CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

http://doi.org/10.5281/zenodo.4432151

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

NANOSUSPENSION TECHNOLOGY: A REVIEW

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Article Received: November 2020 **Accepted:** December 2020 **Published:** January 2021

Abstract:

Solubility is the crucial factor for drug effectiveness, independence of the route of administration. Large proportions of newly discovered drugs are water insoluble, and therefore poorly bioavailable contributing to deserted development effort. These so-called 'Brickellia' candidates can now be delivered by formulating them into Nanosuspension. Nanosuspension technology solved the problem of drugs which are poorly aqueous soluble and less bioavailability. Stability and bioavailability of the drugs can be improved by the Nanosuspension technology. Preparation of Nanosuspension is simple and applicable to all drugs which are aqueous insoluble. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and super critical fluid techniques. Nanosuspension can be prepared by using stabilizers, organic solvents and other additives such as buffers, salts, polyols, osmogent and cryoprotectant. Nanosuspensions can be delivered by oral, parenteral, pulmonary and ocular routes. Nanosuspensions can also be used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels.

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QR code

Please cite this article in press B. Hemalatha et al, ***Nanosuspension Technology : A Review.,*** *Indo Am. J. P. Sci, 2021; 08(1).*

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 new chemical entities than 40% of the being generated through drug discovery programs are lipophilic or poorly water-soluble compounds (Sharma P *et al.*, 2009). 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 (Prasanna Lakshmi *et al.*, 2010). Over the last decades, nano particle engineering has been developed and reported for pharmaceutical applications. 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. Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants. Nanosuspensions consist of the poorly water-soluble drug without any matrix material suspended in dispersion. 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 into a solid matrix. Apart from these advantages, it also has the advantages of liquid formulations over others (Sharma P *et al.*, 2009).

Advantages of Nanosuspension:

1. Enhance the solubility and bioavailability of drugs
2. Suitable for hydrophilic drugs
3. Higher drug loading can be achieved
4. Dose reduction is possible
5. Enhance the physical and chemical stability of drugs
6. Provides a passive drug targeting.

Disadvantages of Nanosuspension:

1) The drug needs to be soluble in at least one solvent (thus excluding all new drugs that are simultaneously poorly soluble in aqueous and in organic media).
2) The solvent needs to be miscible with at least one nonsolvent.
3) Solvent residues need to be removed, thus increasing production costs.
4) It is an Iittle bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction). In general, it is recommended that a second consecutive process has to be performed for particle preservation that is spray drying or lyophilisation.

FORMULATION CONSIDERATION:

a) Stabilizer:

The main function of a stabilizer is to wet the drug particles thoroughly, and to prevent ostwalds ripening and agglomeration of Nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barrier. The type and amount of stabilizer has a pronounced effect on the physical stability and *in vivo* behavior of Nanosuspension. Stabilizers that have been used so far are poloxomers, polysorbates, cellulosics, povidones, and lecithins. Lecithin is the stabilizer of choice if one intends to develop a parentally acceptable and autoclavable nanosuspension (Prasanna Lakshmi *et al.*, 2010).

b) Organic Solvent:

Organic solvents are used in the formulation of Nanosuspension if emulsions or micro emulsions are used as a template. The pharmaceutically acceptable less hazardous water miscible solvent, such as methanol, ethanol, chloroform, isopropanol, and partially water miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol are preferent in the formulation over the conventional hazardous solvents, such as dichloromethane (Harshil M. Patel *et al.*, 2016).

c) Co-Surfactants:

The choice of co-surfactant is critical when using microemulsions to formulate Nanosuspensions. Since cosurfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected micro emulsion composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycerrhizinate as cosurfactants, various solubilizers, such as Transcutol, glycofurol, ethanol

and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions (Rinku Jayaprakash *et al.*, 2016).

d) Other additives:
Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant (N. Arun Kumar *et al.*, 2009).

PREPARATION OF NANOSUSPENSIONS:

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

A. Media milling
B. High pressure homogenization
C. Emulsion diffusion method
D. Supercritical fluid method
E. These are preferred over the precipitation methods.

A. Media milling (Nanocrystals or Nanosystems):
In this method the nanosusensions are produced using high-shear media mills or pearl mills. The media mill consists of a milling chamber, a milling shaft and a recirculation chamber. The milling medium is framed of glass, zirconium oxide or highly cross-linked polystyrene resin. The milling chamber is charged with the milling media, water, drug and stabilizer, and the milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled temperatures. The high energy and shear forces generated as a result of the impaction of the milling media with the drug provide the energy input to break the microparticulate drug into nano-sized particles. The unimodal distribution profile and mean diameter of <200, require a time profile of 30-60 min. The media milling procedure can successfully process micronized and non-micronized drug crystals. Once the formulation and the process are optimized, very short batch-to-batch variation is observed in the quality of the dispersion. A nanosuspension of Naproxen with a mean particle size of 300-600 nm was prepared using pearl milling technique.

