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Review Paper

An Overview of The Nanosuspension Drug Delivery System

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ABSTRACT

Nanosuspension terms divided into two words “Nano” and “suspension”. Nano refers to the particle size in the range of nanometres. Which is usually below 1000nm. While suspension means the particle are suspended/Dispersed into the liquid medium. Which is very finely colloid, dispersed, Biphasic solid drug particles in an aqueous vehicle. Further, the technology which is used for the preparation of the Nano suspension is called a Nanotechnology. Moreover, Nanotechnology is called as a science that deals with the Manufacturing process which occurs at micro level and of nano scale. Nano suspension is prepared by the surfactants and polymer by using different suitable methods for application of drug. it can increased the bioavailability of the hydrophobic drugs. Nanosuspension is a Viable, Efficacious and prospective technology to improve poor solubility and bioavailability of the drugs like BCS class II & IV. Review article describes different techniques of preparation, and its applications of nanosuspensions in the pharmaceutical industries.

INTRODUCTION

The formulation parameters such as suspensibility, dispersibility, solubility and stability at ambient temperature are playing an essential role in the formulation development of any BCS class II & IV drugs. As BCS class II & IV drugs have very poor solubility it is became bottle neck for the preparing a oral dosage form of new drug molecules. More than 40% of the new drugs are being produced through drug discovery programmers and from that almost 90% drugs are poorly water-soluble

compound primarily falling into BCS Class II or IV.^[1] This limits drug dissolution and results in low, erratic bioavailability. Further to this Solubilization of a BCS class II & IV drug has always been a challenging problem for the pharma industry. To bypass or to increase the solubility of the BCS class II & IV drugs there are many conventional methods are available. Such as micronization, solid dispersion technology, Nanotechnology which includes preparation of Nanospheres, Liposomes, Niosomes, Nano particles, Nanosuspension, solubilization using

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co-solvents, surfactant dispersion and precipitation technique has been developed for improving solubility of BCS class II & IV drugs. There are many conventional methods such as micronization, solubilization using co-solvents, surfactant dispersions and precipitation technique have been developed for improving solubility of poorly soluble drugs. But these techniques showed limitation to the drugs which are not soluble in both aqueous and organic solvents. Nanosuspension technology is selected to solve the problems associated with various approaches like solubility enhancements and preparation of stable formulation at ambient temperature. Nanosuspension is nano-sized Active Pharmaceutical Ingredients (API) particles stabilized by surfactants. It is also defined as a bi-phasic colloidal dispersion containing of pure drug particles in an aqueous vehicle. The diameter of suspended particle is Not more than 1000 nm. [2]

Drugs like BCS class II and IV showed that they have very low oral bioavailability, which is due to its poor solubility. There are many approaches to improve the solubility of the poor soluble drugs. Approaches like complex formation with HP beta CD (Beta cyclodextrin) complexes, Hypromellose, Povidones, Polyethylglycols, solid dispersion and drug salts forms. During last two decades a new technology, reducing drug particle size has been developed to increase the solubility of the BCS class II & IV. As the particle size is decreased the surface area of the particle is gets increased and hence the solubility of the drug is got increased. According to Noyes-Whitney equation, Drugs with small particle size have enlarged surface areas which lead to increase solubility/dissolution velocity. Higher the solubility/dissolution rate together with the resulting higher concentration gradient between gastrointestinal lumen and systemic circulation could further increase oral absorption and bioavailability of BCS class II & IV drugs.

