International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
October - November, 2013, Vol. 2, No.6, pp 642-649
ISSN: 2278-0238

Review Article

SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG BY USING NANO-SUSPENSION TECHNOLOGY

Mishra Soumya*, Saurabh Gupta, Rahul Jain, Mazumder R.

Department of Pharmacy, Noida Institute of Engineering and Technology, 19, Knowledge Park-II, Institutional Area, Phase - II, *Greater Noida.*

***Corresponding Author: Email** soumya.mishra1504@gmail.com

(Received: July 14, 2013; **Accepted:** September 10, 2013**)**

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. Nanosuspension technology can be used to improve the stability as well as the bioavailability of poorly soluble drugs. The problem is even more complex for drugs like itraconazole, simvastatin, and carbamazepine which are poorly soluble in both aqueous and nonaqueous media, belonging to BCS class II as classified by biopharmaceutical classification system. Formulation as nanosuspension is an attractive and promising alternative to solve these problems. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. This review article describes the preparation methods, characterization, and applications of the nanosuspension.

Keywords: Bioavailability, colloidal dispersion, solubility enhancement, nanosuspension..

INTRODUCTION

One of the main problems responsible for the low turnout in the development of new molecular entities as drug formulations is poor solubility and poor permeability of the lead compounds. The increasing frequency of poorly water soluble new chemical entities exhibiting therapeutic activity is of major concern to the pharmaceutical industry. Various formulation parameters that play a crucial role for successful formulation are aqueous solubility, stability at ambient temperature and humidity, photostability, compatibility with solvents and excipients, etc. Of these, solubility is the most important property for developing formulations. A major hurdle that has prevented the commercialization of many promising poorly soluble drugs is dissolution rate-limited bioavailability. Over the last decades, nanoparticle engineering has been developed and reported for pharmaceutical applications[1]. Nanotechnology can be used to solve the problems associated with various approaches described earlier. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} m. The drug microparticles /micronized drug powder is transferred to drug nanoparticles by techniques like Bottom-Up Technology and Top-Down Technology[2]. Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants[3]. Nanosuspensions consist

of the poorly water-soluble drug without any matrix material suspended in dispersion[4]. These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. This approach is useful for molecules with poor solubility, poor permeability, or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without any blockade of the blood capillaries. The suspensions can also be lyophilized and into a solid matrix. Apart from these advantages, it also has the advantages of liquid formulations over others [5]. In the present review, we are mainly focusing on the different methods of preparation associated merits, demerits, and its pharmaceutical application as drug delivery system.

ADVANTAGES OF NANOSUSPENSION

- Enhance the solubility and bioavailability of drugs
- Suitable for hydrophilic drugs
- Higher drug loading can be achieved
- Dose reduction is possible
- Enhance the physical and chemical stability of drugs
- Provides a passive drug targeting

Preparation of nano-suspension:

The most common approach that has been used for preparing nanosuspensions is micronization by colloid or jet milling [6]. The method increases the dissolution rate of the drug but does not have any impact on the saturation solubility and thus cannot improve the bioavailability of drugs.

Sucker and co-workers used a precipitation technique to produce nanoparticles by dissolving the drug in a solvent and adding the solvent to a non-solvent that cause precipitation of the fine drug particle [7]. This has the advantage of using relatively simple and low-cost equipment. However, this created problems in stirring and mixing when taken up for large-scale production. The major challenge of this technique is to avoid crystal growth that occurs on storage due to Ostwald ripening. Mainly there are two methods for preparation of nanosuspensions. The conventional methods of precipitation (Hydrosols[25]) are called 'Bottom Up technology'. In Bottom Up Technology the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media[8].

The 'Top Down Technologies' are the disintegration methods and are preferred over the precipitation methods. The 'Top Down Technologies' include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege) [9,10]. Few other techniques used for preparing nanosuspensions are emulsion as templates, microemulsion as templates etc[11]

Methods of Preparation of Nanosuspensions

The following methods are used to prepare nanosuspension:

i. Media milling (Nanocrystal or Nanosystems),
ii. Homogenization in water (Dissocubes),
iii. Homogenization in nonaqueous media (Nanopure),
iv. Combined precipitation and homogenization (Nanoedege),
v. Nanojet technology,
vi. Emulsification-solvent evaporation technique,
vii. Hydrosol method and
viii. Supercritical fluid method.

