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Review Article

FORMULATION AND BIO-AVAILABILITY PARAMETERS OF PHARMACEUTICAL SUSPENSION

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ABSTRACT

The suspension is a biphasic liquid or semi-solid dosage form where the finely divided insoluble solid drug particles are homogeneously dispersed in a liquid or semi-solid medium. The solid drug particles act here as the dispersed phase and the liquid or the semi-solid as the dispersion medium. Suspensions contribute to pharmaceutical dosage form development by supplying drugs that are insoluble in all acceptable medium and often distasteful. Suspension translates such drugs into more bio-available form when compared to capsules, tablets, coated tablets, enteric coated tablets and sustained release products. The dosage form is palatable to the patient and many are doing well when applied to the skin or mucous membrane. This particular dosage form is also applied for injecting drugs into the systemic circulation. Therefore, pharmaceutical suspension finds its application through three different routes of administration namely oral, externally applied suspension and injectable one. The success of any dosage form largely depends on formulation parameters and the factors that influence the bioavailability which ultimately dictate the therapeutic success of the formulated dosage form. Hence, it is obvious to discuss the formulation parameters and the factors influencing bioavailability of suspension for the therapeutic success of it.

Keywords: Formulation, Flocculation, Structured vehicles, Bio-availability factors

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INTRODUCTION

The pharmaceutical suspension is a biphasic liquid or semi-solid dosage form where the finely divided insoluble solid drug particles are homogeneously dispersed in a liquid or semi-solid medium. The insoluble solid drug particles act as the dispersed phase or internal phase. The internal phase solid particles are in the size range of 0.5-5 μm [1]. Its uniform distribution throughout the dispersion medium or vehicle is certain by one or a combination of suitable suspending agents. The therapeutic success of any dosage form depends largely on its successful formulation of the dosage form and the bio-availability of the active medicament or drug in the site of action. It is, therefore, obvious to focus and discuss the parameters that directly influence the formulation of suspension and in turn influence the bio-availability of the drug. Thus the authors have made an attempt to discuss the formulation and the bioavailability parameters of a suspension dosage form in this communication.

A pharmaceutical suspension dosage form would be acceptable if it exhibit the below salient features [2]

i) The suspended drug particles should not settle rapidly.

ii) The particles that settle to the bottom of the container must not form a hard cake and should be redispersed homogeneously upon shaking the container.

iii) The suspension must not be too viscous to pour it from the container.

iv) It should have a smooth and elegant appearance.

v) It should be physically and chemically stable.

vi) It should have acceptable color, odour and taste.

vii) Suspension for external application (e. g. lotion), should be fluid enough to spread easily on the skin and yet should not run off the skin surface.

viii) Injectable suspensions should not loose efficiency during sterilization.

ix) Particle size must remain fairly constant throughout shelf period.

Suspension offers several advantages in comparison to other dosage forms and are listed below [2]

i) The drugs that are unstable or degradable in solution form can be dispensed as suspension.

ii) The suspension is the chosen dosage form for water insoluble drugs and when non-aqueous vehicles are not acceptable, e. g., Corticosteroids suspension.

iii) The suspension is most suitable for drugs having an unpleasant taste and odor e. g., Chloramphenicol palmitate, a bitter tasting drug.

iv) Suspension functioning as reservoir able the drug to be absorbed in the systemic circulation for a sustained period, e. g., Protamine zinc-Insulin.

v) Suspension improves the bioavailability of a drug when compared to the equivalent dose of a tablet or capsule.

Classification of suspension on the basis of route of administration

i) Oral suspension

Oral suspension is biphasic liquid dosage form that contains one or more active ingredients suspended in a suitable vehicle. Suspended solids and or drugs may slowly separate on standing but are easily redispersed upon shaking. These kinds of suspensions are formulated to administer drugs like antibiotics which may contain a dose in the range of 125-500 mg/5 ml of the suspension. In paediatric drops, the concentration of suspended drugs may be relatively higher. Drugs with different activities like antacids, antibacterial, antibiotic, analgesic, antihelminthic, anticonvulsant and antifungal could be formulated as an oral suspension. Azithromycin and Ofloxacin are the examples of drugs dispensed as oral paediatric suspension.

Advantages

(a) It is easy to swallow suspended insoluble powdered drugs especially by the paediatric and geriatric patient than the tablets and capsules.

(b) The suspension ensures faster dissolution needed for absorption compared to the tablets and capsules.

(c) The palatability and stability issues could be answered satisfactorily for the water-insoluble drugs.

