

**PHARMACEUTICAL SUSPENSIONS: PATIENT COMPLIANCE ORAL
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530045.**ABSTRACT**

A pharmaceutical suspension is a coarse dispersion of insoluble solid particles in a liquid medium. The particle diameter in a suspension is usually greater than 0.5 μm . However, it is difficult and also impractical to impose a sharp boundary between the suspensions and the dispersions having finer particles. Suspensions are an important class of pharmaceutical dosage forms. The advantages of suspension dosage forms include effective dispensing of hydrophobic drugs; avoidance of the use of cosolvents; 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. The present review provides an overview of various aspects of suspensions such as classification of suspensions, theories of suspensions, various suspending agents, formulations aspects of suspensions, packaging of suspensions, evaluation of suspensions, stability of suspensions and recent research work that is being carried on suspensions.

KEYWORDS: Suspensions, Suspending agents, Evaluation, Stability.**INTRODUCTION****Definition**

A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout 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.

Classification

1. Based on General Classes

- Oral suspension
- Externally applied suspension
- Parenteral suspension

2. Based on Proportion of Solid Particles

- Dilute suspension (2 to 10% w/v solid)
- Concentrated suspension (50% w/v solid)

3. Based on Electro Kinetic Nature of Solid

- Particles
- Flocculated suspension
- Deflocculated suspension

4. Based on Size of Solid Particles

- Colloidal suspension (< 1 micron)
- Coarse suspension (> 1 micron)
- Nano suspension (10 nm)

Advantages

- ❖ Pharmaceutical 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. bioavailability is in following order,

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 cause 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.

Features Desired in Pharmaceutical

- ❖ 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.

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. Oxytetracycline 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.
- ❖ Vaccines as a immunizing agent are often formulated as suspension.
E.g. Cholera vaccine.
- ❖ X-ray contrast agent are also formulated as suspension.
E.g. Barium sulphate for examination of alimentary tract.

Theory of Pharmaceutical Suspensions

1. Sedimentation Behaviour

Introduction

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

2. Theory of Sedimentation

Velocity of sedimentation expressed by Stoke's equation:

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

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

Where,

v = sedimentation velocity in cm / sec

d = Diameter of particle

r = radius of particle

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

Stoke's Equation Written In Other Form

$$V' = V_{\text{sed.}} \cdot \epsilon^n$$

V' = the rate of fall at the interface in cm/sec.

V = velocity of sedimentation according to Stoke's law

ϵ = represent the initial porosity of the system that is the initial volume fraction of the uniformly mixed suspension which varied to unity.

n = measure of the "hindering" of the system & constant for each system.

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 interference with one another (without collision).
- ❖ Particles with no physical or chemical attraction or affinity with the dispersion medium.
- ❖ But most of pharmaceutical suspension formulation has conc. 5%, 10%, or higher percentage, so there occurs hindrance in particle settling.

Factors Affecting Sedimentation

1. Particle size diameter (d)
2. Density difference between dispersed phase and dispersion media ($\rho_s - \rho_o$)
3. Viscosity of dispersion medium (η)

3. Sedimentation Parameters

Three important parameters are considered:

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

$$F = V_u / V_o \text{ ----- (A)}$$

Where, V_u = final or ultimate volume of sediment

V_o = original volume of suspension before settling.

Sedimentation volume is a ratio of the final or ultimate volume of sediment (V_u) to the original volume of sediment (V) before settling. Some time 'F' is represented as 'Vs' and as expressed as percentage. Similarly when a measuring cylinder is used to measure the volume

$$F = H_u / H_o$$

Where, H_u = final or ultimate height of sediment

H_o = original height of suspension before settling Sedimentation volume can have values ranging from less than 1 to greater than 1; F is normally less than 1. F=1, such product is said to be in flocculation equilibrium. And show no clear Supernatant on standing Sedimentation volume (F) for deflocculated suspension

$$F_v = V_v / V_o$$

Where, F_v = sedimentation volume of deflocculated suspension

V_v = sediment volume of completely deflocculated suspension.

(Sediment volume ultimate relatively small)

V_o = Original volume of suspension

3. Sedimentation Velocity³

The velocity dx / dt of a particle in a unit centrifugal force can be expressed in terms of the Svedberg co-efficient 'S' Under centrifugal force, particle passes from position x at time t to position x at time t.

The Sedimentation Behaviour of Flocculated and Deflocculated Suspensions

Flocculated Suspensions

In flocculated suspension, formed flocks (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. In flocculated suspension the loose structure of the rapidly sedimenting flocs tends to preserve in the sediment, which contains an appreciable amount of entrapped liquid. The volume of final sediment is thus relatively large and is easily redispersed by agitation.

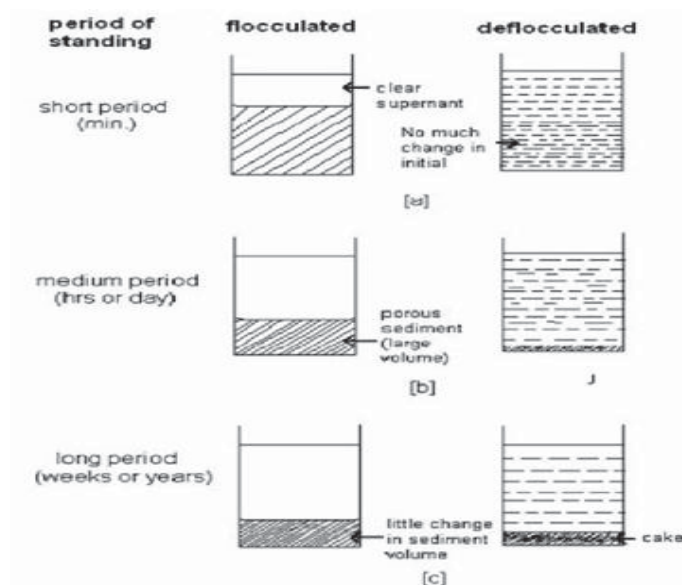


Fig 1.2: Sedimentation Behaviour of Flocculated and Deflocculated Suspensions

Deflocculated suspensions In deflocculated suspension, individual particles are settling, so rate of sedimentation is slow which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation. This phenomenon also called 'cracking' or 'claying'. In deflocculated suspension larger particles settle fast and smaller remain in supernatant liquid so supernatant appears cloudy whereby in flocculated suspension, even the smallest particles are involved in flocs, so the supernatant does not appear cloudy.

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. If the particles (up to about 2 micron in diameter) are observed under a microscope or the light scattered by colloidal particle is viewed using an ultra microscope, the erratic motion seen is referred to as Brownian motion. This typical motion viz., Brownian motion of the smallest particles in pharmaceutical suspension is usually eliminated by dispersing the sample in 50% glycerin solution having viscosity of about 5 cps.

The displacement or distance moved (D_i) due to 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

The radius of suspended particle which is increased Brownian motions become less & sedimentation becomes more important In this context, NSD i.e. 'No Sedimentation Diameter' can be defined. It refers to the diameter of the particle, where no sedimentation occurs in the suspensions systems. The values of NSD depend on the density and viscosity values of any given system.

Electrokinetic Properties

1. 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 shown in figure 1.3, the potential drops off rapidly at first, followed by 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.

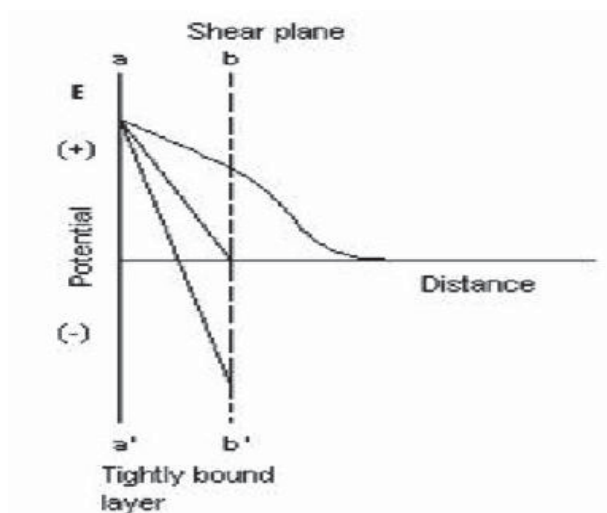


Fig 1.3: Zeta potential

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 (which depends on the particular system being used), 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 deflocculation depends on zeta potential carried by particles. Particles carry charge may acquire it from adjuvants as well as during process like crystallization, grinding processing, adsorption of ions from solution e.g. ionic surfactants. A zeta meter is used to detect zeta potential of a system.

2. Flocculating Agents

Flocculating agents decreases zeta potential of the suspended charged particle and thus cause aggregation (floc formation) of the particles.

Examples of flocculating agents are:

- Neutral electrolytes such as KCl, NaCl.
- Calcium salts
- Alum
- Sulfate, citrates, phosphates salts

- Neutral electrolytes e.g. NaCl, KCl besides acting as flocculating agents, also decreases interfacial tension of the surfactant solution. If the particles are having less surface charge then monovalent ions are sufficient to cause flocculation e.g. steroidal drugs. For highly charged particles e.g. insoluble polymers and poly-electrolytes species, di or trivalent flocculating agents are used.

3. Flocculated Systems

In this system, the disperse phase is in the form of large fluffy agglomerates, where individual particles are weakly bonded with each other. As the size of the sedimenting unit is increased, flocculation results in rapid rate of sedimentation. The rate of sedimentation is dependent on the size of the flocs and porosity. Floc formation of particles decreases the surface free energy between the particles and liquid medium thus acquiring thermodynamic stability.

The structure of flocs is maintained in sediment so they contain small amount of liquid entrapped within the flocs. The entrapment of liquid within the flocks increases the sedimentation volume and the sediment is easily redispersed by small amount of agitation.

Formulation of Flocculated Suspension System

There are two important steps to formulate flocculated suspension

- The wetting of particles
- Controlled flocculation

The primary step in formulation is that adequate wetting of particles is ensured. Suitable amount of wetting agents solve this problem which is described under wetting agents.

Careful control of flocculation is required to ensure that the product is easy to administer. Such control is usually achieved by using optimum concentration of electrolytes, surface-active agents or polymers. Change in these concentrations may change suspension from flocculated to deflocculated state.

Method of Floccules Formation

The different methods used to form floccules are mentioned below:

1. Electrolytes

Electrolytes decrease electrical barrier between the particles and bring them together to form floccules. They reduce zeta potential near to zero value that results in formation of bridge between adjacent particles, which lines them together in a loosely arranged structure.

Electrolytes act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in 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 based on electrophoretic mobility potential because of the strong force of repulsion between adjacent particles, the system is peptized or deflocculated. By preparing series of bismuth subnitrate suspensions containing increasing concentration of monobasic potassium phosphate co-relation between apparent zeta potential and sedimentation volume, caking and flocculation can be demonstrated.

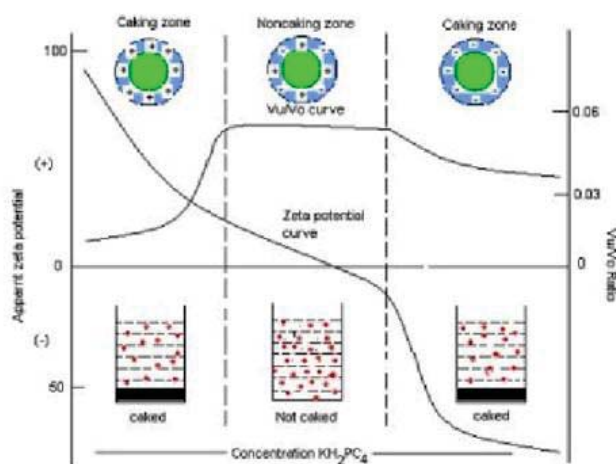


Fig 1.4: Caking Diagram, Showing the Flocculation of a Bismuth Subnitrate Suspension by Means of the Flocculating Agent.

The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease owing to the adsorption of negatively charged phosphate anion. With continued addition of the electrolyte, the zeta potential eventually falls to zero and then increases in negative directions.

Only when zeta potential becomes sufficiently negative to affect potential does the sedimentation volume start to fall. Finally, the absence of caking in the suspensions correlates with the maximum sedimentation volume, which, as stated previously, reflects the amount of flocculation.

2. Surfactants

Both ionic and non-ionic surfactants can be used to bring about flocculation of suspended particles. Optimum concentration is necessary because these compounds also act as wetting agents to achieve dispersion. Optimum concentrations of surfactants bring down the surface free energy by reducing the surface tension between liquid medium and solid particles. This tends to form closely packed agglomerates. The particles possessing less surface free energy are attracted towards to each other by van der waals forces and forms loose agglomerates.

3. Polymers

Polymers possess long chain in their structures. The part of the long chain is adsorbed on the surface of the particles and remaining part projecting out into the dispersed medium. Bridging between these later portions, also leads to the formation of flocs.

4. Liquids

Here like granulation of powders, when adequate liquids are present to form the link, compact agglomerate is formed. The interfacial tension in the region of the link, provide the force acting to hold the particles together. Hydrophobic solids may be flocculated by adding hydrophobic liquids.

Important Characteristics of Flocculated Suspensions

- Particles in the suspension are in form of loose agglomerates.
- Flocs are collection of particles, so rate of sedimentation is high.
- The sediment is formed rapidly.
- The sediment is loosely packed. Particles are not bounded tightly to each other. Hard cake is not formed.
- The sediment is easily redispersed by small amount of agitation.
- The flocculated suspensions exhibit plastic or pseudo plastic behavior.
- The suspension is somewhat unsightly, due to rapid sedimentation and presence of an obvious clear supernatant region.

- The pressure distribution in this type of suspension is uniform at all places, i.e. the pressure at the top and bottom of the suspension is same.
- In this type of suspension, the viscosity is nearly same at different depth level.
- The purpose of uniform dose distribution is fulfilled by flocculated suspension.

