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Review Article

A REVIEW ON NANOSUSPENSIONS IN DRUG DELIVERY

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Abstract

Poorly water soluble drug candidates remains a major obstacle to their development and clinical application. Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages. Nanosuspensions have been extensively developed for a wide range of drugs and have been evaluated for in vitro and in vivo applications by various routes: parenteral, oral, pulmonary, topical. They have also been used for drug targeting. The unique features of nanosuspensions have enabled their use in various dosage forms, including specialized delivery systems such as mucoadhesive hydrogels. Rapid strides have been made in the delivery of nanosuspensions by parenteral, per-oral, ocular and pulmonary routes. Currently, efforts are being directed to extending their applications in site-specific drug delivery.

Keywords: Nanosuspensions, hydrogels , mucoadhesive

INTRODUCTION

Nanosuspensions are colloidal dispersions and biphasic system consisting of drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate due to increased surface area and saturation solubility[1]. The use of nanotechnology to formulate poorly water soluble drugs as nanosuspension offers the opportunity to address nature of the deficiency associated with this class of drugs[2]. The formulation of nano-sized particles can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and hence partition into gastrointestinal barrier. Micronization is used for class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility[3]. Nano is a Greek word, which means 'dwarf'. Nano means it is the factor of 10-9 or one billionth. Some comparisons of nanoscale are given below,

0.1 nm = Diameter of one Hydrogen atom.
2.5 nm = Width of a DNA molecule
1 micron = 1000 nm.
1 nm = 10-9m= 10-7 cm = 10-6 mm.
Micron = 10-6m= 10-4 cm = 10-3mm 4.

For a long duration of time micronization of poorly soluble drugs by colloid mills or jet mills was preferred.The overall particle size distribution ranges from 0.1µm to approximately 25µm, only negligible amount being below 1µm in the nanometer range[4].

There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization, solubilisation using co-solvents, salt form8, surfactant dispersions, precipitation technique, and oily solution. Other techniques are like liposomes, emulsions microemulsion, solid dispersion and inclusion complexation using cyclodextrins show sensible achiever, but they lack in universal applicability to all drugs. These techniques are not applicable for those drugs which are not soluble in aqueous and organic solvents.[5]

Various approach to produce nanosuspension:

There are two methods for preparation of

nanosuspension. They are 'Bottom up technology' and 'Top down technology' For the production of nanoparticles in Bottom up technology the drug is dissolved in a solvent, which is then added to non-solvent that causes precipitation of the fine drug particles.All-Trans retinoic acid nanosuspensions were prepared with a precipitation method. Use of simple and low cost equipment and also benefit for higher saturation solubility is the advantage for precipitation technique compared to other methods of nanosuspension preparation. Precipitation technique is not applicable to drugs which are poorly soluble in aqueous and non aqueous media. In this technique, the drug needs to be soluble in atleast one solvent which is miscible with nonsolvent. The major challenge is to avoid crystal growth due to Ostwald ripening being caused by different saturation solubilities in the vicinity of differently sized particles. The top down technologies include media milling, high pressure homogenization, emulsion diffusion method, supercritical fluid method and these are preferred over the precipitation methods[5].

Method of preparation of nanosuspension:

1. Emulsions as templates:

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. There are two ways of fabricating drug nanosuspensions by the emulsification method. In the first 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. Originally, organic solvents such as methylene chloride and chloroform were used (Bodmeier & McGinity 1998). However, environmental hazards and human safety concerns about residual solvents have limited their use in routine manufacturing processes. Relatively safer solvents such as ethyl acetate and ethyl format can still be considered for use[6].

2. Supercritical fluid process

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 CO2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry[7].

3. Precipitation

The most common method of precipitation used is anti solvent addition method in which the drug is dissolved in an organic solvent and this solution is mixed with a miscible anti solvent. Mixing processes vary considerably. Precipitation has also been coupled with high shear processing. The NANOEDGE process relies on the precipitation of friable materials for subsequent fragmentation under conditions of high shear or thermal energy. Rapid addition of a drug solution to a solvent leads to sudden super saturation of the mixed solution,and generation of fine crystalline or amorphous solids[7].

