SUSPENSIONS

7th week

Preparation of Suspensions

The preparation of suspension includes three methods:
(1) use of controlled flocculation
(2) use of structured vehicle
(3) combination of both of the two previous methods

The following is the general guidelines to suspension formulation.

1) Structured Vehicles

Structured vehicles are generally aqueous solutions of polymeric materials, such as the hydrocolloids, that are usually negatively charged in aqueous solution.

Typical examples;
Methylcellulose, Carboxymethylcellulose, Bentonite, Carbomer.

The concentration employed will depend on the consistency desired for the suspension that, in turn, will relate to the size and density of the suspended particles. They function as viscosity-imparting suspending agents and, as such, reduce the rate of sedimentation of dispersed particles.

Suspending agents that have been used in the formulation of pharmaceutical suspensions

Type of Polymer	Examples	Commercial Names
Cellulose derivates		
Anionic	Carboxymethylcellulose (CMC) Microcrystalline cellulose blends	Avicel
Nonionic	Methylcellulose (MC) Ethylcellulose (EC) Hydroxyethylcellulose (HEC) Hydroxypropylcellulose (HPC) Hydroxypropylmethylcellulose (HPMC)	Methocel Ethocel Natrasol Klucel Methocel
Natural polymers		
Anionic	Alginates, Carageenan, Xanthan gum, Acacia, Tragacanth, Locust Bean Gum, Guar gum	
Synthetic polymers		
Anionic	Carbomers	Carbopol
Nonionic	Polyvinyl pyrrolidone (PVP) Polyvinyl alcohol (PVA) Poloxamer	Povidone, Kollidon
Clays	Magnesium aluminum silicate (Veegum) Bentonite Hectorite	

2) Controlled Flocculation

Controlled flocculation of particles is obtained by adding flocculating agents, which are (a)electrolytes (b)surfactants (c)polymers.

The aim is to control flocculation by adding that amount of flocculating agent that results in the maximum sedimentation volume.

a) Flocculation using Electrolytes

Electrolytes are probably the most widely used flocculating agents. They act by reducing the electrical forces of repulsion between particles, thereby allowing the particles to form the loose flocs so characteristic of a flocculated suspension.

As the ability of particles to come together and form a floc depends on their surface charge, zeta potential measurements on the suspension, as an electrolyte is added, provide valuable information as to the extent of flocculation in the system.

b) Flocculation by Polymers

Polymers can play an important role as flocculating agents in pharmaceutical suspensions. As such, polymers can have an advantage over ionic flocculating agents in that they are less sensitive to added electrolytes. This leads to a greater flexibility in the use of additives such as preservatives, flavoring and coloring agents that might be needed for the formulation.

- The effectiveness of a polymer as a stabilizing agent for suspension primarily depends on the affinity of the polymer for the particle surface as well as the charge, size and orientation of the polymer molecule in the continuous phase.
- It is believed that the primary mechanism by which polymers act as flocculants is due to the bridging of the polymer between the surfaces of two different particles.

c) Flocculation Using Detergents (Surfactants)

- Both ionic and nonionic detergents can be used to produce flocculation in suspensions.
- Ionic detergents can produce flocculation in a manner that is similar to other electrolytes; they can reduce the zeta potential of the dispersed particles.
- Relatively high concentrations of nonionic detergents can form a hydrated layer around particles that can lead to deflocculation via a mechanism that is similar to steric stabilization described for polymers.

3) Flocculation in Structured Vehicles

- The ideal formulation for a suspension would seem to be when flocculated particles are supported in a structured vehicle.
- The process involves dispersion of the particles and their subsequent flocculation. Finally, a lyophilic polymer is added to form the structured vehicle.
- In developing the formulation, care must be taken to ensure the absence of any incompatibility between the flocculating agent and polymer used for the structured vehicle.

Commonly Used Ingredients in Pharmaceutical Suspensions

1. Active Pharmaceutical Ingredient

Ideally, the active pharmaceutical ingredient (API) should be insoluble in the continuous phase.

However, many APIs are sufficiently soluble in the continuous phase for solubility to be a problem. The problem is a consequence of storage temperature variations which can lead to super-saturation and crystal growth (Ostwald ripening).

This phenomenon can be counteracted by the use of crystallization inhibitors such as povidone and other polymers. The specific inhibitor for a particular application will depend on the API and the other components of the formulation.

The appearance of the final product is always a factor. Patients require pharmaceutically elegant products. With medium to high dose drugs, the API is often present in sufficient quantity to form an acceptable, elegant suspension. However, for low dose APIs, the concentration of the API in the suspension is low and may be insufficient to produce a pharmaceutically elegant suspension.

