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Pharmaceutical suspensions: A review

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Abstract
The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product. The drug and pharmaceutical materials utilized must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer and safe. The product should be manufactured under appropriate measures of quality control and packaged in containers that contribute to product stability. The product should be labeled to promote correct use and be stored under conditions that contribute to maximum shelf life.
Methods for the preparation of specific types of dosage forms and drug delivery systems are described in subsequent chapters. This chapter presents some general considerations regarding pharmaceutical ingredients, drug product formulation, and standards for good manufacturing practice.

Keywords: Pharmaceutical, physical, chemical, biological

Introduction
Suspensions are an important category of pharmaceutical formulation and present many challenges to formula development personnel because of their inherent instability of structure and manufacturing and packaging problems. Suspensions may be meant for oral administration, external application or parenteral use. They generally consist of a finely divided solid (individual particles ranging in size from 0.5 to 5.0µ) suspended in a liquid or semi-solid vehicle which constitutes the continuous phase. Many suspensions are these days marketed as dry powders which are 'constituted' before use by incorporation of specified amounts of a vehicle. Such 'suspensions' are produced mainly on account of considerations of stability.
The particle size of the disperse phase is a very important consideration in suspension formulation. Suspensions for topical application should have very small particle size to avoid a gritty feel on application and to provide greater coverage and protection to the area to which the suspension is applied. In case, the solid substance is meant for skin penetration, its small size will give a quicker rate of dissolution and hence of the penetration. In suspensions, meant for introduction into the ophthalmic cavity, the particle size should not go beyond 10µ. Below this size the patient feels no pain but above this the suspension may give a feeling of pain or discomfort. Injectable suspensions should have a particle size that can easily pass through the syringe needle. The needle shaped particles generally give a sustained action and hence are preferable in 'depot' type products [1].

Types of suspensions
1. According to the route of administration
- Oral suspensions should be taken by oral route and therefore must contain suitable flavoring and sweetening agents.
- Topical suspensions meant for external application and therefore should be free from gritty particles.
- Parenteral suspensions should be sterile and should possess property of syringability.
- Ophthalmic suspensions should be sterile and should possess very fine particles

2. According to nature of dispersed phase and methods of preparation
The suspensions are classified as suspensions containing diffusible solids, indiffusible solids, poorly wettable solids, precipitate forming liquids and products of chemical reactions.

3. According to nature of sediment

- **Flocculated Suspensions**

In this type the solid particles of dispersed phase aggregate leading to network like structure of solid particles in dispersion medium. The aggregates form no hard cake. These aggregates settle rapidly due to their size as rate of sedimentation is high and sediment formed is loose and easily redispersible. The suspension is not elegant, as dispersed phase tends to separate out from the dispersion medium. Therefore it is desired that flocculation should be carried out in a controlled manner so that a balance exists between the rate of sedimentation and nature of sediment formed and pourability of the suspension.

- **Non flocculated Suspensions**

In this type the solid particles exist as separate entities in dispersion medium. The sediments form hard cake. The solid drug particles settle slowly as rate of sedimentation is low as sediments are formed eventually there is difficulty of redispersion. The suspension is more elegant as dispersed phase remain suspended for a long time giving uniform appearance [2].

Approaches for developing suspensions

- **Structured Vehicles**

The approach employed in the preparation of physically sable suspensions involve the use of structured vehicle so that particles remain deflocculated and applying the principles of flocculation to produce floccules that settle rapidly with ease of dispersibility with a minimum agitation. Structured vehicles act by entrapping the deflocculated particles so that no settling occurs. Practically some degree of sedimentation usually takes place. The Shear-thinning property of these vehicles facilitates the reformation of a uniform dispersion when shear is applied. Thus the product must flow readily from the container and possess a uniform distribution of particles in each dose. Controlled Flocculation from stability point of view a suspension in which all the particles remain discrete are regarded to be stable, However in pharmaceutical suspension solid particles are coarser and sedimentation is due to size of the particles. The electrical repulsive forces between the particles allow to form a closely packed sediment at the bottom, whereas the smaller particles fills within the voids of larger particles leaving a cloudy supernatant liquid due to colloidal particles. The particles, which form the lowest layer in the pack, are pressed by the weights of the particles above them thus overcoming the repulsive barrier. Whereas in the case of particles in the secondary minimum, which is a desirable state for a pharmaceutical suspension, the particles form a lose aggregates known as floccules. The sedimentation of floccules is rapid leading to loosely packed high volume sediment which are easily redispersible.