1. Media milling (Nanocrystal or Nanosystems)

The method is first developed and reported by Liversidge et.al. (1992).The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days). The milling medium is composed of glass, Zirconium oxide or highly cross-linked polystyrene resin. The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting

into breaking of microparticulate drug to nanosized particles[12, 13].

Advantages:

1. Media milling is applicable to the drugs that are poorly soluble in both aqueous and organic media.
2. Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity.
3. Nanosize distribution of final nanosize products.

Disadvantages:

1. Nanosuspensions contaminated with materials eroded from balls may be problematic when it is used for long therapy.
2. The media milling technique is time consuming.
3. Some fractions of particles are in the micrometer range.
4. Scale up is not easy due to mill size and weight.

B) Homogenization In Water (Dissocubes)

R.H.Muller developed Dissocubes technology in 1999. The instrument can be operated at pressure varying from 100 – 1500 bars (2800 –21300psi) and up to 2000 bars with volume capacity of 40ml (for laboratory scale). For preparation of nanosuspension, we have to start with the micronized drug particle size less than 25 µm to prevent blocking of homogenization gap hence it is essential to prepare a pre suspension of the micronized drug in a surfactant solution using high speed stirrer[14].

Principle

In piston gap homogenizer particle size reduction is based on the cavitation principle. Particles are also reduced due to high shear forces and the collision of the particles against each other. The dispersion contained in 3 cm diameter cylinder; suddenly passes through a very narrow gap of 25µm. According to Bernoulli's Law the flow volume of liquid in a closed system per cross section is constant. The reduction in diameter from 3 cm to 25 µm leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Due to this water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached. The size of the drug nanocrystals that can be achieved mainly depends on factors like temperature, number of homogenization cycles, and power density of homogenizer and homogenization pressure.

Advantages

1. It does not cause the erosion of processed materials[15].
2. Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity[16].
3. It is applicable to the drugs that are poorly soluble in both aqueous and organic media.
4. It allows aseptic production of nanosuspensions for parental administration[17].

Disadvantages

1. Preprocessing like micronization of drug is required.
2. High cost instruments are required that increases the cost of dosage form.

C) Homogenisation In Nonaqueous Media (Nanopure)

The drugs that are chemically labile can be processed in such nonaqueous media or water-miscible liquids like polyethyleneglycol-400 (PEG), PEG1000 etc. The homogenization can be done at room temperature, 0° C and below freezing point (-20° C)[14].

D) Combined Precipitation And Homogenization (Nanoedege)

The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystals. 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[14].

3. PRECIPITATION

Precipitation has been applied for years to prepare submicron particles within the last decade[18,19], especially for the poorly soluble drugs. Typically, the drug is firstly dissolved in a solvent. Then this solution is mixed with miscible antisolvent in the presence of surfactants. Rapid addition of a drug solution to the antisolvent (usually water) leads to sudden supersaturation of drug in the mixed solution, and generation of ultrafine crystalline or amorphous drug solids. This process involves two phases: nuclei formation and crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate but low growth rate is necessary. Both rates are dependent on temperature:

the optimum temperature for nucleation might lie below that for crystal growth, which permits temperature optimization[20]

Nanojet technology: This technique, called opposite stream or nanojet technology, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction. Equipment using this principle includes the M110L and M110S micro fluidizers . Dearn prepared nanosuspensions of atovaquone using the micro fluidization process. [21]The major disadvantage of this technique is the high number of passes through the micro fluidizer and that the product obtained contains a relatively larger fraction of micro particles.