4. Lipid emulsion/microemulsion template

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. Another way to produce nanosuspensions is to use an emulsion which is formed by the conventional method using a partially water miscible solvent as the dispersed phase. Nanosuspensions are obtained by just diluting the emulsion. Moreover, microemulsions as templates can produce nanosuspensions. Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by intimate mixing. Suitable dilution of the microemulsion yields the drug nanosuspension. An example of this technique is the griseofulvin nanosuspension which is prepared by the microemulsion technique using water, butyl lactate, lecithin and the sodium salt of taurodeoxycholate. The advantages of lipid emulsions as templates for nanosuspension formation are that they easy to produce by controlling the emulsion droplet and easy for scale-up. However, the use of organic solvents affects the environment and large amounts of surfactant or stabilizer are required[8].

5. Milling:

Recently, nanosuspensions can be obtained by dry milling techniques. Nanosuspensions are produced by using high-shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft and a recirculation chamber. An aqueous suspension of the drug is then fed into the mill containing small grinding balls/pearls. As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combined forces of friction and impact produce a high degree of particle size reduction. The milling media or balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. Planetary ball mills (PM100 and PM200; Retsch GmbH and Co., KG, Haan, Germany) is one example of an equipment that can be used to achieve a grind size below 0.1μm. A nanosuspension of Zn- Insulin with a mean particle size of 150 nm was prepared using the wet milling technique. Media milling is a further technique used to prepare nanosuspensions. Nanocrystal is a patent protected technology developed by Liversidge et al. In this technique, the drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generated as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate. The major concern with this method is the residues of milling media remaining in the finished product could be problematic for administration[9].

6. **Nanojet technology:**

This technique is also called as "opposite stream" uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure upto 4000 bar at high velocity of 1000m/s. The high shear force produces during the process result in particle size reduction[10].

7.Emulsification- solvent evapouration techniques -

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[10].

8. Dry co-grinding:

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 polyvinyl pyrrolidone (PVP) and Sodium dodecyl sulfate (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. Recently, nanosuspensions can be obtained by dry milling techniques. Dry co-grinding can be carried out easily and economically and can be conducted without organic solvents. The co-grinding technique can reduce particles to the submicron level and a stable amorphous solid can be obtained. However, if all the ingredients that are used for the production of the nanosuspension are present in a concentration acceptable for the desired route of administration, then simple centrifugation or ultracentrifugation is sufficient to separate the nanosuspension[11].

9. Nanoedge technology:

Nanoedge technology involves on the precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy`. This also includes the combination of rapid precipitation and high-pressure homogenization. In this technique the precipitated suspension is further homogenized to get smaller particle size and avoid crystal growth. It produces nanosized stable dispersion with a short period of time as well it avoids crystal growth. Nanoedge technology is a registered trademark of Baxter International Inc. and its subsidiaries[12].

Advantages of nanosuspensions

1. Improved biological performance:

An increase in the dissolution velocity and saturation solubility of a drug leads to an improvement in the in-vivo performance of the drug irrespective of the route used. The advantages related to various routes are discussed later in detail.

2. Ease of manufacture and scale-up:

Unlike nanoparticulate carriers such as polymeric nanoparticles, which were investigated earlier, nanosuspensions are easy to manufacture. The production processes described earlier are easily scaled up for commercial production. The introduction of nanosuspension products such as Rapamune and the Nanocrystal colloidal ketoprofen is sufficient to substantiate this[13]

• Provides ease of manufacture and scale-up for large scale production.

• Long-term physical stability due to the presence of stabilizers.

• Oral administration of nanosuspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability.

• Rapid dissolution and tissue targeting can be achieved by IV route of administration.

• Reduction in tissue irritation in case of subcutaneous/intramuscular administration.

• Higher bioavailability in case of ocular administration and inhalation delivery.

• Drugs with high log P value can be formulated as nanosuspensions to increase the bioavailability of such drugs.

• Improvement in biological performance due to high dissolution rate and saturation solubility of the drug.

• Nanosuspensions can be incorporated in tablets, pellets, hydrogels and suppositories are suitable for various routes of administration.

• The flexibility offered in the modification of surface properties and particle size, and ease of post production processing of nanosuspensions enables them to be incorporated in various dosage forms for various routes of administration, thus proving their versatility[14].

