

Review Article

Nanosuspension – A Novel Carrier For Lipidic Drug Transfer

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Abstract: Solubility is the crucial factor for drug effectiveness, independence of the route of administration. Large proportion of newly discovered drugs are water insoluble & therefore poorly bioavailable contributing to desert development effort. Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophilic drugs because of their versatile features & unique advantages. The reduction of drug particles into submicron range leads to a significant increase in dissolution rate & therefore enhances bioavailability. Nanosuspension contain submicron colloidal dispersion of the pharmaceutical active ingredient particles in a liquid phase stabilised by surfactant. Nanosuspensions can be delivered by oral & non-oral route of administration. Study is focused on various methods of preparation with advantages & disadvantages, characterization properties, applications.

Keywords: Nanosuspension, Bioavailability, Colloid, Surfactant, Solubility enhancement.

INTRODUCTION

A nanosuspension is a submicron colloidal dispersion of drug particles. A pharmaceutical nanosuspension is defined as a very finely colloid, biphasic, dispersed, solid drug particles in aqueous vehicle, size below 1 μm , without any matrix material, stabilised by surfactants & polymers, prepared by suitable methods for drug delivery applications, through various routes of administration like oral, topical, parenteral, ocular & pulmonary routes. A nanosuspension not only solves the problem of poor solubility & bioavailability but also alters the pharmacokinetics of drug & that improves safety & efficacy. Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point & dose. Nanosuspension has been reported to enhance adsorption & bioavailability it may help to reduce the dose of the convectional oral dosage forms. Drug particle size reduction leads to an increase in surface area & consequently in the rate of dissolution as described by Nernst-Brunner & Levich modification of the Noyes-Whitney equation. In addition, an increase in saturation solubility is postulated by particle size reduction due to an increase dissolution pressure explained by the Ostwald-Freundlich equation. Depending on the production technique applied changes in crystalline structure of the drug particles may also occur. An increasing amount of amorphous drug fraction could induce higher saturation solubility. Furthermore, a general adhesiveness to tissue has been described for nanoparticles. The aim of present study were to evaluate whether providing drug in the form of a nanosuspensions will enhance drug flux resulting from higher transmembraneous concentration gradients.

Nanosuspensions differ from nanoparticles [11]. Nanoparticles are commonly polymeric colloidal carrier of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the crystalline state with reduced particle size, leading to increase dissolution rate & therefore improved bioavailability. Drugs encapsulated within nanosuspensions exist in pharmaceutically accepted crystalline or amorphous state. Nanosuspensions can successfully formulate the brick dust molecules for improved dissolution & good absorption [18].

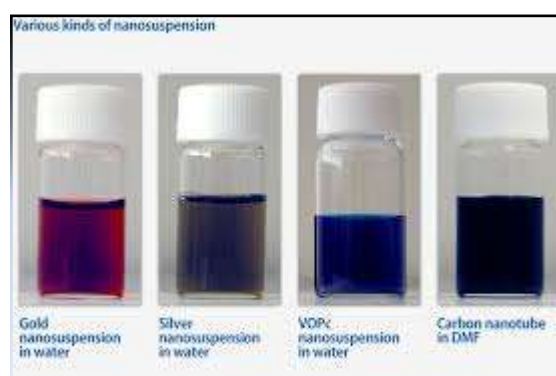


Fig. 1- Various kinds of nanosuspensions.

Advantages of Nanosuspension Drug Delivery System-

1. Its general applicability to most drugs & simplicity
2. Can be applied for poorly water soluble drugs.
3. Can be given by any route
4. Reduced tissue irritation in case of subcutaneous/ intramuscular administration.