Supercritical fluid methods: Various methods like rapid expansion of supercritical solution (RESS) process, supercritical antisolvent process, and precipitation with compressed antisolvent (PCA) process are used to produce nanoparticles. In RESS technique, drug solution is expanded through a nozzle into supercritical fluid, resulting in precipitation of the drug as fine particles by loss of solvent power of the supercritical fluid. By using RESS method, Young *et al*. prepared cyclosporine nanoparticles having diameter of 400 to 700 nm. In the PCA method, the drug solution is atomized into the CO_2 compressed chamber. As the removal of solvent occurs, the solution gets supersaturated and finally precipitation occurs. In supercritical antisolvent process, drug solution is injected into the supercritical fluid and the solvent gets extracted as well as the drug solution becomes supersaturated[22]

LIPID EMULSION/MICROEMULSION TEMPLATE.

Another way to produce nanosuspensions is to use an emulsion which is formed by theconventional method using a partially water miscible solvent as the dispersed phase.Nanosuspensions are obtained by just diluting the emulsion[23]. Moreover, microemulsions as templates can produce nanosuspensions. Micro emulsions 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 preformed micro emulsion can be saturated with the drug by intimate mixing. Suitable dilution of the micro emulsion 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 [24].

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.

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. *In vivo* pharmacokinetic performance and biological function of nanosuspension strongly depends on its particle size and distribution, particle charge (zeta potential), crystalline state, and particle 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 [26]. 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 fairly narrow size distribution, and PI value more than 0.5 indicates a very broad distribution [27] .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[28]. 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.[25]

Crystalline State and Particle Morphology

Polymorphic or morphological changes of nanosized particles can be checked by assessing the crystalline state and particle morphology[25]. As nanosuspension requires high-

pressure homogenization, change in crystalline structure of formulation occurs which may be converted to either amorphous or other polymorphic forms[26]. Alteration in the solid state of the drug particles and the extent of the amorphous portion is determined by X-ray diffraction analysis [29] and supplemented by differential scanning calorimetry analysis[25].

Surface Charge (Zeta Potential)

Surface charge properties of the nanosuspensions are studied through zeta potential. The value of particle surface charge indicates the stability of nanosuspensions at the macroscopic level. A minimum zeta potential of ±30 mV is required for electrostatically stabilized nanosuspensions[30], [31] and a minimum of ±20 mV for steric stabilization [32] The zeta potential values are commonly calculated by determining the particle's electrophoretic mobility and then converting the electrophoretic mobility to the zeta potential. [33] Electroacoustic technique is also used for the determination of the zeta potential in the areas of material sciences. [34]

Evaluation of nanosuspensions[35,36]:–

A) In-Vitro Evaluations

1. Particle size and size distribution
2. Particle charge (Zeta Potential)
3. Crystalline state and morphology
4. Saturation solubility and dissolution velocity

B) In-Vivo Evaluation

C) Evaluation for surface-modified Nanosuspensions[36]

1. Surface hydrophilicity
2. Adhesion properties
3. Interaction with body proteins

1) Mean particle size and size distribution

The mean particle size and the width of particle size distribution (called Polydidpersity Index) are determined by Photon Correlation Spectroscopy[37] (PCS). Particle size and polydispersity index (PI) governs the saturation solubility; dissolution velocity and biological performance. It is proved that change in particle size changes saturation solubility and dissolution velocity. PCS measures the particle size in the range of 3nm- 3 µm only. PI governs the physical stability of nanosuspension and should be as low as possible for long-term stability.(Should be close to zero). PCS is a versatile technique but has low measuring range. In addition to PCS analysis nanosuspensions are analyzed by Laser Diffractometry (LD) measures volume size distribution and measures particles ranging from 0.05- 80µm upto 2000 µm. Atomic Force Microscopy[38] is used for visualization of particle shape.

2) Particle charge (Zeta Potential)

Particle charge determines the stability of nanosuspension. For electro statically stabilized nanosuspension a minimum zeta potential of ±30mV and for combined steric and electrostatic stabilization it should be a minimum of ±20mV.