(d) The bitter taste of the drug can be masked by incorporating a suitable flavouring and sweetening agent in the formulation.

ii) Injectable suspension [3]

Injectable suspensions are heterogeneous systems consisting of the drug dispersed in a liquid medium. They are sterile, pyrogen free and physically and chemically stabile over the intended shelf-life. They are administered through the subcutaneous and intramuscular routes. They are not administered intravenously as it may lead to vaso-occlusion. They may usually contain a drug concentration in between 0.5-5.0% which passes easily through the hypodermic needle. So, a particle size of less than 5µm facilitates syringe ability. The viscosity of the medium is also kept optimum to avoid any kind of interference with particles flow. Procaine benzyl penicillin, known as Procaine penicillin G and Benzathine benzylpenicillin were also known as benzathine penicillin G are the examples of antibiotics which are injected intramuscularly. A sterile suspension of insulin modified by the addition of zinc chloride and protamine sulfate known as Protamine Zinc-Insulin suspension is another example of an antidiabetic agent used for the prolonged availability of the drug in the systemic circulation. Vaccines are immunising agents which are a dispersion of killed causative microorganism (e. g. Cholera vaccine) and toxoids, on the other hand, are chemically modified toxins from the pathogenic microorganism, which is no longer toxic but possess the antigenic property to stimulate the anti-toxin formation, for e. g. Diphtheria, Botulism and Tetanus toxoids. Toxoids are adsorbed onto the substrate like aluminium hydroxide or phosphate and made into a suspension type dosage form.

Advantages

(a) Therapeutic use of drugs those are insoluble in conventional solvents (i.e. water, water miscible and water immiscible).

(b) Increase chemical stability when compared to solution dosage forms.

(c) Possible for depot formation.

(d) First-pass effect can be by-passed.

iii) Externally applied suspension

Externally applied suspensions are used topically and designed for dermatological, cosmetic and protective purposes. Such kind of suspension should spread easily and must not be too fluidic to run off the skin surface. Calamine lotion is a classic example of such suspension applied for protective rationale but it also possesses a cosmetic feel. Many lotions with a suspension structure are meant for application on broken skin and must be free from microorganisms. Suspensions as lotion architecture are easy to apply and less messy compared to other semi-solid external preparations. The application of suspension is not confined as a lotion but extends as inhalations, ear drops and ophthalmic products.

Advantages

(a) Suspensions of insoluble drugs may also be used externally, often as protective agents.

Classification of suspension on the basis of electro-kinetic nature of solid particles [4]

i) Flocculated suspension

Flocculation is an architecture which results from the lowering of the electrical forces of repulsion between the dispersed particles of suspension along with dominant attraction force. Under this condition, the particles with reduced repulsive force approach each other resulting into a loosely aggregated structure popularly known as *floc*. As the *floc* or *floccule* is composed of many individual particles resulting in a large network of individual particles, the rate of sedimentation is always rapid. The floccules have loose porous structure and the dispersion medium can flow through them during sedimentation. The floccules also entrap a large amount of the liquid phase. Therefore, the volume of the final sediment will still be large and facilitate re-dispersion with ease by moderate shaking. Though the floccules settle rapidly than individual discrete particles, flocculated particles form a lattice type structure that resists complete settling and thus are less prone to compaction and cake formation.

ii) Deflocculated suspension

In a deflocculated suspension, the individual particles remain as discrete separated units and settle slowly. The slow rate of settling of particles prevents the individual particles of this suspension to entrap any liquid medium and becomes compacted leading to cake formation. This cake may be very difficult to re-disperse by moderate agitation. This phenomenon of caking is a very serious physical stability issue encountered in suspension. Another characteristic feature of this suspension is that the supernatant remains cloudy for sufficient time after shaking. This is primarily attributed to the very slow settling rate of the smallest particles of the suspension.

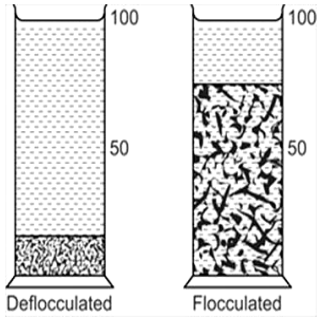

Fig. 1: Schematic representation of deflocculated and flocculated suspension

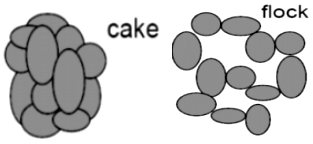

Fig. 2: Schematic representations of cake and flock formed in deflocculated and flocculated suspension respectively

Table 1: A comparative scenario between flocculated and deflocculated suspension is depicted

Flocculated suspension	Deflocculated suspension
Particles form a loose aggregate (floccules) and form a network-like structure.	Particles exist as separate entities and do not form floccules.
The rate of sedimentation is high.	The rate of sedimentation is slow.
Sediment is easy to re-disperse.	Sediment is difficult to re-disperse.
Sediment is loosely packed and does not form a hard cake.	Sediment is tightly packed and forms a hard cake.
The supernatant is clear.	The supernatant is hazy.
Floccules stick to the sides of the bottle.	Particles do not stick to the sides of the bottle.
The suspension is not pleasing in appearance.	The suspension is pleasing in appearance.