Important Characteristics of Deflocculated Suspensions

- In this suspension particles exhibit as separate entities.
- Particle size is less as compared to flocculated particles. Particles settle separately and hence, rate of settling is very low.
- The sediment after some period of time becomes very closely packed, due to weight of upper layers of sedimenting materials.
- After sediment becomes closely packed, the repulsive forces between particles are overcome resulting in a non-dispersible cake.
- More concentrated deflocculated systems may exhibit dilatant behavior.
- This type of suspension has a pleasing appearance, since the particles are suspended relatively longer period of time.
- The supernatant liquid is cloudy even though majority of particles have been settled.
- As the formation of compact cake in deflocculated suspension, Brookfield viscometer shows increase in viscosity when the spindle moves to the bottom of the suspension.
- There is no clear-cut boundary between sediment and supernatant. Flocculation is necessary for stability of suspension, but however flocculation affects bioavailability of the suspension.

Rheological Behaviour

Generally viscosity is measured as a part of rheological studies because it is easy to measure practically. Viscosity is the proportionality constant between the shear rate and shear stress, it is denoted by $\eta = S/D$

Where, S = Shear stress & D = Shear rate

Viscosity has units dynes-sec/cm or g/cmsec
or poise in CGS system.

SI unit of Viscosity is N-sec/m

1 N-sec/m = 10 poise

1 poise is defined as the shearing stress required producing a velocity difference of 1 cm/sec between two parallel layers of liquids of 1cm area each and separated by 1 cm distance.

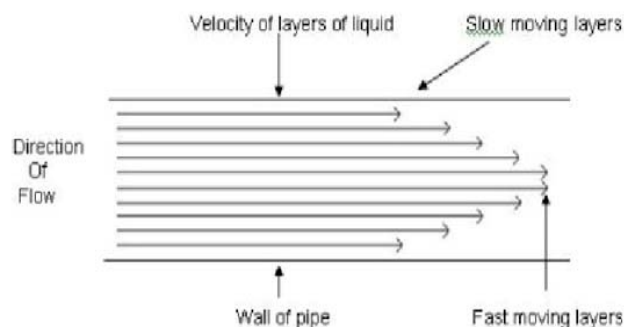


Fig 1.5: Figure Showing the Difference in Velocity of Layers

As shown in the above figure, the velocity of the medium decreases as the medium comes closer to the boundary wall of the vessel through which it is flowing. There is one layer which is stationary, attached to the wall. The reason for this is the cohesive force between the wall and the flowing layers and inter-molecular cohesive forces. This inter-molecular force is known as Viscosity of that medium. In simple words the viscosity is the opposing force to flow, It is characteristic of the medium.

Viscosity of Suspensions

Viscosity of suspensions is of great importance for stability and pourability of suspensions. As we know suspensions have least physical stability amongst all dosage forms due to sedimentation and cake formation.

As the sedimentation is governed by Stoke's law,

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

Where, v = Terminal settling velocity

d = Diameter of the settling particle

ρ_s = Density of the settling solid (dispersed phase)

ρ_l = Density of the liquid (dispersion medium)

g = Gravitational acceleration

η = Viscosity of the dispersion medium

So as the viscosity of the dispersion medium increases, the terminal settling velocity decreases thus the dispersed phase settle at a slower rate and they remain dispersed for longer time yielding higher stability to the suspension. On the other hand as the viscosity of the suspension increases, its pourability decreases and inconvenience to the patients for dosing increases. Thus, the viscosity of suspension should be maintained within optimum range to yield stable and easily pourable suspensions. Now a day's structured vehicles are used to solve both the problems.

Thixotropy

Thixotropy is defined as the isothermal slow reversible conversion of gel to sol. Thixotropic substances on applying shear stress convert to sol(fluid) and on standing they slowly turn to gel (semisolid).

Thixotropic substances are now a day's more used in suspensions to give stable suspensions. As Thixotropic substances on storage turn to gel and thus that their viscosity increases infinitely which do not allow the dispersed particles to settle down giving a stable suspension. When shear stress is applied they turn to sol and thus are easy to pour and measure for dosing. So Thixotropic substances solve both the problems, stability and pourability.

Negative Thixotropy and Rheopexy

Negative Thixotropy is a time dependent increase in the viscosity at constant shear. Suspensions containing 1 to 10% of dispersed solids generally show negative Thixotropy.

Rheopexy is the phenomenon where sol forms a gel more rapidly when gently shaken than when allowed to form the gel by keeping the material at rest. In negative Thixotropy, the equilibrium form is sol while in Rheopexy, the equilibrium state is gel.

Different Approaches to Increase the Viscosity of Suspensions

Various approaches have been suggested to enhance the viscosity of suspensions. Few of them are as follows:

1. Viscosity Enhancers

Some natural gums (acacia, tragacanth), polymers, cellulose derivatives (sodium CMC, methyl cellulose), clays(bentonite) and sugars (glucose, fructose) are used to enhance the viscosity of the dispersion medium. They are known as suspending agents.

2. Co-solvents

Some solvents which themselves have high viscosity are used as co-solvents to enhance the viscosity of dispersion medium.

Effects of Viscosity on Properties of Suspensions

As viscosity increases the sedimentation rate decreases, thus physical stability increases. Clinical effectiveness of Nitro furantoin suspension increases as the viscosity of the suspension increases. Viscosity strongly affects the retention time of polymeric suspensions in the pre-corneal area of human eye.^[3] Clearance rate of colloidal solutions from the nasal cavity can be decreased by increasing their viscosity.^[4] Per-cutaneous absorption of Benzocaine increases as the viscosity of suspension increases.

Suspension Syringeability

Parenteral suspensions are generally deflocculated suspensions and many times supplied as dry suspensions, i.e. in one bottle freeze dried powder is supplied and in another bottle the vehicle is supplied and the suspension is to be reconstituted at the time of injection. If the parenteral suspensions are flocculated one, their syringeability will be less i.e. difficult to inject for the doctor or nurse and painful to patient due to larger floccule size. Parenteral suspensions are generally given by intra muscular route. Now a days intravenous suspension are also available with particle size less than 1 micron, termed as nano-suspension. Viscosity of suspensions should be within table range for easy syringeability and less painful to patient.

Colloidal Properties

Colloids in suspension form chemical compounds such as ions in the solution, So the suspension characteristics of colloids are generally ignored. Generally, colloids are held in suspension form through a very slight Electro-negative charge on the surface of each of the particle. This charge is called Zeta Potential. These minute charge called Zeta-potential is the main function that determines ability of a liquid to carry material in suspension. As this charge (Electro-negative charge) increases, more material can be carried in suspension by liquid. As the charge decreases, the particles move closer to each other and that causes liquid to decrease its ability to carry out material in suspension. There is a point where the ability to carry material in suspension is exceeded and particles begin to clump together with the heavier particles materials dropping out of the liquid and coagulating. Colloids in suspension determine the ability of all liquids particularly water-based liquids to carry material. This also applies to semisolids and solids.

Formulation of Pharmaceutical Suspensions

Structured Vehicle

For the need of a stable suspension, the term 'Structured vehicle' is most important for formulation view and stability criteria. The main disadvantage of suspension dosage form that limits its use in the routine practice is its stability during storage for a long time. To overcome this problem or to reduce it to some extent, the term 'Structured vehicle' has got importance. The structured vehicle is the vehicle in which viscosity of the preparation under the static condition of very low shear on storage approaches infinity. The vehicle behaves like a 'false body', which is able to maintain the particles suspended which is more or less stable.

The 'Structured vehicle' concept is applicable only to deflocculated suspensions, where hard solid cake forms due to settling of solid particles and they must be redispersed easily and uniformly at the time of administration. The Structured Vehicle concept is not applicable to flocculated suspension because settled floccules get easily redispersed on shaking. Generally, concept of Structured vehicle is not useful for Parenteral suspension because they may create problem in syringeability due to high viscosity.

In addition, Structured vehicle should possess some degree of Thixotropic behaviour viz., the property of GEL-SOL-GEL transformation. Because during storage it should be remained in the form of GEL to overcome the shear stress and to prevent or reduce the formation of hard cake at the bottom which to some extent is beneficial for pourability and uniform dose at the time of administration.

Preparation of Structured Vehicle

Structured vehicles are prepared with the help of Hydrocolloids. In a particular medium, they first hydrolyzed and swell to great degree and increase viscosity at the lower concentration. In addition, it can act as a 'Protective colloid' and stabilize charge.

Density of structured vehicle also can be increased by:

- Polyvinylpyrrolidone
- Polyethylene glycols
- Glycerin

Other Formulation Aspects

A perfect suspension is one, which provides content uniformity. The formulator must encounter important problems regarding particle size distribution, specific surface area, inhibition of crystal growth and changes in the polymorphic form. The formulator must ensure that these and other properties should not change after long term storage and do not adversely affect the performance of suspension. Choice of pH, particle size, viscosity, flocculation, taste, color and odour are some of the most important factors that must be controlled at the time of formulation.

Table 1.1: Various Components used Insuspension Formulation

Components	Function
API	Active drug substances
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 aadjust 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.

List of Suspending Agents used for Manufacturing Suspensions

- Alginates
- Methylcellulose
- Hydroxyethylcellulose
- Carboxymethylcellulose
- Sodium Carboxymethylcellulose
- Microcrystalline cellulose
- Acacia
- Tragacanth
- Xanthan gum
- Bentonite
- Carbomer

- Carageenan
- Powdered cellulose
- Gelatin

Most suspending agents perform two functions i.e. besides acting as a suspending agent they also imparts viscosity to the solution. Suspending agents form film around particle and decrease interparticle attraction.

A good suspension should have well developed thixotropy. At rest the solution is sufficient viscous to prevent sedimentation and thus aggregation or caking of the particles. When agitation is applied the viscosity is reduced and provide good flow characteristic from the mouth of bottle.

Preferred suspending agents are those that give thixotropy to the media such as Xanthan gum, Carageenan, Na CMC/MCC mixers, Avicel RC 591 Avicel RC 581 and Avicel CL 611.^[3]

Avicel is the trademark of FMC Corporation and RC 591, RC 581 and CL 611 indicates mixture of MCC and Na CMC. The viscosity of thixotropic formulation is 6000 to 8000 cps before shaking and it is reduced to 300 to 800 cps after being shaken for 5 seconds.^[3]

For aqueous pharmaceutical compositions containing titanium dioxide as an opacifying agent, only Avicel RTM RC-591 microcrystalline cellulose is found to provide thixotropy to the solution, whereas other suspending agents failed to provide such characteristics to the product. Most of the suspending agents do not satisfactorily suspend titanium dioxide until excessive viscosities are reached. Also they do not providethixotropic gel formulation that is readily converted to a pourable liquid with moderate force for about five seconds.^[13]

The suspending agents/density modifying agents used in parenteral suspensions are PVP (polyvinylpyrrolidone), PEG (Polyethylene glycol) 3350 and PEG 4000.^[4]

The polyethylene glycols, having molecular weight ranging from 300 to 6000 are suitable as suspending agents for parenteral suspension. However, PEG 3350 and PEG 4000 are most preferably used.^[4]

PVPs, having molecular weight ranging from 7000 to 54000 are suitable as suspending agents for parenteral suspension. Examples of these PVPs are PVP K 17, PVP K 12, PVP K 25, PVP K 30. Amongst these K 12 and K17 are most preferred.^[4]

The selection of amount of suspending agent is dependent on the presence of other suspending agent, presence or absence of other ingredients which have an ability to act as a suspending agent or which contributes viscosity to the medium. Stability of the suspensions depends on the types of suspending agents rather than the physical properties of the drugs. This evidence is supported through the study by Bufgalassi S et. al. They formulated aqueous suspension of three drugs (Griseofulvin, Ibuprofen, Indomethacin). The suspending agents used were Na CMC, MCC/CMC mixer and jota carageenan (CJ). Evaluation of suspension was based on the physical and physico-chemical characteristics of the drugs, the rheological properties of the suspending medium, corresponding drug suspension and the physical and chemical stability of the suspension. They noted that the physical stability of suspension was mainly dependent on the type of suspending agent rather than the physical characteristics of the drug. The suspending agents which gave highest stability were jota carageenan (having low-temperature gelation characteristics) and MC/CMC (having thixotropic flux).

Table 1.2: 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%
Methyl cellulose	3-11	1-2%
Hydroxyethylcellulose	2-12	1-2%
Hydroxypropylcellulose	6-8	1-2%
Hydroxypropylmethyl cellulose	3-11	1-2%
CMC	7-9	1-2%
Na-CMC	5-10	0.1-5%
Microcrystalline Cellulose	1-11	0.6-1.5%
Tragacanth	4-8	1-5%
Xanthangum	3-12	0.05-0.5%
Bentonite	P ^H >6	0.05-5.0%
Carageenam	6-	0.5-1%
Guar gum	4-10.5	1-5%
Colloidal silicone Dioxide	0-7.5	2-4%

as thickening agents. They increase in viscosity of the solution, which is necessary to prevent sedimentation of the suspended particles as per Stoke's's law. The suspension having a

viscosity within the range of 200 -1500 milipoise are readily pourable.^[3] Use of combination of suspending agents may give beneficial action as compared to single suspending agent. Hashem F et al. carried out experiment to observe effect of suspending agents on the characteristics of some anti-inflammatory suspensions.^[23] For Glafenine, the combination of 2% veegum and 2% sorbitol was best as compared to other formulation of Glafenine. The physical stability of Mefenamic acid and Flufenamic acid was improved by combining 2% veegum, 2% sorbitol and 1% Avicel. Excellent suspension for Ibuprofen and Azapropazone was observed by combining 1% veegum, 1% sorbitol and 1% alginate.

Some important characteristics of most commonly used suspension are mentioned below:

1. Alginates

Alginate salts have about same suspending action to that of Tragacanth. Alginate solution loses its viscosity when heated above 60°C. Due to depolymerization. Fresh solution has highest viscosity, after which viscosity gradually decreases and acquires constant value after 24 hrs. Maximum viscosity is observed at a pH range of 5-9. It is also used as bulk laxative and in food industry. Due to significant thickening effect, alginate is used at lower concentration to avoid problem of viscosity. High viscosity suspensions are not readily pourable. 1% solution of low viscosity grade of alginate has viscosity of 4-10 mPas at 20°C. Chemically alginates are polymers composed of mannuronic acid and glucuronic acid monomers. The ratio of mannuronic acid to glucuronic acid determines the raft-forming properties. High ratio (e.g. 70% glucuronic acid) forms the strongest raft. Protanal LFR 5/60 is the alginate having high levels of glucuronic acid used in the cimetidine suspension formulation. The concentration of alginate is optimized by raft-forming ability of the suspension in order to avoid pourability problem by too much increase in viscosity of suspension. In practice, alginate is used at concentration less than 10% w/w, particularly at 5% w/w.

