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A Review on Pharmaceutical Suspension and Its Advancement

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Abstract

Pharmaceutical formulation such as suspensions are plays an important role in drug delivery. Due to their inherent instability of structure many challenges are present at the time of formula development. They generally include fine solid particles (size from 0.5 μm to 5.0 μm) which are suspended into a desirable vehicle i.e., liquid or semi liquids acts as a continuous phase. Suspensions are used and marketed for years but there are stability related limitations which are conquer using modern approaches and methodologies such as polymer coating suspension, Nanosuspension, encapsulation.

Keywords: Drug delivery; Encapsulation; Pharmaceutical formulation; Polymer coating suspension; Suspensions

Introduction

We can say suspensions are those course dispersions in which internal phase i.e., coarse powder is dispersed into the external phase i.e., liquid vehicle. Internal phase that consists of solid particles that are uniformly suspended in sufficient amount of vehicle by the addition of individual or combined form of suspending agents. Vehicles in external phase are commonly aqueous in nature in oral preparation, on the other side organic and oily liquids are used for non-oral preparations. Nowadays, many suspensions are marketed in the form of powder which are suspended into specified amount of vehicle just before use because of stability considerations [1]. Insoluble particles must be uniformly dispersed in ideal suspensions. The solid particles are isolated from the liquid as sediments in a standing state. Usually, the volume of sediment should be re-dispersed evenly in the system while shaking. The settling rate can be enhanced with the help of agents which increase viscosity. For preparing elegant and smooth product suspended particles should be smaller in size and avoid gritty texture [2]. In the dispersed phase particle size is very important to consider in suspensions. Suspensions that are used for external/ topical applications should contain very small number of particles because large molecules can produce gritty feel and skin irritation. Small particle size enhances the coverage and provide protection of that area at which suspension is applied [3]. Small size of particles also enhances the skin penetration and increase the dissolution rate. Suspensions that are used for ophthalmic purpose, must contain particle size not beyond 10 μm, if the size above than this range then patient feels discomfort and pain during the administration. Suspension used for parenteral route must contain particle of smaller size which can easily pass from the needle of syringe [4].

Types of Suspensions

According to route of administration

Oral suspensions: These suspensions are given through oral route therefore they contain flavoring and sweetening compounds for masking of bitter taste of drug [5].

Topical suspensions: These are applied on external surface of body, and must be free from any type of gritty particles so that they can't cause irritation on skin [6].

Parenteral suspensions: These suspensions are administered through parenteral routes like intravenously or intramuscularly that's why they should be sterile and free from foreign particles [7].

Ophthalmics suspensions: Ophthalmic suspensions are used to treat eyes disorder that's why these should also be sterile and should be free from foreign particles [8].

On proportion of solid particles

Dilute suspension: In dilute suspensions the concentration of solid particles is in concentration

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of 2% to 10% w/v.

Concentrated suspensions: In concentrated suspension the number of solid particles are in concentration about 50% w/v [9].

On the basis of particles size of solid

Colloidal suspension: size of particle <1 micron.

Coarse suspension: size of particle >1 micron.

Nano suspension: particle size is 10 ng.

According to the nature of dispersed phase and method of preparation

- Suspension containing diffusible solids
- Suspensions containing in diffusible solid
- Pooling wettable solids
- Precipitate forming liquids

According to the nature of sedimentation rate

Flocculated suspensions: In flocculated suspension the dispersed phase formed clusters and produced a network like structure of solid particles in the medium. These clusters do not form a hard cake. They settle down rapidly due to their size results in high sedimentation rate. In flocculated suspension sediment is loosely bound and easily re-dispersible. To balance between the rate of sedimentation and the nature of the sediment formed it should be taken care that the flocculation must be formulate in a controlled manner [10].

Non-flocculated suspension: In non-flocculating suspensions the solid particles are present in a separate manner in the dispersion medium. These segments are prepared as a hard cake. The solid particles slowly settle down, sedimentation rate is also low, due to which hard cake formation takes place and it is difficult to re-disperse [11].