Formulation of suspension [2]

The formulation of a suspension depends on whether the suspension is flocculated or deflocculated in nature. The subject of formulation could be conceptualised by a flow chart as depicted below in fig. 3. However, there are three common approaches that are applied to formulate a suspension. These are 1) Controlled flocculation, 2) Structured vehicle and 3) Controlled flocculation in the structured vehicle. The formulation approaches are represented schematically in fig. 3.

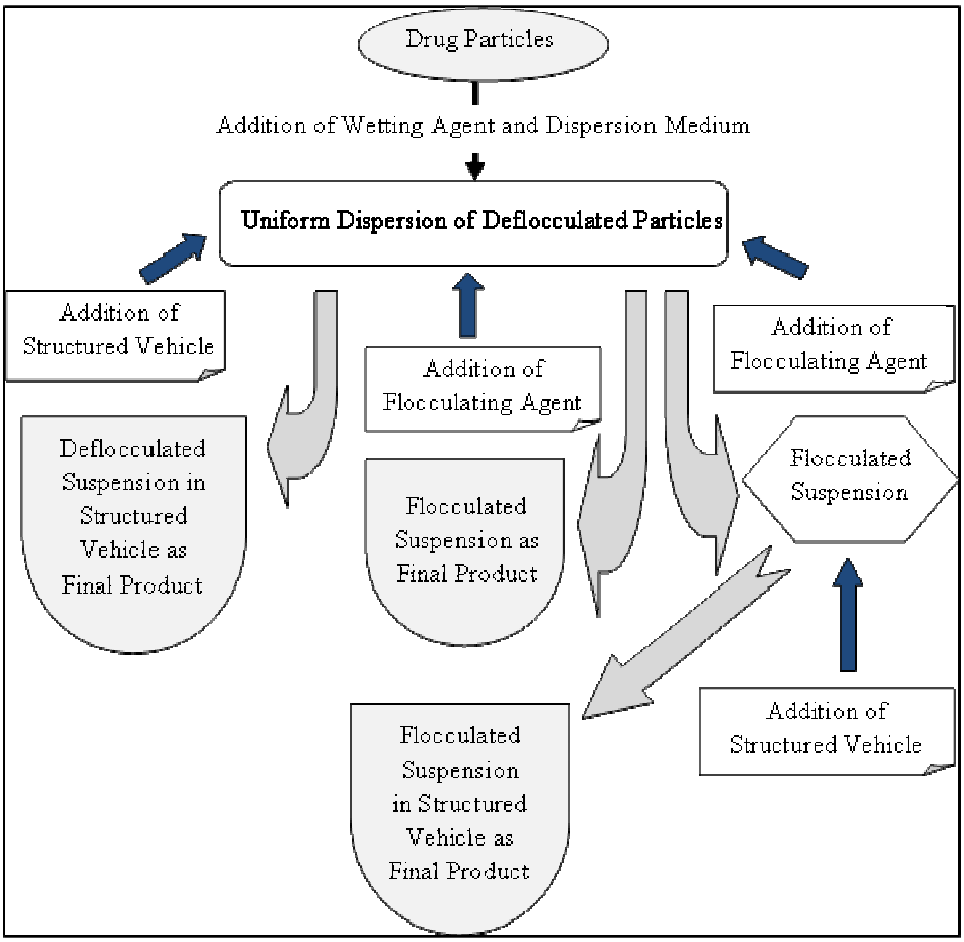

Fig. 3: Flow chart focusing the approaches for formulation of suspension

1) Controlled flocculation

Flocculation is a process of making loose contact or adhesion of the particles dispersed in a liquid medium. This phenomenon is materialized by a precise balance of attractive and repulsive forces between the dispersed particles of the liquid medium. This flocculation may be controlled by the optimum elevation of the force of attraction over the force of repulsion, resulting into a larger size cluster or a network like structure. The term flocculation may carry a negative connotation but in many cases, by controlling this flocculation we may actually produce a more desirable featured suspension than the de-flocculated one. An uncontrolled flocculation, on the other hand, may cause too much precipitate, reduce gloss and increase the viscosity. Thus it is very important to control the flocculation to make a stable and therapeutically effective dosage form.