5. Rapid dissolution & tissue targeting can be achieved by IV route of administration.
6. Oral administration of nanosuspension provide rapid onset, reduced fed/fasted ratio & improved bioavailability.
7. The absorption form absorption window can be increased, due to reduction in the particle size.
8. Higher bioavailability & more consistent dosing in case of ocular administration & inhalation delivery.
9. Drug with higher log P value can be formulated as nanaosuspensions to increase the bioavailability of such drugs.
10. Improvement in biological performance due to high dissolution rate & saturation solubility of the drugs.
11. Long term physical stability (due to absence of Ostwald ripening).
12. Nanosuspensions can be incorporated in tablets, pellets, hydrogel & suppositories are suitable for various routes of administration.
13. Increasing the amorphous fraction in the particles leading to a potential change in the crystalline structure & higher solubility.
14. Possibility of surface-modification of nanosuspension for site specific delivery.
15. Possibility of large-scale production, the pre-requisite for the introduction of delivery system to the market [26].

Disadvantages for Nanosuspension Drug delivery system

1. Physical stability, sedimentation & compaction can cause problems.
2. It is bulky sufficient care must be taken during handling & transport.
3. Improper dose.
4. Uniform & accurate dose cannot be achieved [32].

Techniques for Nanosuspensions-

Current techniques used to obtain drug nanoparticles can be divided into two categories:

Bottom up techniques

It is the technique in which nano size is obtained by increasing the size of particle from molecular range to nano range [21]. The convectional method of precipitation (Hydrosol) are called as Bottom up techniques. Using a precipitation technique, the drug is dissolved in an organic solvent & this solution is mixed with miscible anti-solvent. In the water solvent mixture, the solubility is low & drug precipitates. Basic challenge is that during the precipitation procedure growing of the crystals need to be controlled by addition of surfactant to avoid formation of microparticles. The use of simple & low cost equipments is the advantage of bottom up technique. But the drug needs to be soluble in at least one solvent & the solvent needs to be miscible with non-solvent. Moreover, it is not applicable to the drugs, which are poorly soluble in both aqueous & non-aqueous media.

Top down techniques

The techniques in which nano size range of particles is obtained by reduction in size of larger particles.

Methods for preparation of Nanosuspension-

There are different methods for the preparation of nanosuspensions [22],

1. Homogenization in water (Disso Cubes).
2. Media milling (Nanocrystal).
3. Homogenization in non-aqueous media (Nanopure).
4. Combined precipitation & homogenization (Nanoedge).
5. Nanojet technology.
6. Emulsifying-solvent evaporation technique.
7. Hydrosol method.
8. Supercritical fluid method.
9. Dry co-grinding.
10. Emulsion as template.

High pressure homogenization (Disso Cubes) -

Disso cubes are engineered using piston-gap-type high pressure homogenizers [19]. High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The instrument can be operated at pressure varying from 100-1500 bars & upto 2000 bars with volume capacity of 40ml. The concern with this method is the need for small sample particles before loading & the fact that many cycles of homonization are required. Before subjecting the drug to the homogenization process, it is essential to form a pre-suspension of the microsized drug in a surfactant solution using high speed stirrer. During the homogenization process, the drug suspension is pressed through the homogenization gap in order to achieve nanosizing of the drug. In piston gap homogenizer, particle size reduction is based on the cavitation principle. A piston-gap homogenizer like APV Gaulin type has been shown. Particles are also reduced due to high shear forces & the collision of the particles against each other. The dispersion contained in 3cm diameter cylinder, suddenly passes through a very narrow gap of 25 μ m. The reduction in diameter of 3cm to 25 μ m leads to increase in dynamic pressure & decrease of static pressure below the boiling point of water at room temperature. Due to this water starts boiling at room temperature & forms bubbles, which implode when the suspension leaves the gap & normal air pressure, are reached [22].

Media milling (Nano Crystals) -

In this method, the nanaosuspensions are produced using high-shear media mills or pearl mills. The media mills consists of a milling chamber, a milling shalf & a recirculation chamber. The milling chamber charged with polymeric media is the active component of the mill. The mill can be operated in a batch or recirculation mode. Crude slurry consisting of drug,

water & stabilizer is fed into the milling chamber & processed into nano-crystalline dispersion & the milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled

temperatures. The typical residence time generated for a nanometer-sized dispersion with a mean diameter of <200nm is 30-60min [19].

