CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Review Article*

NANOSUSPENSIONS – A REVIEW

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Article Received: December 2019 **Accepted:** January 2020 **Published:** February 2020

Abstract:
The interest in the preparation and application of nanometer-sized materials is increasing due to their tremendous potential as a drug delivery system with wide range of applications. Recently, nanoscale systems have received much interest as a way to resolve solubility issues because of their cost-effectiveness and technical simplicity compared to liposomes and other colloidal drug carriers. Nanosuspensions have proven to be a better alternative over other approaches currently available for improving bioavailability of number of drugs with low solubility. 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. Different preparation methods for nanosuspensions and their application are being reported and patented. In fact, the number of products based on nanosuspension in the market and under clinical study is higher than that of other nanotechnology-based applications. A surprisingly large proportion of new drug candidates emerging from drug discovery programs are water insoluble, and therefore poorly bioavailable, leading to abandoned development efforts. These so-called 'brickdust' candidates can now be rescued by formulating them into crystalline nanosuspensions.
Key words: nanosuspension, bioavailability, solubility enhancement, polymers.

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*Please cite this article in press K. Malleswari et al., **Nanosuspensions – A Review.,** Indo Am. J. P. Sci, 2020; 07(02).*

INTRODUCTION:

A range of parameters like solubility, stability at room temperature, compatibility with solvent, excipient, and photostability play a critical role in the successful formulation of drugs. Till date, more than 40% of the new chemical entities being generated through drug discovery programs are lipophilic or poorly watersoluble compounds. [1,2] Many formulation approaches are available to solve the problems of low solubility and low bioavailability of drugs. The conventional approaches include micronization, use of fatty solutions, use of penetration enhancer or cosolvents, surfactant dispersion method, salt formation, precipitation, etc., but still, these techniques having limited utility in solubility enhancement
for poorly soluble drugs. Additional approaches are vesicular system like liposomes, dispersion of solids, emulsion and microemulsion methods, and inclusion complexes with cyclodextrins, which show beneficial effect as drug delivery system but major problems of these techniques are lack of universal applicability to all drugs.[3] Over the last decades, nanoparticle engineering has been developed and reported for pharmaceutical applications.[4] 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.[5] Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants.[6] Nanosuspensions consist of the poorly water-soluble drug without any matrix material suspended in dispersion.[7] 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.

CLASSIFICATION OF SUSPENSION [8]

I. Based On General Classes

- Oral suspension
- Externally applied suspension
- Parenteral suspension

II. Based On Proportion Of Solid Particles

- Dilute suspension (2 to10%w/v solid)
- Concentrated suspension (50%w/v solid)

III. Based on Electrokinetic Nature of Solid Particles

- Flocculated suspension
- Deflocculated suspension

IV. Based On Size Of Solid Particles

- colloidal suspension (< 1 micron)
- Coarse suspension (>1 micron)
- Nano suspension (10 ng)

The nanosuspensions can also be lyophilized or spray dried and the nanoparticles of a nanosuspension can also be incorporated in a solid matrix. Apart from this, it has all other advantages of a liquid dosage form over the solid dosage forms. The present review is focused on various methods of preparing nanosuspensions, critical parameters to be characterized and the application of nanosuspension formulations. Most of the drugs are not soluble in water and they create major problem during formulation they also show poor bioavailability. Reduction in particle size of such drugs enhances the dissolution rate and bioavailability. Nano suspension a promising delivery used to enhance the solubility of hydrophobic drugs. Media milling and high-pressure homogenization technique are used commercially to produce nano suspensions. Recently emulsion and micro emulsion as templates are used to produce nano suspension. They are administered by Parenteral, per oral, ocular and pulmonary routes. Now their application also extended to site specific delivery.

This review describes the methods of pharmaceutical production, formulations and pharmaceutical applications in drug delivery as well as the marketed products. Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion.