To achieve *controlled flocculation* the flocculating agents that may be needed [5], a) *electrolytes* b) *surfactants* and c) *polymers*.

a) Electrolytes

The electrolytes act by altering the zeta potential of the dispersed particles of the suspension. The zeta potential is the difference in potential between the surface of the tightly bound layer (shear plane) of the dispersed particle and the electro-neutral region of the bulk. When the electrolytes lower the zeta potential to a particular value, the electrical barrier between the dispersed particles reduces and the particles approach each other. This results into flocculation in place. The flocculation ability of an electrolyte depends on its valency. The divalent ions are ten times more effective then the monovalent ions while trivalent ones are thousand times more effective. Being more efficient, the application of trivalent ions is limited because of their toxicity. The most widely used electrolytes as flocculating agent include sodium salts of chlorides, acetates, phosphates and citrates. The concentration of the electrolytes must be optimum to achieve flocculation otherwise, any excess quantity may cause a reversal of this and may lead to deflocculation. In the fig. 4, the flocculated and the deflocculated condition of Bismuth subnitrate is shown to be depended on the concentration of an electrolyte, monobasic potassium phosphate (KH2PO4).

When the particles of bismuth subnitrate are dispersed in water, the positive surface charge contributed by bismuth ions yield strong force of repulsion between adjacent particles. The bismuth subnitrate suspension thus takes a deflocculated texture. When a series of bismuth subnitrate suspensions are prepared to contain an increasing concentration of monobasic potassium phosphate a strong correlation is observed between the apparent zeta potential and sedimentation volume, caking and flocculation. As the electrolyte concentration increased, the positive zeta potential of the suspension decreases due to the adsorption of negatively charged phosphate anion supplied by monobasic potassium phosphate. At a particular concentration range of monobasic potassium phosphate,

the deflocculated bismuth subnitrate suspension becomes flocculated. This conversion is evident by the absence of caking with a concomitant increase in sedimentation volume. With further addition of the electrolyte, the zeta potential of the suspension eventually falls to zero and then increases in the negative direction. When the zeta potential becomes sufficiently negative, all the bismuth subnitrate particles behave like a negatively charged species and the repulsive force again dominate. The suspension becomes deflocculated and the sedimentation volume starts to fall. Finally caking is observed which is a clear indication of deflocculated texture of the suspension.

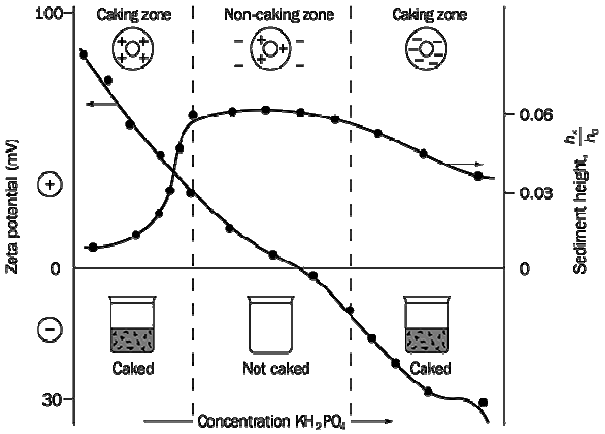

Fig. 4: Typical relationships between caking, zeta potential and sedimentation volume, as a negatively charged flocculating agent is added to a suspension of positively charged particles

b) Surfactants

Both ionic and non-ionic surfactants are capable of doing flocculation of the suspended particles. At a particular concentration, the surfactants trim down the surface free energy by reducing the interfacial tension between the liquid medium and solid drug particles. This may lead to form closely packed agglomerates. However, at a particular surfactant concentration, when the particles possess less surface free energy, they are attracted towards each other by Van der Waal's force and form a loose agglomerate. Ionic surfactants cause flocculation by neutralizing the charge on each particle, resulting into a flocculated suspension. When the surfactants reduce the interfacial tension, the liquid becomes capable of displacing the adsorbed film of air from the surface of solid drug particle and facilitating wetting. Hence, the concentration of surfactant needs to be adjusted very carefully as it facilitates the wetting and also functions as a deflocculating agent to achieve dispersion. Table 2 enlist all types of surfactants that may be used to produce controlled flocculation.