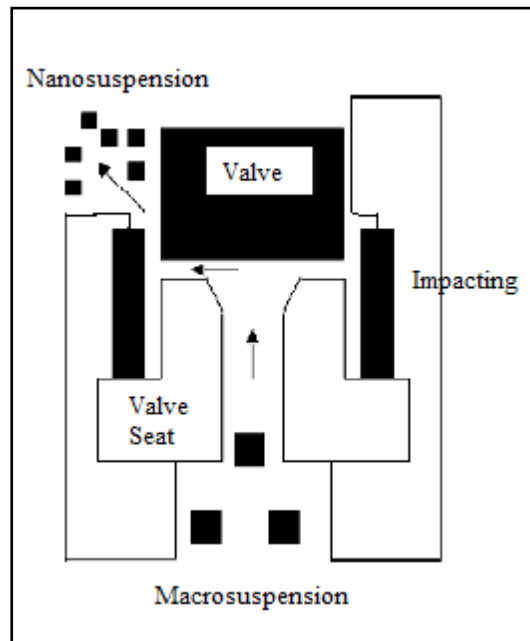


Fig.2- Schematic representation of high-pressure homogenizer process

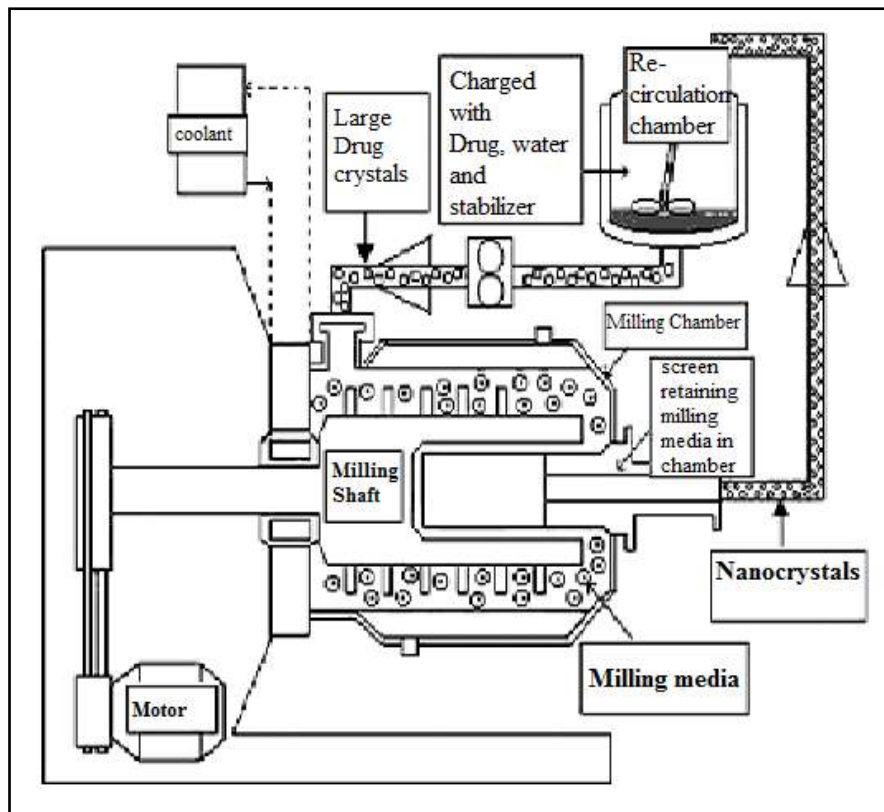


Fig. 3- Schematic representation of the media milling process.

