

Nanosuspensions in Pharmaceutical Sciences: A Comprehensive Review

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ABSTRACT

Regardless of the method of administration, the solubility of drugs is essential to their efficiency. However, many newly discovered drugs suffer from poor water solubility and low bioavailability, leading to limited development efforts. Nanosuspension technology offers a solution for these "Brickellia" candidates by enhancing their solubility and bioavailability. Nanosuspensions improve medication stability and can be easily prepared for water-insoluble drugs using techniques such as high-pressure homogenizers, wet mills and emulsion solvent evaporation. Additives like stabilizers, solvents, buffers, salts, and cryoprotectants can be used. Nanosuspensions can be administered orally, parenterally, intravenously, and can be combined with ocular inserts and mucoadhesive hydrogels for targeted drug delivery.

Keywords: Saturation solubility, Surfactant, Nanosuspension, Dissolution, Solubility enhancement.

INTRODUCTION

A significant portion, comprising more than 40%, of newly discovered chemical entities in the development of drugs display either water insolubility or lipophilic properties. Overcoming the challenge of formulating drugs with poor solubility in water has been a complex task for pharmaceutical scientists. One approach to enhance solubility and facilitate absorption through the gastrointestinal barrier involves the use of nanosized particles to formulate therapeutic molecules classified as BCS class II or IV. Micronization is employed for class II drugs in the BCS, which exhibit good permeability but low solubility. Various traditional methods have been utilised to improve the solubility of drugs that have poor solubility, including micronization, solubilization with cosolvents, salt formation, surfactant dispersions, precipitation processes, and oily solutions.^[1-4] While alternative approaches such as microemulsions, emulsions,

liposomes, solid dispersion, and cyclodextrin-based inclusion complexation have shown promising results, they are not universally applicable to all drugs. Furthermore, these methods are ineffective for drugs that are insoluble in both aqueous and organic solvents. Nanotechnology offers a potential solution to overcome the limitations of conventional techniques for improving solubility and bioavailability. Specifically, nanosuspensions are well-suited for substances that are not soluble in water but soluble in oil, exhibiting high values for log P, melting point, and dosage.^[5-7]

Considerations for Strategic Implementation of the Nano Suspensions Approach

1. When dealing with compounds characterized by a high log P value, indicating solubility in oil but insolubility in water, the preparation of nano

- suspensions emerges as a favoured method.
2. Nanosuspensions are the preferred choice for formulating drugs not soluble in both water and organic media, eliminating the need for lipidic systems.
 3. When drugs show poor solubility in organic media or water, nanosuspensions provide an alternative formulation approach that surpasses the use of lipidic systems.
 4. While liposomes or emulsions are commonly employed for drugs which are poorly soluble in water but soluble in oil, these lipid-based methods may not be suitable for all the drugs. It is preferable to use nanosuspensions in such situations.^[8,9]

Advantages of Nanosuspension Technology in Enhancing the Solubility of Drugs with Limited Solubility

1. Nano suspensions are suitable for water-insoluble compounds soluble in oil. They are also effective for formulating compounds insoluble in both water and oil, providing an alternative to lipidic systems.
2. The reduction in particle size achieved through nanosuspension technology leads to an improved drug dissolution rate and enhanced drug absorption, resulting in increased bioavailability, faster onset of action, and higher peak drug levels. Additionally, it minimizes the variability in drug response and the impact of food intake on drug efficacy.
3. In nanosuspensions the drug is in contact with the gastrointestinal mucosa for a longer period, stimulating better absorption.
4. Nanosuspensions offer versatility in drug delivery and various routes can be used to administer them, including parenteral, oral, dermal, pulmonary and ocular routes, providing treatment options that are flexible.
5. Nanosuspensions offer important benefits for ocular applications. As a result, it is possible to administer drugs