2. Methyl Cellulose

Methyl Cellulose 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. Adding Methyl Cellulose in hot water and cooling it with constant stirring gives clear or opalescent viscous solution. Methyl Cellulose is stable at pH range of 3- 11. As methyl Cellulose is non-ionic, it is compatible with many ionic adjuvants. On heating to 50°C, solution of Methyl Cellulose is converted to gel form and on cooling, it is

again converted to solution form. Methyl Cellulose is not susceptible to microbial growth. It is not absorbed from G.I tract and it is non-toxic.

3. Hydroxyethyl Cellulose

Hydroxyethyl Cellulose (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.

4. Carboxymethyl Cellulose (CMC)

Carboxymethyl Cellulose is available at different viscosity grades. Low, medium and high viscosity grades are commercially available. The choice of proper grade of CMC is dependent on the viscosity and stability of the suspension. In case of HVCMC, the viscosity significantly decreases when temperature rises to 40⁰C from 25⁰C. This may become a product stability concern. Therefore to improve viscosity and stability of suspension MV-CMC is widely accepted. This evidence was supported through an experiment by change HC et al. They developed topical suspension containing three active ingredient by using 1% MV-CMC and 1% NaCl. The viscosity stability was improved by replacing HV-CMC by 1% MV-CMC and 1% NaCl.

5. Sodium Carboxymethylcellulose (NaCMC)^[3,6]

It is available in various viscosity grades. The difference in viscosity is dependent on extent on polymerization. It is soluble in both hot and cold water. It is stable over a pH range of 5-10. As it is anionic, it is incompatible with polyvalent cations. Sterilization of either powder of mucilage form decreases viscosity. It is used at concentration up to 1%.

6. Microcrystalline Cellulose (MCC; Trade name- Avicel)^[3,6,8]

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. Colloidal MCC (attrited MCC) is used as a food additive, fat replacer in many food products, where it is used alone or combination with other additives such as CMC.

It is found that MCC: alginate complex compositions are excellent suspending agents for water insoluble or slightly soluble API. The advantages of MCC: alginate complex compositions are that they provide excellent stability. Further suspensions prepared with

them are redispersible with small amount of agitation and maintain viscosity even under high shear environment.

7. Acacia^[6]

It is most widely used in extemporaneous suspension formulation. Acacia is not a good thickening agent. For dense powder acacia alone is not capable of providing suspending action, therefore it is mixed with Tragacanth, starch and sucrose which is commonly known as Compound Tragacanth Powder BP.

8. Tragacanth^[6,2]

The solution of Tragacanth is viscous in nature. It provides thixotropy to the solution. It is a better thickening agent than acacia. It can also be used in extemporaneous suspension formulation, but its use in such type of formulation is less than that of Acacia. The maximum viscosity of the solution of Tragacanth is achieved after several days, because several days to hydrate completely.

9. Xanthan Gum^[3]

Xanthan gum may be incorporated at a concentration of 0.05 to 0.5% w/w depending on the particular API. In case of antacid suspension, The Xanthan concentration is between 0.08 to 0.12% w/w. For ibuprofen and acetaminophen suspension, Xanthan concentration is between 0.1 to 0.3% w/w.

Wetting Agents^[6,7]

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 it finds less difficulty in wetting by water. Inability of wetting reflects the higher interfacial tension between material and liquid. The interfacial tension must be reduced so that air is displaced from the solid surface by liquid.

Non-ionic surfactants are most commonly used as wetting agents in pharmaceutical suspension. Non-ionic surfactants having HLB value between 7-10 are best as wetting agents. High HLB surfactants act as foaming agents. The concentration used is less than 0.5%. A high amount of surfactant causes solubilization of drug particles and causes stability problem.

Ionic surfactants are not generally used because they are not compatible with many adjuvant and causes change in pH.

Surfactants

Surfactants decrease the interfacial tension between drug particles and liquid and thus liquid is penetrated in the pores of drug particle displacing air from them and thus ensures wetting. Surfactants in optimum concentration facilitate dispersion of particles. Generally we use non-ionic surfactants but ionic surfactants can also be used depending upon certain conditions. Disadvantages of surfactants are that they have foaming tendencies. Further they are bitter in taste. Some surfactants such as polysorbate 80 interact with preservatives such as methyl paraben and reduce antimicrobial activity.

All surfactants are bitter except Pluronics and Poloxamers. Polysorbate 80 is most widely used surfactant both for parenteral and oral suspension formulation. Polysorbate 80 is adsorbed on plastic container decreasing its preservative action. Polysorbate 80 is also adsorbed on drug particle and decreases its zeta potential. This effect of polysorbate 80 stabilizes the suspension. In an experiment by R. Duro *et al.*, polysorbate 80 stabilized the suspension containing 4% w/v of Pyrantel pamoate. Polysorbate 80 stabilized suspensions through steric mechanism. At low concentration of polysorbate 80, only partial stabilization of suspension was observed. In absence of polysorbate 80, difficulty was observed in re-dispersion of sedimented particles.

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.
- Less foaming tendencies however it should be used at concentration less than 0.5%.
- Compatible with most of the adjuvant.

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, pectin, gelatin, wool fat, egg yolk, bentonite, Veegum, Methylcellulose etc.

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^[6,3,4]

To encounter stability problems all liquid formulation should be formulated to an optimum pH. Rheology, viscosity and other property are dependent on the pH of the system. Most liquid systems are stable at pH range of 4-10. This is the most important in case where API consists of ionizable acidic or basic groups. This is not a problem when API consists of neutral molecule having no surface charge.e.g. Steroids, phenacetin, but control of pH is strictly required as quality control tool.

Buffers are the materials which when dissolved in a solvent will resist any change in pH when an acid or base is added. Buffers used should be compatible with other additives and simultaneously they should have less toxicity. Generally pH of suspension should be kept between 7-9.5, preferably between 7.4-8.4. Most commonly used buffers are salts of weak acids such as carbonates, citrates, gluconates, phosphate and tartrates.

Amongst these citric acid and its pharmaceutically acceptable salts, phosphoric acid and its pharmaceutically acceptable salts are commonly used in suspension formulation. However, Na phosphate is most widely used buffer in pharmaceutical suspension system. Citric acid is most preferable used to stabilize pH of the suspension between 3.5 to 5.0.

L-methionine is most widely used as buffering agent in parenteral suspension. Usual concentration of phosphoric acid salts required for buffering action is between 0.8 to 2.0% w/w or w/v. But due to newly found super-additive effect of L-methionine, the concentration of phosphoric acid salts is reduced to 0.4% w/w or w/v or less.

Buffers have four main applications in suspension systems that are mentioned below:

- Prevent decomposition of API by change in pH.
- Control of tonicity
- Physiological stability is maintained
- Maintain physical stability

For aqueous suspensions containing biologically active compound, the pH can be controlled by adding a pH controlling effective concentration of L-methionine. L-methionine has synergistic effects with other conventional buffering agents when they are used in low concentration. Preferred amount of buffers should be between 0 to 1 grams per 100 mL of the suspension.

Osmotic Agents^[6,3]

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 for ophthalmic suspensions are dextrose, mannitol and sorbitol.

The tonicity-adjusting agents used in parenteral suspension are sodium chloride, sodium sulfate, dextrose, mannitol and glycerol.

Preservatives^[3,4,5,6,7]

The naturally occurring suspending agents such as tragacanth, acacia, xanthan gum are susceptible to microbial contamination. If suspension is not preserved properly then the increase in microbial activity may cause stability problem such as loss in suspending activity of suspending agents, loss of color, flavor and odor, change in elegance etc. Antimicrobial activity is potentiated at lower pH.

The preservatives used should not be

- Adsorbed on to the container
- It should be compatible with other formulation additives.
- Its efficacy should not be decreased by pH.

This occurs most is commonly in antacid suspensions because the pH of antacid suspension is 6-7 at which parabens, benzoates and sorbates are less active. Parabens are unstable at high pH value so parabens are used effectively when pH is below 8.2. Most commonly observed incompatibility of PABA (Para amino benzoic acid) esters is with non-ionic surfactant, such as polysorbate 80, where PABA is adsorbed into the micelles of surfactant. Preservative efficacy is expected to be maintained in glass container if the closure is airtight, but now a days plastic container are widely used where great care is taken in selection of preservative. The common problem associated with plastic container is permeation of preservatives through container or adsorption of preservatives to the internal plastic surface. The use of

cationic antimicrobial agents is limited because as they contain positive charge they alter surface charge of drug particles.

Secondly they are incompatible with many adjuvants.

Most common incidents, which cause loss in preservative action, are,

- Solubility in oil
- Interaction with emulsifying agents, suspending agents
- Interaction with container
- Volatility

Active form of preservative may be ionized or unionized form.

For example active form of benzoic acid is undissociated form. The pKa of benzoic acid is 4.2. Benzoic acid is active below pH 4.2 where it remains in unionized form.

$\text{Fraction of undissociated preservative} = \frac{1}{1 + \text{antilog}(\text{pH} - \text{pKa})}$
--

The combination of two or more preservative has many advantages in pharmaceutical system such as

- Wide spectrum of activity
- Less toxicity
- Less incidence of resistance
- Preservatives can be used in low concentration.

For example, older formulation of eye drops, contain combination of methyl and propyl paraben, which provide antifungal and antibacterial property. Now a days, combination of phenylethyl alcohol, phenoxetol and benzalkonium chloride are used in eye drops. EDTA (ethylenediaminetetra-acetate) is also used in combination with other preservative. Propylene glycol is added to emulsions containing parabens to reduce loss to micelles.

Table 1.3: Preservatives and their Optimal Concentration

Name of the preservatives	Concentration range
Propylene Glycol	5-10%
Disodium edetate	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

Cetrimide	0.005%
Chlorobutanol	0.5%
Phenyl mercuric acetate	0.001-0.002%
Potassium sorbate	0.1-0.2%
Sodium benzoate	0.02-0.5%
Sorbic acid	0.05-0.2%
Methyl paraben	0.015-0.2%

Flavoring and Coloring Agents

They are added to increase patient acceptance. There are many flavoring and coloring agents are available in market. The choice of color should be associated with flavor used to improve the attractiveness by the patient. Only sweetening agent are not capable of complete taste masking of unpleasant drugs therefore, a flavoring agents are incorporated. Color aids in identification of the product. The color used should be acceptable by the particular country.

Most Widely used Flavouring Agents are as Follows:

Table 1.4: Flavouring agents

Acacia	Lavender oil	Orange flower water
Ginger	Vanilla tincture	Corriander oil
Saraparilla syrup	Cinnamon(Oil, water)	Peppermint(oil,spirit,water)
Anise oil	Lemon oil	Dextrose
Glucose	Tolu balsam syrup	Raspberry
Spearmint oil	Citric acid syrup	Ethyl acetate
Benzaldehyde	Mannitol	Rose(oil,water)
Glycerin	Wild cherry syrup	Ethyl vanillin
Thyme oil	Citric acid	Rosemary oil
Caraway oil	Nutmeg oil	Fennel oil
Glycerrhiza	Clove oil	Saccharin sodium
Tolubalsam		
Cardamom(oil,tincture,spirit)	Methyl salicylate	Cocoa syrup
Honey	Cocoa	Cherry syrup
Vanilla	Orange oil	

Coloring Agents

Colors are obtained from natural or synthetic sources. Natural colors are obtained from mineral, plant and animal sources. Mineral colours (also called as pigments) are used to color lotions, cosmetics and other external preparations. Plant colours are most widely used for oral suspension. The synthetic dyes should be used within range of 0.0005% to 0.001% depending upon the depth of colour required and thickness of column of the container to be viewed in it.

Most widely used colours are as follows.

- Titanium dioxide (white)

- ✓ Brilliant blue (blue)
- ✓ Indigo carmine (blue)
- ✓ Amaranth (red)
- Tartarazine (yellow)
- ✓ Sunset yellow (yellow)
- ✓ Carmine (red)
- Caramel (brown)
- Chlorophyll (green)
- ✓ Annatto seeds (yellow to orange)
- ✓ Carrots (yellow)
- ✓ Madder plant (reddish yellow)
- ✓ Indigo (blue)
- ✓ Saffron (yellow)

Sweetening Agents

They are used for taste masking of bitter drug particles.

Examples of sweetening agents are:

- ❖ Sweeteners
- ❖ Bulk sweeteners
- ❖ Sugars such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose
- ❖ Hydrogenated glucose syrup
- ❖ Sugar alcohols such as sorbitol, xylitol, mannitol and glycerin
- ❖ Partially hydrolysed starch
- ❖ Corn syrup solids
- ❖ Artificial sweetening agents
- ❖ Sodium cyclamate
- ❖ Na saccharin
- ❖ Aspartame
- ❖ Ammonium glycyrrhizinate

A bulk sweetener is used at concentration of 15-70% w/w of the total weight of the suspension. This concentration is dependent on presence of other ingredient such as alginate, which have thickening effect.

For example, in presence of alginate, sorbitol is used at concentration of 35-55% particularly at 45% w/w of the total suspension composition. Hydrogenated glucose syrup can be used at concentration of 55-70% w/w, when alginate is absent. Combination of bulk sweeteners can also be used. e.g. Combination of sorbitol and hydrogenated glucose syrup or sucrose and sorbitol. Generally the taste-masking composition consists of at least one sweetening agent and at least one flavouring agent. The type and amount of flavouring and colouring agent is dependent on intended consumer of such suspension e.g. pediatric or adult.

Sugar sweetener concentration is dependent on the degree of sweetening effect required by particular suspension. The preferred amount of sugar sweetener should be between 40 to 100 gm per 100 mL of the suspension. Water soluble artificial sweeteners can also be added in place of sugar sweetener or in addition to them. The amount of artificial sweetening agents should be between 0 to 5 gms per 100 mL of suspension. Optimum taste-masking of API in the suspension can be obtained by limiting the amount of water in the suspension, but the amount of water must not be too low to hydrate MCC, Na CMC or other suitable suspending agent. The low amount of water should provide a sufficient aqueous base to impart desired degree of viscosity. The preferred total amount of water contained in the suspension should be between 30 to 55 grams per 100 mL of suspension.