Homogenization in non-aqueous media (Nanopure) - Nanopure is suspension homogenized in water free media or water mixtures i.e. the drug suspensions in the non-aqueous media were homogenized at 0°C or even

below the freezing point & hence are called “deep-freeze” homogenization. The result obtained were comparable to disscubes & hence can be used

effectively for thermolabile substance at milder conditions.

Combined precipitation & homogenization (Nanoedge) -

The drug is dissolved in an organic solvent & this solution is mixed with a miscible anti-solvent for precipitation. In the water-solvent mixture the solubility is low & the drug precipitates. Precipitation has also been coupled with high shear processing. The basic principles of Nanoedge are the same as that of precipitation & homogenization. A combination of these techniques results in smaller particle size & better stability in a shorter time [26].

Nanojet technology –

This technique is also called as ‘opposite stream’ uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure upto 4000 bar at high velocity of 1000m/s. The high shear force produces during the process result in particle size reduction [25].

Emulsification-solvent evaporation techniques -

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug [20].

Supercritical fluid method –

Supercritical fluid technology can be used to produce nanoparticles from drug solutions. The various methods attempted are rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process & 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. In the PCA method, the drug solution is atomized into a chamber containing compressed CO₂. As the solvent is removed, the solution gets supersaturation & thus precipitates as fine crystals. The supercritical anti-solvent process uses a supercritical fluid in which a drug is poorly soluble & a solvent for the drug that is also miscible with the supercritical fluid. The drug solution is injected into the supercritical fluid & the solvent gets extracted by the supercritical fluid & the drug solution gets supersaturated. The drug is then precipitated as fine crystals [26].

Dry co-grinding –

Nanosuspensions prepared by high pressure homogenization & media milling using pearl ball mill are wet –grinding processes. Recently, nanosuspensions can be obtained by dry milling techniques. Successful work in preparing stable nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers & copolymers after dispersing in a liquid media has been reported. Many soluble polymers & co-polymers

such as PVP, PEG, HPMC has been used. Physicochemical properties & dissolution of poorly water soluble drugs were improved by co-grinding because of an improvement in the surface polarity & transformation from a crystalline to an amorphous drug. Dry co-grinding can be carried out easily & economically & can be conducted without organic solvents. The co-grinding technique can reduce particles to the submicron level & a stable amorphous solid can be obtained [18].

Emulsion as template –

Apart from the use of emulsion as a drug delivery vehicle, they can also be used as template to produce nanosuspensions. The use of emulsion as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvents. Such solvents can be used as the dispersed phase of the emulsion. There are two ways of fabricating drugs nanosuspensions by emulsification method. In the first method, an organic solvent or mixture of solvents loaded with drug is dispersed in the aqueous phase containing suitable surfactant to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitates instantaneously to form a nanosuspension stabilized by surfactants. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion. Optimizing the surfactant composition increases intake of organic phase & ultimately the drug loading in the emulsion. Originally, organic solvents such as methylene chloride & chloroform were used.

Characterization of Nanosuspension-

1) Mean particle size & particle size distribution.

The mean particle size & the width of particle size distribution are important characterization parameters as they govern the saturation solubility, dissolution velocity, physical stability & even biological performance of nanosuspensions [27].

2) Crystalline state & particle morphology.

The assement of the crystalline state & particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. Additionally, when nanosuspensions are prepared drug particles in an amorphous state are likely to be generated. Hence, it is essential to investigate the extent of amorphous drug nanoparticles generated during the production of nanosuspensions. The changes in the physical state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis & can be supplemented by differential scanning calorimetry. In order to get a actual idea of particle morphology, scanning electron microscopy is preferred [6].

3) Particle charge (Zeta potential)

The determination of zeta potential of nanosuspension is essential as it gives an idea about the physical stability of the nanosuspension. The zeta potential of a nanosuspension is governed by both the stabilizer & the drug itself. In order to obtain a nanosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension a minimum zeta potential of 30mV is required whereas in the case of a combined electrostatic & steric stabilization, a minimum zeta potential of 20mV is desirable [28].