Advantages

- Suspension can improve chemical stability of certain drug.
- Drug in suspension exhibits higher rate of bioavailability than remaining formulations.
- Duration and onset of action can be controlled.
- Suspension can mask the unpleasant/ bitter taste of drug.

Disadvantages

- Physical stability, sedimentation and compaction can causes problems.
- It is bulky sufficient care must be taken during handling and transport.
- Uniform and accurate dose cannot be achieved unless suspension are In a proper dose.

Feature Desired In Pharmaceutical Suspensions

- The suspended particles should not settle rapidly and sediment produced must be easily re-suspended by the use of moderate amount of shaking.
- It should be easy to pour yet not watery and no grittiness.
- It should have pleasing odour, colour and palatability.
- Good syringeability.
- It should be physically, chemically and microbiologically stable.
- Parenteral/Ophthalmic suspension should be sterilizable.

Applications

- Suspension is usually applicable for drug which is insoluble or poorly soluble.
- To prevent degradation of drug or to improve stability of drug.

CLASSIFICATION [8]

There are three general classes of pharmaceutical suspensions:

- Orally administered (sometimes referred to as mixtures)
- Externally applied (topical lotions)
- Injectable(parenteral)

ORAL ADMINISTERED:

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.[40] In case of azithromycin nanosuspensions, more than 65% drug was found to be dissolved in 5 hours as compared with 20% of micronized drugs. 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.

TOPICAL SUSPENSIONS

Historically, the externally applied ‘‘shake lotion’’ is the oldest example of a pharmaceutical suspension. The protective action and cosmetic properties of topical lotions usually require the use of high concentrations of the dispersed phase, often in excess of 20%. Therefore, topical lotions represent the best example of suspensions that exhibit low settling rates. Various pharmaceutical vehicles have been used in the preparation of topical lotions, including diluted oil-in-water or water-in-oil emulsion bases, dermatological pastes, magmas, and clay suspensions. Safety and toxicity are import combination for dermatological acceptability. some time, the drug particles settled slowly, forming tightly packed sediment that was almost impossible to resuspend even with vigorous shaking. Primary particles or small aggregates, reaching the bottom of the container during sedimentation (settling), slipped past each other and produced compact layers of solids. The inter particle interaction in such compact sediments is relatively high because the inter particle distances are small, and the weak van der Waals forces of attraction. Such conditions frequently lead to the undersirable phenomenon of ‘‘caking or claying’’ and require extensive agitation for resuspension. The physical instability of these early deflocculated suspensions led to other methods of producing physically stable pharmaceutical suspension.

PARENTAL DRUG DELIVERY

The present approaches for parental delivery include micellar solutions, salt formation, solubilization using cosolvents, cyclodextrin complexation, and more recently vesicular systems such as liposomes and niosomes. But these methods have limitations like solubilization capacity, parental acceptability, high manufacturing cost, etc. To solve the above problems, the nanosuspension technology is used. Nanosuspensions are administered through various parental routes such as intraarticular, intraperitoneal, intravenous, etc. Additionally, nanosuspensions increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspension was reported to have their superiority in reducing the median tumor burden. Clofazimine nanosuspension showed an improvement in stability as well as efficacy above the liposomal clofazimine in *Mycobacterium avium*-infected female mice.Rainbow *et al*. showed that intravenous nanosuspension of itraconazole

enhanced efficacy of antifungal activity in rats relative to the solution formulation.[9-11]

NANOSUSPENSION-AN APPROACH TO ENHANCE SOLUBILITY OF DRUGS

In recent years, there has been a considerable interest in the development of novel drug delivery systems using particulate delivery systems like nanoparticles. Nanoparticles represent a promising drug delivery system of controlled and targeted release. In this context, nanosuspensions will be effective in increasing the solubility, bioavailability of poorly soluble drugs. The review focuses on advantages, method of preparation, physical characteristics and evaluation of nanosuspensions. A large proportion of new chemical entities coming from drug discovery are water insoluble, and therefore poorly bioavailable, leading to hurdles in formulation development efforts. There are number of formulation approaches like micronisation, solubilization using cosolvents, precipitation techniques etc., to resolve the problems of low solubility and low bioavailability. Each of them have their own limitations. Other techniques like micro emulsions, solid dispersions and inclusion complexes using cyclodextrins even though showed increased solubility, but not applicable for drugs which are insoluble in both aqueous and organic media. The next development stepis transformation of the micronized drug to drug nanoparticles and nanosuspensions. [12,13]

