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Nanosuspension Formulation by High Pressure Homogenization (HPH)

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ABSTRACT

In recent years many scientists are focusing to develop nano formulation to enhance bioavailability of poorly soluble drug. Nanosuspensions is one of the approach to increase solubility and bioavailability of BCS class 2 and Class 4 drug. There are many technique to formulate nanosuspensions but High Pressure Homogenization method is most widely used as it applicable for many drug and having several advantages over other methods. Formulated nanosuspension can be evaluated by parameters like Particle size, Surface charge (Zeta potential),Crystalline state and particle morphology, Saturation solubility and Dissolution velocity, pH, Viscosity. Nanosuspensions have many applications and it is used by various route viz Oral, Parenteral, Pulmonary, Occular, Topical.

Keywords : Nanosuspension, High Pressure Homogenization, Bioavailability

I. INTRODUCTION

Nanosuspensions are aqueous suspensions containing submicronsized drug substances and appropriate stabilizers. A very finely dispersed solid drug particles in an aqueous vehicle in which diameter of suspended particle is less than 1 um in size, stabilized by surfactants, which is given by oral,topical, parentral or pulmonary administration. Due to reduced particle size it shows increased dissolution rate which ultimately shows improvement in bioavailability. Average particle size ranges from 200-600 nm.

Bioavailability is the rate and extent to which drug substance absorbed from a drug product and is available at the site of action.Due to poor solubility less amount of drug get absorbed from site of action. Dissolution within the gastrointestinal tract is necessary for good oral bioavailability.Improvement of bioavailability of poorly water-soluble drug is one of the challenging aspects of drug development. Nearly 40% of new chemical entities discovered by the pharmaceutical industry are poorly water compounds.

Advantages of Nanosuspension over conventional dosage form:

1. Formulation of nanosuspensions is easy also manufacturing process can be applied at large scale.
2. Nanosuspensions is quite stable for longer duration due to use of Stabilizers,
3. It can be orally administered which shows rapid onset of action improved bioavailability

4. IV route of administration of nanosuspension increases dissolution and tissue targeting it also shows less tissue irritation.
5. Ocular administration of Nanosuspensionsshows more bioavailability.
6. Nanosuspensionsshows increase in the bioavailability of drugs which have high log P value
7. Biological performance of drug get increased due toincrease in dissolution rate and saturation solubility.
8. It can can be delivered various route of administration like oral, parenteral, topical by incorporating in different dosage form.

Drug selection Criteria for nanosuspensions

Nanosuspension can be prepared for the API that is having either of the following proprties:

a. Water insoluble but which are soluble in oil
b. Drug with high log P or API whicih insoluble in both water and oils
c. Drugs which have low tendency of the crystal to dissolve
d. Drug which have high dose.

Formulation Consideration for nanosuspension

Stabilizers: It helps to wet drug particles also prevent Ostwald's ripening andagglomeration of nanosuspensions, providing a steric or ionic barrier. e.g Soya Lecithins, Poloxamers188/407, Polysorbate 80, HPMC E-15/E-50, PVP K-25/K-30.

Co-surfactants : It influence phase behavior when microemulsions are used to formulate nanosuspensions.e.g Bile salts, DipotassiumGlycyrrhizinate, Transcutol, Ethanol, Isopropanol

Organic solvent :These should be pharmaceutically acceptable and less hazardous solvent for preparation of formulation. e.g Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, Ethyl formate, Butyl lactate, Triacetin, Propylene carbonate, Benzyl alcohol.

Various Methods Fornanosuspension Manufacturing

Those methods are generally classified into three categories as

(1) top-down technology,

(2) bottom-up technology, and

(3) combination technology.

Other preparation techniques, such as supercritical fluid technology, emulsification-solvent evaporation method, and melt emulsification method.

As mentioned above there are various methods of Nanosuspension formulation but High Pressure Homoginization have its own advantages over othermethods.

High Pressure Homoginization

This method is known as top down approach because larger size particles are broken into smaller one into stabilizer solution which ranges size in nano scale. There are two main methods like high energy High Pressure Homogenization and low energy Media milling.

This method is most widely used for nanosuspension formulation as it is very easey method and applicable for most of drug which are water insoluble. This method consist of three steps. In first step pre suspension of drug powder is prepared then in second step pre suspension is homogenised at lower pressure and higher pressure which known as pre milling. In the final step 10 to 25 cycles performed at higher pressure unless get desired size of particle.

Different types of High Pressure Homoginization

a)Homogenization in aqueous media (Disso cubes):

Disso cube is sub type of High P pressure homoginization which involve use of aqueous media. In this method suspension is forcefully passed

through a small gap where 1500 bar pressure is applied. This results in decrese in the static pressure and increase in thedynamic pressure at whcich water start to boil this will generate bubbles.

