These are

- 1. Diffusible solids – these sediment sufficiently slowly to enable satisfactory doseremovalafterredispersion.eg. Light kaoline, magnesium tricilcate.

- Indiffusible solids- eg. sulphadimidine and chalk.These sediment too rapidly and require the addition of other materials to reduce sedimentation rate to an acceptable level

Disadvantages

- Physical stability, sedimentation and compaction can causes problems.

- It is bulky sufficient care must be taken during handling and transport.

- It is difficult to formulate.

- Uniform and accurate dose cannot be achieved unless suspension are packed in unit dosage form

Desired features of suspension

- 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.

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 to10%w/v solid)

Eg: cortisone acetate, predinisolone 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.

Coarse dispersion Barium sulphate

Nano suspensions (10 ng)

➢Suspensions are the biphasic colloidal dispersions of nanosized drug particles stabilized by surfactants.

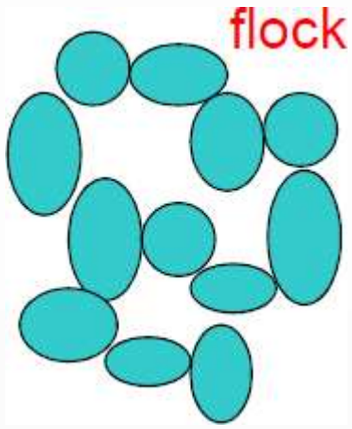
➢Size of the drug particles is less than 1mm.

Flocculated Suspensions

- In flocculated suspension, formed flocs (loose aggregates) will cause increase in sedimentation rate due to increase in size of sedimenting particles.

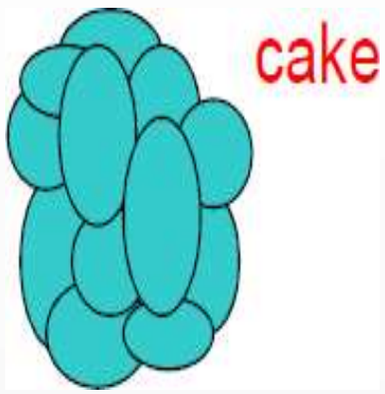
- Hence, flocculated suspensions sediment more rapidly.

- Here, the sedimentation depends not only on the size of the flocs but also on the porosity of flocs.