In such cases the number of particles in suspension may be increased by adding a suitable excipient in a finely divided form to provide sufficient disperse phase to achieve an acceptable, elegant suspension. Examples of such excipients include finely divided microcrystalline cellulose, added either co-processed with carmellose sodium (so-called "colloidal" grade microcrystalline cellulose) or as a fine milled grade, or very fine crospovidone.

2. Inorganic Clays

The inorganic clays are typically complex hydrated silicates and include smectites (formerly known as montmorillonites), kaolinites (e.g. kaolin) and palygorskite (attapulgite). These are naturally occurring minerals and are mined and purified for use in pharmaceuticals.

The clays hydrate in water and form gels or sols depending on the concentration. After hydration is complete and the small platelets have separated, they form chains and networks of platelets linked through the difference in charge, between the positive edges of the platelets and their negative faces. This linked platelet structure traps the continuous and disperse phases, and slows sedimentation of the disperse phase through hindered settling. These clays do not form gels in the absence of water.

The hydration time can be reduced by using mechanical energy, e.g. high shear and heat.

As a general rule for the best chance of timely hydration, the clay is added slowly to the water rather than adding water to the clay.

3. Water-Soluble Hydrocolloids

There are many water soluble hydrocolloids that can act as suspending agents in the formulation of pharmaceutical suspensions. They can be of natural, semi-synthetic or synthetic origin.

In suspensions, water-soluble hydrophilic colloids work by increasing the viscosity of the aqueous continuous phase, and thereby hindering the sedimentation of the disperse phase.

Water-soluble hydrophilic colloids for use as suspending agents

Acacia	Hydroxyethyl cellulose	Polyethylene glycol
Agar	Hydroxypropyl cellulose	Poly (vinyl alcohol)
Alginic acid	Hydroxypropyl starch	Potassium alginate
Carbomer	Hypromellose	Povidone
Carmellose sodium	Maltodextrin	Pregelatinized starch
Carrageenan	Methylcellulose	Propylene glycol alginate
Dextrin	Modified starch	Sodium alginate
Gelatin	Pectin	Tragacanth
Gellan gum	Poloxamer	Xanthan gum
Guar gum	Polycarbophil	

4. Bulking Agents (Auxiliary Suspending Agents)

In some instances, there are insufficient drug particles in a unit dose of suspension to make a pharmaceutically elegant suspension. This is particularly true for the more highly active drugs, where the unit dose is small.

Under such circumstances, the formulator will need to add more particles to improve the appearance of the final product and also to help stabilize the suspension. The different excipients that may be used include inorganic solids, insoluble cellulose derivatives and insoluble synthetic polymers.

Bulking agents/auxiliary suspending agents

Calcium carbonate	Magnesium carbonate
Calcium hydroxide	Magnesium hydroxide
Cellulose	Microcrystalline cellulose
Crospovidone	Silica (silicon dioxide)
Dibasic calcium phosphate	Titanium dioxide

5. Surfactants / Wetting Agents

Surfactant is a general name for materials that possess surface activity; in solution they tend to orient at the surface of the liquid.

There are several general classes of surfactants: anionic, cationic, amphoteric and non-ionic.

Surfactants are amphiphilic molecules, i.e. part of the molecule is hydrophilic, and part is lipophilic.

This combination of the two opposite affinities in the same molecule causes them to orient to the interface and thereby reduce the interfacial tension between the continuous and disperse phases, such as in emulsions and suspensions.

Ionic surfactants work primarily through electrostatic forces, whereas non-ionic surfactants work primarily through steric forces.

Types of non-ionic surfactants used in pharmaceutical suspensions

Generic name	Synonyms/*sample trade names*
Polyoxyethylene sorbitan fatty acid esters	Polysorbate, *Tween®*
Polyoxyethylene 15 hydroxystearate	Macrogol 15 hydroxystearate, *Solutol HS15®*
Polyoxyethylene castor oil derivatives	*Cremophor® EL, ELP, RH 40*
Polyoxyethylene stearates	*Myrj®*
Sorbitan fatty acid esters	*Span®*
Polyoxyethylene alkyl ethers	*Brij®*
Polyoxyethylene nonylphenol ether	*Nonoxynol®*

6. pH Modifiers and Buffers

There is often an optimum pH range for both the physical and chemical stability of aqueous pharmaceutical suspensions. This may require modification of the pH during formulation and manufacture, because of the components that render the preparation too acidic or too basic.

Simply adding an acid or a base may give the required pH, but this may not hold during storage since ions may be adsorbed onto the suspended particles with a consequent drift in pH.

Buffer systems are better able to tolerate slight changes in ionic strength and yet maintain the pH within the required range. Typically, the better buffer systems use salts of weaker polyvalent acids, e.g. sodium salts of citric acid, or combinations of sodium salts of citric acid with sodium salts of phosphoric acid.