Nanoparticulate drug delivery system may offer plenty of advantages over conventional dosage forms which include improved efficacy, reduced toxicity, enhanced biodistribution and improved patient compliance. Nanosuspension technology offers novel solution for these poorly soluble drugs. Nanosuspension consists of pure poorly water-soluble drugs with or without any matrix material suspended in dispersion. They can be surfactant free; can also comprise surfactants or stabilizers or both. Nanosuspensions differ from nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nano capsules), and from solid-lipid nanoparticles (SLN), which are lipidic carriers of drug. Nanosuspensions are distinctive and commercially feasible approach to solve the problems of hydrophobic drug such as poor solubility and poor bioavailability. For large-scale production of nanosuspensions, media milling and high-pressure homogenization technology have been successfully used. Striking characteristics, like improvement of dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification, and ease of postproduction processing, have widened the applications of nanosuspensions for various routes of administration**.** More than 40 percent of the drugs coming from High-through output screening are poorly soluble in water. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms.

One of the critical problems associated with poorly soluble drugs is too low bioavailability and or erratic absorption. These techniques for solubility enhancement have some limitations and hence have limited utility in solubility enhancement. [14,15] 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 demerits, characterization and evaluation parameters. A nanosuspension not only solve the problems of poor solubility and bioavailability but also alter the pharmacokinetics of drug and thus improves drug safety and efficacy.

PREPARATION OF NANOSUSPENSION [17,18]

The most common approach that has been used for preparing nanosuspensions is micronization by colloid or jet milling. [10] This 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. [8] 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. The principle techniques used in recent years for preparing nanosuspensions can be classified into four basic methods: (a) wet milling, (b) homogenization, (c) emulsification solvent evaporation and (d) supercritical fluid method.

a. Wet milling [19]

Nanosuspensions are produced by using highshear 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 0.1 µm. A nanosuspension of Zn-Insulin with a mean particle size of 150 nm was prepared using the wet milling technique. The major drawbacks of this technology include the erosion of balls/pearls that can leave residues as contaminants in the final product, degradation of the thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles ≥5 µm.

b. Homogenization Dissocubes [20,21]

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. Dissocubes was developed by Muller et al. in 1999. In this case, the suspension of the drug is made to pass through a small orifice that results in a reduction of the static pressure below the boiling pressure of water, which leads to boiling of water and formation of gas bubbles. When the suspension leaves the gap and normal air pressure is reached again, the bubbles implode and the surrounding part containing the drug particles rushes to the center and in the process colloids, causing a reduction in the particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of drug, the desired mean particle size and the required homogeneity. This principle is employed in the APV Gaulin Micron LAB 40 Homogenizer (APV Homogenizer, Lóbeck, Germany) and the NS 1001L-Panda 2K highpressure homogenizer . prepared atovaquone naanosuspensions using this technique. An aqueous suspension of atovaquone was dispersed using an Ultra turrax T25, IKA-Werke GmbH& Co. KG, Staufen, Germany and was further homogenized in a Gaulin Micron Lab 40 highpressure homogenizer. After subjecting to pressures of 1.5 x 10^7 (two cycles), 5 x 10^7 (two cycles) and 1.5 x 10^8 (20 cycles) Pa, a nanosuspension of atovaquone with a mean diameter of 279 ± 7 nm and mean polydispersity index of 0.18 ± 0.001 was obtained. To produce a nanosuspension with a higher concentration of solids, it is preferred to start homogenization with very fine drug particles, which can be accomplished by pre-milling. The major advantage of high- pressure homogenization over media milling is that it can be used for both diluted as well as concentrated suspensions and also allows aseptic production.