c) Polymers

Polymers are high molecular weight compounds with long-chain in their structure. They play an important role as a flocculating agent. The mechanism of polymer induced flocculation is less well understood than the inorganic electrolytes. The function of a polymer in place depends on its affinity for the particle surface as well as charge, size and orientation of it in the continuous medium. Many polymers have polar functional groups in its hydrocarbon backbone. As a result of this, the polymer molecule may adsorb on the particle surface and maintain a degree of interaction with the liquid continuous medium. Polymers can produce both flocculated and deflocculated suspensions. An ionic polymer has the potential to affect the zeta potential of a particle in a manner similar to inorganic electrolytes. The flocculating role of a polymer is due to the bridging of the polymer between the surfaces of different particles. At a higher concentration, sufficient binding sites are available on the particles, permitting additional inter-particle attachments to form. At this intermediate concentration, optimum flocculation and sedimentation volume takes place. At high concentration, complete coverage of the particle surface with polymer occurs and insufficient binding sites remains to permit interparticle bridging which results into a low degree of flocculation. This high concentration of polymer also prevents the close association of individual particles by a phenomenon known as *steric stabilization*. Steric stabilization is the ability of adsorbed polymers to prevent close approach and cohesion of dispersed particles due to the energetically unfavourable conditions. Suspension formulated with a relatively high concentration of polymer would be deflocculated with small sedimentation volume (fig. 5). The conformation of the polymer in the continuous phase may also have an effect on the degree of flocculation. At concentration where flocculation occurs, polymers having a linear conformation in the continuous phase will be more effective flocculants than the polymers that are coiled. In many cases, a combination of polymer and inorganic electrolyte are used to achieve flocculation. Generally, the sensitivity of the dispersed solid particles for flocculation is enhanced by electrolytes when used in presence polymers.

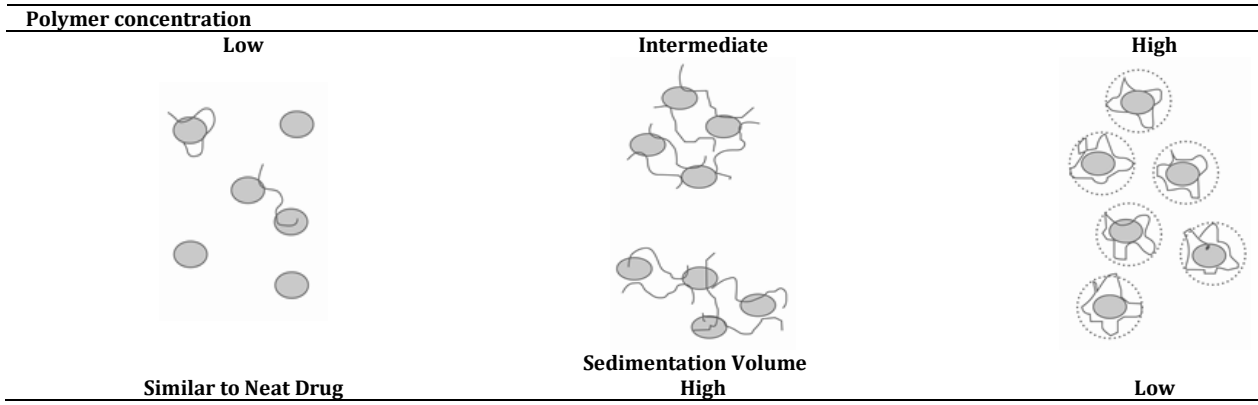

Fig. 5: Flocculation by hydrophilic polymers. The optimal degree of flocculation and sedimentation volume occurs when a large number of interparticle bridges are formed. High concentrations of polymer result in a deflocculated suspension via steric repulsion

2) Structured vehicle

Structured vehicles are aqueous dispersions of natural and synthetic gums. When the gums are dispersed homogeneously in the aqueous medium, its viscosity increases. That is why they are also known as thickening agents. This thickness of the continuous medium retards the settling of the individual particles of a suspension. Hence the structured vehicles are also known as suspending agents. It is important to note that too high viscosity may cause causes difficulty in pouring and administration. It may also affect the absorption of

the drug since the polymeric counterparts are adsorbed onto the surface of the particle and thus suppress the rate of dissolution.

