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**Original Research Article**

# An Overview on Nanosuspension Technology

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**Abstract:**

Nanosuspension is a colloidal dispersion of submicron-sized particles (typically in the nanometer range) of an active pharmaceutical ingredient (API) in a liquid medium, often water or a water-miscible solvent. This review article provides an in-depth overview of nanosuspensions, a promising drug delivery system with its various advantages. We have discussed various techniques employed for preparing nanosuspensions. In this review article different types of evaluation parameters are discussed like organoleptic properties, particle size distribution, zeta potential, crystal morphology, dissolution velocity and saturation solubility, pH, droplet size, drug content along with viscosity measurement which can be used for the evaluation of nanosuspension.

**Key words:** Nanosuspension, API, zeta potential, crystal morphology.



## Introduction

Nanotechnology is an emerging field in all areas of science, engineering and technology. It's a novel interdisciplinary area of comprehensive research that combines medicine and other life sciences. It offers a potential for unique and novel approaches with broad spectrum of application in cancer treatment including areas such as diagnostics, therapeutics and prognosis. The main advantage of particles in the nano-metric range is its improved physical and chemical properties. [1]

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 μm in size. [2]

Nanosuspension have revealed their potential to solve the problem associated with the delivery of poorly water-soluble and poorly water and lipid soluble drugs. It enhances the absorption and bioavailability and helps to reduce the dose of conventional oral dosage forms. Drug particle size reduction leads to an increase in the surface area and consequently the rate of dissolution as described by the Noyes Whitney equation. In addition, an increase in saturation solubility is postulated by the particle size reduction due to an increased dissolution pressure explained by the Ostwald-Freundlich equation. [3,4]

**Advantages of Nanosuspension** [5,6]

- ❖ It can be useful for poorly water-soluble drugs.
- ❖ It can be given by any route.

- ❖ Reduced tissue irritation in the case of subcutaneous/intramuscular administration.
- ❖ Rapid dissolution and tissue targeting can be reached by the IV route of administration.
- ❖ Oral administration of nanosuspensions provides fast onset, reduced fed/fasted ratio and improved bioavailability.
- ❖ The absorption from the absorption window of the drugs can be increased due to a reduction in the particle size.
- ❖ In case of ocular administration and inhalation delivery, higher bioavailability and more consistent dosing.
- ❖ Enhancement in biological performance due to high dissolution rate and saturation solubility of the drug.
- ❖ Ease of manufacture and little batch-to-batch variation.
- ❖ Long term physical stability.
- ❖ Nanosuspensions can be incorporated in tablets, pellets, hydrogel, and suppositories are suitable for various routes of administration.

**Techniques Employed for Preparing Nanosuspensions [7,8,9,10]**

a. Solvent evaporation
b. Milling techniques
c. High-pressure homogenization
d. Precipitation
e. Emulsification-solvent
f. Melt emulsification method
g. Supercritical fluid process
h. Lipid emulsion/microemulsion template

**A. Solvent evaporation**

In the solvent evaporation method, the solutions of the polymer are prepared in volatile solvents and emulsions. The emulsion is converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. The particle size was influenced by the concentration of polymer, stabilizer and the speed of homogenizer. In the conventional methods, two main strategies

are being used for the formation of emulsions, the preparation of single emulsions, e. g., oil-in-water (o/w) or double-emulsions, e. g., (water-in-oil)-in-water, (w/o)/w.

**B. Milling techniques**

In this technique, the drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generated as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process, the milling chamber is charged with the milling media, water or a suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate.

**C. High-pressure homogenization**

In this technique, the drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generated as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process, the milling chamber is charged with the milling media, water or a suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate.

**D. Precipitation**

Precipitation method has been used for long years for the preparation of submicron particles. It is mainly used for the poorly soluble drugs. The first drug is dissolved in a suitable solvent. This solution is then mixed with a miscible antisolvent system in the presence of surfactants. Rapid addition

of drug solution into the antisolvent leads to the sudden supersaturation of drug in the mixed solution forms ultrafine drug solids. Precipitation method involves two phases-nuclei formations and crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate and but the low growth rate is necessary. Both rates are depending on temperature. In this technique, the drug needs to be soluble in at least one solvent which is miscible with a nonsolvent.

### E. Emulsification-solvent

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a nonsolvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

### F. Melt emulsification method

In this method, the 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 a temperature controller and the temperature of the 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. Nanosuspension of ibuprofen was prepared by this method. Formulating ibuprofen Nanosuspension by melt emulsification method show greater dissolution rate than formulating by the solvent diffusion method.

### G. Supercritical fluid process

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 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. 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.

### H. Lipid emulsion / microemulsion template

Another way to produce nanosuspensions is to use an emulsion which is formed by the conventional method using a partially water miscible solvent as the dispersed phase. Nanosuspensions are obtained by just diluting the emulsion. Moreover, microemulsions as

templates can produce nanosuspensions. Microemulsions 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 pre-formed microemulsion can be saturated with the drug by intimate mixing. Suitable dilution of the microemulsion 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. 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.

**Evaluation of Nanosuspension [11-16]**

**a. Organoleptic properties**

These characteristics are especially important in orally administered formulation. Variations in taste, especially of active constituents, can offered be attributed to changes in particle size, crystal habit and subsequent particle dissolution. Changes in color, odor and taste can also indicate chemical instability.

**b. Particle Size Distribution**

Particle size distribution determines the physiochemical behavior of the formulation, such as saturation solubility, dissolution velocity, physical stability, etc. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer.

**c. Zeta potential**

Zeta potential is an indication of the stability of the suspension. For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of ±30 mV is required whereas in case of a combined electrostatic and steric stabilizer, a zeta potential of ±20 mV would be sufficient.

**d. Crystal morphology**

To characterize the polymorphic changes due to the impact of high-pressure homogenization in the crystalline structure of the drug, techniques like X-ray diffraction analysis in combination with differential scanning calorimetry or differential thermal analysis can be utilized. Nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high-pressure homogenization.

**e. Dissolution Velocity and Saturation Solubility**

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. These two parameters should be determined in various physiological solutions. The assessment of saturation solubility and dissolution velocity helps in determining the in vitro behavior of the formulation. Böhm et al. reported an increase in the dissolution pressure as well as dissolution velocity with a reduction in the particle size to the nanometer range. Size reduction leads to an increase in the dissolution pressure.

**f. pH**

The pH of the nanosuspension can be easily measured by means of the use of a pH meter

**g. Droplet Size**

The droplet size distribution of micro emulsion vesicles can be determined by either light scattering technique or electron microscopy. Dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm.

**h. Drug Content**

The drug content material of nanosuspension formulation can be carried out with the aid of extracting the nanosuspension in the appropriate solvent mixture, like Methanol: THF (1:1) mixture, shaken well and then centrifuged. The supernatants can be separated and diluted with the same solvent combination, and the absorbance can be measured at appropriate λmax. The drug content then can be calculated the usage of the calibration curve.

### i. Viscosity Measurement

The viscosity of lipid-based formulations of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 370C by a thermo bath and the samples, for the measurement are to be immersed in it.

## Conclusion

Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. It has therapeutic advantages, such as simple method of preparation, less requirement of excipients, increased saturation solubility and dissolution velocity of drug. A nanosuspension not only improves the solubility and bioavailability but also modifies the pharmacokinetics of drug and thus improves drug safety and efficacy.

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