- that are poorly water-soluble and to achieve minimal drug doses, sustained drug release, a reduction in systemic toxicity, a prolongation of corneal residence time, and higher drug concentrations in infected tissues.
6. Utilising nanosuspensions improves the safety profile overall since they lessen the likelihood of side effects connected to the excipients employed in the formulation.
7. Nanosuspensions do not require the dissolution of compounds and help preserve the crystalline state of drugs for pharmaceutical use.
8. Nanosuspensions have improved physical stability and decreased particle settling due to their increased resistance to oxidation and hydrolysis.
9. Nanosuspensions enable the administration of lower volumes of the drug, making them suitable for ophthalmic, intramuscular and subcutaneous applications.
10. Nanosuspensions possess the ability for passive targeting, allowing for the concentration of drugs at precise locations within the body where they exert their intended effects.^[10,11]

Techniques for Nanosuspension Preparation

There are primarily two approaches to preparing nanosuspensions. The traditional method, referred to as "bottom-up technology," involves precipitation to form hydrosols. Conversely, "top-down technologies" are disintegration methods that are preferred over precipitation techniques. These "top-down technologies" include media milling for nanocrystals, high-pressure homogenization in water for dissocubes, high-pressure homogenization in non-aqueous media for nanopores, and a combination of precipitation and high-pressure homogenization known as nano edge.

1. Bottom-up technology:

An approach known as "bottom-up technology" begins at the molecular level

and develops through molecular association to produce solid particles. This method uses conventional precipitation approaches, such as changing the temperature or adding a nonsolvent to change the solvent's quality. In pharmaceutical chemistry and technology, precipitation is a well-known process.^[12,13]

Advantages:

- Simple as well as cost-effective equipment can be used.
- Precipitation offers higher saturation solubility when compared with methods used in the preparation of nanosuspension.

Disadvantages:

- The drug must exhibit solubility in at least one solvent, which excludes new drugs with poor solubility in both aqueous and organic media.
- At least one non-solvent must be miscible with the solvent being utilised.
- Removal of residues of solvent increases production costs.
- Preserving the particle characteristics, particularly size and the amorphous fraction, can be challenging. To maintain particle integrity, a subsequent process such as lyophilization or spray drying is often recommended.^[14,15]

2. Top-down technology:

The top-down technologies encompass two methods:

a) Media milling:

Nanosuspensions can be prepared by utilizing pearl mills. This process involves utilizing a recirculation chamber, a milling shaft, and a milling chamber. Initially, a drug suspension is introduced into the mill, along with an aqueous medium, and combined with pearls or small grinding balls. At a high shear rate balls rotate, leading to friction and impact within the grinding jar, effectively reducing the size of the particles.^[16] The milling media, typically made of durable materials such as zirconium oxide, demonstrate excellent resistance to wear and tear. Advanced equipment like planetary ball

mills, such as the PM200, PM100 models can achieve particle sizes below 0.1 μm . In a specific study, researchers employed a wet milling technique to produce a nanosuspension that consists of Zn-Insulin, resulting in particle size that is about 150 nm. However, it's important to note that media milling has its limitations, including potential contamination from milling material erosion, the risk of thermolabile drug degradation due to heat generation, and the occurrence of particles that are around 5 μm in size.^[17]

Advantages:

- Straightforward technology
- Milling process is cost-effective
- To a certain extent, achieving extensive manufacturing is possible through the utilization of batch processing.

Disadvantages:

- There is a credible possibility that the erosion of milling material could result in the contamination of the product.
- The process duration may not be optimal for efficient production.
- Potential for microbial growth in the water phase during prolonged milling periods
- The duration and expenses related to the milling material's separation from the nanosuspension pose significant considerations, particularly in the production of sterile parenteral products.^[18,19]

b) High pressure homogenization

It is a technique that involves passing a drug suspension through a narrow valve under pressure. This process utilizes cavitation and implosion of gas bubbles to reduce particle size. Pre-milling of fine drug particles is recommended for higher solid concentrations. High-pressure homogenization provides several benefits, including its applicability to both diluted and concentrated suspensions and the capability for aseptic manufacturing.^[20]

Nanopure

Nanopure is a method of homogenization that employs media or mixtures without water.