De-Flocculated Suspensions

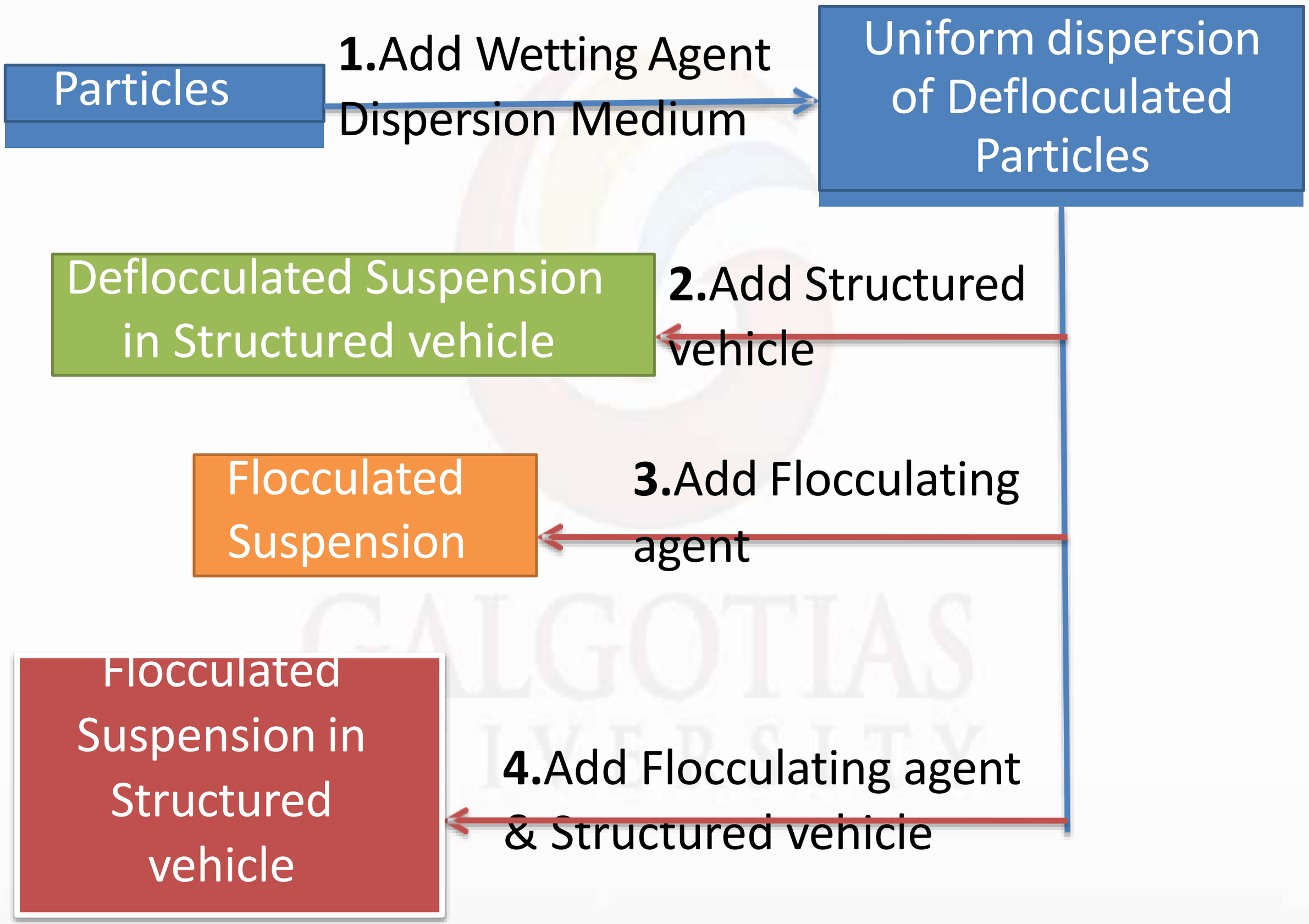
- In deflocculated suspension, individual particles are settling.
- Rate of sedimentation is slow , which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation.
- This phenomenon called ‘caking’ or ‘claying’.
- In deflocculated suspension larger particles settle fast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



Formulation of suspension

- Theformulation of a suspension depends on whether the suspension is flocculated or deflocculated.
- Different approaches are commonly involved
  - Use of structured vehicle
  - Use of controlled flocculation

FORMULATION OF SUSPENSION:



Step-1: Dispersion of solids:

Water (solvent) + Insoluble solids (Hydrophobic) → Difficult to disperse.

Small particles adsorb air and **float** on solvent surface.