- **Rheological Behaviour**

Plastic or pseudoplastic flow is exhibited by flocculated suspension depending upon concentration. The apparent viscosity of flocculated suspensions is high when applied shearing stress is low but decreases as the applied stress increases and the attractive forces resulting in flocculation are overcome. The dialant flow is exhibited by the concentrated deflocculated suspensions. The apparent viscosity is low at low shearing stress however it increases as the applied stress increases. The rheological consideration are of interest to investigate the viscosity of a suspension as it affects the settling of dispersed particles, transformation of flow properties while a suspension is shaken and product is poured out of bottle and the lotion when it is applied to effected area [3].

Applications of suspensions

- Drugs that have very low solubility are usefully formulated as suspensions.
- If people have difficulty swallowing solid dosage forms, the drug map need to be dispersed into a liquid form.
- Drugs that have an unpleasant taste in their soluble form can be made into insoluble derivatives, and formulated as a suspension, which will be more palatable. For example chloramphenicol (soluble), chloramphenicol palmitate (insoluble.)
- In oral suspensions the drug is delivered in finely divided form, therefore dissolution occurs immediately in the gastrointestinal (GI) fluids. The rate of absorption of a drug from a suspension is usually faster than when delivered as a solid oral dosage form, but slower than the rate from solution. The rate of availability of drug from as suspension is dependent on the viscosity; the more viscous the product, the slower the release of drug.
- Insoluble forms of drugs may prolong the action of a drug by preventing rapid degradation of the drug in the presence of water.
- When the drug is unstable in contact with the vehicle, suspensions are prepared immediately prior to handing out to the patient in order to reduce the amount of time that the drug particles are in contact with the dispersion medium. For example with ampicillin suspension, water is added to powder or granules, prior to giving out to the patient. A 14- day expiry date is given, if kept in the fridge [4].

Properties of a good pharmaceutical suspension

- There is ready redispersion of any sediment produced on storage.
- After gentle shaking, the medicament stays in suspension long enough for a dose to be accurately measured.
- The suspension is pourable.
- Particles in suspension are small and relatively uniform in size, so that the product is free from a gritty texture.

Theories involved in disperse phase

- **Interfacial phenomenon**

Smaller solid particles are used to disperse in a continuous medium. Smaller particle size and large surface area is associated with a surface free energy making it thermodynamically unstable. Thus the particles possess high energy which leads to grouping together to reduce surface free energy thus leading to formation of floccules. These floccules are held together among themselves and within by weak van der walls forces. However in cases where particles are adhered by stronger forces to form aggregates forming hard cake. These phenomena occur in order to make system more thermodynamically stable. In order to achieve a state of stability the system tend to reduce the surface free energy, which may be accomplished by reduction of interfacial tension that is achieved by use of surfactants.

- **Electrical double layer and zeta potential**

Most surfaces acquire a surface electric charge when they come in contact with aqueous surface. A solid charged surface when in contact with an aqueous medium possesses positive and negative.

The equation of stokes' law reflects that larger particles exhibit greater velocity of sedimentation. The velocity of sedimentation is inversely proportional to the viscosity of dispersion medium.

- **DLVO Theory**

According to DLVO (Derjaguin Landau and overbeek) theory, in a dispersed system the interactions involved between particles are electrical repulsion and van der walls attraction. The total potential energy of interaction is addition of these parameters [5].

Formulation of suspensions

The three steps that can be taken to ensure formulation of an elegant pharmaceutical suspension are:

- Control particle size. on a small scale, this can be done using a mortar and pestle, to grind down ingredients to a fine powder
- Use a thickening agent to increase viscosity of vehicle, using suspending agents of viscosity- increasing agents
- Use a wetting agent [6].

Preservation of supensions

Water is the most common source of microbial contamination. All pharmaceutical preparations that contain water are therefore susceptible to microbial growth. Also the naturally occurring additives such as acacia and tragacanth may be sources of microbes and spores. Preservative action may be diminished because of adsorption of the preservative onto solid particles of drug, or interaction with suspending agents. Useful preservatives include chloroform water, benzoic acid and hydroxybenzoates.

The dispensing of suspensions

The method of dispensing of suspensions is the same for most, with some differences for specific ingredients.

- Crystalline and granular solids are finely powdered in the mortar. The suspending agent should then be added and mixed thoroughly in the mortar. Do not apply to much pressure, otherwise gumming or caking of the suspending agent will occur and heat of friction will make it sticky.
- Add a little of the liquid vehicle to make a paste and mix well until smooth and free of lumps. Continue with gradual additions until complete [7, 8].