Advantages of Suspension

- Duration of drug and onset of drug can be controlled.
- It masks the bitter taste of drugs example chloramphenicol.
- In the comparison of other doses form suspension have higher rate of bioavailability. Order of bioavailability is as follow: solution >suspension >capsule >compressed tablets >coated tablet.
- Chemical stability of some drugs can improve by making suspension E.g., penicillin G.
- Efficient in intramuscular depot therapy.
- Use of co-solvents can be avoided.
- Easy to swallow for elder patients [12].

Disadvantages of Suspension

- Difficulties in formulating the formulation.
- During handling and transportation sufficient care is required.
- Sedimentation and stability can cause problems.
- Chances of non-uniformity and non-accuracy of dose.

Applications of Suspensions

- People who have difficulty in swallowing of solid dosage forms like tablets can be takes oral suspensions easily.
- The absorption rate of drug from gastrointestinal tract is quicker in suspension because drug is delivered in finely divided form.
- Drugs which have low solubility can be formulated in suspension.
- Some drugs which are unstable in aqueous vehicle for long period are marketed in the form of powder, so that suspension can be prepare at the time of administration.
- Contrast media use for the diagnosis purpose is also given in the form of suspension. E.g., barium sulphate for examination of alimentary canal [13].

Approaches for the Development of Suspensions

Structured vehicle

Structured vehicles are used for preparation of physically stabilized suspensions so that the solid particles remain deflocculated. The principle of flocculation is applied so that a minimum aggregation of floccules takes place which can be easily re-dispersed. Structured vehicles entrap the non-flocculating particles so that settling of particle can't occur. The vehicles also have a shear thinning property that facilitates the formation of a uniform dispersal whenever shear is applied. The product must be readily flow from the container and retain a uniformly distribution of particles in every dose [14].

Rheological behavioral

Plastic or pseudoplastic flow is exhibited by flocculated suspension which is depend on the concentration of solid particles. When the applied shear stress is low then the viscosity of flocculated suspension is high. The dilatant flow is exhibited by the concentrated deflocculated suspensions. The rheological consideration are of interest to investigate the viscosity which affects the settling of dispersion of solid particles. Flow properties are transformed whenever a suspension has been shaken [15].

Theories Involved in Disperse Phase

Interfacial phenomenon

Very small size solid particles are used in continuous medium. Smaller size of particles and large surface area is correlated with a surface free energy that makes it thermodynamically unstable [16]. High energy particles grouped together which leads to formation of floccules. Weak van der wall forces plays important role in it. In other cases where particles are bonded with strong forces are aggregate to form a hard cake. To achieve high stable product the system tends to reduce the surface free energy of particles, which is gained by reduction of interfacial tension by adding surface active agents [17].

Electrical double layer and zeta potential

Zeta potential is known as the potential between the solution's electron neutral region and the surface of the close boundary layer, i.e., the shear plane. Most surfaces gain a charge i.e., this is called electrical surface charge. In contact with the water, a charged solid surface creates two opposite poles one is positively and other is negatively charged [18]. The Zeta potential has a functional application in suspension stability involving solid dispersion. Zeta potential has a practical application in stability of the suspension containing solid dispersed particles. Whenever the zeta potential is reduced under a

certain value, the attractive forces exceed the repulsive forces so that the particles come closer, this process is known as flocculation. We can say that the flocculated suspension has zeta potential in the range of -20 to +20 mv [19].

DLVO theory (Derjaguin Landau and Overbeek Theory)

According to this theory the total potential energy of interaction is the addition of electrical repulsion forces and van der walls attraction that are involve in dispersed system.

Formulation of Pharmaceutical Suspensions

Structured vehicles

To formulate stable suspensions saturated vehicle is the important part of formulation from stability criteria. The main drawback of suspensions is that stability considerations during storage for long duration of time period. To reduce this difficulty the term "structured vehicle" gets introduced. Structured vehicle is also known as thickening agent. The vehicle behaves like a "false body", which is able to maintain the particles suspended which is more or less stable [20]. Structured vehicles are only feasible on deflocculating suspensions, where the solid particles settle down and formed a hard cake that must be dispersed uniformly and easily at the time of admission. Saturated vehicles are not applicable on flocculating suspension because the settled molecules redispersed on shaking of container. Structured vehicles are not used in the formulation of parenteral suspensions because of their viscosity enhancer property that creates a problem during administration through syringe [21]. Structure vehicle also consist of some thixotropic properties i.e., GEL-SOL-GEL transformation. Preparation of saturated vehicle: In particular medium hydrocolloids firstly hydrolyzed and swell to 2 degree and increase the viscosity at the lower concentration. Density of structured vehicle also increased by: Polyethylene glycol, glycerin [22].