- 4) **pH**
The pH of the nanosuspensions can be easily measured by using pH meter [26].
- 5) **Osmolarity**
Practically, osmolarity of nanosuspension can be measured by using Osmometer [26].
- 6) **Saturation solubility & Dissolution velocity**
Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. The saturation solubility of the drug in different physiological buffer as well as at different temperature should be assessed using methods described in the literature. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over convectional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs. The assessment of saturation solubility & dissolution velocity helps in determining the *in vitro* behaviour of the formulation [1].
- 7) **Surface Hydrophilicity**
For intravenous injected nanosuspensions, additional parameters need to be determined which affect the *in vivo* fate of the drug nanoparticles. Surface hydrophilicity is considered as one of the important parameters affecting the *in vivo* organ distribution after *i.v.* injection. The surface hydrophobicity determines the interaction with cells prior to phagocytosis & in addition, it is a relevant parameter for the adsorption of plasma proteins the key factor for organ distribution. To avoid artefact, the surface hydrophobicity needs to be determined in the original environment of the drug nanoparticles, which means in aqueous dispersion medium. A suitable technique is hydrophobic interaction chromatography (HIC), previously employed to determine the surface hydrophobicity of bacteria, & then transferred to the characterization of nanoparticulate drug carriers.

Applications of Nanosuspensions-

- 1) **Oral Drug Delivery**
The oral route is the preferred route for drug delivery because of its numerous well-known advantages. Orally administered antibiotics such as atovaquone & bupravaquone reflect this problem very well. Nanosizing of such drugs can lead to a dramatic

increase in their oral absorption & subsequently bioavailability. The oral administration of naproxen nanoparticles leads to an area under the curve of 97.5 mg-h/l compared with just 44.7 mg-h/l for naprosyn suspensions & 32.7 mg-h/l for anapro tablets. Oral administration of gonadotrophin inhibitor Danazol as a nanosuspensions leads to an absolute bioavailability of 82.3 & the convectional dispersion only to 5.2%. A nanosuspension of Amphotericin B developed by Kayser *et al.* showed a significant improvement in its oral absorption in comparison with the convectional commercial formulation [6].

2) **Parenteral Drug Delivery**

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 co-solvent, improving the therapeutic effect of the drug available as convectional oral formulations & targeting the drug to macrophages & the pathogenic micro-organism residing in the macrophages. Injectable nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using convectional solubilising techniques, such as use of surfactants, cyclodextrins *etc.* To improve bioavailability [2].

3) **Pulmonary Drug Delivery**

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizer for lung delivery. Basically the nanosuspensions can be used in all nebulizers. The dispersions can be relatively high concentrated. Due to presence of many small particles instead of a few large microparticles, all aerosol droplet are likely to contain drug nanoparticles. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspension for pulmonary delivery. A good relationship was obtained between increasing the drug concentration in the formulation & the number of micrograms of drug delivered per actuation. In addition, buparvaquone nanosuspensions were formulated for treatment of lung infections by using nebulizers [18].

4) **Topical Formulations**

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

5) **Ocular Drug Delivery**

Nanosuspension can be boon for drug that exhibit poor solubility in lachrymal fluids. Nanosuspensions, by their inherent ability to improve the saturation solubility of drug, represented an ideal approach for ocular delivery of hydrophobic drugs & nanoparticulate nature

of the drug allows its prolonged residence in the cul-de-sac, giving sustained release of the drug [10].

CONCLUSION

Nanosuspensions appear to be unique & yet commercially viable approach to combating problems such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. The dissolution problems of poorly water soluble drugs have been largely solved to improve drug absorption & bioavailability. Nanosuspension technology can be combined with traditional dosage forms: tablets, capsules, pellets, & can be used for parenteral products. To take advantage of nanosuspension drug delivery, simple formulation technologies & variety applications, nanosuspensions will continue to be interest as oral formulations & non-oral administration develop in the future.

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