Humectants

Humectants absorb moisture and prevent degradation of API by moisture. Examples of humectants most commonly used in suspensions are propylene glycol and glycerol. Total quantity of humectants should be between 0-10% w/w. Propylene glycol and glycerol can be used at concentration of 4% w/w.

Antioxidants

Suitable antioxidants used are as follows.

- ❖ Ascorbic acid derivatives such as ascorbic acid, erythorbic acid, Na ascorbate.
- ❖ Thiol derivatives such as thioglycerol, cysteine, acetylcysteine, cystine, dithioerythritol, dithiothreitol, glutathione
- ❖ Tocopherols
- ❖ Butylated hydroxyanisole (BHA)
- ❖ Butylated hydroxytoluene (BHT)

- ❖ Sulfurous acid salts such as sodium sulfate, sodium bisulfite, acetone sodium bisulfite, sodium metabisulfite, sodium sulfite, sodium formaldehyde sulfoxylate and sodium thiosulfate.
- ❖ Nordihydroguaiaretic acid

4) Drug Release and Dissolution Study of Suspensions

Introduction

The drug release from suspensions is mainly through dissolution. Suspension share many physico- chemical characteristic of tablet & capsules with respect to the process of dissolution. As tablets and capsules disintegrate into powders and form suspension in the biological fluids, it can be said that they share the dissolution process as a rate limiting step for absorption and bioavailability.

Principles of Drug Release

Diffusion Controlled Dissolution:

The dissolution of suspension categorized in two ways:

- ✓ Dissolution profile for monodisperse system
- ✓ Dissolution profile for polydispersed system.

The basic diffusion controlled model for suspended particle was developed by Noyes & Whitney and was later modified by Nernst.

$$DQ/dt = DA (C_s - C_b)/h$$

Where, dQ/dt = Dissolution rate

h = Diffusion layer thickness

C_s = solubility

C_b = bulk area of particle

This model represents the rapid equilibrium at the solid-liquid interface that produces a saturated solution which diffuses into the bulk solution across a thin diffusion layer.

In this model the heterogeneous process of dissolution is limited to a homogeneous process of liquid phase diffusion. For spherical particle with a changing surface area, cube-root relationship which is derived by Hixson & Crowell.

Formulation Factors Governing Drug Release**Wetting**

Wetting of suspended particles by vehicle is must for proper dispersion.

Air entrapment on the particle promotes particles that rise to the top of the dispersion medium, particle de-aggregation or other cause of instability. Poor wetting on drug particle leads poor dissolution of particles and so retard release of drug.

Viscosity

The total viscosity of the dispersion is the summation of the intrinsic viscosity of the dispersion medium and interaction of the particles of disperse phase.

As per Stokes-Einstein equation,

$$D = KT/6\pi\eta r$$

Intrinsic viscosity of medium affects the dissolution rate of particles because of the diffusion effect. On enhancement of viscosity the diffusion coefficient decreases, which gives rise to a proportionate decreases in rate of dissolution.

Effect of Suspending Agent

Different suspending agents act by different way to suspend the drug for example suspension with the highest viscosity those made by xanthan gum and tragacanth powder shows inhibitory effects on the dissolution rate. The suspension of salicylic acid in 1% w/v dispersion of sodium carboxymethylcellulose and xanthan gum indicating effect of viscosity on hydrolysis of aspirin in GIT is not significant from a bioavailability point of view.

Bioavailability of Suspensions From Different Sites**1. Oral Suspensions**

The bio-availability of an oral suspension is determined by the extent of absorption of drug through GIT tract. Oral suspensions vary in composition. The vehicle varies in viscosity, pH and buffer capacity. In short, the bio-availability of the oral suspension can be optimized by selecting the appropriate drug particle sizes, site of optimal absorption, particle densities and vehicle viscosities.

2. Rectal Suspensions

The administration of the drug suspension by the rectum was accomplished by enema system. Enemas are in large volume (50-100 ml) & limited patient compatibility. The bioavailability of rectal suspension depends on absorption from rectal tissues and rectal blood flow.

3. Ophthalmic Suspensions

The viscosity of the vehicle and the particle size of the suspended drug particles affect the bioavailability of ophthalmic suspension. Polymers (polyvinyl alcohol, polyvinyl pyrrolidone, cellulose derivatives) used to impart the adequate viscosity and so the particle settling is retarded. The particle size must be below 10 micron to retard the absorption from cornea. The particle size is related with dissolution rate as well as retention within the conjunctival sac. Particles either dissolves or are expelled out of the eye at the lid margin or at the inner canthus. The time required for the dissolution and corneal absorption must be less than the residence time of the drug in the conjunctival sac just for retention of particles. The saturated solution of a suspension absorbed by cornea produce initial response, where as the retained particles maintain the response as the particles dissolves and drug is absorbed. In case of suspension having high particulate content, a greater mass of drug remains in the cul-de-sac following drainage of the applied volume and remaining particles then dissolves in the tear fluids and provide an additional drug in force, that transport the drug across the corneal into the aqueous humor.

4. Parenteral Suspensions

Suitable vehicle in suspension for subcutaneous and intramuscular administration are water, non-toxic oils (sesame, peanut, olive), organic solvent (propylene glycol, polyethylene glycol, glycerin. When water is used as vehicle dissolved drugs rapidly diffuse into body tissue leaving a depot of undissolved drug at the injection site. In case of parenteral suspension the dissolution characteristic of drug at the site of injection controlled the rate at which drug is absorbed in to the systemic circulation and its resulting bioavailability.

5. Dissolution Testing

Two methods are used for dissolution testing of suspensions.

1. Official Methods (Conventional Methods)

It is known as paddle method. Dissolution profile of the 500 mg sample suspension is determined at 37degC in 900 ml of pH 7.2 phosphate buffer using the FDA paddle method at

25 RPM. 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 at 37degC. 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 2 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 um membrane and analyze.

2. Non-Official Methods (Non-Conventional Methods)

(Experimental Design Based Dissolution Apparatus for Suspensions)

Several types of apparatus were used for dissolution testing of suspensions but there is drawback of retention of dissolving material within the confines of dissolution chamber & sampling. Edmundson & Lees develop an electronic particle counting device for suspension containing Hydrocortisone acetate.

To explain the dissolution of commercially available Prednisolone suspension by a magnetically driven rotating filter system.^[33]

A methodology to determine the dissolution-rate profile of suspensions employing the FDA's two bladed paddle method.^[35]

Flow Through Apparatus for Dissolution of Suspensions

This method, which is based on the mass between solid and liquid phase in an exchange column, is shown to avoid some disadvantage of the commonly used beaker method employing fixed liquid volumes. Determination of dissolution rate profile of suspension using the FDA's two bladed paddle method.^[35]

Dialysis System

In the case of very poorly soluble drugs, where perfect sink condition would necessitate a huge volume of solvents with conventional method, a different approach, utilizing dialysis membrane, was tried as a selective barrier between the fresh solvent compartment and the cell compartment containing the dosage form.

6. Dissolution Models' Studies

The following assumptions are employed for these models:

The effective particle shape approximates a sphere. The diffusion co-efficient is concentration independent. Sink condition exists. The interpretation of the apparent thickness of the diffusion layer fundamentally differentiates each model.

Model	Equation	Characteristic
I	$d_a/d_t = -2DC_s/l$	Static
II	$d_a/d_t = -2DC_s/K_a$	a
III	$d_a/d_t \propto \rho$	a

Where,

a= particle diameter (cm)

t= time (sec)

D= diffusion co-efficient (cm /sec)

l= thickness of diffusion layer (cm)

r= density (g/cm)

In model I diffusion layer thickness is constant over the life time of the particle. For model II & III the diffusion layer thickness is proportional to the one-half of first power of the particle diameter.

In-Vivo In-Vitro Co-Relationship (IVIVC)^[3]

- *In Vivo* Data *In Vitro* Data
- Peak plasma/serum concentrations Percent drug dissolution profiles
- AUC (plasma/serum) concentration Dissolution rate profiles
- Profile (To-T)
- Estimated AUC (plasma/serum) Intrinsic dissolution rates
- Plasma Concentration profile (To-∞)
- Pharmacokinetic modeling Dissolution-rate constants and Absorption-rate constant (K_a)
- Dissolution half-lives
- Absorption half-life
- Elimination half-life
- Drug excreted in the urine (T) Time for a certain percentage of Drug to dissolve
- (e.g. T_{30%}, T_{50%}, T_{90%}, etc).
- Cumulative amount of drug excreted as a Parameters resulting from function of time determination of dissolution Kinetics
- Percent drug absorbed-time profiles

- First order percent remaining to be dissolved-time profiles
- Amount of drug absorbed per milliliter of Logarithmic probability plots the volume of distribution percent drug dissolved-time profiles
- Statistical moment analysis Statistical moment analysis
- Mean residence time (MRT) Mean residence time (MRT)
- Mean absorption time (MAT) Mean dissolution time (MDT)

5) Quality Assurance and In-Process Quality Control (Ipqc) of Suspensions^[1,2,3]

5.1 Introduction

Quality Assurance (QA) is a broad concept which takes into consideration all factors that individually or combinely affect the quality of a product. It is a system which keeps a Critical look on what has happened yesterday, what is happening today and what is going to happen tomorrow so that it can ensure right quality of final product.

Quality Control (QC) is a small part of QA and it is concerned with sampling, testing and documentation during manufacturing and also after completion of manufacturing. Quality control is the monitoring process through which manufacturer measures actual quality performance, compares it with standards and acts on the causes of deviation from standard to ensure quality product not once but every time.

Quality control system can be divided into two parts on basis of its function:
In Process Quality Control, and Final Quality control.

5.2 In Process Quality Control (Ipqc) of Suspensions

In process quality control is a process of monitoring critical variables of manufacturing process to ensure a quality of the final product and to give necessary instruction if any discrepancy is found. In process manufacturing controls are established and documented by quality control and production personnel to ensure that a predictable amount of each output cycle falls within the acceptable standard range.

For proper function of In process Quality control the following must be defined.^[2]

Which process is to be monitored and at what phase?

Number of samples to be taken for analysis and frequency of sampling?

Quantitative amounts of each sample, Allowable variability, etc.

Objectives of IPQC Tests^[2]

- To minimize inter-batch and intra-batch variability.
- To ensure quality of final product.
- To ensure continuous monitoring of process variables which are going to affect the quality of product.
- To ensure implementation of GMP in manufacturing.
- To give indication of existence of a functional Quality assurance system.

IPQC Tests of Suspensions

The tests are carried out during the manufacturing of suspension to ensure a stable, safe and quality product. These include:

Appearance of Phases

This test is done for the dispersed phase and dispersion medium. For preparation of dispersion phase for suspension usually purified water and syrup are used. The particle size distribution, clarity of syrup, the viscosity of gum dispersion, quality control of water is monitored to keep an eye on the product quality.

Viscosity of Phases

Stability of a suspension is solely dependent on the sedimentation rate of dispersed phase, which is dependent on the viscosity of the dispersion medium. So this test is carried out to ensure optimum viscosity of the medium so a stable, redispersible suspension can be formed. The viscosity of the dispersion medium is measured before mixing with dispersed phase and also viscosity after mixing is determined using Brooke field viscometer. The calculated values are compared with the standard values and if any difference is found necessary corrective action are taken to get optimized viscosity.

Particle Size of Dispersed Phase

Optimum size of drug particle in the dispersed phase plays a vital role in stability of final suspension. So this test is carried out to microscopically analyze and find out particle size range of drug then it is compared with optimum particle size required. If any difference is found, stricter monitoring of micronisation step is ensured.

pH Test

pH of the phases of suspension also contribute to stability and characteristics of formulations. So pH of the different vehicles, phases of suspension, before mixing and after mixing are monitored and recorded time to time to ensure optimum pH environment being maintained.

Pourability

This test is carried out on the phases of suspension after mixing to ensure that the final preparation is pourable and will not cause any problem during filling and during handling by patient.

Final Product Assay

For proper dosing of the dosage form it is necessary that the active ingredient is uniformly distributed throughout the dosage form. So samples are withdrawn from the dispersed phase after micronisation and after mixing with dispersion medium, assayed to find out degree of homogeneity. if any discrepancy is found out it is suitably corrected by monitoring the mixing step to ensure a reliable dosage formulation.

Zeta Potential Measurement

Value of Zeta potential reflects the future stability of suspensions so it monitored time to time to ensure optimum zeta potential. Zeta potential is measured by either Zeta meter or micro-electrophoresis.

Centrifugation Test

This test tells us about the physical stability of suspension. The product is checked for uniform distribution of color, absence of air globules before packing.

Final Quality Control of Suspensions

The following tests are carried out in the final quality control of suspension:

- ✓ Appearance
- ✓ Color, odor and taste
- ✓ Physical characteristics such as particle size determination and microscopic photography for crystal growth
- ✓ Sedimentation rate and Zeta Potential measurement
- ✓ Sedimentation volume
- ✓ Redispersibility and Centrifugation tests

- ✓ Rheological measurement
- ✓ Stress test
- ✓ pH
- ✓ Freeze-Thaw temperature cycling
- ✓ Compatibility with container and cap liner
- ✓ Torque test

Stability of Suspensions

1. Introduction

Pharmaceutical suspensions are thermodynamically unstable system, so they always tend towards the ultimate loss of stability. What one examines at a time is only the apparent stability of the product.

Stability of suspension can be considered in two ways:

- ✓ Physical
- ✓ Chemical

2. Physical Stability

The definition of physical stability in context of suspensions is that the particles do not sediment for a specific time period and if they sediment, do not form a hard cake. To achieve this desired target, one must consider the three main factors affecting the physical stability.

A. Particle-Particle Interaction and its Behaviour

Derjaguin, Landau, Verwey & Overbeek explained a theory of attractive & repulsive forces in context of lyophobic colloids viz., DLVO theory. This theory allows us to develop insight into the factors responsible for controlling the rate at which the particles in the suspension will come together to produce aggregate to form duplets or triplets. The process of aggregation will accelerate the sedimentation and affect the redispersibility.