Suspending agent

Suspending agent are compounds that form film around solid particles and reduce the inter-particle attraction. Some suspending agents perform other function such as imparting viscosity to the solution. At resting condition, the solution must be sufficiently viscous in nature for the prevention of sedimentation and cake formation of particles [23]. Agents which provide a thixotropic property are preferable suspending agent. E.g., Xanthan gum, sodium carboxymethyl cellulose, Avicel RC591, etc. In parenteral suspensions the suspending density modifying agents are used such as PEG (Polyethylene Glycol) 3350, PEG 4000 etc., The PEG having molecular weight ranging about 300 g/mol to 6000 g/mol are suitable as suspending agent for parenterals. The amount of the suspending agent is depends on the presence of other components which may contributes viscosity to the medium [24]. In comparative studies it was found that combination of suspending agents are more beneficial than individual. Some important and most commonly used suspending agents are as follow.

Methyl cellulose

There are many types of viscosity grades of methyl cellulose present. Owing to variations in methylation and polymer chain length, these differences exist. It is soluble in both hot and cold forms of water. When we add methyl cellulose to hot water and cooled it, a transparent and opalescent viscous solution is formed with a continuous stirring. It is stable in the 3 to 11 pH range. At temperatures above 500°c, the solution is transformed into gel. When it cooled down it becomes solution. Methyl cellulose is not absorbed by gastrointestinal tract and it is nontoxic too [25].

Hydroxyethyl cellulose

Hydroxyethyl Cellulose (HEC) is a strong suspending agent and like methyl cellulose, has similar properties. HEC is soluble in hot and cold water, but like methyl cellulose, does not form gel when heated [26].

Carboxymethyl cellulose

Carboxymethyl cellulose is available in various viscosity grades and is used in low, medium and high viscosity grades. The selection of the right CMC grade depends on the stability and viscosity of the suspension [27].

Sodium carboxymethyl cellulose

Sodium carboxymethyl cellulose depends on the degree of polymerization. It is found in various viscosities. It is soluble in hot and cold water and stable in the 5 to 10 pH range. It is incompatible with polyvalent cations [28].

Tragacanth

By nature, tragacanth is viscous. It converts the solution into thixotropic solution. It is better thickening agent than acacia. The maximum viscosity of solution is achieved after several days, because it takes several days to hydrate completely [29].

Xanthan gum

Concentration of xanthan gum is depends on the active pharmaceutical ingredient. The xanthan concentration is about 0.08% w/w to 0.12% w/w. The concentration for paracetamol suspension is between 0.1% w/w to 0.3% w/w.

Wetting agents

Wetting agents are a material that decreases water's surface tension such that it spreads drops on to the surface and improves liquid spreading abilities. Hydrophilic surfaces are quickly moistened by water, but non-polar liquids moisten hydrophobic compounds. Wetting with water depends on the material's hydrophilicity. Wetting inability means that there is a strong interfacial tension between liquid and particles [30]. In the preparation of pharmaceutical suspensions nonionic surface-active agents are used instead of ionic surfactants because they are incompatible with some adjuvants and cause changes in the pH. They have HLB value between 7 to 10. If the HLB value is high then it acts as forming agents [31].

Surface active agents

Surface active agents are certain substances that reduce the interfacial tension between solid particles. Nonionic surface-active agents are commonly used but ionic surfactants are often used depending upon certain conditions. Instead of pluronics and Poloxamers, all surfactants are typically bitter in flavor. Surfactant Polysorbate 80 is commonly used for oral and parental formulation. The explanation behind polysorbate 80's widespread use is that it is non-ionic, so it does not change with pH, non-toxic, compatible with adjuvants and safe for oral use [32].

Buffering agents

Buffers are the compounds which resist the changes in the pH. For the stability purpose all liquids formulations should be formulated on an optimum pH. Other properties like rheology and viscosity are also depends on pH of the system. In the formulation in which API consist of ionizable acidic or basic groups are stable at pH 4 to 10.

