

REVIEW ON NANOSUSPENSION: A MODERN APPROACH FOR DRUG DELIVERY

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ABSTRACT:

Nanosuspensions are submicron colloidal dispersions of pharmaceutically active ingredients in a liquid medium, stabilized with surfactants. Poor water solubility remains a significant challenge in formulation development. Reducing drug particle size increases surface area, which in turn enhances bioavailability. Nanosuspensions can be prepared through various methods, including techniques like media milling and high-pressure homogenization, which are commonly used in commercial production. The distinct characteristics of nanosuspensions have made them versatile, enabling their use in a variety of dosage forms and delivery routes, including oral, pulmonary, ocular, topical, and mucoadhesive hydrogel applications. The advantages of nanosuspensions include improved drug dispersibility, enhanced solubilization, increased therapeutic efficacy and reduced toxicity. This review aims to highlight the advancements in nanosuspensions within drug delivery systems, focusing on their ability to improve solubility, stability and bioavailability of drugs.

Key words: Nanosuspension, Particle Size Reduction, High-Pressure Homogenization, Media Milling, Colloidal Drug Delivery System.

INTRODUCTION:

The pharmaceutical industry is constantly striving to identify and develop novel approaches that can effectively improve the oral bioavailability of therapeutic agents. This is particularly critical given that a significant proportion of New Chemical Entities (NCEs), which have demonstrated promising biological activity, are characterized by their low water solubility. This issue presents a considerable challenge in the field of drug

formulation, as many of these NCEs, despite their potential efficacy, cannot be absorbed adequately when administered orally due to their inherent solubility and permeability limitations. Moreover, the increasing prevalence of poorly soluble compounds with therapeutic potential has emerged as a key concern in pharmaceutical research and development. The difficulty in formulating these poorly soluble drugs not only slow down the pace of drug development but also severely impacts the market availability of new molecular entities (NMEs). In essence, the inadequate solubility and poor permeability of lead compounds remain one of the most significant barriers to successful formulation, resulting in a lower yield of viable drug products and contributing to the delay of potentially transformative therapies reaching the patient population.¹

DEFINITION:

Pharmaceutical Nano-suspensions are defined as finely dispersed, biphasic systems consisting of discrete solid drug particles in a colloidal form, suspended within an aqueous medium and stabilized by surfactants. These systems are designed for multiple routes of administration, including parenteral, pulmonary, oral, and topical delivery. By reducing the particle size, Nano-suspensions enhance the dissolution rate of the drug, leading to an improvement in its bioavailability. Typically, the diameter of the suspended particles is less than 1 μm (ranging from approximately 0.1 μm to 1000 μm). The particle size distribution in Nano-suspensions is generally below one micron, with average particle sizes falling within the range of 200 to 600 μm . The dissolution rate of micronized drug particles (those with a size $< 10 \mu\text{m}$) increases due to a corresponding increase in the surface area available for dissolution, which, in turn, accelerates the dissolution velocity. The enhanced dissolution rate in Nano-suspensions is also influenced by the vapour pressure effect, whereby the reduced particle size leads to an increased saturation solubility and consequently a faster dissolution process²

MAJOR ADVANTAGES OF NANO-SUSPENSION:

➤ **Wide Applicability and Simplicity**

Nano-suspensions offer broad applicability across various drug classes due to their straightforward formulation process and ease of preparation.

➤ **Advantageous for Drugs with Limited Water Solubility**

Nano-suspensions are particularly beneficial for drugs exhibiting poor aqueous solubility, facilitating enhanced dissolution rates and improved bioavailability.

➤ **Flexible Administration Routes**

These systems are adaptable to a variety of administration routes, including parenteral, oral, pulmonary, and topical, providing a versatile approach to drug delivery.

- **Reduced Tissue Irritation for Subcutaneous and Intramuscular Injections**
Nano-suspensions, when administered via subcutaneous or intramuscular routes, tend to cause less irritation to the surrounding tissues, thereby improving patient tolerance and comfort.
- **Rapid Dissolution and Targeted Delivery via Intravenous Route**
Administration of Nano-suspensions via the intravenous route ensures rapid drug dissolution and enables more precise, targeted delivery to specific tissues or organs.
- **Enhanced Bioavailability and Consistent Absorption with Oral Administration**
Oral administration of Nano-suspensions results in quicker drug onset, more consistent absorption irrespective of food intake, and an overall improvement in bioavailability.
- **Increased Absorption in the Drug's Optimal Absorption Window**
By reducing the particle size, Nano-suspensions enhance the absorption of the drug within its designated absorption window, promoting more efficient bioavailability.
- **Improved Bioavailability and Consistency in Ocular and Pulmonary Delivery**
Nano-suspensions delivered through ocular or inhalation routes offer superior bioavailability and more consistent dosing, enhancing therapeutic outcomes for targeted treatments.²