Dispersion can be done by

1. Water miscible Co-solvents = Alcohol, Glycerin, PEG

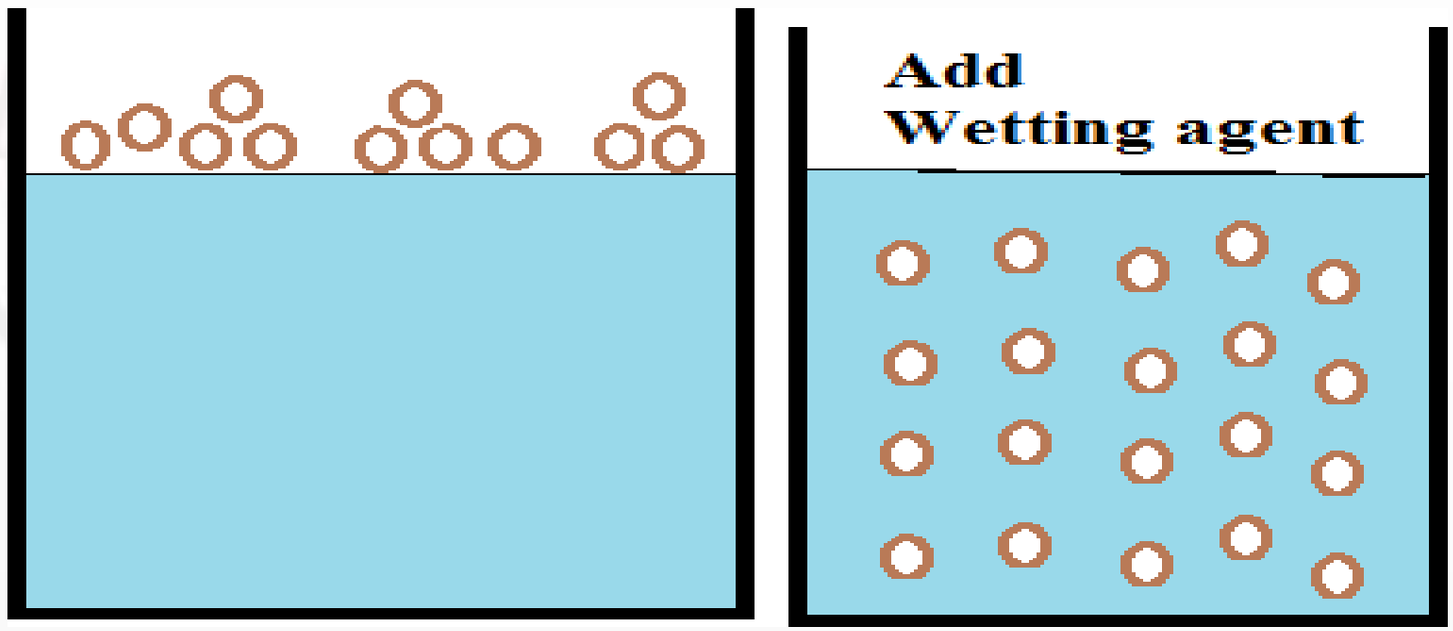
Floating particles + Glycerin → removes air on surface,

forms a coat → ↑Dispersion.

2. Wetting agents:

Surfactants→ ↓IFT, ↓Contact angle(90-0^0) →↑Dispersion.

(HLB= 7-9)



Step-2: Deflocculated Suspension in Structured vehicle:

- **Structured vehicles** are the vehicles which exhibit pseudo plastic/ plastic rheological behavior.
- These also posses thixotropic behavior i.e., gel-sol-gel transformation to improve physical stability of suspension.
- Structured vehicles are hydrocolloids, in low Conc. absorb water, swell to give high viscosity.
- They act as protective colloid to stabilize charge.

Ex: Non-ionic = MC, HPMC

Anionic = Sodium CMC, Carbopol.

Clays = Bentonite

Concentration of suspending agent depends on:

1. Viscosity of vehicle:

Vehicle (low η) + High Conc. suspending agent

Vehicle (high η) + low Conc. suspending agent

2. Amount of solid:

Oral= high solid content + high Conc. S.A (non-ionic)

Parenteral= low solid content + low Conc. S.A (0.5% W/V) If clays are used add preservatives (2-5% W/V)

3. Particle Size:

Small size + low Conc. suspending agent

Large size + High Conc. suspending agent

4. Density of solids:

Structured vehicles + PVP/PEG/Sugars → ↑ viscosity.

5. pH, Ionic strength.

Step-3: Flocculated Suspension (Contorlled flocculation):

Flocculating agent= electrolytes, surfactants, polymers.