The structured vehicle approach brings into play the formulation of a physically stable suspension. The construction of the vehicle ensures the particles to remain as deflocculated. The vehicles act by entrapping the individual particles and translating them into a deflocculated suspension with an endeavour that no settling occurs in a place. But in practice, some degree of sedimentation takes place. As the structured vehicles exhibit pseudo plastic rheological behavior are endowed with shear-thinning property which facilitates the reformation of the suspension to a uniform dispersion. Thus the suspension flows readily from the container when shear is applied and a uniform distribution of particles in each dose could be assured. However, the application of structured vehicles in the formulation of suspensions for the parenteral route is restricted due to their high viscosity and the lack of sufficient syringe ability. The most commonly used polymers in pharmaceutical suspension to function as a structured vehicle are Methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, acacia, gelatin and tragacanth. These polymers are non-toxic, pharmacologically inert and compatible with a wide range of active ingredients.

3) Flocculation in structured vehicles

From the stability point of view, suspensions that contain discrete solid particles may be regarded as stable. But in practice, the sedimentation of the solid particles occurs on long standing due to its size. Smaller the particle size, more the surface free energy. These highly energetic finer particles tend to release the energy associated with them. As a result, the particles approach each other and form a closely packed structure. This structure is heavier and sediment at the bottom and the smaller particles fills within the voids of larger particles leaving a cloudy supernatant liquid due to colloidal particles. The particles of the lowest layer are pressed by the weights of the particles above them thus overcoming the electric repulsive barrier. This leads to the formation of hard cake which is very difficult to redisperse upon shaking.

The construction of structured vehicle ensures the formation of deflocculated suspension. Under such formation, if the principle of flocculation is applied, it may produce floccules that will settle rapidly but the dispersion of it could be achieved with ease. For successful flocculation in the structured vehicle, we need an appropriately charged flocculating agent or flocculent and a hydrocolloid as a protective colloid. To formulate a stable suspension containing positively charged drug particles, first of all, flocks are produced by negatively charged flocculants. Then the negatively charged hydrocolloid suspending agent like Carboxymethylcellulose, Carbopol 934, Veegum, Tragacanth and Bentonite are used. As the flocculent and suspending agent both are negatively charged, they are compatible with each other and a stable suspension was formed. But in case the drug particles are negatively charged, then a positively charged flocculent is needed to make the flocks. Under this situation, if a negatively charged suspending agent is used, an incompatible product will form. It will ultimately deteriorate the flocculating property of the flocculent and the protective property of the suspending agent. To avoid such situation, a positively charged suspending agent like Gelatin, Fatty acid Amine etc. are to be used. Now the flocculent and suspending agent both is positively charged and as they are compatible with each other, a stable suspension will form. There is another approach which may produce a stable suspension. In this approach irrespective to the charge of drug particles whether positive, negative or neutral, it will be coated first with a positively charged protective colloid. This will transform all types of charged particles coated with a colloid of positive charge. At this moment if negatively charged flocculant is used, it will produce a stable suspension.

Table 2: Types of surfactants that may be used to produce controlled flocculation

Surfactants		
	Polymeric Surfactants	The polyxamers (also known as pluronics are a series of neutral synthetic polyoxyethylene polypropylene block copolymers. Eg. Poloxamer 188 (Pluronic F68).
Ionic Surfactants are irritant and toxic to the mucous membrane.	Anionic Surfactants Cationic Surfactants	They also have antimicrobial properties and are the most toxic and irritant, as compared with other surfactants eg. Cetrimide (cetyltri-methylammonium bromide, benzalkonium chloride).
Least toxic surfactants.	Non-Ionic Surfactants	Eg. Tweens, Spans (polysorbates), macrogols.
	Amphoteric Surfactants.	Eg. Phospholipids, Glyceryl monostearate, glyceryl monooleate.

Bio-availability influencing factors of suspension

The major rate-limiting step in the absorption of drugs from suspension dosage form is drug dissolution which is generally rapid due to the large surface area of the particles. Suspensions are expected to demonstrate improved bioavailability compared to the same drug formulated as a tablet or capsule. This is because the suspension already contains discrete drug particles whereas tablet dosage from must undergo disintegration in order to maximize the necessary dissolution process. Frequently antacid suspensions are perceived as being more rapid in action and therefore more effective than an equivalent dose in the form of tablets.

1) Particle size and shape

The particle size of the active pharmaceutical ingredient (API) and inert excipients is a very important parameter that has a huge influence on the bio-availability of a drug from suspension. Particle size affects the formulation, stability and efficacy of the dosage form. Dissolution rate is a direct function of the total surface area for a dispersed phase. The surface area increases inversely with the particles size according to the expression [6]:

$$S_v = \frac{6}{d}$$

Where S_v = specific surface area and d = average particle diameter.

When the particles are non-spherical there is an extra energy indulgence and consequently an increase in the viscosity.