CHARACTERIZATION TECHNIQUES:

The particle size, particle size distribution, and zeta potential affect the safety, efficacy, and stability of nanodrug delivery systems as well as dissolution performance is also altered by solid state of nanoparticles. Thus, characterization of nanoparticles plays a great role in forecasting in vitro and in vivo performance of nanodrug delivery systems.

(I) In-vitro

1. Crystalline State and Particle Morphology:

It is of importance as there are chances of the polymorphism during the storage of the nanosuspensions. Hence it is necessary to study the crystal morphology of the drug in suspension. Differential Scanning Calorimetry (DSC) is most commonly used for such studies[15].

2. Particle size:

The most important charecterization parameter for the nanosuspension are the mean particle size and width of particle size distribution (called polydispersity index) which governs the

physiocochemical properties like saturation solubility, dissolution velocity, physical stability and even biological performance. It is proved that change in particle size changes saturated solubility and dissolution velocity. Different methods for determining particle size distribution are

1. Photon correlation spectroscopy (PCS)
2. Laser diffraction (LD)
3. Coulter counter multisizer

PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of nanosuspensions and should be as low as possible for the long-term stability of nanosuspensions. A PI value of 0.1–0.25 indicates a fairly narrow size distribution where as a PI value greater than 0.5 indicates a very broad distribution.PCS determines the particle size in the range of (3nm to 3 μm) it becomes difficult to determine the possibility of contamination of the nanosuspension by microparticulate drugs (having particle size greater than 3μm)[16].

3. Particle charge (Zeta Potential):

Article charge determines the stability of nanosuspension. For electrostatically stabilized nanosuspension a minimum zeta potential of ±30mV and for combined steric and electrostatic stabilization it should be a minimum of ±20mV[17].

4. Saturation solubility and dissolution velocity:

The nanosuspension increases the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific constant depending upon temperature and the properties of dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility [18].

(II) In-Vivo Biological Performance:

The in-vitro-in-vivo correlations have utmost importance in the case of intravenously injected nanosuspensions. Suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea do in-vivo behaviour. Surface hydrophibicity, qualitative and quantitative measurement of protein adsorption are important in case of in-vivo studies. Surface hydrophobicity was determined by hydrophobic interaction chromatography[19].

Applications of nanosuspensions in drug Delivery

1. Target drug delivery:

Nanosuspensions can also be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product enable the development of commercial viable nanosuspensions for targeted delivery. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Targeting of *Cryptosporidium parvum*, the organism responsible for cryptosporidiosis, was achieved by using surface modified mucoadhesive nanosuspensions of bupravaquone. Similarly, conditions such as pulmonary aspergillosis can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes[20].

2. Oral drug delivery:

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. .Orally administered antibiotics such as atovaquone and bupravaquone reflect this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability[21].

3. Ocular drug delivery:

Nanosuspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. Nanosuspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs and Nanoparticulate nature of the drug allows its prolonged residence in the culdesac, giving sustained release of the drug[21].

4. Parentral drug delivery:

From the formulation perspective, nanosuspensions meet almost all the requirements of an ideal drug delivery system for the parentral route. Since the drug particles are directly nanosized, it becomes easy to process almost all drugs for parentral administration. Hence, nanosuspensions enable significant improvement in the parentrally tolerable dose of

the drug, leading to a reduction in the cost of the therapy and also improved therapeutic performance. The maximum tolerable dose of paclitaxel nanosuspension was found to be three times higher than the currently marketed Taxol, which uses Cremophore EL and ethanol to solubilize the drug[22].

5. Topical formulations:

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin[23].

6. Mucoadhesion of the nanoparticles:

Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as "bioadhesion". From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. 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[23].

Conclusion:

The dissolution problems of poorly water soluble drugs have been largely solved to improve drug absorption and bioavailability. Attractive features, such as reduction of particles size up to submicron level lead to a significant increase in dissolution velocity as well as saturation solubility. Improved bio-adhesiveness, versatility in surface modification and ease of post-production processing have widened the applications of nanosuspensions for various routes.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. surfactants. Nanosuspension drug delivery has obtained great success in the preparation of insoluble drugs.

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