Ideally buffers should be compatible with other excipients and should have less toxic effects. Salts of weekly acids are the most widely used buffers. E.g., carbonates, gluconates, citrates, etc. Buffer prevents decomposition of active pharmaceutical ingredient by changing in pH. Buffer maintains physical and physiological stability [33].

Preservatives

In suspensions natural occurring agents like tragacanth, acacia etc. are quickly degraded by microorganisms. If the suspensions do not preserve properly then the microbes cause stability problems which involves loss in suspending activity of suspending agents, loss of color, flavor and odor. To prevent these activities preservatives are included in the formulation. Preservatives are those compounds which prevents the formulation from the microbial growth. Ideally preservatives are nontoxic, should not affect by pH, should not be e absorbed by the surface of the container and should be compatible with other excipients [34]. The effectiveness of preservatives is supposed to be preserved in airtight glass containers. In plastic containers, the most common issue is that the preservative sticks to the surface of the plastic containers [35]. Combination of two or more preservative are more beneficial in the formulation such as they are less toxic, wide spectrum of activity and can be used in less concentration. For example, nowadays combination of benzalkonium chloride, phenoxetol, and phenylethyl alcohol are used in eye drops. Some examples of preservatives are cetrimide, propylene glycol, disodium edetate, benzoic acid, sorbic acid, methyl paraben, potassium sorbate etc. [36].

Osmotic agents

Osmotic agents are used in the preparation of ophthalmic and parenteral suspensions to maintain the osmotic pressure. Dextrose, sorbitol and mannitol are usually used as osmotic agents in ophthalmic preparations. In parenteral tonicity regulating agents are used like sodium chloride, sodium sulphate and glycerol [37].

Flavoring agents

Flavoring agents are those compounds which provides a flavor and increase the drug acceptance of patient. Flavoring and coloring agents are used to improve the attractiveness and masking of the unpleasant and better taste of the drug. Color and flavor are varied according to country. Examples of flavoring agents are Acacia, ginger, anise oil, glucose, benzaldehyde, glycerin, tolu balsam, honey, vanilla, vanilla tincture, lemon oil, clove oil, orange oil, rose oil, fennel oil, coriander oil etc. [38].

Humectants

Humectants are the compounds which absorbs the moisture and help in prevention of active pharmaceutical ingredient by moisture. Propylene glycol and glycol are most common used humectants and used in the concentration of 4% w/w [39].

Antioxidants

These compounds prevent drug from oxidation and enhance the stability of formulation. Examples: Ascorbic acid derivatives, tocopherol, thiol derivatives like cysteine, thioglycerol etc.

Coloring agents

Coloring agents are those compounds which provide color to the formulation. Natural as well as synthetic sources are used to obtain them. Natural colors are obtained from plants, animals and minerals source; mineral colors are known as pigments. The synthetic dyes should be used under the range of 0.0005% to 0.001%. Example of coloring agents are titanium dioxide (white), indigo carmine (blue), tetrazine (yellow), caramel(brown), Etc. [40].

In-Process Quality Control of Suspensions

To ensure and monitor the final product's quality and also to rectify the existing defect, quality control processes are done by the manufacturer. Production employees implement and document quality control in order to ensure consistent output.

Objectives of in Process Quality Control

- For the prevention of inter - batch and intra-batch variability.
- Ensure that good manufacturing practices are implemented or not.
- To ensure final product quantity.

In Process Quality Control Tests for Suspensions

In Process Quality Control Tests to ensure the stability, safety and quality products. These are as follows.

Phase test for appearance

Appearance tests are frequently performed on the dispersed phase as well as on dispersion medium. Purified water is typically used to prepare the suspension. In this test, the purity of the syrup, solid particle distribution, gum dispersion consistency and water quality are usually monitored. Rheological tests are carried out to guarantee that the medium has the desired viscosity, allowing for the formulation of a stable and re-dispersible suspension. Before mixing of dispersed phase, viscosity of dispersion medium is ensured. Brooke field viscometer is a device that is used for determining the viscosity of suspension. The calculation obtained by test are compared with a standard reference, and an action is taken if the defect is found [41].