In technology involving Dissocubes cavitation is crucial, but when non-aqueous media are employed, the decrease in static pressure is inadequate to induce cavitation. Nanopure achieves homogenization at lower temperatures, even below the freezing point, making it suitable for thermolabile substances. It provides comparable results to Dissocubes in milder conditions.^[21,22]

Nanoedge™

Nanoedge™ combines homogenization and precipitation techniques to achieve smaller particle size that is small and effectively enhances the stability. It addresses the limitations commonly associated with precipitation methods, such as long-term stability issues and crystal growth. Initially here suspension that is precipitated undergoes additional homogenization in order to decrease size of particle and inhibit crystal development. Methanol, ethanol, and isopropanol are just a few examples of water-miscible solvents that can be used in the precipitation process. These solvents can be tolerated in the formulation to some extent, while it is desirable to totally remove them. An evaporation stage may be added to the Nanoedge™ nanosuspension manufacturing process to provide a modified starting material devoid of solvent, which is subsequently homogenised under high pressure.^[23]

Emulsion diffusion method:

In this method, emulsions are used as both a vehicle for delivery of drug and templates for generating nanosuspensions. This technique is suitable only when the drug shows solubility in organic solvents that are volatile in nature or solvents that show partial solubility in water. The dispersed phase of the emulsion contains these solvents, which carry the drug. The mixture of solvent is dispersed within an aqueous phase containing appropriate surfactants, and the

resulting emulsion is stirred. Subsequently, high-pressure homogenization is employed to homogenise the emulsion. Through multiple cycles of homogenization, water is used to dilute the emulsion, and it is further homogenised so that organic solvent gets diffused and droplets get converted into solid particles. By controlling the emulsion's size, the nanosuspension's particle size is adjusted accordingly. The optimisation of the composition of surfactant enhances the absorption of the organic phase, hereby increasing the emulsion's drug loading. Initially, solvents like chloroform, ethanol, ethyl acetate, and methanol were used more commonly in this process.^[24,25]

Advantages:

- It doesn't require any specialised equipment.
- By adjusting the emulsion's droplet size, it is easy to regulate the particle size.
- The formulation can be optimised to ensure scalability.

Disadvantages:

- Drugs whose solubility is limited in organic and aqueous media are not suitable for this method.
- Issues associated with safety may arise due to the use of hazardous solvents during the process. Purifying the drug nanosuspension through ultrafiltration may increase overall costs.
- Relatively larger amounts of surfactant/stabilizer are needed compared to other previously mentioned production techniques.^[26,27]

Microemulsion template:

This method involves dispersing the drug in a combination of organic or inorganic solvents, which must be coupled with an aqueous phase and an appropriately surfactant-containing aqueous phase to form an emulsion. The drug's particles quickly precipitate at low pressure as the organic phase evaporates, creating nanosuspension. The drug particles quickly precipitate and create the nanosuspension by rapidly

evaporating the organic phase at decreased pressure. The stability of the nanosuspension is ensured by the use of surfactants. Triacetin, benzyl alcohol, and butyl lactate are a few examples of solvents that can be used in the dispersion phase as an alternative to employing harmful solvents.^[28]

Advantages:

- It doesn't require any specialised equipment.
- By adjusting the emulsion's droplet size, it is simple to regulate the particle size.
- The scalability of the process is achievable with appropriate formulation optimisation.

Disadvantages:

- Drugs that show low solubility in both media, i.e., organic and aqueous, are not suitable for this technique.
- The purification process of nanosuspension through diultrafiltration may lead to increased process costs.
- Compared to the other manufacturing methods previously described, more surfactant or stabiliser is needed.^[29,30]

Supercritical fluid method:

From drug solutions, it is possible to make drug nanoparticles using supercritical fluid technology. Precipitation using the compressed anti-solvent process (PCA), the rapid expansion of the supercritical solution process (RESS), and the supercritical anti-solvent process are a few of the techniques that have been tested. The RESS technique involves expanding a medicinal solution using a nozzle and a supercritical fluid. As a result of the loss of solvent power, tiny drug particles precipitate. In the PCA technique, compressed CO₂ is used to atomize the drug solution, causing supersaturation and the drug to precipitate as tiny crystals. In the supercritical anti-solvent method, a drug solvent that is miscible with the supercritical fluid and a supercritical fluid in which the medicine is only weakly soluble are both used. The drug is injected into the supercritical fluid, the solvent is withdrawn,

and the drug supersaturates and precipitates as tiny crystals. These methods have been used to produce poorly soluble nanoparticles of numerous medicines.^[31]