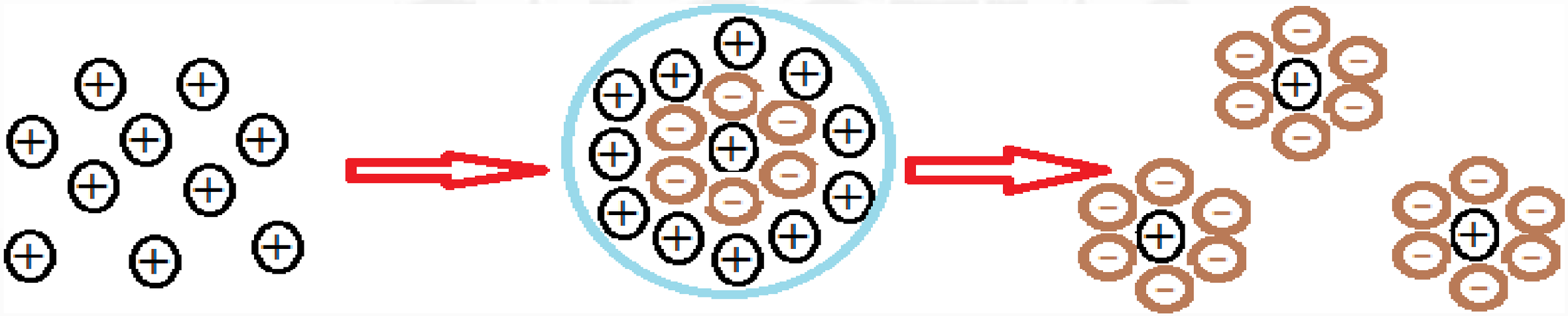
1. **Electrolytes:**

All suspended particles same charge → Repulsive forces

Add electrolytes of opposite charge→Attractive forces→Flocs

Bismuth sub nitrate(+) + water + WA→ Deflocculated suspension + Monobasic potassium phosphate(-) electrolyte → **Flocculated Suspension**.

Flocculated Suspension + extra electrolyte→ all particles (-) charged → repulsions→ Deflocculated suspension

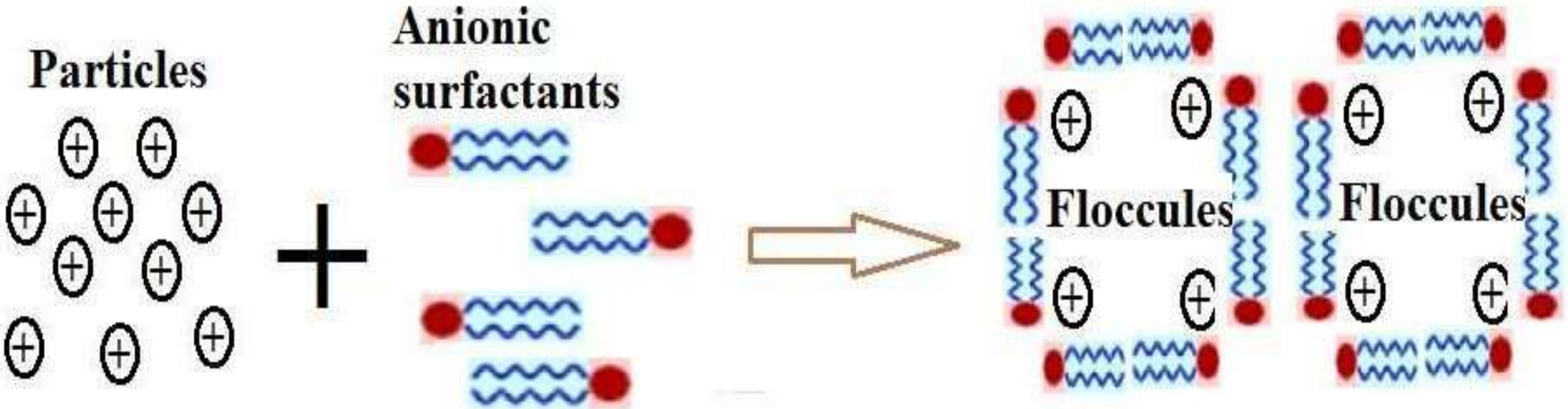


Controlled flocculation:

- ➢ Most dispersed particles posses charge depending on pH of the system.
- ➢ The charge should be adjusted to zero and adjust pH to make flocculated suspension in non-caking zone with optimum zeta potential .