After the suspension leaves the gap and the pressure returns to atmospheric levels, the gas bubbles will collapse, causing the gas bubbles to burst. The drug particles fracture into nano-size as a result of the implosion, collisions, and severe shear. The physical features of the resultant nanosuspensions, such as the particle size distribution, may be influenced by factors such as drug particle hardness, number of homogenization cycles, homogenization pressure used, and temperature. The Dissocubes technique has a number of advantages. There was no erosion of treated materials. Nanosuspensions with extremely low and high concentrations may be made using drug quantities ranging from 1 mg/mL to 400 mg/mL. It also enables aseptic nanosuspension synthesis for ophthalmic and parenteral delivery. Under 20 homogenization cycles, even less than 1 ppm metal contamination was identified when a high pressure of 1500 bar was applied. The fundamental drawback of this procedure is that it takes several cycles of homogenization and pretreatment to get microparticles before homogenization. Another disadvantage is the expensive cost of instruments, which drives up the cost of dose formulation.

b) Homogenization in nonaqueous media (Nanopure):

The nanopure method, which is carried out at low temperatures and is also known as the deep-freeze method, is another high-pressure homogenization procedure. Because of the low vapour pressure of oils or oily fatty acids and their high boiling point, cavitation does not develop when drug nanocrystals are disseminated in water mixes or nonaqueous media. The drug nanosuspensions in nonaqueous medium were homogenised at below the freezing point due to inadequate pressure reduction. As a result, thermo-labile substances can be processed using the nanopure method. Suspensions homogenised in water-free medium or water combinations such as PEG 400, PEG 1000, and others are known as nanopure. The homogenization can be carried out at ambient temperature or at temperatures below freezing (-200C), thus the term "deep freeze" homogenization.

C) Combination Method H69:

This method involve combination of Anti Precipitation and High Pressure Homoginization. Initially drug dissolved in suitable solvent and thissolution is added drop wise to stabilizer solution which result in precipitation. After precipitation it is passed through high pressure homoginization. This process known as H69.

Advantages of High Pressure Homogenization Method

1)It Provide aseptic condition which is useful for parenteral and ophthalmic preparation

2) It does not cause the erosion of processed materials.

3)Low risk of product contamination.

4) It is applicable to the drugs that are poorly soluble in both aqueous and organic media.

5)The disadvantage of precipitation technique such as crystal growth and long term stability can be overcome by using the Nanoedge technology

6) Particles of smaller size and better stability in short time can be achieved.

Evaluation Parameters

Nanosuspension can be evaluated for Particle size, Surface charge (Zeta potential),Crystalline state and particle morphology, Saturation solubility and Dissolution velocity, pH, Viscosity.

1) Mean particle size and particle size distribution:

The saturation solubility, dissolving rate, physical stability, and even invivo behaviour of nanosuspensions are all influenced by the mean particle size and particle size distribution. Photon correlation spectroscopy (PCS), laser diffraction (LD),

and the Coulter counter multisizer may all be used to determine the particle size distribution. PCS may also be used to determine the particle size distribution's width (polydisperity index, PI). A PI value of 0.1-0.25 implies a limited size distribution, whereas a PI value of more than 0.5 indicates a relatively broad distribution.

2. Surface charge (Zeta potential):

The zeta potential provides information on the surface charge characteristics of nanosuspensions as well as their long-term physical stability. A minimum zeta potential of 30 mV is required for a stable suspension stabilised only by electrostatic repulsion, but a zeta potential of 20 mV is adequate for a combination electrostatic and steric stabiliser.

3. Crystalline state and particle morphology:

Understanding the polymorphism or morphological changes that a medication may experience when subjected to nanosizing relies on evaluating the crystalline state and particle morphology. Nanosuspensions can modify their crystalline structure due to high pressure homogenization, which might result in an amorphous or polymorphic state. X-ray diffraction analysis and DSC can be used to determine changes in the solid state of the drug particles and the amount of the amorphous fraction. Scanning electron microscopy is preferable for determining particle morphology.

4. Saturation solubility and Dissolution velocity: The drug's saturation solubility in various physiological buffers and at various temperatures should be determined using techniques published in the literature. The benefits that may be realised over traditional formulations, especially when constructing sustained release dosage forms based on nanoparticulate medicines, are reflected in the examination of the dissolving velocity of nanosuspensions. The assessment of saturation solubility and dissolution velocity aids in assessing the formulation's invitro behaviour.

5) pH: pH can be measured by using pH meter. Most of drugs are stable at pH 4-6.

6) Viscosity:The viscosity of the medium must be addressed since particle settling is affected by it. An ideal suspension would have a high apparent viscosity at low shear rates, allowing suspended particles to settle slowly or remain suspended during storage.

Applications of Nanosuspension

1)Oral Drug Delivery

The oral administration method is chosen over the many alternative medication delivery administration routes due to the numerous advantages it offers. Safety, high patient compliance, simplicity of intake, pain prevention, and adaptability to handle various types of medications are just a few of the benefits. The use of nanosuspension DDS to increase the bioavailability of poorly soluble medicines is advantageous.

The many advantages of nanosuspension DDS for oral administration, such as enhanced dissolution rate and solubility of poorly soluble drugs, high adhesiveness of drug nanocrystalson the epithelial gut wall, prolonged absorption time of drug nanocrystals due to long gastrointestinal tract, and reduced variability caused by food, are the main reasons. Oral administration can be done using both liquid and solid dose forms, such as powder, tablet, pellet, capsule, and film. The produced liquid nanosuspensions can be used in liquid dosage forms for oral administration right away.