Disadvantages:

- The use of toxic solvents and a larger quantity of stabilisers and surfactants compared to other procedures
- Potential particle nucleation overgrowth owing to temporary high supersaturation may lead to the creation of unwanted forms or polymorphs.^[32]

Emulsification melt method:

The drug is heated past its melting point while being dissolved in an aqueous solution of a stabiliser during the melt emulsification process. The mixture is then homogenised to produce an emulsion. The temperature of the emulsion is maintained above the melting point of the medication throughout the operation using a heating tape with a temperature controller. The emulsion is then either slowly cooled to room temperature or immediately chilled in an ice bath.^[33]

Advantage:

- When employing the melt emulsification method, no organic solvents are used at all throughout the production process.^[34]

Dry co-grinding:

Dry milling techniques have lately been used to create nanosuspensions. This approach involves mixing poorly soluble drugs with soluble copolymers and polymers in a liquid environment to produce stable Nanosuspensions. Many soluble polymers and copolymers, such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives, have been subjected to this approach.^[35]

Considerations in Formulating Nanosuspensions:

• **Stabilizer**

A stabiliser's primary function in nanosuspensions is to ensure that drug particles are properly moistened and to

prevent Ostwald's ripening and agglomeration. The physical stability of the formulation is maintained by the provision of steric or ionic barriers. How physically stable and behaved nanosuspensions are greatly depends on the type and quantity of stabiliser used. Common stabilisers include poloxomers, polysorbate, cellulose, povidones, and lecithins. Lecithin is particularly needed for preparing nanosuspensions suitable for parenteral administration and autoclaving.^[36]

- **Organic solvent**

Organic solvents are employed when using emulsions or microemulsions as templates for nanosuspension formulation. It is advised to use less hazardous and water-miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, and propylene carbonate. These solvents include methanol, ethanol, chloroform, isopropanol, and ethanol. These alternatives are chosen over traditional hazardous solvents like dichloromethane.^[37]

- **Co-surfactants**

The right co-surfactant must be chosen when making nanosuspensions with microemulsions. Because they affect how the internal phase is absorbed and how much medicine is placed into the microemulsion, co-surfactants are significant in phase behaviour. Other solubilizers, including transcutool, glycofurol, ethanol, and isopropanol, can be used in microemulsion formulations without concern, despite the fact that co-surfactants such as bile salts and dipotassium glycyrrhizinate have been identified in the literature.^[38]

- **Other additives**

Depending on the needs, nanosuspensions may also include other additives such as buffers, salts, polyols, osmogents, and cryoprotectants.^[39]

Post-production processing

Nanosuspensions require post-production processing when a treatment candidate is

particularly susceptible to hydrolytic cleavage or chemical degradation. Processing could also be necessary if the chosen stabiliser is insufficient to keep the nanosuspension stable for a long time or if the indicated administration route has acceptable restrictions. Nanoscale drug particles can be used in the production of dry, powdery pharmaceuticals using methods like lyophilization and spray drying. Drug characteristics and cost considerations should be taken into account when choosing between two-unit processes, with spray drying typically being more practical and less expensive than lyophilization.^[40]

Nanosuspension Characterization

Techniques:

In-vitro Evaluations:

- **Organoleptic properties:**

These properties need to be considered in formulations that have to be given orally. Changes in particle size, crystal habit, and subsequent particle disintegration can all be used to explain variations in taste, particularly for active compounds. Chemical instability may be indicated by alterations in taste, aroma, and colour.