Buffering agents, pH modifiers and salts used in suspensions

Acetic acid	Proprionic acid	Sodium citrate
Adipic acid	Potassium acetate	Sodium glycolate
Ammonium carbonate	Potassium bicarbonate	Sodium hydroxide
Ammonium hydroxide	Potassium chloride	Sodium lactate
Ammonium phosphate	Potassium citrate	Sodium phosphate
Boric acid[a]	Potassium metaphosphate	Sodium proprionate
Citric acid	Potassium phosphate	Succinic acid
Diethanolamine	Sodium acetate	Sulfuric acid
Fumaric acid	Sodium bicarbonate	Tartaric acid
Hydrochloric acid	Sodium borate[a]	Trolamine
Malic acid	Sodium carbonate	
Nitric acid	Sodium chloride	

7. Preservatives, Antioxidants and Chelating Agents

Antimicrobial Preservatives

Pharmaceutical suspensions with water as the continuous phase are susceptible to microbial spoilage.

The source of the microbial growth may be raw materials, e.g. materials of natural origin such a clays (mined) and alginates (extracted from marine algae), process related (airborne contamination or from operators) or during use by the patient.

In addition, the risk of microbial contamination and subsequent product spoilage is much increased during use by the patient.

For these reasons, pharmaceutical suspension formulations contain preservatives. The preservative system has to be effective against both bacteria and yeasts and molds.

Typically, combinations of preservatives are used.

Antimicrobial agents used in oral suspension products

Alcohols	**Parabens**
Benzyl alcohol	Butyl paraben
Chlorobutanol	Ethyl paraben
Ethanol	Methyl paraben
Phenylethyl alcohol	Propyl paraben
Benzoates	**Phenolics**
Benzoic acid	Chlorocresol
Potassium benzoate	Cresol
Sodium benzoate	Phenol
Quaternary ammonium compounds	**Sorbates**
Benzalkonium chloride	Potassium sorbate
Cetrimonium bromide	Sorbic acid
Cetylpyridinium chloride	

Antioxidants

Some components of pharmaceutical suspensions are susceptible to oxidative degradation. Antioxidant molecules which themselves are preferentially oxidized can be included in the formulation to reduce the degradation of these other components.

The type of antioxidant will depend on the nature of the formulation. Different antioxidants will be required for aqueous and non-aqueous formulations. The choice of antioxidant will depend on the nature of the formulation, the API and the other excipients.

Antioxidants for use in pharmaceutical preparations

Aqueous systems	Non-aqueous systems
Ascorbic acid	Butylated hydroxyanisole
Erythorbic acid	Butylated hydroxytoluene
Sodium formaldehyde	Propyl gallate
Sodium metabisulfite, sodium bisulfite, sodium sulfite	Tocopherol
Potassium metabisulfite	

Chelating Agents

Chelating agents are molecules that have the ability to form stable complexes with metal ions, particularly di-valent and tri-valent metal ions including trace metals and heavy metals. These metal ions are often implicated in API degradation by acting as catalysts. Oxidative degradation is also often catalyzed by heavy metals.

The materials used in pharmaceutical applications as chelating agents are;

-Calcium disodium edetate

-Disodium edetate

-Edetic acid

-Citric acid

8. Sweetening Agents

Palatability of oral medicines is an important factor in compliance.

There are several components to palatability including flavor, mouth-feel and sweetness.

Most patients prefer medicines that are not too bitter but may be slightly "tart" (acidic).

Most APIs are bitter. However, for bitterness to develop, the drug must be sufficiently soluble to interact with taste receptors on the tongue.

For insoluble APIs in the form of suspensions, this begs the question as to why a sweetener is needed.

The answer is straightforward in that many of the minor, but necessary, components of the suspension are also bitter, e.g. preservatives, or very salty, e.g. buffer systems. However, a slight saltiness and a slight bitterness are desirable for palatability.

Traditionally, oral medicines were sweetened using syrup (concentrated sucrose solution) or honey (contains fructose).

However, these materials are inadequate for the formulation of many products because they simply are not able to adequately mask the very bitter taste of many pharmaceutical materials, including APIs and excipients.

Several alternative sweetening agents have been developed over the years to better mask unpleasant tastes in both processed foods and pharmaceuticals.

- Dextrose
- Fructose
- Galactose
- Maltose
- Mannitol
- Saccharin
- Sorbitol
- Sucrose
- Trehalose
- Xylitol
- Aspartame

9. Flavoring Agents

Flavors are used to improve the palatability of oral medicines. One problem that can arise with oral suspensions is that the suspension may produce a "cloying" sensation in the mouth. While this is not the same as a bitter taste, it can nevertheless cause problems for the patient and affect compliance. This can be a particular problem with high levels of inorganic components. Flavors can help reduce this "cloying" taste and thereby improve palatability, and ultimately patient compliance.