For this, the potential energy curves may be used to explain the sedimentation behaviour which generally is indicative of the interaction of the two charged surfaces which gives rise to two types of suspension systems i.e. deflocculated and flocculated.

In deflocculated suspension systems, the particles dispersed carry a finite charge on their surface. When the particles approach one another, they experience repulsive forces. These forces create a high potential barrier, which prevents the aggregation of the particles. But

when the sedimentation is complete, the particles form a closed pack arrangement with the smaller particles filling the voids between the larger ones. And further the lower portion of the sediment gets pressed by the weight of the sediment above. And this force is sufficient to overcome the high energy barrier. Once this energy barrier is crossed, the particles come in close contact with each other and establish strong attractive forces. This leads to the formation of hard cake in a deflocculated system. The re-dispersion of this type of system is difficult as enough work is to be done in order to separate the particle and create a high energy barrier between them.

The another type viz., the flocculated system in which the particles remain in the secondary minimum, which means that the particles are not able to overcome the high potential barrier, so they remain loosely attached with each other. So, the particles here still experience a high energy barrier, but are easily re-dispersible.



Fig 1.9. Potential Energy Curves for Particle Interaction in Suspension Systems.

To conclude, the deflocculated system provides the apparent stability, while the flocculated system is necessary to achieve the long-term stability. And so far for the flocculation to occur, repulsive forces must be diminished until the same attractive forces prevail.

Electrolytes serve to reduce the effective range of the repulsion forces operating on the suspended particles, as evidenced by the decrease in Zeta Potential and the formation of the

bridge between the adjacent particles so as to link them together in a loosely arranged structure.

B. Interfacial Properties of Solids

A good pharmaceutical suspension should not exhibit the settling of suspended particles. This can be achieved by reducing the particle size to a level of 5m to exhibit the Brownian motion. As for the size reduction, work (W) is to be done which is represented as

$$W = \Delta G = \gamma SL \Delta A.$$

Where, ΔG = increase in surface free energy

γSL = interfacial tension between liquid medium & solid particles.

ΔA = increase in surface area of interface due to size-reduction.

'The Size reduction tends to increase the surface-free energy of the particles, a state in which the system is thermodynamically unstable.

In order to approach the stable state, the system tends to reduce the surface free energy and equilibrium is reached when $\Delta G = 0$, which is not desirable.

Thus, the following two approaches are used to retain the stability.

- 1) By reducing the ΔA . Provided that they are loosely attached (flocculated system) and are easily redispersible.
- 2) By reducing the interfacial tension, the system can be stabilized, but cannot be made equal to zero, as dispersion particles have certain positive interfacial tension. Thus, the manufacture must add certain surface-active agents to reduce γ to a minimum value, so that the system can be stabilized.

Poly-Dispersibility: (Variation in Particle Size)

Range of particle size might have an influence on the tendency towards caking. When the drug material is in the dispersed state, the dispersed material will have an equilibrium solubility that varies relative to its particle size. Small particles will have higher equilibrium solubility than the larger particles. So, these small particles will have a finite tendency to solubilize subsequently precipitate on the surface of the larger particles (considering the fluctuations in temperature).

Thus, the larger particle grows at the expense of the smaller particles. This phenomenon is known as "Ostwald Ripening".

This phenomenon could result in the pharmaceutically unstable suspensions (caking) & alter the bio-availability of the product, through an alteration in the dissolution rate.

This problem can be surmounted by the addition of polymer (Hydrophilic Colloid) such as cellulose derivatives, which provides the complete surface coverage of the particles, so that their solubilization is minimized to some extent.

Another way is to have uniformity in particle size of the dispersed material, which is to be considered prior to the manufacturing of suspensions.

C. Chemical Stability of the Suspensions

Most of the drug materials although insoluble, when suspended in a liquid medium has some intrinsic solubility, which triggers the chemical reactions such as hydrolysis, to occur leading to degradation. So, the particles that are completely insoluble in a liquid vehicle are unlikely to undergo chemical degradation. The Chemical stability of the suspensions is governed by the following facts:

It is assumed that the decomposition of the suspension is solely due to the amount of the drug dissolved in aqueous phase. This solution will be responsible for drug decomposition and more drug will be released from insoluble suspended particles within the range of solubility. It behaves like a reservoir depot. So, the amount of the drug in the solution remains constant inspite of the decomposition with time, Thus, primarily suspensions behave as a zero order. But once all the suspended particles have been converted into the drug in the solution, the entire system changes from zero order to first order, as now the degradation depends upon the concentration in the solution. Thus, it can be said that suspension follows apparent zeroorder kinetics.

CONCLUSION

The suspension is stable till the system follows zero order, but once it enters the first order kinetics, the degradation is rapid. But, if the suspension is concentrated, the system will require more time to convert from zero order to first order. And this is the reason that a concentrated suspension is often stable enough to market, but a dilute is not. But a concentrated suspension affects the physical stability of the suspension. So, the manufacturing pharmacist should optimize both physical & chemical parameters of the dispersed particles to achieve the desired stability of the suspensions.

Packaging of Suspensions

Due to the world wide emergence of the drug regulations and increasing sophistication in variety of dosage forms and development of new packaging materials, today pharmacist must aware of wide range of packaging material that relates directly to the stability and acceptability of dosage forms. For example, to optimize shelf life industrial pharmacist must understand inter-relationship of material properties, while the retail pharmacist must not compromise with the storage of the dosage forms. So because of that labeling and storage requirements are important for both patient as well as pharmacist.

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.

1. Glass

Generally soda lime and borosilicate glass are used in preparation of non sterile suspensions. Some times it is advisable to use amber colored glass where light is the cause of degradation of the product. 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.

Table 1.5: Type of Glasses and Additives Giving Amber Colour

Type of Glass	Additive Giving Amber Colour
Soda lime	FeO+ sulfur(in presence of reducing agent)
Borosilicate	FeO+TiO ₂

Disadvantages of Glass Materials

- ✓ They are fragile. difficult.
- ✓ They are very heavy as compared to plastic so handling and transport is difficult.

- ✓ Most important disadvantage of glass is that glass constituents get extracted in to the product.
- ✓ So for sterile dosage forms powder glass test as well as water attack test has to be carried out to ensure the amount of alkali material leached out in the product. Also typical test for extractable material is some time carried out.

Table 1.6: Typical Characteristics of Borosilicate Glass For Example

Assay of Borosilicate Glass	Value
Initial pH	6
Final pH	8
pH change	±0.24
SiO ₂ ppm	21.0
Na ppm	301
K ppm	0.74
Al ppm	1.3
Ba ppm	0.7

Plastic

Due to the negative aspects of glass, coupled with the many positive attributes of the plastic material significantly inroads for the use of plastic as packaging material for sterile as well as non-sterile pharmaceutical suspensions.

Advantages Of Plastic Material:

- ✓ Non breakability.
- ✓ Light weight.
- ✓ Flexibility.

Materials used: - Polyethylene, PVC, polystyrene, polycarbonate etc.

Drug Plastic Consideration

There are mainly five factors which is to be considered during selection of plastic as a packaging material for suspension.

- ✓ Permeation
- ✓ Leaching
- ✓ Sorption
- ✓ Chemical reaction
- ✓ Alteration of the physical properties of plastic.

E.g. Deformation of polyethylene containers is often caused by permeation of gas and vapours from the environment. Also sometimes solvent effect is also found to be the factor

for altering the physical properties of plastic viz., oils has softening effect on polyethylene and PVC.

Closure and Liners

With an exception of ampoules all containers required elastomeric closure.

Factors affecting in selecting closure:

- ✓ Compatibility with product.
- ✓ Effect of processing should not affect the integrity of the closure.
- ✓ Seal integrity.
- ✓ It should be stable throughout the shelf life.
- ✓ Lot to lot variability has to be considered.

Factors Affecting in Selecting Liner

- ✓ Chemical resistance.
- ✓ Appearance
- ✓ Gas and vapour transmission.
- ✓ Removal torque.
- ✓ Heat resistance.
- ✓ Shelf life.
- ✓ Economical factors.

3. FDA Regulations for Packaging

When FDA evaluates drug, the agency must be firmly convinced that package for a specific drug will preserve the drug's efficacy as well as its purity, identity, strength and quality for the entire shelf life.

The FDA does not approve the container as such, but only the material used in container. A list of substance "Generally recognized as safe" (GRAS) have been published by FDA. Under the opinion of qualified experts they are safe in normal conditions. The material does not fall in this category (GRAS) must be evaluated by manufacturer and data has to be submitted to FDA. The specific FDA regulation for the drug states that "container, closure and other components of the packaging must not be reactive, additive or absorptive to the extent that identity, strength, quality, or purity of the drug will be affected".

4. Storage Requirements (Labelling)

- Shake well before use
- Do not freeze
- Protect from direct light (For light sensitive drugs).

5. Innovations in Suspensions**1. 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 can be summarized.

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

Polymer coated drug powders are also used for preparation of reconstitutable powders that means dry powder drug products that are reconstituted as suspension in a liquid vehicle such as water before usage. These reconstitutable polymer coated powders are long shelf-life and once reconstituted have adequate taste masking.

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 for example copolymer of dimethyl ammonium methyl methacrylate). The drug after encapsulation are suspended, dispersed or emulsified in suspending medium to give the final dosage form.

Polymer Coated Drug with a Basic Substance

This method has claimed to give stable taste masked suspensions on reconstitution (taste masked for prolonged period).

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.

Table 1.7: Some Examples of Taste Masked Suspensions:

Nano-Suspension:

S.I No.	Name of the Drug	Taste Masking Approach
01	Risperidone	pH control and polymer coating(with Eudragit RS) The coated drug is suspended in water based liquid constituted at an optimum pH.
02	Roxithromycin-I And ROxithromycin-II	Polymer coating with Eudragit RS 100
03	Diclofenac	Polymer coating with Eudragit RS 100
04	Levofloxacin	Polymer coating (Eudragit 100:Cellulose acetate, 60:40 or 70:30)

Nano-suspension of potent insoluble active pharmaceutical ingredient will become improved drug delivery formulations when delivered to at sizes less than 50 nm.

When delivered I.V. at sizes less than 50 nm, the suspension particles avoids the normal reticulo-endothelial system filtration mechanisms and circulates for long periods. The suspension particles may be insoluble API particles or nanoparticle polymeric carriers of soluble or insoluble drugs and may be useful in delivering genetic therapeutic materials targeted to the cells.

In transdermal delivery application, control of particulates in the 10-50 nm size range should allow the formulation of API in formats that match requirements of delivery rates and for penetration depth target. The drug particulates may involve insoluble active structures or active either soluble or insoluble in degradable polymeric structures.

For oral delivery, nanometer size particles may allow delivery of API through the intestinal wall into the blood stream, at desired rates and with minimal degradation in the GI tract. Insoluble particles at these sizes may be designed to be transportable across this barrier. Another strategy involves encapsulation of active drugs in nano-particulate degradable polymer structures.

Preparation of Nano-Particles

The technology used should produce nanoparticles of insoluble API or of encapsulated APIs. A new reactor system has been developed known as Multiple Stream Mixer or Reactor (MMR) produces nano-particles by several methods.

Principle:- The system (MMR) conducts two or more streams of reactants to an interaction zone where the streams collide at high velocity under extreme pressure.

Designing of Nano-Particle Formulations

Using the MMR, nano-particles formulation can be designed using several approaches.

Direct Reactions

It is carried out if the API is a result of a synthesis which yields an insoluble material. The reactant streams can be fed into the MMR to yield particles of nanometer size.

pH Shift Reaction

Many APIs are soluble as a basic form and insoluble as active acid form. The synthesized material dissolve in a basic medium constitutes one feed stream, into the MMR, which an acidifying element. The result of collision reaction is a nano-particle suspension of insoluble active acid form.

Controlled Re-crystallization

This approach enables preparation of nanosuspension from API feed material made in a kilo lab or other sources of synthesized solution to the problem of producing nanoparticles from any insoluble API feed material. The API is dissolved in a solvent and the dissolved API from one input stream and other stream is either water or water solution which recrystallizes the insoluble active on contact because the recrystallization occurs in a ultra turbulent collision zone, the resultant insoluble API forms as nano-particles. After necessary clean up process the API can be dispersed into the aqueous final formulation (saline for injection) by passage through dispersion or mixing system (micro-fluidized fluid processing system).

Because the intrinsic API crystallizes where formed as nanoparticles, they can be re-dispersed as nanosuspension.

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 enlisted as follows as Ethyl cellulose, Eudragit, Cellulose acetate, etc.