B. Homogenization:
i) Dissocubes:
Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The most commonly used homogenizer in the preparation of nanosuspension is the APV micron LAB 40 (APV Deutschland GmbH, Lubeck, Germany). However, other piston-gap homogenizers from Avestin (Avestin Inc., Ottawa, Canada) and Stansted (Stansted Fluid Power Ltd, Stansted, UK) can also be used. The instrument can be operated at pressures varying from 100 to 1500 bars. In some instruments, a maximum pressure of 2000 bars can be reached. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of the drug, the desired mean particle size, and required homogeneity. High-pressure homogenizers are available with different capacities ranging from 40ml (for laboratory purposes) to a few thousand litres (for large-scale production). Before subjecting the drug to the homogenization process, it is essential to form a presuspension of the micronized drug in a surfactant solution using high-speed stirrers. In the homogenization gap, according to Bernoulli's equation, the dynamic pressure of the fluid increases with the simultaneous decrease in static pressure below the boiling point of water at room temperature. In consequence, water starts boiling at room temperature, leading to the formation of gas bubbles, which go off when the suspension leaves the gap (called cavitation) and normal air pressure is reached again. The implosion forces are sufficiently high to break down the drug microparticles into nanoparticles. Additionally, the collision of the particles at high speed helps to achieve the nano-sizing of the drug. The principle is employed in the APV gaulin micron LAB 40 homogenizer (APV homogenizer, Lubeck, Germany) and NS 100 1L-panda 2K high pressure homogenizer (NIROSUAVI. S.P.A., Parma, Italy).

Effect of homogenization pressure:
As the homogenization pressure increases particle size decreases.

Number of homogenization cycles:

It is anticipated that as the number of homogenization cycles increases the particle size decreases. It is not possible to achieve the desired particle size in single homogenization cycle. Typically multiple cycles are required. The number of cycles depends on the hardness of the drug, required homogeneity, and the desired mean particle size required.

ii) Nanoedge:
The principle involved in Nanoedge is same that of the precipitation and homogenization techniques. This technique has an advantage of getting smaller particle size and greater stability in short period of time. In this technique the precipitated suspension is further homogenized to get smaller particle size and to avoid crystal growth. Precipitation is performed in water using water miscible solvent, such as methanol, ethanol, and isopropanol. It is desired to remove the solvent completely by including evaporation step to provide a solvent free modified starting material followed by high pressure homogenization.

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

C. Emulsion solvent diffusion method:
Apart from the use of emulsion as drug delivering vehicle they can also be used as templates to produce nanosuspension. 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. An organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants with stirring to form an emulsion. The obtained emulsion was further homogenized by high pressure homogenization. After homogenization cycles the emulsion was diluted with water, homogenized by homogenizer to diffuse the organic solvent and convert the droplets into solid particles. 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 methanol, ethanol, ethyl acetate, chloroform are used as organic solvents. However, environmental hazards and human safety concerns about residual solvents have limited their use in routine manufacturing processes (Prasanna Lakshmi *et al.*, 2010).

D. Melt emulsification method:
In this method drug is dispersed in the aqueous solution of stabilizer and heated above the melting point of the drug and homogenized to give an emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with temperature controller and the temperature of emulsion was maintained above the melting point of the drug. The emulsion was then cooled down either slowly to room temperature or on an ice-bath. The main advantage of melt emulsification technique relative to the solvent diffusion method is total avoidance of organic solvents during the production process.

E. Supercritical fluid method:
The organic solvents used in the preparation of conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods are hazardous to environment and physiological systems. To rectify the problem occurred through the conventional method supercritical fluid technology has been investigated for the preparation of biodegradable micro and nanoparticles, because supercritical fluids are environmentally safe. The most common techniques using supercritical fluids are supercritical anti-solvent (SAS), precipitation with compressed anti-solvent process (PCS) and rapid expansion of supercritical solution (RESS). The process of SAS employs a liquid solvent, e.g. methanol, which is completely miscible with the supercritical fluid (CO_2), to dissolve the solute to be micronized; at the process condition, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting in the formation of nanoparticles.

CHARACTERIZATION OF NANOSUSPENSION:

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 (V. B. Patravale *et al.*, 2004).

A. 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. 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. 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 2000 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 (Smita S *et al.*, 2017).

B. Crystalline State and Particle Morphology:

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 and supplemented by differential scanning calorimetry analysis.

C. 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 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 (Roya Yadollahi *et al.*, 2014).

PHARMACEUTICAL APPLICATIONS OF NANOSUSPENSION:

By using postproduction processing, nanosuspensions are prepared into various dosage forms. Nanosuspension increases dissolution rate and absorption of drug due to smaller particle size and larger surface area (Banshraj *et al*., 2013).

A. 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. 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 (Ch. Prabhakar *et al.*, 2011).

Fig No - 1: Nanosuspension for oral drug delivery

B. 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. nanosuspension of itraconazole enhanced efficacy of antifungal activity in rats relative to the solution formulation.