10. Coloring Agents

Pharmaceutical colors come in two types; soluble dyes and insoluble pigments.

For pharmaceutical suspensions intended for oral use, soluble dyes are often used; however, pigments may also be used and would be part of the disperse phase. Soluble dyes have the potential to interact with other components of the formulation.

Stability of Suspensions

A-Physical stability:

1. Appearance, color, odor and taste
2. pH
3. Specific gravity
4. Sedimentation rate
5. Sedimentation volume
6. Zeta potential measurement
7. Compatibility with container
8. Compatibility with cap liner
9. Microscopic examination
10. Determination crystal size
11. Determination uniform drug distribution

B-Chemical stability:

1. Degradation of active ingredient
2. Viscosity change
3. Antimicrobial activity:
    a. Incompatibility with preservative
    b. Degradation of preservative
    c. Adsorption of preservative onto drug particle

Evaluation of Suspensions

Suspensions are evaluated by determining their physical stability. Two useful parameters for the evaluation of suspensions are sedimentation volume and degree of flocculation.

Sedimentation Volume

The sedimentation volume (F) is the ratio of the equilibrium volume of the sediment (V_u) to the total volume of the suspension (V_0).

$F = V_u/V_0$

As the volume of suspension that appears occupied by the sediment increases, the value of F, which normally ranges from nearly 0 to 1, increases.

In the system where F=0.50, for example, 50% of the total volume in the container is apparently occupied by the loose, porous flocs forming the sediment.

When F=1, no sediment is apparent even though the system is flocculated. This is the ideal suspension for, under these conditions, no sediment will occur. Caking also will be absent. Furthermore, the suspension is esthetically pleasing, there being no visible, clear supernatant.

Sediment volume is greater than the original volume (F>1) due to formation of floccules which are fluffy and loose.

Degree of Flocculation

A better parameter for comparing flocculated systems is the degree of flocculation (β) which relates the sedimentation volume of the flocculated suspension (F) to the sedimentation volume of the suspension when deflocculated (F_∞).

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

The degree of flocculation is, therefore, an expression of the increased sediment volume resulting from flocculation.

If, for example, β has a value of 5.0, this means that the volume of sediment in the flocculated system is five times that in the deflocculated state.

If a second flocculated formulation results in a value for β of say 6.5, this latter suspension obviously preferred, if the aim is to produce as flocculated a product as possible.

As the degree of flocculation in the system decreases, β approaches unity, the theoretical minimum value.

Rheological Consideration

Viscosity of suspension affects and controls the settling of dispersed particle. It also affects pouring the product from bottle and spreading qualities in case of lotion.

Best viscosity for suspension is to be high during storage to prevent sedimentation and to be low at high shear to ease the administration. Thus, pseudoplastic / thixotropic and plastic / thixotropic suspending agents could be use for this purpose.

Combination of two suspending agents can enhance the stability of suspension.

Crystal Growth

Also known as Ostwald ripening, crystal growth sometimes is very important for suspension sedimentation, physical stability, redispersibility, appearance, and bioavailability.

Size of all particles in a dispersion may not remain constant throughout its shelf life. One reason for that change would be crystal formation.

Particles in dispersion generally are not monodisperse. Rather, there is a range of particle size, not a single value.

The surface free energy on smaller particles is comparatively more than that on larger particles. Therefore, smaller particles are more soluble in the dispersion medium. If the temperature rises, more materials are dissolved from the smaller particles, decreasing their size even more.

When the temperature goes down, the drug attempts to recrystallize on the surface of existing particles. Thus, gradually the larger particles will increase in size as the smaller particles decrease in size. Thus, a slight fluctuation of temperature may cause the particle size spectrum shift to higher values.

This situation is especially true for slightly soluble drugs. This problem can be initially eliminated by using a narrow particle size range. Surface active agents or polymeric colloids can also prevent crystal growth by being adsorbed on the particle surface.

Crystal growth in pharmaceutical suspension may also happen for polymorphic drugs. Metastable (i.e., the least stable form of the drug) is the most soluble. As the metastable form changes to more stable form, solubility decreases and crystallization occurs.

This problem can be avoided by excluding the metastable form from the dispersion and by using the most stable polymorph of the drug.

Packaging and Storage of Suspensions

1) Suspensions should be packaged in wide mouth containers having adequate air space above the liquid.

2) Suspensions should be stored in tight containers protected from: freezing, excessive heat & light.

3) Label: "Shake Before Use" to ensure uniform distribution of solid particles and thereby uniform and proper dosage.

4) Stored in room temperature if it is dry powder (25°C). It should be stored in the refrigerator after opening or reconstitute (freezing should be avoided to prevent aggregation).