Particle size of dispersed phase test

The size of a drug's particles has a significant impact on the end product's stability. This test is done by analyzing the particles size microscopically. The particle size of the medications is compared to the optimum particle size necessary, and if there is a difference, rigorous action is taken.

Pourability test

This test is carried out to check that final formulation is pourable or not, and do not create any difficulty at the time of filling in container and during handling by patients.

pH test

The pH of the formulation is crucial to its stability. So different types of vehicles and phases of suspensions are monitor before and after mixing. Records are also maintained timely to verify that proper pH can be maintained.

Final product assay test

This test ensures that active components is evenly distributed throughout the formulation or not. In this test the sample is withdrawn and assay is carried out to find out the degree of homogeneity. If a flaw is discovered, it is repaired by closely monitoring the formulation procedures.

Zeta potential management

Zeta potential provide information about the future stability of

the suspension. Microelectrophoresis or a device known as a Zeta meter are used to determine zeta potential [42].

Centrifugation test

A centrifugation test is used to determine the suspension's physical stability. Before packaging, uniform color dispersion and the absence of air globules are examined.

Packaging of Suspension

Packaging materials specifically contributes to the suspension's stability and acceptability. In today's life, pharmacists need to be aware of the broad range of packaging materials due to the advancement of drug regulations worldwide and growing sophistication in terms of dosage type. The industrial pharmacist should understand the interrelationship of material properties to optimize the shelf life of suspension. Pharmaceutical suspensions are commonly packed in wide mouth containers, that have a space to ensure the proper mixing while shaking. Glass ampoules or vials are used to package parenteral suspensions. Ideally the packaging material should be inert. It should be effective to preserve the product from light, air and other factors. It should be cheap and effective in transportation to deliver the product without any difficulty [43].

Materials Used for Packaging

Suspension packaging is typically made of various grades of glass and plastic.

Plastic

Nowadays plastic are widely used for packaging purpose due to too many advantages instead of glass. Plastic are non-breakable, lightweight and are flexible. Materials used for plastic packaging are polyethylene, PVC, polysorbate etc. The following considerations are taken into account when choosing plastic as a suspension packing material: Leaching, permeation, chemical reactions, sorption, and changes in plastic physical qualities [44].

Glass

In most cases, non-parenteral suspensions are made with soda lime and borosilicate glass. The formulations that are degraded by light are packed by amber colored glass containers. Amber glass prevent from the UV light passage through the formulation.

Disadvantages of glasses:

- Difficult in transportation and handling, easily breakable.
- Types of glasses and additives use for providing Amber color
- Soda lime: FeO+ sulfur
- Borosilicate: FeO+ TiO_2

Closure: All containers except ampoules require an elastomeric closure. Closures should be compatible with formulation. The integrity of the closer and seal should not be harmed as a result of processing. Closure can be made up of rubber and plastics [45].

FDA regulations for packaging: FDA evaluates the drugs packaging, they must be firmly convinced that the packaging used for particular drug will preserve the efficacy of the formulation as well as its purity, identity and quality also. FDA published list that are (GRAS) "Generally Recognized as Safe". The substances that are not come under this list must be evaluated by manufacturer and submitted to FDA [46].

Special Labels and Advice for Suspensions

"Shake well before use" is the most important note mentioned on the label of suspension as some sedimentation of medicament would normally be expected. Shaking of container help in redispersion of the medicament and ensure that accurate dose is intake by patients. "Store in cool place" stability is altered with change in temperature. Some suspensions, that are made by reconstituting dry powder, are may be stored in refrigerator.

Innovation in Suspensions

Polymer coating of drugs suspension

Polymer Coating help the patient to perceived the taste of formulation by swallowing the drug particles before the threshold concentrate reached into the mouth. Ethyl cellulose, Eudragit RS 100 as well as Eudragit RS 30 D and some other polymers are used for coating purpose. This process is commonly used for the preparation of reconstitutable powders or the dry powder drugs which are converted into suspension by mixing in liquid vehicle like water just before use. These re-constitute powders coated by polymers have a long shelf-life [47].

