Nanosuspensions: A Versatile Formulation Technique for Drugs with Poor Aqueous Solubility- A Review

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ABSTRACT

BCS class II drugs associated as they are with low aqueous solubility and bioavailability pose an alarming challenge for the pharmaceutical scientists from the point of view of formulation by conventional methods. That is all the more surprising as around forty percent of the new generated drugs exhibit poor water solubility. However , the formulation of such drugs is now being increasingly done through the latest technique of nanosuspension formulation . Among the major advantages of this technique is the fact that nanosuspensions can be formulated for various routes of administration like oral, parenteral, ocular, and pulmonary and targeted drug delivery system. Nanosuspension technology increases the dissolution velocity, saturation solubility, adhesion, and bioavailability that lead to a decrease in the dose and fast-fed variability thereby playing a vital role in drug discovery. Nanosuspensions help in administering huge drug concentration of the poorly water soluble drugs to brain with decreased systemic effects. In fact, nanosuspension technology achieves that target by altering the pharmacokinetics of the drug and improves drug safety and efficacy.

KEYWORDS: Nanosuspensions, Poorly Water Soluble Drugs, Dissolution, Solubility, Drug Delivery Systems, Bioavailibilty

INTRODUCTION

Consequent to recent development of many state-of the-art technologies in the area of drug development such as high-throughput screening, computer aided drug design, it has now become possible to forcast drug candidates possessing desired pharmacotherapeutic profiles (Lenhardt et al [1]). However, the utility of those drug candidates which have poor solubility and poor bioavailability puts a question mark on their therapeutic usage. Solubility is an essential factor for drug effectiveness. In fact, such class of drugs were once called “brick dust” candidates and were even abandoned from pharmaceutical development researches. As a result, patients in the past could not take advantage of their therapeutic usage. Fortunately, new developments have taken place today in the field of formulation development which have now converted the so-called “brick dust” drugs into very useful drugs via nanosuspension technology.

Nanosuspensions are submicron colloidal dispersions of nanosized drug particles which are stabilized by surfactants without any matrix material suspended in dispersion. Nanosuspensions differ from nanoparticles that are polymeric colloidal carriers of the drug. They also differ from solid nanoparticles that are lipidic carriers of the drug.

PREPARATION

Nanosuspension preparation can be done by two methods –, "Bottom up technology"and the"Top down technology", the two popular techniques used for making nanoparticles (Barett et al[2]). While the former is an assembling process converting smaller particles into nanoparticles, the latter is a disintegrating process converting larger particles into nanoparticles . Precipitation, microemulsion, melt emulsification fall under the first category while high-pressure homogenization and milling methods come in the second technique.

Precipitation

First of all, the drug is dissolved in a solvent . The solution obtained is now rapidly mixed with a solvent, generally water in which the drug is insoluble, in the presence of the surfactant, resulting in the formation of ultrafine amorphous or crystalline drug(Metteucci et al [3)] . In fact, the method is based on the temperature dependent formation of the nuclei and crystal growth, with high rate of nucleation and low rate of crystal growth favoring a stable suspension with minimum particle size (Gassman et al [4)].

High-Pressure Homogenization

In this technique, first of all, a presuspension is prepared by dispersing drug powders in a stabilizer solution which is then homogenized by high pressure homogenizer at a low pressure for premilling followed by homogenization at a high pressure for 10 to 25 cycles to yield the desired size nanosuspension (Liversidge et al [5)].

Dissocubes (homogenization in aqueous media)

This technique developed by Muller has been used to prepare nanosuspensions of many drugs like atovaquone, fenofibrate, dexamethasone, prednisolone, carbamazepine, ordinon, melarsoprol, thiomerasol, amphotericin etc.(Moller et al[6]) In this technique, a presuspension of the micronized drug is prepared in a surfactant solution using high speed stirrers to pass through a small orifice that results in a reduction of static pressure below the boiling pressure of water at room temperature (Scholar et al[7]). Consequently, the water starts boiling at room temperature and gas bubbles are formed . When the suspension leaves the gap and normal pressure is reached , the gas bubbles implode. This leads to the reduction of the particle size of the drug. In fact, the size of the drug nanocrystals depends on the number of homogenization cycles, the temperature, the homogenization pressure and the powder density of homogenizer.