2. Surfactants:

- ❖ Reduces surface tension act as wetting agent, deflocculating agent & flocculating agent (Controlled Conc.)
- ❖ Particles + oppositely charges surfactant → Tails form bridges between particles → Floccules



Anionic surfactants – SLS

Cationic surfactants – cetyl trimethyl ammonium bromide

Nonionic surfactants – tweens

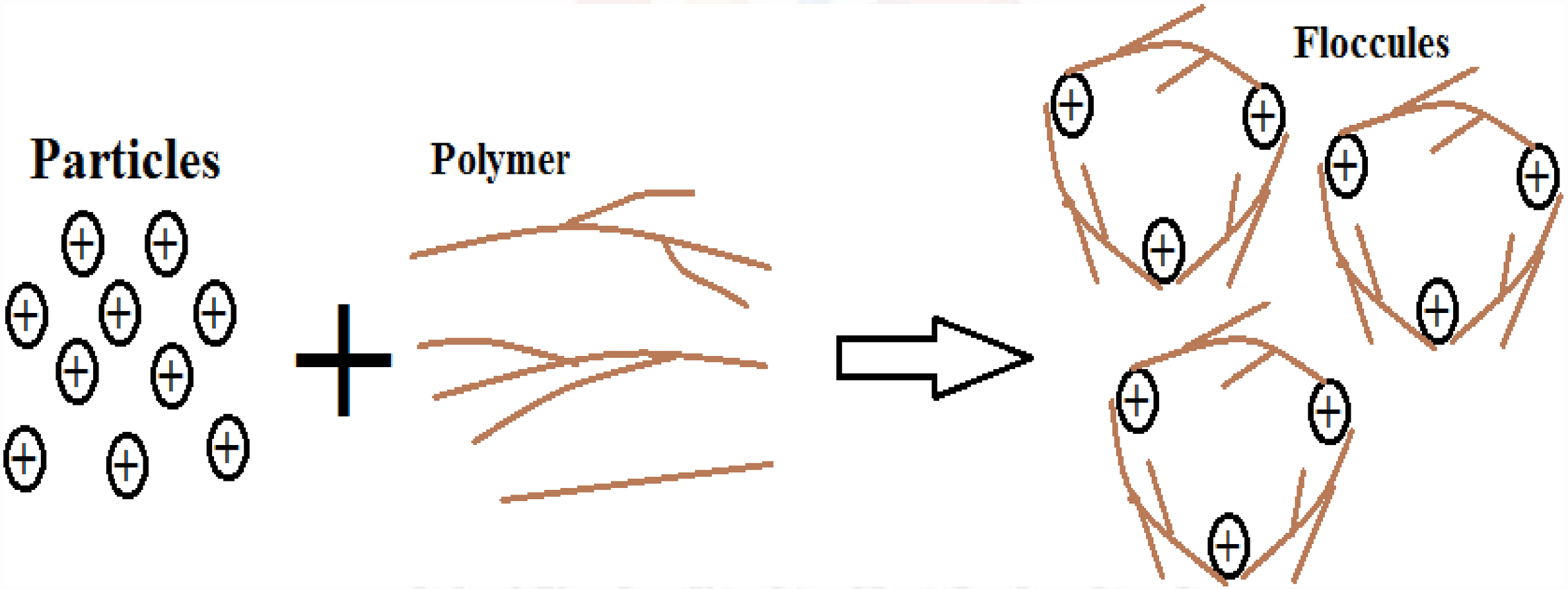
3. Polymers:

Polymers are long hydrocarbon chained molecules.