2) Polymorphism

The effect of the polymorphism on bio-availability is more significant when dissolution is the rate limiting step. Polymorphism of pharmaceuticals is the ability of the molecule to assemble into multiple crystal structures. Different polymorphs have different arrangements of atoms within the unit cell, and this can quite often have a remarkable impact on the physicochemical properties of the crystallized compound. Different polymorphs of a drug can display different physicochemical properties, including stability and reactivity, dissolution rate and solubility. All these parameters can affect the pharmacokinetics and Pharmacodynamics [7]. Amorphous forms are disordered molecular arrangements and do not exhibit 3D crystalline lattice, hence they tend to have higher dissolution rate and solubility. This result into increased rate and extent of oral absorption compared to the crystalline drugs.

3) Wetting agent

It is a prerequisite that the hydrophobic drug particles must be wetted properly for the uniform dispersion in the continuous medium. The

wetting is very important irrespective of the physical nature of the drug, diffusible or in-diffusible. The finely distributed hydrophobic drug particles are coated with a film of air preventing its dispersion in the external medium. If the drug particles are not wetted properly, the suspension may exhibit poor physical stability and poor dissolution properties. As a result, the drugs bioavailability and *in vivo* performances can greatly be at stake. Hence the issue of wetting must be addressed precisely. The wettability is characterized by the contact angle of the liquid (usually water) with the solid surface. The smaller the contact angle, the greater the wettability of the solid (fig. 6). The formation of a well wetted solid surface is a fundamental step in the formation of the acceptable suspension. However, the wettability of a drug substance may vary with crystal form, crystal habit, surface roughness, surface area, porosity and particle size.

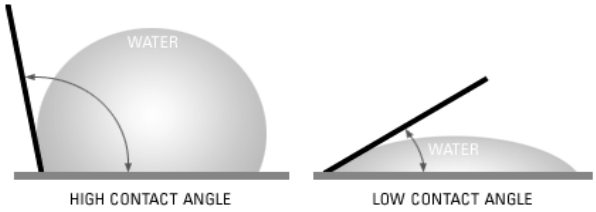

Fig. 6: Schematic representation of water drops creating an angle on the solid surface

There are three kinds of wetting agent that are commonly used i) *Surfactants* ii) *Hydrophilic Polymers* iii) *Water miscible liquids*.

i) Surfactants

They act by reducing the interfacial tension between the surface of the insoluble solid particle and the surrounding water medium. This enables the water to approach towards the solid surface and wetting takes place. The surfactants can be anionic, cationic, amphoteric and even non-ionic in charge. Few examples are polysorbates, sorbitan esters etc.

ii) Hydrophilic polymers

When the hydrophilic polymers coat the insoluble solid particles, the hydrophilic nature of the polymer induces some wetting of the particles. Few examples of polymers are acacia, cellulose derivatives, tragacanth, gum acacia, alginate, pectin, carragenan etc.

iii) Water miscible liquids

There are certain solvents/liquids that are miscible with water and reduce liquid air interfacial tension. Then the liquid penetrates in individual surface and facilitate wetting. Few examples are alcohol, glycerin, propylene glycol etc.

4) Viscosity of the medium

Viscosity or the flow property of the medium is extremely important issues that need to be addressed precisely. The flow property or rheology of the suspension must be characterized and manipulate to ensure the optimal performance of the dosage form. While the less viscous suspension leads to rapid settlement of dispersed drug particles and may lead to caking formation, a bizarre in suspension making technology; on the other hand highly viscous suspension is very difficult to shake and prone to non-uniform dosing. Moreover, higher viscosity of the suspension diminishes the diffusion coefficient of the drug resulting into a slower dissolution rate of the drug. Hence, the viscosity of the medium directly influences the bio-availability of the drug.

The viscosity of the dispersion arises from two sources: a) *Intrinsic viscosity of dispersion medium* and b) *Interaction of the particles of dispersed phase*.

a) Intrinsic viscosity of dispersion

The intrinsic viscosity or the inherent viscosity of the dispersion medium affects the dissolution rate of particles through its effect on the diffusion coefficient, D. Increase in viscosity decrease the diffusion coefficient, which decreases the dissolution rate and ultimately influencing bioavailability and therapeutic success of the dosage form.

The relation of diffusion of drug particles through a liquid medium of low Reynolds number is expressed by Stokes-Einstein equation,

$$D = \frac{k_B T}{6\pi\eta r}$$

Where, D = Diffusion coefficient, η = viscosity of the medium, k_B = Boltzmann's constant. The value of Boltzmann's constant is approximately $1.3807 \times 10^{-}$[23] joules/kelvin. T = Absolute temperature and r = radius of the spherical particle.