Nanopure (homogenization in nonaqueous media)

Nanopure suspension is a suspension homogenized in water –free medium and is prepared for thermolabile compounds (Kipp et al[8]). In fact, nanopure is a deep-freeze homogenization in which homogenization of the drug suspension is carried out in nonaqueous medium at zero degree centigrade or even below that temperature. Due to very high boiling point and low vapour pressure of water, oils, and fatty acids, the drop in static pressure is not sufficient to cause cavitation in this technique.(Noyes et al [9])

Milling techniques

Media miling

In this technique, nanosuspensions are produced by using high-shear media mills or pearl mills. The mill consists of a milling shaft and a recirculation chamber.(Liversidge et al [10]). The milling chamber is charged with the milling media-the drug, stabilizer, and a suitable buffer or water. The chamber is rotated at a very high shear rate to produce the desired suspension. However , residues are left in the final product due to erosion of balls/pearls.

Dry cogrinding

This is actually a dry milling method, an alternative to wet milling method. In this technique, dry grinding of the poorly soluble drug is done with soluble polymers and copolymers after dispersion in liquid medium that generates stable nanosuspensions.(Itoh et al [11]). Examples include poorly water soluble drugs such as griseofulvin, nifedipine using sodium dodecyl sulfate and polyvinylpyrrolidone stabilizer.(Mura et al [12])

Lipid emulsion /microemulsion template

This technique involves the formation of an emulsion of the drug by using a partially water-miscible solvent as the dispersed phase.(Trotta et al [13]). The obtained emulsion is just diluted to form the nanosuspensions of the drug. Microemulsion templates may also contribute to yield the nanosuspensions of the drug. By microemulsions, we mean dispersions of two immiscible liquids like water and oil that have been thermodynamically stabilized by a surfactant or a cosurfactant. Water, butyl lactate, lecithin and sodium taurodeoxycholate have been used to successfully prepare the nanosuspensions of griseofulvin,.

Nanoedge (Micro emulsification High-Pressure Homogenization) method.

The basic principles of nanoedge method are those of precipitation and homogenization. In fact, this method combines microprecipitation with high -pressure homogenization giving us smaller particle size and better stability in a shorter time. What is done is that first of all, a solution of the drug is prepared in an organic solvent. This solution is then added to a solution of the stabilizer

in a solvent in which the drug is insoluble. The addition is carried out under high speed agitation which leads to precipitation of drug particles.(Hintz et al [14]).

Nanojet technology

In this technique, also called opposite stream, a chamber is used wherein a stream of suspension is divided into two or more parts that are allowed to collide with each other at high pressure such that the resultant high shear force leads to reduced particle size production. (Dearna et al [15]).This technique has been used to prepare nanosuspensions of atovaquone using the microfluidization process. A drawback of this method is that the product contains a relatively larger fraction of the microparticles.

Melt emulsification method

This method is principally used to prepare solid lipid nanoparticles. In this four-step method, first of all the drug is added to an aqueous solution containing a stabilizer that is then heated at a temperature above the melting point of the drug followed by homogenization by a high speed homogenizer leading to the formation of the emulsion. Cooling of the emulsion yields the desired nanoparticles. Thus, drug concentration, nature of the stabilizer , cooling temperature etc determine the size of the nanosuspension(Kipp et al[16])