Stability of suspensions

The physical stability of a pharmaceutical suspension is the condition in which the particles do no aggregate and in which they remain uniformly distributed throughout the dispersions. In order to achieve this ideal situation the suspension should have additive, which are added to achieve ease in resuspension by a moderate amount of agitation. Taking a case example; In case of dispersion of positively charged particles that is flocculated by addition of an anionic electrolyte like monobasic potassium phosphate. The physical stability of the system is enhanced by addition of carboxymethylcellulose, Carbopol 934, veegum, tragacanth or bentonite either alone or in combination. No physical incompatibility is recorded as majority of hydrophilic colloids are negatively charged and are compatible with anionic flocculating agents. When a flocculated suspension of negatively charged particles with a cationic electrolyte is prepared (aluminum chloride) the addition of hydrocolloid may result in an incompatible product resulting in stingy mass, which has no suspending action, and settle rapidly. In such a condition protective agent is added to change the sign on the particles from the negative to positive is employed which can also be achieved by the adsorption onto the particle surface by fatty acid amine or gelatin. Thus an anionic electrolyte is used to produce floccules that are compatible with negatively charged suspending agent [9].

Quality control tests for suspensions

- **Sedimentation volume**

Redispersibility is the major consideration in assessing the acceptability of a suspension. The measurement of the sedimentation volume and its ease of redispersion form two of the most common basic evaluative procedures. The sedimentation volume is the simple ratio of the height of sediment to initial height of the initial suspension. The larger the value better is the suspendability.

- **Particle size and size distribution**

The freeze-thaw cycling technique used to assess suspension for stress testing for stability testing result in increase of particle growth and may indicate future state after long storage. It is of importance to study the changes for absolute particle size and particle size distribution. It is performed by optical microscopy, sedimentation by using Andreasen apparatus and Coulter counter apparatus, none of these methods are direct methods. The sedimentation method yields a particle size relative to the rate at which particles settle through a suspending medium.

- **Rheological studies**

Rheologic methods can help in determining the settling behaviour of the suspension. Brookefield viscometer with variable shear stress control can be used for evaluation viscosity of suspensions. It consist of T-bar spindle which is lowered into the suspension and the dial reading is noted which is a measure of resistance the spindle meets at various levels in the suspension. This technique also Indicates in which level of the suspension the structure is greater due to particles aggregates.

Data obtained on aged and stored suspension reveals whether changes have taken place [10].

Preparation of suspensions form dry powders and granules for reconstitution

Suspensions may be prepared from previously manufactured dry powders or granules if the liquid preparation has a limited shelf life because of chemical or physical instability. Powders should firstly be loosened from the bottom of the container by lightly tapping against a hard surface. The specified amount of cold, purified water should then be added, some times in two or more portions, with shaking, until all the dry powder is suspended. The container is usually over-sized in order to allow adequate shaking for reconstitution. Some suspensions may be prepared by the patient immediately before taking from individually packed sachets of powder or from bulk solids.

Containers for suspensions

Suspensions should be packed in amber bottles, plain for internal use and ribbed for external use. There should be adequate air space above the liquid to allow shaking and ease of pouring. A 5 ml medicine spoon or oral syringe should be given when the suspension is for oral use.

Special labels and advice for suspensions

The most important additional label for suspensions is 'Shake well before use', as some sedimentation of medicament would normally be expected. Shaking the bottle will redisperse the medicament and ensure that an accurate or aliquot does can be measured by the patient.

"Store in a cool place.' Stability of suspensions may be adversely affected by extremes and variations of temperature. Some suspensions, such as those made from reconstituting dry powders, may need to be stored in the refrigerator.

Extemporaneously prepared and reconstituted suspensions will have a relatively short shelf life. They are usually required to be recently or freshly prepared, with a 1-4 week expiry date. Some official formulae state an expiry date, but many do not. The pharmacist may have to make judgments about the expiry date for a particular preparation, based on its constituents and likely storage conditions. The manufacturer's literature for reconstituted products will give recommended storage conditions [11, 12].

Conclusion

This paper will consider how suspensions can best be evaluated to see how well they meet the purpose for which they were designed. The performance check of suspensions will not be reviewed from the standpoint of the control chemist who is following a standard set of procedures on a series of production samples and whose curiosity and need are generally satisfied when he has a yes or no answer. Rather, suspensions will be examined at the research and development stage in their evolution and through the eyes of the pharmacists who want to be certain that they have the very best possible formulation for the job at hand.

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