c. Nanopure [22,23]

Nanopure is suspensions homogenized in waterfree media or water mixtures. In the Dissocubes technology, the cavitation is the determining factor of the process. But, in contrast to water, oils and oily fatty acids have very low vapour pressure and a high boiling point. Hence, the drop of static pressure will not be sufficient enough to initiate cavitation. Patents covering disintegration of polymeric material by high- pressure homogenization mention that higher temperatures of about 80 C promoted disintegration, which cannot be used for thermolabile compounds. In nanopure technology, the drug suspensions in the non- aqueous media were homogenized at 0 C or even below the freezing point and hence are called "deep-freeze" homogenization. The results obtained were comparable to Dissocubes and hence can be used effectively for thermolabile substances at milder conditions.

d. Nanoedge

The basic principles of Nanoedge are the same as that of precipitation and homogenization. A combination of these techniques results in smaller particle size and better stability in a shorter time. The major drawback of the precipitation technique, such as crystal growth and long-term stability, can be resolved using the Nanoedge technology. In this technique, the precipitated suspension is further homogenized, leading to reduction in particle size and avoiding crystal growth.Precipitation is performed in water using water-miscible solvents such as methanol, ethanol and isopropanol. It is desirable to remove those solvents completely, although they can be tolerated to a certain extent in the formulation. For an effective production of nanosuspensions using the Nanoedge technology, an evaporation step can be (RESS), supercritical anti-solvent process and precipitation with compressed anti-solvent process (PCA).The RESS involves expansion of the drug solution in supercritical fluid through a nozzle, which leads to loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. Young et al. prepared cyclosporine nanoparticles in the size range of 400-700 nm using this process. In the PCA method, the drug solution is atomized into a chamber containing compressed CO_2. As the solvent is removed, the solution gets supersaturated and thus precipitates as fine crystals. The supercritical anti-solvent process uses a supercritical fluid in which a drug is poorly soluble and a solvent for the drug that

is also miscible with the supercritical fluid. [23,24] The drug solution is injected into the supercritical fluid and the solvent gets extracted by the supercritical fluid and the drug solution gets supersaturated. The drug is then precipitated as fine crystals. Nanoparticles of griseofulvin, a drug with poor solubility, were prepared by Chattopadhyay et al. using this method. [16] The disadvantages of the above methods are use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques, particle nucleation overgrowth due to transient high supersaturation, which may also result in the development of an amorphous form or another undesired polymorph.

Evaluation of nanosuspensions [25]

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

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

Mean Particle Size and Particle Size Distribution [26]

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. API 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. [27,28] 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. 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.

Crystalline State and Particle Morphology [29,30]

Polymorphic or morphological changes of nanosized particles can be checked by assessing the crystalline state and particle morphology. As nanosuspension requires high-pressure homogenization, change in crystalline structure of formulation occurs which may be converted to either amorphous or other 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[34] and supplemented by differential scanning calorimetry analysis.

Surface Charge (Zeta Potential) [31,32]

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 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. Electroacoustic technique is also used for the determination of the zeta potential in the areas of material sciences.

4) Saturation solubility and dissolution velocity [32-35]

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.

CONCLUSION:

The nanosuspension can be proved as a gift as the poorly water-soluble drugs can be easily formulated into nanosuspension. One of the critical problems associated with poorly soluble drugs is too low bioavailability. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability. 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. Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants. Nanosuspension drug delivery has obtained great success in the preparation of insoluble drugs. The nanosuspension technology can confer a series of special characteristics to the drugs, such as the enhanced dissolution rate and saturation solubility. This mini review first described the differences between the nanocrystals and nanosuspensions. Next, the product techniques, the stable measures, the special features, and the routes of administration of the nanosuspensions were reviewed and compared. Finally, some existing shortcomings of the nanosuspensions were mentioned and the perspectives of the nanosuspensions were also made.

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