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NANOSUSPENSION: A PROMISING DRUG DELIVERY SYSTEM

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ABSTRACT

Solubility is an essential factor for drug effectiveness, independent of the route of administration. Poorly soluble drugs are often a challenging task for formulators in the industry. Conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. One of the critical problems associated with poorly soluble drugs is too low bioavailability. Nanosuspension technology can be used to improve the stability as well as the bioavailability of poorly soluble drugs. Nanosuspensions are biphasic systems consisting of pure drug particles dispersed in an aqueous vehicle, stabilized by surfactants. Nanotechnology can be used to resolve the problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10-9 meters. The present article describes the details about nanosuspensions. Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion. The review article includes the methods of preparation with their merits and characterization, application, and parameters.

Keywords: Nanosuspension, Nanotechnology, Solubility enhancement, Bioavailability.

INTRODUCTION[1-11]

Nanosuspension is submicron colloidal dispersion of drug particles. A pharmaceutical nanosuspension is defined as very finely colloid, biphasic, dispersed solid drug particles in an aqueous vehicle, size below 1 μm stabilized by surfactants and polymers prepared by suitable

methods for drug delivery applications. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. An increase in the dissolution rate of micronized particles (particle size < 10 μm) is related to an increase in the surface area and consequently the dissolution velocity.

Nanosuspension have revealed their potential to solve the problem associated with the delivery of poorly water soluble and poorly water and lipid soluble drugs. It enhances the absorption and bioavailability and help to reduces the dose of conventional oral dosage forms. Drug particle size reduction leads to an increase in the surface area and consequently the rate of dissolution as described by the noyes whitney equation. In addition an increase in saturation solubility is postulated by the particle size reduction due to an increased dissolution pressure explained by the ostwald-freundlich equation. Depending upon the production technique applied changes in the cristaline structure of the drug particle may occur. An increase amount of amorphous drug fraction could induce higher saturation solubility. Nanosuspension not only solves the problem of poor solubility and poor bioavailability but also alters the pharmacokinetics of the drug and improves the drug safety and efficacy.

Need of Nanosuspension[12-15]

More than 40% of drugs are poorly soluble in water, so they show problems in formulating them in conventional dosage forms. Also, for class II drugs which are poorly soluble in aqueous and organic media, the problem is more complex. Preparing nanosuspension is preferred for such compounds that are insoluble in water (but are soluble in oil) with high log P value. Various approaches to resolve problems of low solubility and low bioavailability micronization, co-solvency, oily solution, salt formation- some other techniques are liposomes, emulsions, microemulsion, solid dispersion, ß- cyclodextrin inclusion complex etc. But, many of these techniques are not universally applicable to all drugs. In these cases nanosuspensions are preferred. In case of drugs that are insoluble in both water and in inorganic media instead of using lipidic systems, nanosuspensions are used as a formulation approach. It is most suitable for the compounds with high log P value, high melting point, and high dose. Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound increases and the maximum plasma level is reached faster (e.g., oral or

intravenous (IV) administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. It is useful for molecules with poor solubility, poor permeability or both, which poses a significant challenge for the formulators.

Major Advantages of Nanosuspensions[15]

a) Its general applicability to most drugs and its simplicity.
b) Can be applied for the poorly water soluble drugs.
c) Can be given by any route.
d) Reduced tissue irritation in case of subcutaneous/intramuscular administration.
e) Rapid dissolution and tissue targeting can be achieved by IV route of administration.
f) Oral administration of nanosuspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability.
g) The absorption from absorption window of the drugs can be increased, due to reduction in the particle size.
h) Higher bioavailability and more consistent dosing in case of ocular administration and inhalation delivery.
i) Drugs with high log P value can be formulated as nanosuspensions to increase the bioavailability of such drugs.
j) Improvement in biological performance due to high dissolution rate and saturation solubility of the drug.
k) Ease of manufacture and little batch-to-batch variation.
l) Long term physical stability (Due to absence of Ostwald ripening).
m) Nanosuspensions can be incorporated in tablets, pellets, hydrogel and suppositories are suitable for various routes of administration.
n) Increasing the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility.
o) Possibility of surface-modification of nanosuspension for site specific delivery.
p) Possibility of large-scale production, the pre-requisite for the introduction of a delivery system to the market.

Preparation Methods of Nano- suspension[10]

There are different methods of Nanosuspensions preparation

a) Homogenization in water (DissoCubes).
b) Media milling (Nanocrystal or NanoSystems).

c) Homogenization in non-aqueous media (Nanopure).
d) Combined precipitation and homogenization (Nanoedge).
e) Nanojet technology.