2)Parenteral Administration

In emergency cases such as cardiac arrest and anaphylactic shock, parenteral injection is favoured above alternative medication delivery methods. This method of administration has various benefits, including avoiding first-pass metabolism, improved bioavailability, and consistent dose. Parenteral administration has better control over the dosage and pace than oral administration, resulting in more predictable pharmacodynamic and pharmacokinetic characteristics. The size of medication particles supplied should be less than 5 m in order to minimise capillary obstruction.When compared to the standard

form of Oridonin, a study on the potential of oridoninnanosuspension to suppress tumour development found that Oridoninnanosuspension may considerably increase the rate of tumour inhibition by over 20%. With the help of nanosuspension, therapeutic efficiency is increased while costs are drastically decreased.

3) Pulmonary Drug Delivery

Several respiratory ailments, such as chronic obstructive pulmonary disease and asthma, can be effectively treated with pulmonary medication delivery. When compared to the previously described oral and parenteral drug delivery methods, pulmonary medication administration has its own set of benefits. The medicine is administered directly to the site of action in pulmonary drug administration. The dose must be reduced, and the adverse effects have improved. Traditional pulmonary drug delivery has a number of flaws, including a lack of selectivity, a short drug residence period, and quick drug release.

By delivering the medicine directly to the afflicted pulmonary cells via the nanosuspension method, the problems of low drug solubility and lack of selectivity can be addressed. Nanosuspensions adhere more strongly to mucosal surfaces, resulting in a longer residence duration at the target region, enhancing selectivity and minimising drug loss. Because nanosuspensions can improve drug solubility and diffusion rate, preventing unwanted drug deposits in the tongue and mouth, pulmonary delivery methods often result in enhanced bioavailability.

4)Dermal Delivery

Nanocrystals have better permeability and bio-adhesiveness as a result of their greater penetration into membranes. The injectability and rapid dissolution of intravenous formulations must be examined before they can be developed. For years, however, researchers have been unable to harness the benefits of adhesion, rapid breakdown, and greater penetration in cutaneous and mucosal applications. The concentration of the poorly soluble medication was raised, which might result in a higher concentration gradient between the formulation and the skin, enhancing drug nanocrystal penetration.

5)Occular Drug Delivery

Traditional eye therapeutic approaches have various drawbacks, such as poor drug solubility in lachrymal fluids, many adverse effects from systematic drug absorption, and the need for recurrent instillation. With the use of nanosuspensions, these constraints posed by the traditional administration method can be circumvented. This nanosuspension technique has a number of advantages, including a longer ocular drug residence time and improved bioavailability.Furthermore, positively charged nanoparticles in nanosuspension adhere strongly to negatively charged mucin, allowing for longer drug release. In ocular medication administration, for example, chitosan is used as a mucoadhesive cationic polymer to bind to negatively charged mucin, resulting in a significantly longer drug residence duration. The drug nanoparticles' intrinsic adhesiveness may help to reduce medication loss.

6) Targeted Drug Delivery

The surface features of the drug particles, such as surface hydrophobicity, charge, and the presence and concentration of particular functional groups, influence their organ distribution. As a result, the fact that Tween 80-coated nanocrystals can be employed for brain targeting is startling. A noteworthy example is the use of atovaquonenanocrystals coated with Tween 80 to treat toxoplasmosis.

Changing the particle size can alter the in vivo behaviour of drug nanoparticles. The surface characteristics of particles alter as their size changes. As a result, the nanosuspension method may be utilised to deliver drugs to specific locations. To prevent phagocytotic absorption of nanocrystals, smart crystals, such as drug particles smaller than 100 nm, can be employed in the DDS. Because of its simplicity, nanosuspension may be developed for targeted medication delivery.

Mucoadhesivenanosuspension was employed to target Cryptosporidium parvum, according to reports (Kayser, 2001).

7) Enhancement Of Bioavailability

Poor bioavailability can be caused by a variety of factors, including drug solubility, permeability, and stability in the gastrointestinal tract (GIT). The problem of low solubility and permeability across the membrane can be remedied by converting medication particles into nanosuspensions.Kayser et al. found that nanosuspension of Amphotericin B improved oral absorption significantly when compared to the standard formulation. Because oleanolic acid is a weakly soluble hepatoprotective drug, its bioavailability was enhanced by using a nanosuspension.

II. Conclusion

Nanosuspension is a one of the best possible approach to solving the poor solubility as well as poor bioavailability problems of the drugs. A nanosuspension not only improves the solubility and bioavailability but also modifies the pharmacokinetics of drug and thus improves drug safety and efficacy.Hhigh-pressure homogenization technologies have been effectively employed for large-scale manufacture of nanosuspensions. Better dissolving velocity, enhanced saturation solubility, improved bioadhesivity, diversity in surface modification, and simplicity of postproduction processing have broadened the applicability of nanosuspensions for multiple administration routes. Although applications in pulmonary and ocular distribution have yet to be studied, nanosuspensions have a long history of use in oral and parental routes.

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