Nanosuspension is a nanosized colloidal dispersion of the drug particles which are stabilized by surfactants. Nanosuspension are defined as very finely dispersed solid drug particles in water vehicle for oral, Topical, parenteral or pulmonary administration. The particle size of the solid particles in nanosuspension is usually not more than 1000 nanometre with an average particle size distribution ranging between 100 nm to 700nm. In nanotechnology nanosuspension of BCS class II & IV drug is retained in the required crystalline state with decreased particle size, which will increase the absorption & dissolution rate and hence improved bioavailability. [3]

Criteria for selection of drug for nanosuspension

Nanosuspension can be prepared for the BCS class II & IV drugs that are having either of the following characteristics:

- Either water insoluble and soluble in oil or soluble in oil and water insoluble.
- Drugs with reduced tendency of the crystal to dissolve, regardless of the solvent
- Drugs with very large dose. [4]

Advantages of Nanosuspension drug delivery system

- Particle size reduction can be achieved by using Nanosuspension technology. Which leads to an improved solubility rate, drug dissolution rate and enhanced drug absorption, resulting in increased absorption, bioavailability, faster onset of action, and higher peak drug levels. It also minimizes the variability in drug responses.
- Nanosuspension which are given through oral drug delivery are contact with the gastrointestinal mucosa for a longer period, stimulating better absorption.



- Nano suspensions are suitable for Drugs which are water insoluble and soluble in oil. They are also effective for formulating Drugs insoluble in both water and oil, providing an alternative to lipidic systems.
- Preparation of the Nanosuspension is feasible for the potent drugs. Hence it is useful for intramuscular, subcutaneous and ophthalmic application.
- Utilising nanosuspensions improves the safety profile overall since they lessen the likelihood of side effects connected to the excipients employed in the formulation.
- Nanosuspensions offer versatility in drug delivery and various routes can be used to administer them, including parenteral, oral, dermal, pulmonary and ocular routes, providing treatment options that are flexible.
- Nanosuspensions offer more advantages for ocular applications. As a result, it is possible to administer BCS class II & IV drugs that are poorly water- soluble and to achieve minimal drug doses, sustained drug release, a reduction in systemic toxicity, a prolongation of corneal residence time, and higher drug concentrations in infected tissues.
- Nanosuspensions help to retain polymorphic form of drugs for pharmaceutical use.
- Nanosuspensions possess the ability for passive targeting, allowing for the concentration of drugs at precise locations within the body where they exert their intended effects: [5]
- It will decrease the sedimentation rate of the particles and improved the physical stability.

Techniques of preparation of Nanosuspensions

Nanosuspension can be prepared by two different methods. They are Top-down and Bottom-up technologies. Usually the Top-down technology is preferred over the Bottom-up technology. In bottom-up technique during the precipitation

procedure the growing of the API crystals need to control by addition of surfactant to avoid formation of microparticles. Bottom-up technology is an assembling method to form nanoparticles like microemulsion, melt emulsification and precipitation method. While top-down technology involves the breakdown of larger particles into small particles like nanoparticles, examples of high-pressure homogenizer are ultra turrex, Silverson, Remi stirrer and milling method are equipment like Ball mill, Colloid mill, Microfluidizer etc.

Precipitation Method

Precipitation methods are common method to prepare the submicron particles size of BCS class II & IV drugs. In precipitation method drug is dissolved in solvent (generally non-aqueous) and then solution is mixed with solvent (generally water) to which drug is insoluble in the presence of surfactant. Fast addition of solution to solvent (generally water) leads to quick supersaturation of API in the solution, and formation of fine amorphous or crystalline API. This method involves crystal growing which are mainly dependent on temperature. Low crystal growing rate is primary requirements for preparing a stable suspension with lower particle size. [6]

High-Pressure Homogenization

High-pressure homogenization follows three steps: In first step, API powders are dispersed in a stabilizer solution for formation of pre-suspension; In second step, pre-suspension is homogenized either at high pressure or at low pressure. In third step, homogenized pre-suspension at a high pressure for 1 to 30 cycles until the required particle size nanosuspensions are formed.

High-Pressure Homogenization (dissocubes)

In these method Active pharmaceuticals ingredients (API) powders are dispersed in a stabilizer solution for formation of pre-suspension;



after that, pre-suspension is forced by a pressure plunger pump through a narrow valve under extreme pressure. When the pre-suspension is allowed to pass through the orifice the static pressure will be reduced below its boiling pressure of water which results in the boiling of water and formed gas bubbles and finally When it leaves the orifice pressure will be normal and bubbles will implode. So surrounding particles will rush into the surface which causes the size reduction.