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

Recent Literature on Suspensions

Sl.No.	Drug	Reason for Formulating into Suspensions	Suspending Agents used	Result	References
1.	Acetaminophen	The ability of polyvinyl pyrrolidone (PVP) and bovine serum albumin (BSA) in inhibition of crystal growth in suspensions containing acetaminophen as a model drug was evaluated.	Avicel	Bovine Serum Albumin above a critical concentration in combination with Poly Vinyl Pyrrolidone induces its inhibitory effect on crystal growth.	[41]
2.	Aceclofenac	Extraction of pectin from waste of orange fruit peel and further characterization for useful alternative pharmaceutical excipient.	Orange peel pectin powder	The release rate of drug is decreased with increase in the orange peel pectin powder percentage in the formulation. Orange peel pectin powder showed good binding and suspending properties at 10%w/w and 2%w/v respectively.	[42]
3.	Aceclofenac	Extraction of mucilage from banana peel and further characterization for useful as alternative pharmaceutical excipient.	Banana peel mucilage powder, Sodium CMC	The release rate of drug is decreased with increase in the banana peel mucilage powder percentage in the formulation. Banana peel mucilage powder showed good binding and suspending properties at 10%w/w and 2%w/v respectively.	[43]
4.	Albendazole	To apply the sensory	Viscocoel,	Sensory evaluation as well	[44]

		test of difference and analysis could be an useful methodology in quality control of oral liquid pharmaceutical formulations.	Veegel, Sodium CMC	as chemical, physicochemical and microbiological tests would be necessary for quality-control of drugs, mainly in the liquid-oral pharmaceutical formulations.	
5.	Artemether	To mark its bitter taste, followed by the study of its dissolution behaviour at pH 6.8 of the oral cavity and pleasant taste perception test.	Xanthan gum	The granules of carbopol prepared by sodium metabisulphite and methyl paraben sodium and coated by opadry® enteric had maximally reduced the bitterness of artemether.	[45]
6.	Ambroxol HCL	To evaluate different concentration of suspending agents for their suitability for the formulation of sustained release suspension containing ambroxol HCL microcapsules.	Xanthan gum	The suspension prepared with xanthan gum(0.3%w/v) as a suspending agent showed a optimum drug release and was found to be ideal for sustained release preparation.	[46]
7.	Ambroxol hydrochloric acid	To prepare taste masked suspension of Ambroxol Hydrochloride by obtaining the intensely bitter taste of Ambroxol Hydrochloride.	Xanthan gum	Drug-resin complexes effectively masked bitter taste of Ambroxol HCL	[47]
8.	Azithromycin Ambroxol HCL	To develop dry suspensions for reconstitution like Azithromycin and Ambroxol HCL using powder blends techniques.	Xanthan gum, Sodium CMC, Acacia	Formulation with xanthan gum (5% and 2.5%) showed excellent sedimentation volume and degree of flocculation.	[48]
9.	Azithromycin	Pediatric Azithromycin suspension formulated by employing various suspending agents exhibited good suspendability and give higher dissolution rate than those formulated with Azithromycin.	HPMC sodium, CMC, Acacia, Gum tragacanth	Among the formulated suspensions (HPMC) showed better <i>in vitro</i> drug release profile as well as better physical stability compared to other formulated suspensions.	[49]
10.	Azithromycin	To prepare an acceptable suspension	Xanthan Gum, HPMC,	The dry physically mixed powder (HPMC) was more	[50]

		either as dry physical mixture powder or granules to be reconstituted, Through studying the effect of various type and concentration of suspending agent on the release profile of the drug.	Colloidal Silicone Dioxide	stable than the granular suspension (Colloidal Silicone Dioxide) since the expiration date for dry and granular suspension were 3.24 and 2.7 years respectively.	
11.	Barium Sulphate	To study the rheological and sedimentation behaviour of BSS in the presence of various additives in order to prepare a stable radio-opaque colloid that can be used for medical investigations.	Sodium CMC, Bentonite,	A new Barium sulphate opaque suspension was developed by sodium CMC, tri sodium citrate, which gave good contrast both in acidic and alkaline region for fluoroscopic survey of gastro intestinal tracts.	[51]
12.	Calcium carbonate	To search for a cheap and effective natural excipient that can be used as an effective alternative for the formulation of pharmaceutical suspensions.	Acacia, Tribulus terrestris mucilage	Tribulus terrestris mucilage could be used as a suspending agent. They have low rate of sedimentation, high viscosity, slightly basic pH and are easily redispersible.	[52]
13.	Cefuroxime axetil	To mask the taste of the cefuroxime axetil and to improve patient compliance.	Indion 214, Indion 204, Indion 234	CA forms complex with Indion-214 by two methods like batch method and kneading using. The product which showed best taste masking and drug release was formulated into suspension. Suspension was again evaluated and in vivo studies were carried out to check the bioavailability of suspension.	[53]
14.	Cefuroxime axetil	To formulate for oral cefuroxime axetil suspensions.	Xanthan gum	Considering the ideal characteristics of prepared suspension formulations, this product can be added to drug market.	[54]
15.	Cefuroxime axetil	To mask the taste of the Cefuroxime axetil by dry suspension formulation using	Xanthan gum	The granules were prepared by using different ratios of Cefuroxime axetil to lubritabshow good taste	[55]

		lipophilic vehicle such as Hydrogenated Cotton Seed oil (Lubritab) as taste masking agent.		masking property for Cefuroxime axetil shows good taste as compared to market preparation.	
16.	Cefixime trihydrate	To search for a natural excipient which is cost effective that can be used as an alternative for the formulation of pharmaceutical suspensions.	Acacia and Eulophia herbacea mucilage	Eulophia herbacea mucilage could be used as a suspending agent. They have low rate of sedimentation, high viscosity, Weak acidic pH and are easily redispersable.	[56]
17.	Cephalexin Mono hydrate	To improve the chemical stability, increase the bioavailability and controlled the duration and onset of action of the drug	Piperine	Improved chemical stability, bioavailability and controlled the duration and onset of action of the drug was achieved by employing Piperine.	[57]
18.	Chlorpheniramine maleate	To formulate tasteless complexes of chlorpheniramine maleate with indion 234 and attempt was made to develop stable and taste masked suspension formulation.	Veegum, Sodium Carboxy Methyl cellulose	Chlorpheniramine maleate was successfully taste masked and formulated into suspension formulation.	[58]
19.	Ciprofloxacin	To investigate the effect of structural vehicles and other formulating factors on physical stability and rheological behaviour of ciprofloxacin suspension.	Sodium CMC, HPMC, Veegum.	The formulation containing NaCMC (0.25% w/v), veegum (0.1%w/v) and Nacl (0.05%w/v) was the most stable formulation by alternating the amount ratios of formulation factors, the best rheological behaviour and the most proper thixotropy may be achieved.	[59]
20.	Clarithromycin	To restrict greatly the further development of oral preparations and clinical applications of these drugs.	Xanthan gum	Eudragit L 100 shown better release profile and good taste masking property at 1:3 drug and polymer ratio and shown taste as compared to marketed preparation.	[60]
21.	Dextromethorphan hydrobromide	To mask the intensely bitter taste of Dextromethorphan	Xanthan gum	Drug-Resin complexes effectively masked bitter taste of Dextromethorphan	[61]

		Hydrobromide using ion exchange resin and to formulate oral suspension of the taste masked drug.		Hydrobromide.	
22.	Diclofenac	To develop a stable suspension formulation of Diclofenac.	Hydroxy Ethyl Cellulose	The suspension were prepared with HPMC were stable and easily redispersable.	[62]
23.	Fluconazole	To develop a niosomal drug delivery system for fluconazole, A triazole antifungal drug that acts by inhibition of the ergosterol component of the fungal cell membrane, Because neosomal formulations have better permeability due to presence of hydrophilic and lipophilic moieties. Hence a delivery system based on cholesterol and non ionic surfactant may have an advantage in the antifungal activity of fluconazole.	Span-60	Niosomes are comparatively stable at lower temperatures. Thus on the basis of studies conducted we can state that niosomes possess great potential as drug delivery carriers and hence the formulated fluconazole niosomal suspension can be further evaluated for its <i>in vitro</i> performance.	[63]
24.	Furosemide	To extract, Evaluate and to findout the potentials as a suspending agent of natural mucilage obtained from the nutlets of the plant Lallelantia royleana(balango).	Butea monospermama and Leucaena leucocephala, Xanthan gum	The mucilage of Lallelantia royleana has good properties to be used as a suspending agent and the performance is comparable with that of chitosan and xanthan gum since it is of natural origin, nontoxic, and of good biocompatibility.	[64]
25.	Gatifloxacin	Formulation and evaluation of gatifloxacin suspension by adding acacia powder in different ratio an all five formulations.	Hydroxypropyl methylcellulose (HPMC) and Acacia	On increasing the concentration of acacia powder in suspensions improved the physical stability.	[65]
26.	Hydrochlorthiazide	To evaluate the effects of polymers with different ionic	Sodium CMC, HPMC	Sodium CMC showed the best diuretic effect in rats, with increase of urine	[66]

		characteristics on the physicochemical parameters of developed pharmaceutical suspensions containing HCTZ for pediatric use.		volume and of electrolyte excretion. HPMC showed caking formation, that result in a product lacking in dose consistency because of failure to obtain and maintain a good degree of dispersion.	
27.	Ibuprofen	Evaluation of grewia polysaccharide gum as a suspending agent by comparing the suspending ability to xanthan gum, Sodium CMC, Acacia gum.	Xanthan gum, Sodium CMC, Acacia	Grewia polysaccharide gum (freeze-dried) may provide a suitable alternative to sodium CMC or Acacia as suspending agent in pharmaceutical oral suspensions, Providing a really available and affordable option in the countries where it is found growing abundantly, Wild or cultivated.	[67]
28.	Isopropyl antioyrene	To evolve a physically chemically stable and elegant and palatable suspension using suspending agents in varying proportions.	Sodium CMC, Veegum	Formulation with sodium CMC has better stable, bioavailability when compared to veegum and marketed preparation.	[68]
29.	Itraconazole	The physical and chemical stability of a phospholipid stabilized suspension of itraconazole crystals employed as a model water-insoluble drug dispersion.	Lipoid E80, Sodium oleate	The phospholipid hydrolysis kinetics and mechanisms proposed at liquid-liquid interfaces are consistent with the results obtained at the solid-liquid junction.	[69]
30.	Lamotrigine	To investigate the combined effect of viscosity enhances and anti-flocculant using full factorial design.	Locust bean gum, Sodium alginate	The eight formulations were made by factorial design, later optimized batch was prepared after desirability analysis and validated the obtained value with predicted showing good reliability of the design, highest r^2 and lowest sum of squares of residual was observed for the responses. The prepared suspension showed high sedimentation volume, High redispersibility and optimum viscosity	[70]

				following Non-Newtonian type behaviour.	
31.	Metronidazole	To prepare palatable liquid formulation by masking the intensely bitter taste of metronidazole.	Xanthan gum	Drug-Resin complexes effectively masked bitter taste of metronidazole.	[71]
32.	Metronidazole	To study the suspending property of holy basil seed mucilage by formulating suspension of metronidazole.	Holy basil seed mucilage	The mucilage powder with the minimum concentration of 0.8% w/v formed a stable metronidazole suspension and thus proved to be a good natural suspending agent.	[72]
33.	Metronidazole	To isolate the mucilage using microwave assisted extraction technique and to evaluate its excepiant properties.	Vigna mungo (black gram)	The mucilage can be isolated effeciently by using microwave irradiation from Vigna mungo(Black gram seeds) and can be used as an effective suspending agent and tablet binder in oral pharmaceutical formulations.	[73]
34.	Methanol(70%v/v) extracts of capparis aphylla aerial part (MECA), Carica papaya leaves (MECP) and Feronia limonia fruit(MEFL)	To develop combinational herbal oral male contraceptive suspensions containing potential antifertility agents from ethnomedicinal plants.	Tween-80	The methanol extracts of Capparis aphylla aerial part, Carica papaya leaves and Feronia limonia fruit could be formulated as combinational herbal oral suspensions with convincing quality control parameters.	[74]
35.	Nimesulide	To isolate a natural pharmaceutical excepiant from tamarind seed and to check its utility as an effective suspending agent in the formulation of pharmaceutical suspensions.	Tamarind seed polysaccharide	The isolated TSP powder can be used as an effective suspending agent in suspensions and the formulated suspension shown drug release and easily re-dispersable.	[75]
36.	Nimesulide	Isolation of natural pharmaceutical excepiant from the seeds of Plantago Ovata as a natural suspending agent.	Isapgol mucilage powder	The Isapgol mucilage powder can be used as an effective suspending agent in suspensions and the formulated suspension were stable.	[76]
37.	Norfloxacin	To formulate norfloxacin suspension using norfloxacin	-----	The product had acceptable physical properties and the ingredients used in the	[77]

		powder and to evaluate the physical and chemical stability of the formulation.		formula did not affect chemical stability of the drug under the studied conditions.	
38.	Nystatin	To investigate the influence of type and concentration of cellulosic suspending agents on the physical and chemical stability of nystatin in suspensions.	SCMC 358 cp, SCMC 1485 cp, SCMC 1240 cp, Avicell RC 591	The shelf-lives of the buffered suspensions were more or less the same but much higher than that of the unbuffered suspensions.	[78]
39.	Ondansetron hydrochloric acid	To improve the patient compliance of drug, an attempt was made to sustain the release and to mask the taste of the ODH using ion exchange resin (Indion 244).	Micro crystalline cellulose, Sodium CMC, Guar gum	Formulated sustained release suspension restricts the release of ODH which may reduce the dosing frequency. Na CMC was giving better suspending property as compared to Guar gum and MCC.	[79]
40.	Oxcarbazepine	The possibility of developing a level correlation between percent drug released and percent drug absorbed for oxcarbazepine suspension.	Targum and sodium alginate	IV/IVC developed by level A correlation makes oxcarbazepine dissolution profile meaningful, as it allows predicting in-process quality control of Oxcarbazepine suspension.	[80]
41.	Paracetamol	To study the comparative dissolution behaviour of marketed paracetamol suspensions.	Sodium CMC 10000CPS Avicel RC 591	The importance of dissolution testing for suspensions and proper selection of the suspending agents during their formulations should be duly emphasized to ensure batch-to-batch reproducibility and consistent pharmacological/biological activity.	[81]
42.	Paracetamol	To search for cheap and effective natural excipients that can be used as an effective alternative for the formulation of pharmaceutical suspensions.	Ocimum basilicum mucilage, tomato powder and tragacanth gum.	The mucilage from <i>osimum basilicum</i> seeds may be used as a pharmaceutical adjuvant and as suspending agent at 2%w/v, depending on its suspending ability and the stability of the resulting suspension.	[82]
43.	Paracetamol	To formulate and evaluate a new, cheap and effective natural	Trigonella foenum graecum	The extracted mucilaginous substance of Trigonella foenum graecum is edible,	[83]