Emulsification-solvent evaporation technique.

a) Hydrosol method.
b) Supercritical fluid method.
c) Dry co-grinding.
d) Emulsion as template.
e) Microemulsion as template.

Homogenization[15]

a) High pressure homogenization (DissoCubes)

DissoCubes are engineered using piston-gap-type high-pressure homogenizers. High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The instrument can be operated at pressure varying from 100-1500 bars (2800-21300 psi) and up to 2000 bars with volume capacity of 40 ml (for laboratory scale). The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required. Before subjecting the drug to the homogenization process, it is essential to form a pre-suspension of the micronized drug in a surfactant solution using high-speed stirrers. During the homogenization process, the drug suspension is pressed through the homogenization gap in order to achieve nano-sizing of the drug.

Advantages

1. Both diluted and concentrated suspension can be formulated.
2. Does not cause erosion of processed material.
3. Applicable to the drugs which are poorly soluble in both aqueous and organic solvent.

Disadvantages

1. Micronisation may occur.
2. High cost of instrument.

b) Homoginisation in nonaqueous media (nanopure)[16]

It is homoginised in water free media or water mixture. Temperature will be 0^0c or even at freezing point. So it is known as deep freeze homoginisation. It is the best method for the thermolabile substances.

c) Nanoedge[17,18]

The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystal. They need to be processed with high-energy forces (Homogenisation). The are in completely amorphous, partially amorphous or completely crystalline which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step.

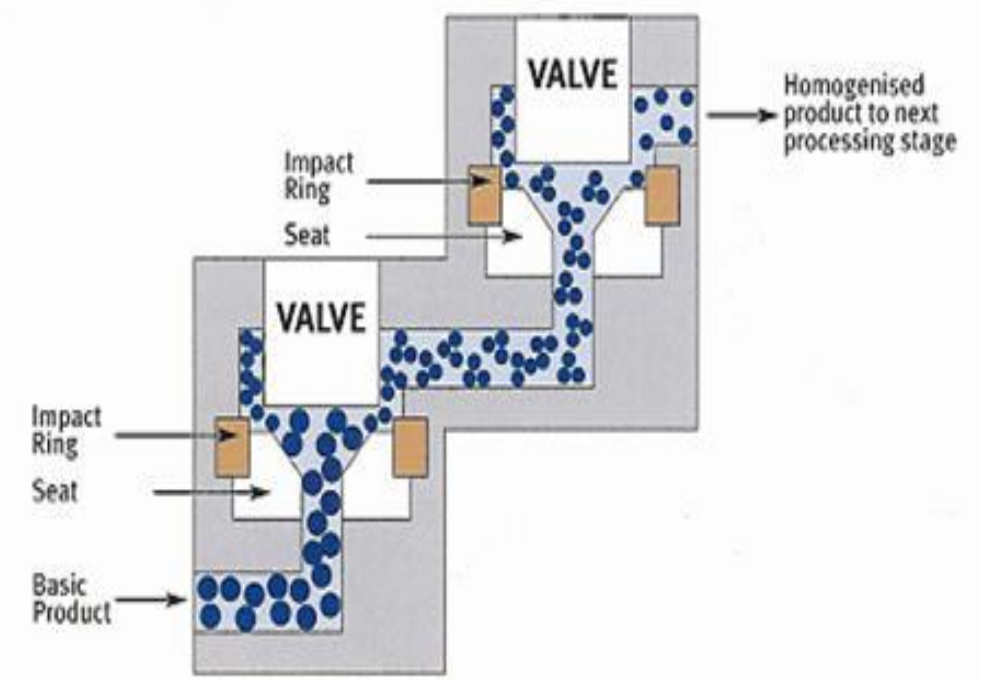

Figure 2: High pressure homogenization.

Media milling[19]

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 is made up of ceramic sintered aluminium oxide or zirconium oxide. Milling chamber charged with milling media, water, drug, stabilizer. Balls rotated at high shear rate under control temperature the balls have an impact on the sample. Due to the both forces of friction and impact particle size reduction occurs and nanosized particles will obtained.