Half chain – adsorbed on particle

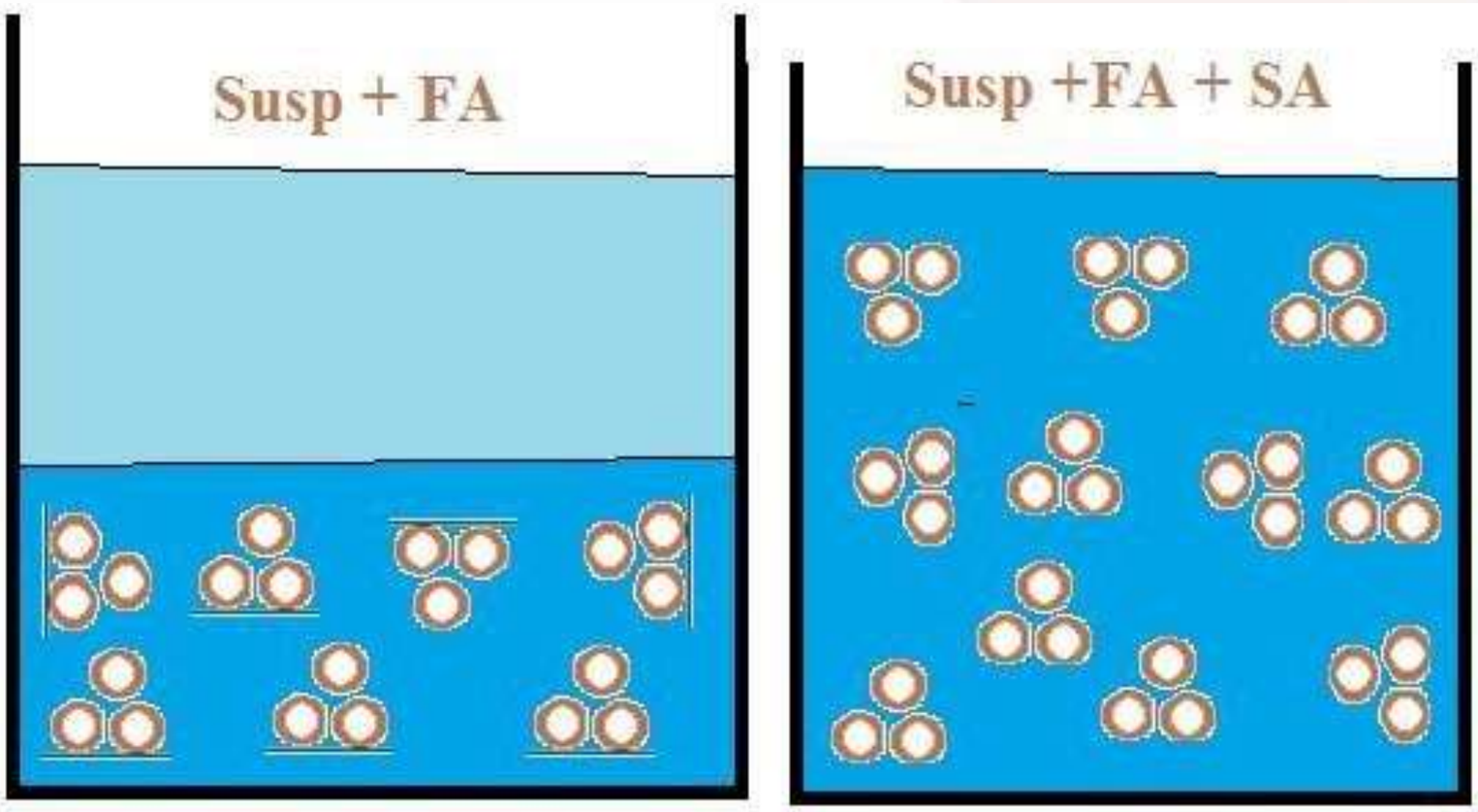
Other half chain – outside form brides with chains➔ Flocs.