Homogenization in non-aqueous media (nanopure)

It is homogenised in without water media or containing mixture of water and other non-aqueous solvent. Temperature will be 0°C or even at freezing point. So, it is known as deep freeze homogenisation. It is the best method for the thermolabile substances.

Wet Milling

Nanosuspensions are formulated by high shear media mills or pearl mills. It consists of milling chamber, recirculation chamber and milling shaft. Milling media consists of balls or pearls which are made up of ceramic sintered aluminium oxide or zirconium oxide. Milling chamber charged with milling media, water, drug, and stabilizer. Balls rotated at high mixing rate under control temperature the balls have an impact on the sample. Due to both forces of friction and impact particle size gets decreased and nanosized particles will form.

Dry Milling

Since last few years, nanosuspensions are prepared through wet milling processes by using pearl ball, mill. Nowadays, nanosuspensions can be prepared by dry milling methods. Stable nanosuspensions are prepared by using dry milling of BCS class II & IV drug with soluble copolymers and polymers

after dispersing in liquid medium. Itoh *et al.* have described the colloidal particles formation of many BCS class II & IV drugs like Atovaquone, Tafamendis, griseofulvin, nifedipine and Glibenclamide with sodium lauryl sulphate and polyvinylpyrrolidone as stabilizer.^[7]

Microemulsion

Nanosuspensions are also prepared by just diluting the emulsion, Which was formed by using a partially water-miscible solvent as the dispersed phase. The emulsion technique is applicable for Active pharmaceuticals ingredients (API) which are either soluble in volatile organic solvents or partially water miscible. Furthermore, microemulsion can also produce nanosuspensions. Microemulsions are dispersions of two immiscible liquids like water and oil. Microemulsions are stabilized thermodynamically by cosurfactant or surfactant. The drug is either loaded into internal phase or preformed of microemulsion. It can be saturated by intimate mixing of drugs. Griseofulvin nanosuspension is prepared by the microemulsion technique by using water, butyl lactate, lecithin, and the sodium salt of Taurodeoxycholate.^[8]

Nanoedge

Nanoedge is prepared by microprecipitation and high-pressure homogenization techniques. Hence it is Nanoedge is a combination of high-pressure homogenization and microprecipitation techniques. Method includes precipitation of fragile/friable materials followed by fragmentation under high speed and/or heat (Thermal).

Melt emulsification method

Melt emulsification method is used for preparation of the Nanoparticles. Mostly with Melt emulsification method SLNs (Solid Lipid Nanoparticles) are prepared. Kipp and coworkers firstly prepare nanosuspensions of ibuprofen by



using melt emulsification method. It is a four-step procedure. Drug is mixed with the Lipid polymer. Then mixture is heated at temperature higher than the melting point of the drug and lipid polymer. Then this melted solution is added in to the water in which melted solution is immiscible. Then it is homogenized by high-speed homogenizer for the formation of emulsion. The temperature is maintained above the melting point of the drug during overall process. Lastly, the emulsion is cooled at room temperature to precipitate the particles. The particle size of nanosuspension mainly depends on parameters like drug concentration, concentration and type of lipid polymer/ stabilizers used, cooling temperature, and homogenization process.^[9]

Characterization techniques

Characteristics such as Particle size distribution (PSD), Individual particle size, and surface charge (zeta potential) affect the efficacy, safety and stability of nanodrug delivery systems. It will also affect the dissolution performance. Which will ultimately affect the absorption and bioavailability of the BCS class II & IV drugs. Thus, characterization of nanoparticles plays crucial role in forecasting in vivo and in vitro performance of nanodrug delivery systems. In vivo biological function and pharmacokinetic performance of nanosuspension strongly depends on its particle size distribution (PSD), individual particle size, particle charge (zeta potential), polymorphic form and morphology.