From the above equation, it is clear that the diffusion coefficient of the drug is inversely related with the viscosity of the medium. Diffusion coefficient of the drug decreases proportionately with the increased viscosity of the medium and vice versa. This viscosity of the medium is primarily attributed to the random Brownian movement of the polymer chain resulting into an entangled structure. This polymeric entanglement entraps the water molecules inside the lattice and viscosity increases. Upon agitation i.e. when the shear stress (Force/Area) is applied the polymeric entanglement disrupts and disentanglement initiates, translating into a parallel orientation of the polymer chain. As a result of this the entrapped water molecules are liberated to the surrounding atmosphere and viscosity of the medium decreases.

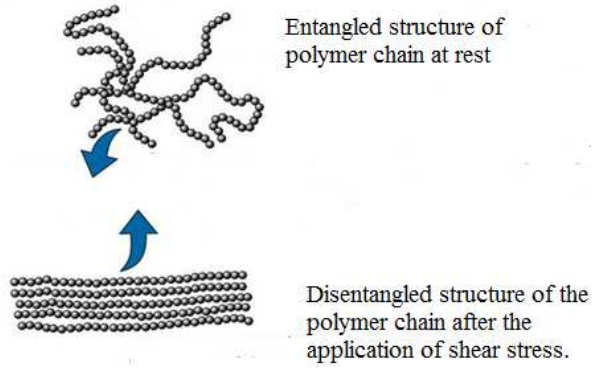

Fig. 7: Polymer chain orientation before and after the application of shear stress

Hence, the concentration of the polymer material must be optimized to achieve desirable diffusion rate of the drug in the surrounding medium followed by its availability in the blood circulation. In addition to that to formulate a stable suspension with a desirable sedimentation rate, the optimization of polymer concentration is very essential. However, high viscosity may retard the rate of gastric emptying and reduce drug absorption.

b) Interaction of the particles of dispersed phase

The Stokes-Einstein equation also expresses that smaller the radius of the particle, higher the diffusion coefficient. Hence, the smaller particles size for a good suspension may be advocated. From the previous discussion, it is also clear that smaller particles exhibit enormous surface area which is an essential prerequisite for faster/better dissolution. When the particles are non-spherical there is an extra energy indulgence and consequently an increase in the viscosity. In dilute suspensions this increase is reflected by the intrinsic viscosity as per Einstein equation, $\eta_r = 1+[\eta]\phi$

Where ϕ = volume fraction of the particles and $[\eta]$ = intrinsic viscosity of the particles. The value of $[\eta]$ depends on particles shape, being 2.5 for rigid spheres [8]. Hence, the above equation clarifies that the intrinsic viscosity of the suspension depends on the volume fraction of the particles. So, more number of drug particles

in the suspension, higher is the intrinsic viscosity. So drug's concentration is an important issue that also influences the bio-availability.

4) Suspending agent

A stable suspension should have a desirable sedimentation rate. To control the sedimentation rate suitable suspending agent are required. An ideal suspending agent should exhibit high viscosity at a negligible shear rate and low viscosity at high shear rate. From the rheological point of view, the agents should exhibit pseudoplastic flow behavior and show thixotropy. The carboxymethyl cellulose and micronized bentonite show the above rheological properties if mixed in 50:50 ratio. Hydrocolloids like methyl cellulose, sodium carboxymethyl cellulose, gelatin, tragacanth or alginates are the polymers mostly used as suspending agents exhibit pseudoplastic flow behavior. They increase the viscosity of the suspension and retards settling. However, such polymer if used inappropriately may reduce the *in vivo* diffusion rate, the dissolution rate and finally the absorption rate of the drug may also be reduced. Thixotropic agents such as sodium bentonite magma, colloidal silicon dioxide are incorporated in the suspension to confer high apparent viscosity and produce a yield value. At rest, this high viscosity retards sedimentation because below the yield value there is no flow. However, when the suspension is shaken at a shear stress above the yield value, the thixotropic structure breakdown and the apparent viscosity reduces. When the container is kept in shelf the thixotropy predominates and the *sol*-like consistency of the suspension converts to *gel* like consistency.

CONCLUSION

Today pharmaceutical suspension has occupied a vast space among the dosage forms. It can administer through different routes like oral, external and injectable. Hence, the optimization of formulation parameters of this dosage form is a very challenging task. The rationale of optimized formulation for a particular therapeutic target would only be achieved if the bio-availability issues are addressed properly.

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CONFLICT OF INTERESTS

Declared none

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