Encapsulation with basic substance

In this process drug having bitter taste is mixed with basic substance. After that this mixture is encapsulated with polymers (cellulose derivatives, vinyl derivatives etc.). Now this encapsulated product is suspended and dispersed in suspending medium to obtained a final product [48].

Coating and pH control

In pH control method, those drugs which are soluble at low pH are preferably maintained in suspension at a high pH where the drug particles are insoluble and vice-versa. By applying polymeric coating, we can avoid the solubilization of drug and taste masking can also achieved [49].

Nano-Suspensions

Nano-suspensions will improve the potency of drugs which are insoluble and less drug membrane permeability which delivered at a size of less than 50 nm. During formulation of I.V. suspension, particle size should be less than 50 nm, the suspension particles circulate for long period by avoiding the normal reticuloendothelial system filtration mechanisms. In the case of oral delivery system, the nanometer size molecules are may be allowed to deliver the active pharmaceutical ingredient through gastrointestinal tract into the blood, at minimum degradation in GIT and with high desirable rate. To cross the barriers, insoluble particles of this size are designed. Nanoparticulate degradable polymer structures is one of another strategy that involve encapsulation of active drug [50].

Advantages of nano-suspension

- It helps in poorly water-soluble drugs.
- In case of intra-cutaneous and intramuscular administration it helps in reducing the tissue irritation.
- Quick resolution and quick targeting can be achieved through intravenous route.
- When we administer through oral route nano-suspensions provide rapid and better bioavailability.
- Due to presence of stabilizers long term stability can be

achieved.

- Nanosuspensions are also incorporated in tablets, pallets, suppositories.

Disadvantages of Nanosuspensions

- Difficulty in achieving uniform and accurate dose.
- Due to bulky nature that's why sufficient care must be taken for the handling and transportation.

Applications of Nano-formulations

- Parenteral administration
- Parenteral route is preferred for those drugs which are not absorbed by GIT or undergoes first-pass metabolism. Parenteral route has very fast action and low quantity of drug is required from this route because of high bioavailability.
- Bioavailability enhancement
- The bioavailability of oral route is less because of low solubility in the GIT.
- Pulmonary administration
- Water soluble nanosuspensions can be directly delivered in lungs by the help of nebulizers. Due to small size of particles, it is likely that each drop must contain at least one particle of drug that leads to more uniform distribution of drugs in lungs.

Targeted Drug Delivery

It is mainly used for targeting antimicrobial and antifungal drugs.

Sustained Release Suspensions

In this method duration of action of drug is increased without affecting its onset action. In the case of suspension, sustained release is affected by the polymer coating of drug formulation. Polymer coating help in masking of bitter drugs and also increase the duration of action. The main advantage of this method is that it reduced the dose frequency. Some examples of polymer which are used in the sustained release suspension are: Ethyl cellulose, Eudragit, Cellulose acetate etc. In the novel drug delivery development multi-unit formulations like microparticles have more beneficial instead of single unit formulations. Multi-unit formulations can also be formulated in the form of liquid suspensions that allows the adjustment of flexibility and swallowing for pediatric and aged patients.

Advantages of sustained release suspensions

- Improve patient's compliance by reducing frequency of dosing.
- They are economically fit.
- It enables increased reliability of therapy
- Efficacy improved.

Mechanism of Drug Release from Matrix Device

Dissolution controlled release

The simplest to make is a sustained release oral product that uses dissolution as the time limiter. If dissolution rate is high then it is feasible to convert into the tablet having low dissolution rate with the help of carrier [51].

Dissolution control formulations are categorized as:

- Encapsulation dissolution control
- Matrix dissolution control
- Diffusion controlled release
- Encapsulation diffusion controlled
- Matrix diffusion controlled

Conclusion

Recent advancement in pharmaceutical suspension such as polymer coating suspension, Nanosuspension, encapsulation with basic compounds, etc. helped in overcoming limitations of traditional suspension. This advancement helped in improving in drug release, dissolution time, membrane permeability, bioavailability, drug disposition, and also improved physiochemical limitations of traditional suspension. Vigorous research work has been conducting on developing new dosage formulation and improving existing dosage forms to overcome the limitations and increase patient compatibility. Suspensions has been an effective dosage form from long time and recent advancement shows its potential in target treatment therapeutics, patient compatibility and effectiveness.

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