3) Crystalline state and particle morphology

Differential Scanning Calorimetry[39] (DSC) determines the crystalline structure. When nanosuspensions are prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. The X-Ray Diffraction[40] (XRD) is also used for determining change in physical state and extent of amorphous drug.

4) Saturation solubility and dissolution velocity

The nanosuspension increase 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.

Applications of Nanosuspensions

1. Intravenous administration

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.[41]

2. Oral Drug Delivery

Poor solubility, incomplete dissolution, and insufficient efficacy are the major problem of oral drug administration. Due to smaller particle size and much larger surface to

volume ratio, oral nanosuspensions are specially used to increase the absorption rate and bioavailability of poorly soluble drugs. [42] In case of azithromycin nanosuspensions, more than 65% drug was found to be dissolved in 5 hours as compared with 20% of micronized drugs. [43] The nanosuspension have advantages like improved oral absorption, dose proportionality, and low intersubject variability. By using standard manufacturing techniques, drug nanosuspensions can be simply incorporated into various dosage forms like tablets, capsules, and fast melts. The nanosuspension of Ketoprofen was successfully incorporated into pellets for the sustained release of drug over the period of 24 hours. [44]

3. Ocular administration.

Ocular delivery of the drugs as nanosuspensions to provide a sustained release of drug. Pignatello *et al.* prepared Eudragit retard nanosuspensions of cloricromene for ocular Delivery [45] .They observed that the drug showed a higher availability in rabbit aqueous humor and the formulation appeared to offer a promising means of improving the shelf-life and the bioavailability of this drug after ophthalmic application.

4. Bioavailability Enhancement

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. The oral administration of naproxen nanoparticles lead to an area under the curve (AUC) (0-24 h) of 97.5 mg-h/l compared with just 44.7 mg-h/l for naprosyn suspensions and 32.7 mg-h/l for anaprox tablets. [46] Oral administration of the gonadotrophin inhibitor Danazol as a nanosuspension leads to an absolute bioavailability of 82.3 and the conventional dispersion (Danocrine) only to 5.2%. [47] A nanosuspension of Amphotericin B developed by Kayser *et al.* showed a significant improvement in its oral absorption in comparison with the conventional commercial formulation.[48]

5. TARGETED DRUG DELIVERY

Nanosuspensions can 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. The engineering of stealth nanosuspensions (analogous to stealth liposomes) by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. [49] Kayser formulated a nanosuspension of Aphidicolin to improve drug targeting against leishmania infected macrophages. He stated that the drug in the conventional form had an effective concentration (EC 50) of 0.16 mcg/ml whereas the nanosuspension formulation had an enhanced activity with an EC (50) of 0.003 mcg/ml. Scholer et al. showed an improved drug targeting to the brain in the treatment of toxoplasmic encephalitis in a new murine model infected with Toxoplasma gondii using a nanosuspension formulation of Atovaquone.

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. [50] 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*. Bupravaquone nanosuspensions have been reported to demonstrate an advantage in TRC- alpha-deficient mice infected with *Cryptosporidium parvum* oocytes. The bioadhesion can also be improved by including a mucoadhesive polymer in the formulation. [51]

CONCLUSION

Nanosuspensions of pure drug offer a method to formulate poorly soluble drug and enhance the bioavailability of several drugs. It has many formulations and therapeutic advantages, such as simple method of preparation, less requirement of excipients, increased dissolution velocity and saturation solubility, improved adhesion, increases the bioavailability leading to a decrease in the dose and fast-fed variability and ease of large-scale manufacturing. Nanosuspensions can be formulated for various routes of administration, such as oral, parenteral, ocular, topical and pulmonary routes. This technology is gaining significance as

the number of molecules with solubility and bioavailability related problems are increasing day by day. Thus, nanotechnology can play a vital role in drug discovery programs to increase aqueous solubility as well as bioavailability of poorly soluble drugs.

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How to cite this article:

Soumya M., Gupta S., A review on "Solubility enhancement of poorly water soluble drug by using nano-suspension technology", Int. J. Res. Dev. Pharm. L. Sci., 2013, 2(6), pp.642-649.