		suspending agent that can be used as an effective alternative for traditional suspending agent.	Acacia, tragacanth.	has the potential as a suspending agent even at lower concentration (1-3% w/v) and can be used as a pharmaceutical adjuvant.	
44.	Paracetamol	To investigate the effect of <i>Adansonia digitata</i> as a suspending agent in pharmaceutical formulations using paracetamol as the model drug.	Sodium carboxy methyl cellulose, <i>Adansonia digitata</i> gum	The profiles of paracetamol pediatric suspensions containing AD appeared to be better than those of Na CMC, suggesting its potential as a suspending agent in formulation of pharmaceutical suspensions.	[84]
45.	Paracetamol	To search for a cheap and effective natural excipient that can be used as an effective alternative for the formulation of pharmaceutical suspensions.	Tragacanth gum, gum acacia, tamarind gum.	All concentrations employed, compound tragacanth gum had the strongest suspending ability relative to the other materials due to the high viscosity of compound tragacanth gum, it can be a stabilizer of choice when high viscosity is desired & also serve as good thickening agent in both pharmaceutical & food industries.	[85]
46.	Paracetamol	The suspending properties of <i>Khaya senegalensis</i> gum were evaluated comparatively with those of <i>Acacia sieberiana</i> and <i>Acacia senegal</i> gums at a concentration range of 0.2 to 5.0%w/v in 2.4%w/v paracetamol suspension.	<i>Acacia sieberiana</i> and <i>Acacia senegal</i> , a standard reference but <i>Khaya senegalensis</i> gum.	<i>Acacia sieberiana</i> at concentrations above 5%w/v may be used to dissolve paracetamol powder, <i>Khaya</i> gum has potential to suspend paracetamol and may provide a substitute excipient in the liquid formulation of paracetamol and perhaps curb the problem of paediatric mortalities associated with organic chemicals used as solubilizing agents in paracetamol.	[86]
47.	Paracetamol	To develop cheap and effective natural excipient that can be used as an effective alternative for the formulation of pharmaceutical	Cactus mucilage (<i>Opuntia ficus indica</i> , <i>Opuntia stricta</i>)	The mucilages of <i>Opuntia</i> spp. (<i>Opuntia ficus-indica</i> and <i>Opuntia stricta</i>) can be used as alternatives to Na CMC as suspending agents in suspension formulations.	[87]

		suspensions.			
48.	Paracetamol	To search for a cheap and effective natural excipient that can be used as an effective alternative for the formulation of pharmaceutical suspensions.	Abelmoschus esculentus mucilage, sodium CMC, tragacanth gum.	The extracted mucilage of Abelmoschus esculentus is non toxic, has the potential as a suspending agent even at lower concentration (4%w/v) and can be used as a pharmaceutical adjuvant.	[88]
49.	Paracetamol	To investigate indigenous plant sources containing polysaccharides, devise a cost effective extraction procedure and evaluate its use as a multi-functional excipient.	Mucilage of psyllium polysaccharide (pps), sodium CMC	The psyllium polysaccharide (PPS) mucilage was found to have a promising potential for its use as a suspending agent when compared to the other suspending agents.	[89]
50.	Paracetamol	To search for a cheap and effective natural excipient and to evaluate the mucilage obtained from the endosperm of Borassus flabellifer as a suspending agent that can be used as an effective alternative for the formulation of pharmaceutical suspension.	Compound tragacanth powder, Lepidium sativum mucilage.	The extracted mucilage of Lepidium sativum has the potential as a suspending agent even at lower concentrations and can be used as a pharmaceutical adjuvant.	[90]
51.	Paracetamol	To evaluate Lepidium sativum mucilage as a suspending agent, compare this with suspension prepared by using tragacanth as a suspending agent and marketed paracetamol suspension.	Compound tragacanth powder, Lepidium sativum mucilage.	The extracted mucilage of Lepidium sativum has the potential as a suspending agent even at lower concentrations and can be used as a pharmaceutical adjuvant.	[91]
52.	Rifampicin	To prepare a stable suspension for rifampicin through preparation of different formulas of rifampicin aqueous suspension either as ready to use or as granular powder to be reconstituted.	Methyl cellulose, Sodium CMC, Xanthan gum.	The MC had better dissolution rate compared with the other suspension and the rheogram showed that the MC was less viscous than the other suspension, it was found that the granular rifampicin was more stable than the ready to use suspension,	[92]

				since the expiration date of granular rifampicin was 2.6 years, while the expiration date of ready to use suspension was 1.8 years.	
53.	Rifampicin	To overcome the problem of bitter taste, degradation & sedimentation, the various trails of rifampicin oral suspension were developed by using four different suspending agents and then it was evaluated for their physic-chemical parameters.	Tween-80 Sodium CMC Carbomer-934, Sodium starch glycollate, Xanthan gum.	The suspension (Xanthan gum as a suspending agent) was considered as stable, uniform, pleasant tasting and readily redispersible Rifampicin oral suspension.	[93]
54.	Rofecoxib	To assess physical stability of that prepared formulations according to ICH guide lines.	Sodium alginate, Veegum(0.4%), Xanthan gum.	The suspension containing veegum, calcium chloride was the best formulation among all the suspension prepared.	[94]
55.	Sulphamethoxazole	The manufacture of suspension cassia roxburghii seed gum were evaluated by comparing with Acacia gum and compound Tragacanth gum at concentration 2.5 and 3%w/v in sulphamethoxazole suspension.	Acacia compound, Tragacanth, Xanthan gum.	The Cassia roxburghii filtered mucilage as a novel suspending agent in the preparation of sulphamethoxazole suspensions and could be employed as stabilizer and thickener of choice in pharmaceutical suspension preparation.	[95]
56.	Sulphamethoxazole	To determine the rheological and stability properties of sulphamethoxazole suspension using cedrela gum as a suspending agent.	Cedrela gum	A suspension of ideal characteristics of high viscosity at negligible shear and low viscosity upon agitation was obtained with cedrela gum and HPMC as a suspending agents, Cedrela gum could be substituted for synthetic and more expensive HPMC in the formulation of pharmaceutical suspensions.	[96]
57.	Sulphadimidine	To assess the suspending ability of the gum from Sesamum indicum leaves for	Compound tragacanth, Acacia, Sesamum gum	Sesamum indicum was compared with acacia gum and mainly tragacanth, a commonly used suspending	[97]

		utilization in pharmaceutical suspensions. Suspensions were prepared with sesamum gum in comparison to tragacanth(mainly) and acacia.		agent on pharmaceutical suspensions. It produced acceptable suspensions which would yield uniform dose due to its ease of redispersibility and no formation of aggregates & can be employed as a thickener and suspending agent for formulation of pharmaceutical suspensions.	
58.	Sulphadimidine	To search for a cheap and effective natural excipient that can be used as an effective alternative for the formulation of pharmaceutical suspensions.	Albizia gum, Compound, tragacanth, Acacia gum, Gelatin	Zygia>Compound Tragacanth gum> Acacia gum> Gelatin> Albizia zygia gum had the strongest suspending ability relative to the other gums.	[98]
59..	Spironolactone	To extemporaneously formulate a liquid dosage form from commercially available tablets and establish the chemical stability of the drug.	Sodium CMC, Veegum, Sodium acetate	The spiranolactone solubility is low that an accurate estimate of thermodynamic parameters cannot be ascertained using the conditions in the study.	[99]
60.	Theophylline	To provide a microparticle containing oral liquid sustained release dosage form for use in pediatric and geriatric patients.	Tragacanth	The formulated suspension can be used as a sustained-release formulation for theophylline in treatment of obstructive pulmonary disorders.	[100]
61.	Temozolomide	To determine the pharmaceutical acceptability and chemical stability of drug in two extemporaneously compounded suspension formulations prepared from capsule.	Povidone	Temozolomide oral suspensions may allow oral patients who are unable to swallow capsules to receive temozolomide treatment,& if compounded in a suitable environment, could reduce the potential for drug exposure to health workers and family members from opening capsules.	[101]
62.	Tinidazole	To mask the intensely bitter taste of tinidazole (TNZ) and to formulate a palatable liquid formulation of the taste-masked drug, by	Xanthan gum	Drug-resin complexes effectively masked bitter taste of tinidazole.	[102]

		novel Ion exchange resin method to overcome taste problem with traditional system.			
63.	Zidovudine	To isolate a novel bio material from the seeds of Buchanania Lanza and to evaluate their potential for sustained drug delivery by formulating various nano suspension using methylene chloride as organic solvent and biomaterial.	Biopolymer	The isolated bio polymer has shown its potentiality for formulating nano suspension. The polymer can serve as potential polymer for formulating various drug loaded nano suspensions.	[103]
64.	Zinc Oxide	To select a new cheap, effective alternative natural suspending agent for pharmaceutical suspensions.	Leucaena Latisiliqua seed gum, Tragacanth, Acacia	The suspending ability of the suspending agents were in the order of Leucaena Latisiliqua gum > Compound Tragacanth > Acacia. Then the gum of Leucaena Latisiliqua can be employed as stabilizer and thickener of choice when high viscosity is desired.	[104]
65.	Zinc Oxide	To isolate and investigate the pharmaceutical properties of the isolated mucilage from Spinacia oleracea L. Leaves, to assess its suitability as a new innovative suspending agent in a pharmaceutical formulation.	Mucilage of Spinacia oleracea L. Leaves	The mucilage of S.oleracea L. Leaves could be used as a suspending agent, and the performance was found to be superior to both tragacanth and bentonite.	[105]
66.	Zinc Oxide	The gum of Moringa oleifera has got properties to be used as a suspending agent and the performance in comparable with that of gum tragacanth.	Moringa oleifera	The suspensions are pseudoplastic in their behaviour and their viscosity decreases with increase in shear rate, which is an essential property in the formulation of Moringa oleifera gum suspension. The suspending properties of Moringa oleifera gum is comparable with that of gum tragacanth.	[106]

REFERENCES

1. Martin A, Coarse Dispersion, Physical Pharmacy, Lippincott Williams and Wilkins, Philadelphia, Fourth Edition, 2001; Page No. 479-481.
2. Cooper & Gun, "Dispersed System" Tutorial Pharmacy, Sixth Edition, Page No. 75- 78.
3. Aulton M.E. "Suspension" Pharmaceutics-the Science of Dosage Form Design, Churchill Livingstone, Edinburgh Second Edition, 2002; Page No. 84-86, 273.
4. Banker G.S. Rhodes C.T. "Dispersed Systems" Modern Pharmaceutics, Marcel Dekker, Inc. New York, 1979; 72: Page No. 345-346.
5. Subramanyam C.V.S, "Suspensions" Text Book of Physical Pharmaceutics, Second Edition, Page No. 374-387.
6. Ansel C, Allen L.V, Popovich N.G. "Disperse Systems" Pharmaceutical Dosage Forms & Drug Delivery Systems, Lippincott Williams and Wilkins, Philadelphia, Eighth Edition, 2005; Page No. 387-389, 398.
7. A. Martin and J. Swarbrick, In Sprowls, American Pharmacy, Lippincott, Philadelphia, Sixth Edition, 1966; Page No. 205.
8. Soci M. M. and Parrot E. L, J Pharm Sci, 1980; 69-403.
9. Ludwig A. and Ooteghen M. Van, Drug Dev Ind Pharm, 1988; Page No. 142-267.
10. Pennington A. K, Ractlife J. H, Wilson C. G and Hardy J. G, Int J Pharm, 1988; Page No. 43-221
11. Dicolo G, Carelli V, Giannacciini B, Serafini M. F, and Bottari F, J Pharm Sci, 1980; Page No. 69-387.
12. Lachman L, "Pharmaceutical Suspension" The Theory and Practice of Industrial Pharmacy, Verghese Publishing House, Bombay, Third Edition, 1996; Page No:488-489.
13. Jani G.K. "Liquid Dosage Forms" Pharmaceutics-II (Dispensing Pharmacy), B. S. Shah Prakashan, Fourth Edition, Ahmedabad 2004; Page No. 202.
14. "Pharmaceutical Formulations" U.S. Patent No 4, 996, 222.
15. "Cefazolin Suspension for Parenteral Administration" U.S. Patent No 4, 029, 782.
16. Wade Ainley, Weller J. Paul, Hand Book of Pharmaceutical Excipients, Second Edition, Page Nos. 1, 24, 76, 78, 84, 215, 219, 223, 229, 306, 428, 532, 562.
17. Aulton E, Michael Second Edition, "Suspension" Pharmaceutics, The Science of Dosage Form Design, Churchill Livingstone Edinburgh, 2002; Page No. 271-278.
18. Libermann A. Herbert, "Oral Aqueous Suspension" Pharmaceutical Dosage Forms, Dispersed Systems, Marcell Dekker, Inc, New York, 1989; 2: Page No. 246-250.
19. "Mcc: Alginate Pharmaceutical Suspensions" U.S. Patent No. 5, 840, 768.

20. "Taste Stable Aqueous Pharmaceutical Suspensions" U.S. Patent No, 4, 195, 084.
21. Remington, Twentieth Edition, "Pharmaceutical Necessities" The Science and Practice of Pharmacy, Lippincott Williams and Wilkins, Philadelphia 2000; Page No: 1017-1021.
22. "Thixotropic Compositions Easily Converted to Pourable Liquids" U.S Patent No 4, 427, 681.
23. Hashem F, Ramden E, "Effect of Suspending Agents on the Characteristics of Some Anti-Inflammatory Suspension" Pharmazie, 1987; 3(5): Page No. 732-735.
24. Williams R. O. et al, "Formulation and Stability of Suspensions For Pre-Clinical Study" Bull.Chem. Pharm, 1997; 2(3): Page No. 628-634.
25. Chang H. C, et al, "Development of A Topical Suspension Containing Three Active Ingredients" Drug Dev Ind Pharm, 2002; 3(1): Page No. 29-39.
26. Duro R, et al, "Adsorption of Polysorbate 80 On Pyrantel Palmoate: Effects on Suspension Stability" Int J Phar, 1998; 9(1): Page No. 211-216.
27. Rambhau D, et al, "Bio-Avaialability of Sulphathiazole from Flocculated and Deflocculated Suspensions and its Implications" Ind J Phsio Pharmacol, 1983; 5(6): Page No. 217-220.
28. Abdou H. M, First Edition "Dissolution of Suspension" Dissolution Bio-Availability and Bio-Equivalence, Mack Publishing House, Easton, 1989; Page No. 173-184.
29. Liebermann H. A. Reiger M. M, Banker G. S, "Bio-Availability of Disperse Systems" Pharmaceutical Dosage Forms- Dispersed System, 1: Page No. 338- 364.
30. Banakar U. V, "Dissolution of Suspensions" Pharmaceutical Dissolution Testing, Vol-49.
31. The United States Pharmacopoeia-24, The National Formulary-19, 1944; Page No. 724.
32. Edmundson I. C. and Less K. A, "Method For Determining Solution Rate of Fine Particles" J Pharm Pharmacol, 1965; 4(2): Page No. 17-193.
33. Shah A. C, Peot C. B, and Ozhs J F, "Design and Evaluation of Rotating Filter Stationary Basket *In-Vitro* Dissolution Test Apparatus-I, Fixed Fluid Volume System, J Pharm Sci, 1972; 5(2): Page No. 62-671.
34. Langenbucher F, "In-Vitro Assessment of Dissolution Kinetics: Description and Evaluation of Column Type Model" J. Pharm. Sci. 1969; Page No. 58-265.
35. Strum J.D, Colizzi J.L, Goehl T.J, Jaffe Z.M, Pitlick W.H. Shah V.P, Poust R.I, J. Pharm. 1978; Page No. 67-1399.
36. Sharma P.P, First Edition, "Quality Assurance" How To Practice Gmp, Vandana Publications, New Delhi. Page No. 20, 45, 208.