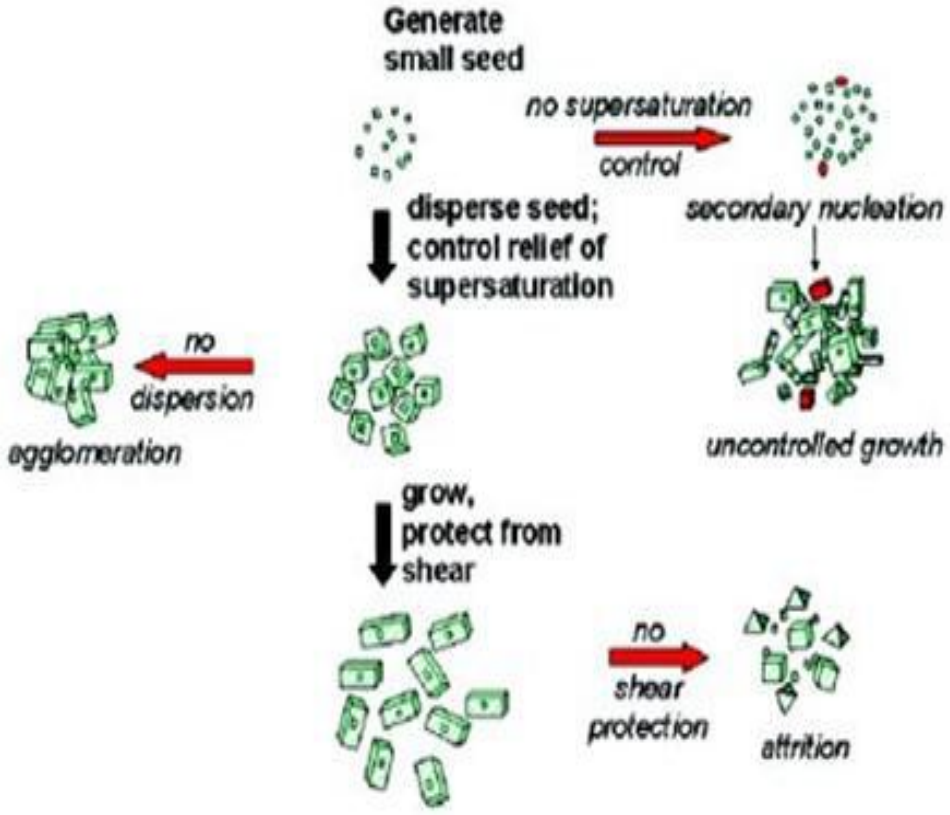

Figure 1: Media milling process.

Precipitation technique (solvent-antisolvent method)[20]

Precipitation method has been used for long years for the preparation of submicron particles. It is mainly used for the poorly soluble drugs. First drug is dissolved in a suitable solvent.This solution is then mixed with a miscible antisolvent system in the presence of surfactants. Rapid addition of drug solution in to the antisolvent leads to the sudden supersaturation of drug in the mixed solution forms ultrafine drug solids. Precipitation method involves two phases - nuclei formation & crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate and but low growth rate is necessary. Both rate are depend on temperature. In this technique the drug needs to be soluble in at least one solvent which is miscible with nonsolvent.

Nanojet technology[21]

Nanojet technology is also called as opposite stream technology. In this technique a stream of suspension in two or more divided parts were passed with high pressure were made to colloid with each other, due to the high shear forces produced during the process results in the reduction of particle size.

Emulsification-solvent evaporation technique[18,22]

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

Supercritical fluid process[21,23,24]

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. A supercritical fluid (SF) can be defined as a dense non condensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). A SCF process allows micronization of drug particles within narrow range of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm in diameter. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO_2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry.

Dry co-grinding[25-29]

Nanosuspensions prepared by high pressure homogenization and media milling using pearl-ball mill are wet–grinding processes. Recently, nanosuspensions can be obtained by dry milling techniques. Successful work in preparing stable nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported. Itoh *et al* reported the colloidal particles formation of many poorly water soluble drugs; griseofulvin, glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodium dodecylsulfate (SDS). Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used. Physicochemical properties and dissolution of poorly water soluble drugs were improved by co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug. Dry co-grinding can be carried out easily and economically and can be cosnducted without organic solvents. The co-grinding technique can reduce particles to the submicron level and a stable amorphous solid can be obtained.

Emulsion as template[10,15]

Apart from the use of emulsions as a drug delivery vehicle, they can also be used as templates to produce nanosuspensions. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. Such solvents can be used as the dispersed phase of the emulsion. In this method, an organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate instantaneously to form a nanosuspension stabilized by surfactants. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion. Optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion.

Microemulsion as template/Lipid emulsion[6]

Lipid emulsions as templates are applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. This technique follows an organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the nanosuspension which is stabilized by surfactants.

Characterization of Nanosuspension[11]

Nanosuspensions are evaluated as same as conventional suspensions such as appearance, colour, odour, assay, related impurities etc. Along with that particle size, zeta potential, morphology, dissolution study, in-vivo studies are also performed.