Mean Particle Size and Particle Size Distribution

The mean particle size and particle size distribution affects saturation solubility, dissolution rate, physical stability, and in vivo performance of nanosuspensions. The particle size distribution and its range named polydispersity index (PI) can be determined by laser diffraction

(LD), photon correlation spectroscopy, microscope, and coulter counter. PI gives the physical stability of nanosuspensions and should be as lower as possible for the long-time stability of nanosuspensions. A PI value of 0.1 to 0.25 shows a narrow size distribution, and PI value more than 0.5 indicates a very broad distribution. LD can detect and quantify the drug microparticles during the production process. It also gives a volume size distribution and can be used to measure particles ranging from 0.05 up to 2 000 μm .^[10] The coulter counter gives the absolute number of particles per volume for the different size classes. It is more efficient and suitable than LD to quantify the contamination of nanosuspensions.

Polymorphic form and Morphology

Polymorphic form of nanosized particles can be confirmed by the X-ray diffraction or differential scanning calorimetry and Morphology of the nanosized particles can be confirmed by particle morphology. As nanosuspension requires high-pressure homogenization, change in polymorphic form of formulation occurs which may be converted to either amorphous or any other crystalline polymorphic forms. Alteration in the solid state of the drug particles and the extent of the amorphous portion is determined by X-ray diffraction analysis^[10] and supplemented by differential scanning calorimetry analysis.

Surface Charge (Zeta Potential)

Surface charge properties of the nano particles are studied through zeta potential. The value of particle surface charge indicates the stability of nano particles at the macro level. A minimum zeta potential of ± 30 mV is required for electrostatically stabilized nanosuspensions and a minimum of ± 20 mV for steric stabilization. The zeta potential values are commonly calculated by determining the particle's electrophoretic mobility



and then converting the electrophoretic mobility to the zeta potential.^[11] Electroacoustic technique is also used for the determination of the zeta potential in the areas of material sciences.

APPLICATIONS OF NANOSUSPENSION

Oral Drug Delivery

The numerous advantages oral route is the most preferable route for mostly all type of the drugs especially in the case of orally administering antibiotics such as atovaquone and buparvaquone. By making it in nano size, its bioavailability and solubility will increase. The oral administration of naproxen nanoparticles leads to an area under the curve (AUC) (0-24 h) of 97.5 mg/h compared with naproxen nanosuspension and naproxen tablets. In the case of danazol (gonadotrophin inhibitor) nanosuspension has absolute bioavailability of 82.3 and the conventional dispersion only 5.2.^[12]

Parenteral Drug Delivery

Clofazimine is given as iv, the concentration in the liver, spleen and lungs reached a high level i.e.; greater than minimum inhibitory concentration, for mostly all of the mycobacterium avium strains. Tarazepide is formulated as nanosuspension to overcome the use of surfactants and cyclodextrins to improve the bioavailability.^[13]

Pulmonary Drug Delivery

Here we are using nano-preparations for the drugs which have poor solubility in pulmonary secretions. For the lung delivery it is nebulised by mechanical or ultrasonic nebulizer. E. g: budesonide.^[14]

Ocular Drug Delivery

These mainly applied for BCS class II & IV drugs. It increases the residence time include sac. The best example of nanosuspension is ibuprofen. The

anti-inflammatory activity of ibuprofen increased compared with the aqueous preparation.^[15]

CONCLUSION

Nanosuspensions formulation majorly resolved the solubility a problem which will also resolve dissolution problem and hence it will improve drug absorption. Nanosuspensions are commercially feasible approach to solve the problems of BCS class II & BCS class IV drugs which has poor solubility and poor bioavailability. For large-scale production of nanosuspensions, generally wet milling and high-pressure homogenization technology have been successfully used. It has therapeutic advantages such as simple method of preparation; less requirements of excipients increase saturation solubility and ultimately increase dissolution rate. Commercially Nanosuspension preparation is feasible approach to solve the poor solubility as well as poor bioavailability problems of the BCS class II & IV drugs.

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