Supercritical fluid Technology

This method is used for forming nanosuspensions from solutions of drugs.Three methods are known-the rapid expansion of supercritical solution process (RESS), the supercritical anti-solvent process (SASP), and precipitation with compressed anti-solvent(PCA). (Young et al[17]) In the RESS technique, the drug solution is expanded through a nozzle in the supercritical fluid. That results in the formation of fine particles of the drug. This method was used by Young and co-workers to produce nanoparticles with diameters in the range 400-700 nm. The drug solution is atomized into the CO_2 compressed chamber in the PCA method. The solution becomes supersaturated due to removal of the solvent leading to the formation of the precipitates as fine crystals. In the third method called SASP, the drug solution is injected into the supercritical fluid such that the solvent gets extracted and the drug solution becomes supersaturated and gets precipitated as fine crystals. The nanoparticles of the drug griseofulvin which is a drug with poor solubility have been prepared by this method.

CHARACTERISATION OF NANOSUSPENSIONS

These techniques are of utmost importance as these enable the researchers to discover whether or not the nanosuspensions have been formed and what are their particle sizes. The other parameters evaluated are zeta potential, the crystalline morphology, dissolution investigations like dissolution velocity and saturation solubility etc.

Particle Size Distribution

The mean particle size and particle size distribution determine the physiological behavior like the dissolution velocity, physical stability of the formulation in hand.(Liversidge et al [5)]. Therefore, it is clear that the characterization of nanosuspensions is of significance both for the in vitro as well as in vivo evaluation of the drug delivery systems of nanosuspensions. The particle size distribution and its polydispersity index(PI) can be determined by photon correlation spectroscopy(PCS), laser diffraction (LD), microscope and coulter counter. While LD technique can measure .05 to 80 μm, the PCS can measure a size range of 3mm to 3nm.The absolute number of the particles per volume can be determined by coulter counter method which is, in fact, a more efficient method in comparison to the LD method for the quantification of the contaminants of the nanosuspensions. (Young et al[17]). Field emission low voltage scanning electron microscopy can be used to image individual particles and atomic force spectroscopy for visualization of particle shape. The sedimentation rate studies are done with near infrared investigations and online monitoring of particle size can also be done with DSC.(Bond et al [18])

Zeta Potential

Zeta potential investigations assist us to unravel the significant surface charge characteristics such as stability of the nanosuspensions at the microscopic level.(Yang et al [19]). Thus , a minimum zeta potential of + 30 mv is needed for electrostatically stabilized nanosuspensions. Similarl, a minimum zeta potential of +20mv is sufficient for steric stabilization. Generally , the zeta potential values are calculated on the basis of electrophoretic mobility . Another technique called electroacoustic technique is widely used for determining the zeta potential in material sciences.

Crystal Morphology

You can investigate the morphological and polymorphic changes occuring due to high-pressure homogenization in the crystalline state of the formulation.(Setler et al[20]). The changes that can occur include the conversion into either the amorphous or into other polymorphic forms. X-ray diffraction analysis and differential scanning calorimetry and differential thermal analysis can be used for these purposes. In case no changes are observed between the raw material and the nanosuspensions, it is clear that the crystal structure has remained intact during the high pressure homogenization process.

Dissolution velocity

The dissolution velocity and saturation solubility are two very important parameters that have to be determined for knowing the in vitro behavior of the nanosuspensions.(Bohm et al[21]). An increase in both the dissolution as well as the dissolution velocity were noted by Bohm upon reduction of the drug into the nano size range. Clearly, a reduction in size causes an increase in the dissolution pressure as well as saturation solubility.

APPLICATIONS OF NANOSUSPENSIONS TO PHARMACEUTICAL SCIENCES

The major applications of nanosuspensions include the following.

Oral Drug Delivery

The oral drug delivery administration , though a preferred rout , suffers from some major limitations like poor solubility, incomplete dissolution etc. (Liversidge et al[22-23]) Antibiotics such as azithromycin very clearly exhibit such problems but these problems .have now been circumvented by making their oral nanosuspensions . Consequently, drugs of this type have exhibited improved absorption rates as well as bioavailability. In fact, such nanosized drugs have been presented in dosage forms like tablets, capsules and fast melts . For instance, the nanosuspensions of ketoprofen and danazol have been used as pellets for sustained drug release.