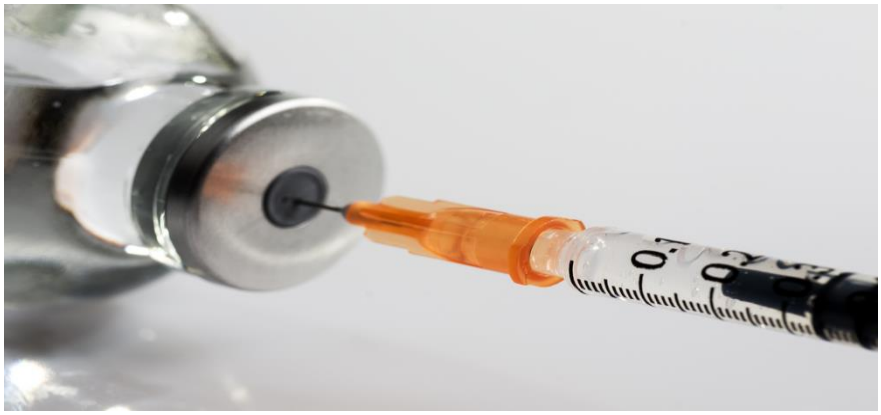

Fig No - 2: Nanosuspension for parentral drug delivery

C. Pulmonary Drug Delivery:

For pulmonary delivery, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Budesonide corticosteroid has been successfully prepared in the form of nanosuspension for pulmonary delivery. Aqueous suspensions of the drug can be easily nebulized and given by pulmonary route as the particle size is very small. Different types of nebulizers are available for the administration of liquid formulations. Some of the drugs successfully tried with pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc.

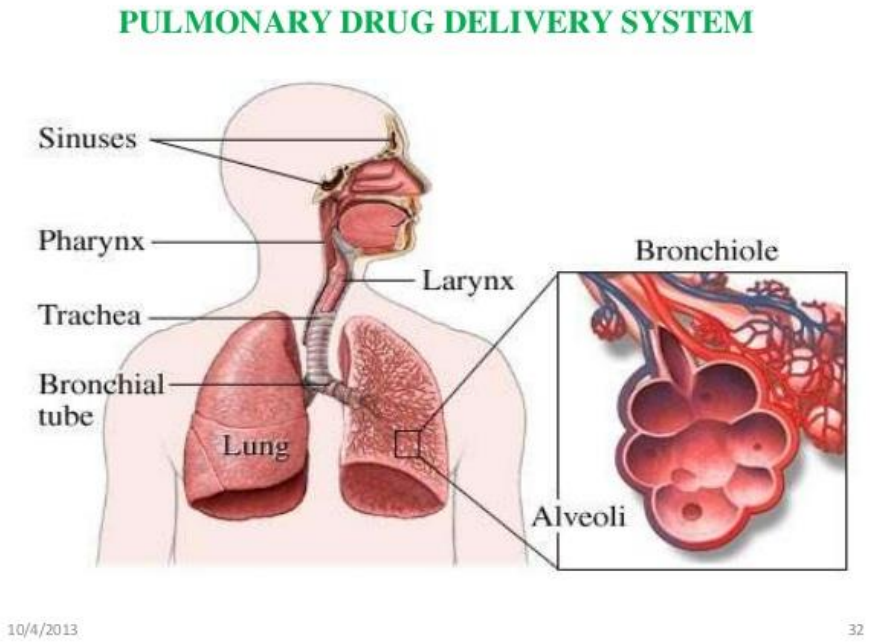

Fig No - 3: Nanosuspension for pulmonary drug delivery

D. Ocular Drug Delivery:

Nanosuspensions are used in ocular delivery of the drugs for sustained release. Liang and co-workers prepared cloricromene nanosuspension for ocular delivery using Eudragit. Experiment showed higher availability of drug in aqueous humor of rabbit eye. Thus, nanosuspension formulation offers a promising way of improving the shelf-life and bioavailability of drug after ophthalmic application (Mayuri Yadav *et al.*, 2014).

Fig No - 4: Nanosuspension for ocular drug delivery

E. Targeted Drug Delivery:

Nanosuspensions are suitable for targeting particular organs because of their surface properties. Along with this, it is easy to alter *in vivo* behavior by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery. This can be used for targeting antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens persist intracellularly. Kayser formulated an aphidicolin nanosuspension that improved the drug targeting to macrophages which were Leishmania infected.

MARKETED PRODUCTS:

Product	Drug	Indication	Company
Triglide	Fenofibrate	Treatment of hypercholesterolemia	First Horizon
Tricor	Fenofibrate	Treatment of hypercholesterolemia	Abbott
Megace	Megestrol aceyate	Appetite stimulant	PAR-Pharmaceutical
Rapamune	Sirolims	Immunosuppressant	Wyeth

CONCLUSION:

Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Productions techniques such as media milling and high pressure homogenizer are used for large scale production of Nanosuspensions. Nanosuspensions can be administered 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.

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