37. Willings S.H, Tuckerman M.M. and Hitchings W.S. Second Edition, "Quality Assurance and Quality Control" Good Manufacturing Practices For Pharmaceuticals: A Plan For Total Quality Control, Marcel Dekker, Inc, New York, Vol-16.
38. Liebermann H.A, Reiger M.M. Banker G.S, "Quality Assurance" Pharmaceutical Dosage Form and Disperse Systems, 3: Page No. 423-424, 457-467.
39. Remington, Twentieth Edition, "Colloidal Dispersions" The Science and Practice of Pharmacy, Lippincott Williams and Wilkins, Philadelphia, 2000; Page No. 298-307.
40. Japanese Patent No:80, 129, 224.
41. Martin, A, Bustamante, P, Chun, A.H.C, Physical Pharmacy, 4th. Edition, Lea and, Febiger, Philadelphia, 1993; Page No. 426, 431, 477.
42. Mann As, Jain Nk, Kharya Md, Evaluation of The Suspending Properties of Cassia Tora Mucilage on Sulphadimidine Suspension, Asian Journal of Experimental Sciences, 2007; Page No: 63-67.
43. Femi-Oyewo Mn, Adedokun Mo, Olusoga To, Evaluation of The Suspending Properties of Albizia Zygia Gum on Sulphadimidine Suspension, Tropical Journal of Pharmaceutical Research, 2004; 3(1): Page No: 279-284.
44. Meilgaard, M; Civille, C.V, Carr, B.T, Sensory Evaluation Techniques, 3rd Edition, Crc Pressflorida, 1999; Page No: 416.
45. Al-Omranm Mf, Al-Suwayeh Sa, El-Helw Am, Saleh Si, Taste Masking of Diclofenac Sodium Using Microencapsulation, Journal of Microencapsulation, 2002; 19: 45-52.
46. Martindale, The Extra Pharmacopoeia, 29th Edition, The Pharmaceutical Press, London, 1989; Page No: 906.
47. Isah Ab, Abdulsamad A, Gwarzo Ms, Abbah Hm, Evaluation of The Disintegrant Properties of Microcrystalline Starch Obtained From Cassava In Mnz, Nigerian Journal of Pharmaceutical Sciences, 2009; 8: 26-35.
48. Ansel C, Allen L.V, Popovich N.G Eighth Edition, Disperse Systems, Pharmaceutical Dosage Forms & Drug Delivery Systems, Lippincott Williams and Wilkins, Philadelphia, 2005; Page No: 387-389, 398.
49. K.P.R Chowdary And L. Srinivas, Physical Stability and Dissolution Rate of Ibuprofen Suspensions Formulated Employing Its Solid Dispersions, Indian Journal of Pharmaceutical Sciences, 2000.
50. Ansels, Pharmaceutical Dosage Forms and Drug Delivery System (8th Edition.), 2005; Chapter6, Page No: 14, 187, 386.

51. Miller R E, Diagnosis of Gastric and Duodenal Ulcer By Barium Meal, Radiology, 1977; 117: 743-749.
52. The Ayurvedic Pharmacopoeia of India, Ministry of Health & Family Welfare, Government of India, Department of Indian System of Medicine & Homoeopathy, 1, Page No: 1, 260.
53. Sohi H Sultana Y, Khar Rk, Taste Masking Technologies in Oral Pharmaceuticals, Recent Development and Approaches, Drug Development & Industrial Pharmacy, 2004; Page No: 429-448.
54. Dhumal R, Biradar V, Yamamura Sh, Paradkar R, York P. Preparation of Amorphous Cefuroxime Axetil Nanoparticles by Sonoprecipitation for Enhancement of Bioavailability, European Journal of Pharmaceutics & Biopharmaceutics, 2008; Page No: 109-115.
55. Schallenberger Rs, Acree Te, Handbook Of Sensory Physiology Iv-2, Beidler Lm Ed, Spingerverlag, Berlin, Newyork, 1971; Page No: 221-277.
56. Bruneton J. Pharmacognosy Phytochemistry Medicinal Plants, Lavoisier Publishing, New York, 1999, 2nd Edition, Page No: 90-91.
57. Vijaykumar Sing, Vikash kumar mishra, Jayanth kumar Maurya, Formulation and Evaluation of Cephalexine Monohydrate Reconstititional Oral suspension With Piperine and their Antibacterial Activity, Journal of Pharmacy and Technology, 2014; 3(5): 821-831.
58. Abuzarue Aloul R, Gjellan K, Sjolund M, Graffner C, Critical Dissolution Tests of Oral Systems Based on Statistically Designed Experiments. I. Screening Of Critical Fluids and In Vitro/ In Vivo Modelling Of Extended Release Coated Spheres, Drug Development & Industrial Pharmacy, 1995; 23(8): 749-760.
59. J. Catania, F. Gales, D. Alton, Taste Masking Composition of Bitter Pharmaceutical Agents, European Patent Specification, 1993; Page No: 1-9.
60. Affolter and Heidi, Liquid Oral Formulations of Diclofenac, Us Patent 5079001, 1992.
61. Arunothayanum, P, Uchegbu, I.F, Craig, D.Q.M, Turton, A.T, Florence, A.T, Florence, A.T, In Vitro/In Vivo Characterization of Polyhedral Niosomes, International Journal of Pharmaceutics, 1999; 183: 57-61.
62. Bharadia Pd, Patel Mm, Patel Gc, Patel Gn, A Preliminary Investigation on Sesbania Gum As a Pharmaceutical Excipient, International Journal of Pharmaceutical Excipients, 2004; 3: 99-102.

63. Atyabi F, Sharma HL, Mohammad Ha and Fell Jt, Controlled Drug Release From Coated Floating Ion Exchange Resin Beads, *Journal Of Controlled Release*, 1996; 42: 25-28.
64. Litwin, M, J. Antoniewicz, A. niemirska, A. Wierzbička, J. Daszkowska, Z.T. Wawer, R.Janas & R.Grenda, *Americal Journal Of Hypertension*, 2007; 20: 875-82.
65. Billany M R, Suspensions and Emulsions, In Aulton, Me, Editor. *Pharmaceutics; the Design and Manufacture Of Medicines*, 3rd Edition Philadelphia, Churchill Livingstone, 2007; 383-405.
66. Tripathi, K.D. *Essentials of Medical Pharmacology*, 3rd Edition, Jaypee Brothers, Newdelhi, 1994; Page No: 441.
67. R. Brown, R.A. Querica, R. Sigman, Total Nutrient Admixture: A Review, *Jpen*, 1986; 10: 650-658.
68. L.Mladena, P. Ana, G.K. Svetlene and G.B. Ksenija, Comparision Of Dissolution Profiles and Serum Concentrations of Two Lamotrigine Tablet Formulations; *Drugs In R&D*, 2011; 53-60.
69. Nahata M. Lack of Paediatric Drug Formulations. *Pediatrics*, 1999; 104: 607-609.
70. Jafar M, Aejaz A, Studies on Ready Mix Suspension of Ampicillin Trihydrate: Development, Characterization and Invitro Evaluation, *International Journal of Pharmaceutical Sciences*, 2010; 109-12.
71. Amit Kumar Nayak, Dilip Kumar Pal, Dipti Ranjan Pany, Biswaranjan Mohanty, *Journal of Advanced Pharmaceutical Technology & Research*, 2010; 338-341.
72. Nadeem, M, Dandiya, P.C, Pasha, K.V, Imran, M, Balani, D.K, Vohora, S.B, *Indian Drugs*, 1996; 390-396.
73. Zografi G, Schott H, Swarbrick J, *Disperse Systems In Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co, Easton, Pa, 1990; 257.
74. *Oral Liquids*, *British Pharmacopoeia*, London, 1998; 1440-1441.
75. Martin A, *Physical Pharmacy*, 4th Edition, Lea and Febiger, Philadelphia P A, 1993; 453-467.
76. *Martindale's the Complete Drug References*, 34th Edition, Pharmaceuticalpress, 2005; Page No: 406-407.
77. Strickley R.G, Iwata Q, Sylvia W, Dahl T. C, *Pediatric Drugs A Review of Commercially Available Oral Formulations*, *Journal of Pharmaceutical Sciences*, 2007; 1731-1774.
78. Amidon GI, Lennernas H, Shah VP, Crison Jr, *A Theoretical Basis for a Biopharmaceutical Drug Classification, the Correlation of Invitro Drug Dissolution and In vivo Bioavailability*, *Pharmaceutical Research*, 1995; 12: 413-419.

79. Mathur, L.K, Jaffe, J.M, Poust, R.I, Harry, H, Goehl, T.J, Shah, V.P, Colaizzi, J.L, Bioavailability and Dissolution Behaviour Of Trisulfapyrimidines Suspensions, Journal of Pharmaceutical Sciences, 1979; 68: 699-701.
80. Martin A, Swarbrick J, Cammarata A, Physical Pharmacy, Lea and Febiger, Philadelphia and London, 1993; 4th Edition, Page No: 477-511.
81. V.Senthil, R.Suresh Kumar, D. Nagasamy Venkatesh, G.N.K. Ganesh and N.Jawahar, Formulation and Evaluation of the Suspending Properties Of Natural Suspending Agent on Paracetamol Suspension Research, Journal Of Pharmacy and Technology, 2009; 719-722.
82. Ogaji I, Hoag Sw, Effect of Grewia Gum As a Suspending Agent on Ibuprofen Paediatric Formulation, American Association of Pharmaceutical Scientists Pharm Sci Tech, 2011; 07-13.
83. Femi-Oyewo Mn, Adedokun Mo, Olusoga To, Evaluation of the Suspending Properties of Albizia Zygia Gum on Sulphadimidine Suspension, Tropical Journal of Pharmaceutical Research, 2004; Page No: 279-284.
84. Anekant J, Yashwant G and Sanjay K.J, Perspectives of Biodegradable Natural Polysaccharides for Site-Specific Drug Delivery To The Colon, Journal of Pharmaceutical Sciences, 2007; 86-128.
85. Azam Mg and Haider Ss, Evaluation of Dissolution Behaviour of Paracetamol Suspensions, Dhaka University Journal of Pharmaceutical Sciences, 2008; 7: 53-58.
86. Zografi G, Schott H, Swarbrick J. In 'Remingtons Pharmaceutical Sciences (18th Edition) Published by Philadelphia College of Pharmacy and Science, 1990; 257.
87. Singh B, Psyllium As Therapeutic and Drug Delivery Agent, International Journal of Pharmaceutical Sciences, 2007; Page No: 334.
88. Bummer P.M, Remington: The Science and Practice of Pharmacy, Philadelphia College of Pharmacy and Science, 2005; 21st Ed, Page No: 280.
89. Patel Dm, Prajapati Dg, Patel Nm, Seed Mucilage From Ocimum Americanum as Disintegrant In Tablets, Seperation and Evaluation, Indian Journal of Pharmaceutical Sciences 2007; 69: 431-434.
90. British Pharmacopoeia, Genearal Notice (Ph Eur Monograph 1163) Eye Preparations Comply With the Requirements of The European Pharmacopoeia, 2007.
91. Indian Pharmacopoeia, Ministry of Health and Family Welfare, Government of India, the Indian Pharmacopoeial Commission, Ghaziabad, 2007; I.

92. Ansel H.C, Allen L.V. and Popovich, N.G, Pharmaceutical Dosage Forms and Drug Delivery System, 17th Edition, 1999; 13: 347-364.
93. Rosen J, Wething and It's Modification By Surfactant In, Surfactant and Interfacial Phenomenon, Jhonwiley & Sons, Newyork, 1978; 174-176, 262-269.
94. A.K. Kulshreshta, O.N. Singh, G.M. Wall, Pharmaceutical Suspension In From Formulation Development to Manufacturing, Usa, 2010; Page No. 323.
95. M.E. Aulton. "Suspension" Pharmaceutics-The Science of Dosage Form Design, 2nd Edition, Edinburgh, Churchill Livingstone, 2002; Page No: 84-86, 273.
96. Zografi, G Schott, H. and Swarbrick, J, In Remington's Pharmaceutical Sciences (18th Edition) Published by Philadelphia College of Pharmacy and Science, 1990; Page No: 257.
97. Anroop B, Ghosh B, Parcha V, Vasanthi S, Studies on Ocimum Gratissimum Seed Mucilage, Evaluation of Binding Properties, International Journal of Pharmaceutics, 2006; Page No. 191-193.
98. Purkiss R, Kayes Ajb. A Survey of Extemporaneous Oral Liquid Formulations, Pharmaceutical Journal, 1981; Page No: 234,588.
99. Akbuga J, Furosemide-Loaded Ethyl Cellulose Microspheres Prepared by Spherical Crystallization Technique, Morphology and Release Characteristics, International Journal of Pharmaceutics, 1991; 76: 193-198.
100. Temodar (Package Insert), Kenilworth, New Jersey, Schering Corporation, 2004.
101. Nahata M, Lack Of Pediatric Drug Formulations, Pediatrics, 1999; 104: 607-609.
102. The Bio Pharmaceutics Classification System (Bcs) Guidance, Office of Pharmaceutical Science. Available From [Http://Www.Fda.Gov/Cder/Ops/Bcs-Guidance.Htm](http://www.fda.gov/cder/ops/bcs-guidance.htm) on 2008.
103. Edwin J, Edwin S, Dosi S, Raj A, Gupta S, Application of Hibiscus Leaves Mucilage As Suspending Agent, Indian. Journal of Pharmaceutical Education & Research, 2007; 41: 373-375, 701.
104. Whistler, R.L, In Industrial Gums, Academic Press, New York, 2nd Edition, 1973; 13,16.