1. Particle size[30]

Particle size and particle size distribution are two important parameters since it will affect the saturation solubility, dissolution rate, stability, and in vivo behavior of nanosuspensions. Any change in the particle size will leads to the change in the solubility and dissolution. Particle size determines the physiochemical behavior of the drug. Particle size can be determined by sem or tem analysis. Particle size distribution can be determined by photon correlation spectroscopy (pcs) or laser diffraction (ld).Particle size distribution will be expressed in polydispersity index (pi).pi value of 0.1-0.25 indicates fairly nanosize distribution where as its value greater than 0.5 indicates a very broad distribution.

2. Particle charge (Zeta potential)[31]

Zeta potential is an indication of the stability of the suspension. For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of +/-30 mV is required whereas in case of a combined electrostatic and steric stabilizer, a zeta potential of +/-20 mV would be sufficient.

3. Crystalline state and particle morphology[32]

Nanosuspension can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high pressure homogenization. X-ray diffraction analysis in combination with differential scanning calorimetry, scanning electron microscopy is used to determine the polymorphic changes due to impact of high pressure homogenization in the crystalline structure of the drug.

4. Saturation solubility and dissolution velocity[11,30]

Nanosuspension will increase the solution solubility and dissolution velocity. It also help for the in vitro behavior of the formulation. When the particle size reduced to nanometric range, dissolution velocity and dissolution pressure will increase which leads to the solution solubility due to the change in the surface tension.

Applications

Nanosuspensions have wide range of applications especially in the case of low solubility and low bioavailability drugs. They are mentioned below.

1. Bioavailability enhancement[30,31]

The poor oral bioavailability of the drug may be due to poor solubility, poor permeability or poor stability in the gastrointestinal tract (GIT). Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a nanosuspension formulation. The therapeutic effect was significantly enhanced, which indicated higher bioavailability. This was due to the faster dissolution (90% in 20 min) of the lyophilized nanosuspension powder when compared with the dissolution from a coarse powder (15% in 20 min).

2. Oral Drug Delivery[11]

Nanosuspensions for Oral Drug Delivery Because of the numerous advantages oral route is the most preferable route for many of the drugs especially in the case of orally administering antibiotics such as atovaquone and bupravaquone. By making it in nanosize, its solubility and bioavailability will increase.

3. Intravenous administration[31,33]

The parenteral route of administration provides a quick onset of action, rapid targeting and reduced dosage of the drug. It is the preferred route for drugs undergoing first-pass metabolism and those that are not absorbed in the GIT or degraded in the GIT. One of the important applications of nanosuspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic cosolvents, improving the therapeutic effect of the drug available as conventional oral formulations and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages.

4. Pulmonary administration[31,34]

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Because of their small size, it is likely that in each aerosol droplet at least one drug particle is contained, leading to a more uniform distribution of the drug in lungs. They also increase adhesiveness and thus cause a prolonged residence time. Budenoside drug nanoparticles were successfully nebulized using an ultrasonic nebulizer.

Ophthalmic drug delivery[32,35]

Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the intrinsic dissolution rate of the drug in lachrymal fluids governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. The best example of nanosuspension is ibuprofen. The anti inflamatory activity of ibuprofen increased compared with the aqueous preparation.

5. Targeted Drug Delivery[11,36]

Nanosuspensions also used for targeting their surface properties and changing of the stabilizer can easily alter the in vivo behavior. The drug will be up take by the mononuclear phagocytic system to allow regional specific drug delivery. This can be used for targeting antimycobacterial, fungal drugs to the macrophages. Atovaquone is used as targeting nanosuspension to the brain.

6. Mucoadhesion of the Nanoparticles[31,37]

Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface.The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT, e.g.,Cryptosporidium parvum. Mucoadhesive bupravaquone nanosuspensions, because of their prolonged residence at the infection site, revealed a 10-fold reduction in the infectivity score of Cryptosporidium parvum as compared to the bupravaquone nanosuspensions without mucoadhesive polymers.

Topical formulations[21,38-40]

Drug nanoparticles can also be incorporated into water free ointments and creams, which have an increased saturation solubility and enhanced diffusion of drug into the skin.

CONCLUSION

Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Productions techniques such as media milling and high pressure homogenizer are used for large scale production of nanosuspensions. Nanosuspensions can be administerd through oral, parenteral, pulmonary, ocular and topical routes. Since nanotechnique is simple, less requirements of excipients, increased dissolution velocity and saturation solubility many poor bioavailability drugs are formulated in nanosuspension form. It is yery good approach for future development.

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