- **Particle size distribution:**

The particle size has an impact on the physicochemical characteristics, such as dissolving rate, saturation solubility, and physical stability. Several techniques, including the Coulter counter multisizer, laser diffraction (LD), and photon correlation spectroscopy, can be used to determine the particle size distribution. In contrast to LD, which has a measuring range of 0.05–80 m, PCS can measure particles with a size range of 3 nm to 3 m. In contrast to LD, which offers a relative size distribution, the Coulter counter multisizer generates a set number of particles. In order to avoid issues like capillary obstruction and embolism, it is preferable for particles used for intravenous (IV) usage to be smaller than 5 m, given that the lowest capillary size is around 5–6 m.

- **Zeta potential:**

The suspension's stability can be measured using zeta potential. A stable suspension that relies only on electrostatic attraction needs a zeta potential of at least 30 mV. However, it is believed that when both steric and electrostatic stabilising mechanisms are active, a zeta potential of 20 mV is enough.

- **Crystal morphology:**

Techniques like X-ray diffraction analysis combined with differential thermal analysis or differential scanning calorimetry can be used to examine the impact of high-pressure homogenization on the drug's crystalline structure. In nanosuspensions, high-pressure homogenization may result in crystalline structural alterations, including the emergence of amorphous or other polymorphic morphologies.

- **Dissolution velocity and saturation solubility:**

In comparison to other methods, nanosuspensions have a significant benefit since they have the potential to increase saturation solubility and dissolving velocity. To completely comprehend the in vitro behaviour of the formulation, these features must be examined in a variety of physiological solutions. According to Böhm et al., increasing the particle size to the nanoscale region may increase the pressure and speed of dissolution. It has been demonstrated that when size decreases, the pressure of dissolution increases.

- **Density:**

An essential factor to take into account is a formulation's specific gravity, often known as density. If the density decreases, air that got stuck inside the formulation structure may be the cause of the issue. It is suggested to use a homogeneous, well-mixed mixture for determining density at a certain temperature. Density can be measured using precision hydrometers.

- **pH Value:**

An aqueous formulation's pH value must be determined at a certain temperature to avoid "pH drift" and electrode surface coating brought on by suspended particles, as well as to ensure equilibrium has been attained. For pH stability, it is suggested not to include electrolytes in the formulation's exterior phase.

- **Droplet size**

Electron microscopy can be used to discover the distribution of droplet sizes in microemulsion vesicles. In a dynamic light scattering spectrophotometer, a neon laser with a wavelength of 632 nm can be used for this.

- **Measurement of viscosity:**

Using a rotational viscometer of the Brookfield type, the viscosity of lipid-based formulations with varied compositions may be assessed at various shear rates and temperatures. The samples for measurement should be submerged in the thermobath-controlled sample chamber of the instrument, which should be kept at 37°C.

- **Stability of Nanosuspension:**

Because nanosuspensions have tiny particle sizes, they have high surface energies, which can cause drug crystals to aggregate. By producing a steric or ionic barrier, stabilisers are essential for thoroughly wetting the drug particles, avoiding agglomeration and Ostwald ripening, and forming a formulation that is physically stable. Nanosuspensions frequently employ cellulose, poloxamers, polysorbates, lecithin, polyoleate, and povidones as stabilisers. When creating parenteral nanosuspensions, lecithin is frequently chosen as the ingredient.

- **In-vivo biological performance:**

Regardless of the route and method of delivery, an in vitro/in vivo correlation needs to be developed in order to monitor a drug's effectiveness in the body. It is significant in the context of intravenously delivered nanosuspensions since the organ distribution

is reliant on the drug's surface properties, such as surface hydrophobicity and interactions with plasma proteins, which in turn are dependent on the in vivo behaviour of the drug. It is commonly accepted that significant factors influencing organ distribution include the size and kind of protein absorption pattern that is seen after intravenous injection of nanoparticles. It is crucial to employ the right methods to assess surface features and protein interactions in order to understand in vivo behaviour. One method for assessing surface hydrophobicity is hydrophobic interaction chromatography, while another method is 2-D PAGE for quantifying and evaluating the adsorption of protein in animals after administration through the intravenous route.^[41-44]

Versatile Implementations of Nanosuspensions

• Oral administration:

Oral administration is preferred mode of administration. The limited solubility and absorption of some drugs, however, restricts their bioavailability and reduces their efficacy. In such cases, nanosuspensions can provide a solution by improving the dissolution rate and absorption through increased surface area and enhanced adhesiveness. Nanosuspensions can also extend gastrointestinal transit time through enhanced mucoadhesion, thereby increasing bioavailability. The enhanced oral bioavailability is attributed to factors such as increased adhesiveness, saturation solubility, and surface area of the nanosuspension. Furthermore, nanosuspensions facilitate easy taste masking of particulate systems.^[45]

• Parenteral administration:

Non-injectable drugs that show low solubility need to be converted into formulations appropriate for intravenous delivery using nanosuspensions. It is essential to create nanosuspensions for parenteral usage, and recent developments in this field have shown that they work well for injectable formulations. With today's highly regulated technologies for making

nanosuspensions, it is possible to produce particles which are uniform and have better control over the maximum particle size. The usefulness of nanosuspensions for parenteral delivery is emphasised in several study publications.^[46]

• Ocular delivery:

A potential method for administering drugs with low lachrymal fluid solubility is nanosuspensions. Given that they increase the saturation solubility of drugs that are hydrophobic in nature, they constitute the perfect technique for ocular drug administration. For some drugs, such as glucocorticoids, researchers have created effective nanosuspension delivery devices, including Kassem et al.

• Pulmonary delivery:

Drugs with low pulmonary secretion solubility may benefit from delivery using nanosuspensions. The limitations of current pulmonary delivery techniques, such as dry powder inhalers and aerosols, include limited diffusion at the intended spot and a brief residence duration. These restrictions can be bypassed via nanosuspensions. Examples include the successful formulation of budesonide and fluticasone as nanosuspensions for pulmonary administration.^[47]

• Dermal application:

Drugs in nanocrystalline form can enhance saturation solubility, which results in enhanced penetration of the drug. Because of their greater membrane penetration, improved permeability, and adhesiveness, nanocrystals are well suited for cutaneous applications.^[48]

• Targeted delivery:

The size of the drug's nanoparticles affects how well they are absorbed. Targeted delivery is made possible by altering in vivo behaviour of nanoparticles by changing their characteristics, such as their surface. Targeted drug delivery systems may be created using techniques like creating smart

crystals or stealth nanocrystals with particle sizes under 100 nm. Due of its simplicity, the creation of nanosuspensions is an economically feasible approach for targeted delivery. Particle surface properties, such as surface hydrophobicity, charge, and the presence or concentration of specific functional groups, have an impact on how the particles are distributed throughout the body. The ability of tween 80-coated nanocrystals for brain targeting has been demonstrated by the successful use of atovaquone nanocrystals coated with tween 80 for efficient parasite elimination in the brain during toxoplasmosis treatment.^[49]

• **Mucoadhesion:**

When given orally as a suspension, nanoparticles disperse in the liquid medium and quickly come into contact with the mucosal surface. The process of "bioadhesion" immobilises the particles at the gut surface. This concentrated solution serves as a particle reservoir and has a quick adsorption process. Direct contact between the intestinal cells and the particles, made possible by the bioadhesive phase, is the first stage of particle absorption.^[49-52]

Future perspectives:

Nanosuspension technology is a novel and state-of-the-art approach to overcome challenges with the administration of hydrophobic drugs, such as those with limited solubility in both aqueous and organic environments. Techniques such as media milling proved successful in the mass production of nanosuspensions. Nanosuspension technology enables the use of parenteral goods as well as conventional dosage forms, including pills, capsules, and pellets. Due to its straightforward formulation procedures and wide range of applications, the area of nanosuspension drug delivery will continue to grow and be of interest for both non-oral routes and oral of administration.

CONCLUSION

Nanosuspensions have been used to treat drugs with low bioavailability and solubility problems in both organic and aqueous solutions. Using methods like high-pressure homogenization and media milling, it is now possible to create nanosuspensions on a massive scale. Nanosuspensions can be administered parenterally, topically, ocularly, or orally. Due to their simplicity of use, reduced need for excipients, faster rate of dissolution, and saturation solubility, nanosuspensions have emerged as the formulation of choice for medications with limited bioavailability.

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