Ex: Sulfaguanidine + Xanthan gum ➔Floccules



Step-4: Flocculated Suspension in Structured vehicle:

- Flocculated suspension have clear supernatant, undesirable property.
- Add structured vehicle/ suspending agent → Good Suspension.
- Flocculating agent – uniform sized floccules.
- Structured vehicle/ suspending agent – prevent settling of floccules



Incompatibility:

Charges of

1. Particle
2. Flocculating Agent
3. Suspending Agent

Adjuvants for suspension

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.**

List of SuspendingAgents

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

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 hydrophillicity 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

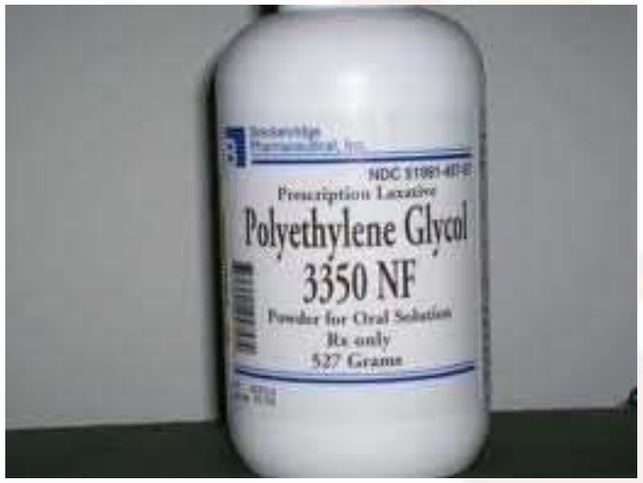
- Hydrophilic colloids coat hydrophobic drug particles in one or more than one layer.

- This will provide hydrophillicity 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.**

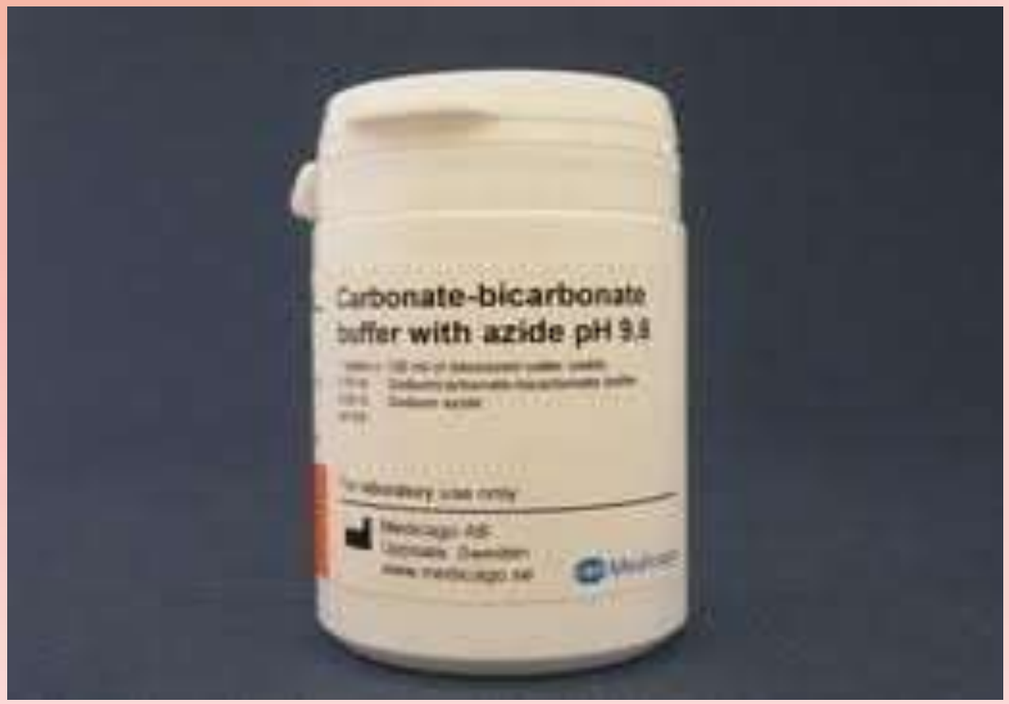
➢To encounter stability problems all liquid formulation should be formulated to an optimum pH.

➢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.



OsmoticAgents

➢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.

Mannitol

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

Disodium EDTA

benzalkanonium

Flavoring And ColoringAgents

➢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)**

SweeteningAgents

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 transformed to a graduated cylinder, the mortar is rinsed with successive portion 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.

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.**

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 **20-25^{0}c**

References

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