Parenteral Drug Delivery

Parenteral route serves as an important drug delivery system and nanosuspensions are best suited for such a system as they fulfill all the requirements expected of such an ideal drug delivery system from the point of view of formulation.(Rainbow et al[24]). Because of their size, nanaosuspensions enhance the efficacy of the drugs administered through parenteral route. They enhance the parenterally tolerable dose of the drug and hence reduce the cost of the therapeutic treatment . Thus, the paclitaxel nanosuspension reduced the median tumor burden to a significant level.(Liang et al[25]). Relative to its solution formulation, the IV itraconazole nanosuspension exhibited enhanced antifungal activity in rats . Further , the maximum tolerable dosage of paclitaxel nanosuspension was discovered to be almost three times greater compared to Taxol. Similarly, the injectable nanaosuspensions form of tarazepide, a poorly soluble drug have proved to be highly efficient.(Jacob et al[26])

Ocular Drug delivery

Drugs that show poor solubility in lachrymal fluids have proved to be far superior as nanosuspensions in their therapeutic action. (Kayser et al[27]). Nanosuspensions are used for sustained release ocular delivery of the drugs. The nanoparticle nature of the drug permits prolonged residence of the drug in the cul-de-sac leading to its sustained release as expected . Nanaosuspensions can be prepared in a hydrogel base, a mucoadhesive base and in ocular inserts as well.

Pulmonary Drug Delivery

Drugs that exhibit poor solubility in pulmonary secretions also show improved profiles as nanaosuspensions . (Heidi et al[28]). These drugs are currently delivered in the form of suspension aereosols or as dry powder inhalers. The nanosuspensions are nebulized via mechanical or ultrasonic nebulizers. It is clear that each aereosol droplet would carry a minimum of one drug

particle due to reasons of its small size. Consequently, that would lead to a uniform distribution of the drug in lungs. (Hernandez-Trejo et al[29]). Evidently, it is the nanoparticle nature of the drug that permits faster diffusion as well as the dissolution of the drug at the absorption site. These effects coupled with the enhanced adhesiveness of the drug prolong the residence time of the drug on the mucosal surfaces , the twin important features that are urgently needed for the efficient treatment of pulmonary diseases. Examples include budenoside now available as efficient nebulized nanosuspensions formulations. (Kaysor et al[30])

Targetted Drug Delivery.

Because of their suitable surface properties as well as the ease to alter the in-vivo-behaviour by changing either the stabilizer or the milieu, the nanosuspensions can be used for targeted delivery. A nanosuspension of the the drug, aphidicolin has been shown to improve the drug targeting against leishmania-infected macrophages. Thus, while the conventional form of this drug had EC 0.16μg/mL, the nanosuspension showed EC 50 of .003ug/mL. Similarly, an enhanced drug targeting to brain in the treatment of toxoplasmic encephalitis in a new murine model infected with Toxoplasma gondii was shown by atovaquone nanosuspension formulation.

CONCLUSION

Nanosuspensions have proved to be a boon in controlling the poor solubility and bioavailabilty of hydrophobic drugs which were because of these reasons once upon a time called brick dust candidates. Nanosuspension technology has been able to convert them into drugs with good pharmacological performance. Another beauty of nanosuspensions is that they can be administered through any means of administration. Moreover, nanosuspensions are commercially viable. Media-milling, high-pressure homogenization techniques are available for the commercial production of such drugs. Furthermore, any drug can be converted into nanometer range. Nanosuspensions enhance not only dissolution and drug availability but they also improve bioadhesivity, versatility in surface characteristics. They alter pharmacokinetics and improve drug safety and efficacy. In view of these authors, as time passes on we will learn more and more about the applications of nanosuspensions through all possible routes of drug administration. The authors believe that the nanosuspensions technology can , in theory , be applied successfully to hydrophilic drugs as well for further improvement in their therapeutic actions.

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