NEED FOR NANOSUSPENSION:

Oral bioavailability, often as a result of their poor aqueous solubility. To enhance the dissolution rate of such drugs, a variety of traditional pharmaceutical strategies have been employed, including dissolution in aqueous-organic solvent mixtures, the formation of β - cyclodextrin complexes, the development of solid dispersions, and the conversion to drug salt forms. Over the past two decades, a novel approach focused on particle size reduction has been introduced as an effective method to significantly improve the dissolution rate and, consequently, the bioavailability of these drugs.³ However, pharmacokinetic evaluations of BCS Class II drugs have revealed that these compounds exhibit limited bioavailability of these drugs.³ According to the Noyes-Whitney equation, drugs with reduced particle size exhibit an increased surface area, which consequently enhances the dissolution rate. A higher dissolution rate, coupled with the resultant concentration gradient between the gastrointestinal lumen and systemic circulation, can further augment the oral bioavailability of the drug. A Nano-suspension refers to a submicron colloidal dispersion of drug particles that are stabilized by surfactants.⁴ A pharmaceutical Nano-suspension is characterized as a colloidal dispersion of finely divided solid drug particles suspended in an aqueous medium, designed for administration via oral, topical, parenteral, or pulmonary routes. The particle size distribution of the suspended drug particles typically remains below one micron, with an average diameter ranging from 200 to 600 nm. In Nano-suspension technology, the active pharmaceutical ingredient is retained in its desired crystalline form while the particle size is reduced, thereby enhancing the dissolution rate and, consequently, improving bioavailability.⁵

TABLE- Various phytochemicals used in nanosuspensions:

SL NO.	PHYTOCHEMICAL CONSTITUENTS	SOURCE	ACTIVITY
1.	Curcumin	Turmeric	Anti-inflammatory, Antioxidant &Anticancer
2.	Resveratrol	Grapes	Antioxidant, Anti-aging &Cardioprotective
3.	Apigenin	Chamomile, parsley and oranges	Anticancer, antidiabetic, anti-inflammatory and antioxidants
4.	Capsaicin	Chili peppers	Analgesic, anti-obesity, anti-inflammatory
5.	Paclitaxel	Pacific yew tree	Potent chemotherapeutic agent against breast, ovarian, and lung cancers
6.	Naringin /Naringenin	Grapefruit and citrus fruits	Redundant ROS production, anti-inflammatory
7.	Quercetin	Red onions, apples and green tea	Antihistamine, potent antioxidant and anti-inflammatory
8.	Berberine	Barberry	Antimicrobial, anti- diabetic and cardioprotective
9.	Silymarin	Milk Thistle	Hepatoprotective, anti-fibrotic and antioxidants
10.	Epigallocatechin Gallate (EGCG)	Green tea	Neuroprotective, anti-amyloid, aggregation

FORMULATION CONSIDERATION:

The formulation of Nano-suspensions typically necessitates the inclusion of stabilizers or surfactants, an appropriate solvent system, and additional excipients for its preparation.

- **Stabilizer:**

Stabilizers play a crucial role in the formulation of Nano-suspensions. In the absence of an appropriate stabilizer, the high surface energy of nanosized particles may lead to agglomeration or aggregation of the drug crystals. The primary function of a stabilizer is to effectively stabilize the drug particles, preventing Ostwald's ripening and agglomeration, thereby ensuring the production of a stable formulation. This is achieved by providing steric or ionic barriers that maintain dispersion stability. The type and concentration of stabilizer significantly influence both the physical stability and in vivo behaviour of the Nano-suspension. In certain instances, a combination of stabilizers may be required to achieve optimal stability. The drug-to-stabilizer ratio typically varies from 1:20 to 20:1, and must be tailored for each specific formulation. Examples of stabilizers include lecithins, PVPK30, PVA, SLS, cellulose, poloxamers, polysorbates and povidones.⁶

- **Organic Solvents:**

Organic solvents are frequently employed in the preparation of Nano-suspensions, particularly when emulsion or micro-emulsion techniques are utilized as the formulation approach. While these solvents pose significant risks to both physiological systems and the environment, less hazardous, water-miscible solvents such as methanol and ethanol are often considered as safer alternatives.⁷

- **Surfactants:**

Surfactants are incorporated into the formulation to improve dispersion by lowering interfacial tension. Additionally, they function as wetting agents or de-flocculants. Commonly utilized surfactants include Tweens and Spans.⁸

- **Co-surfactants:**

The selection of co-surfactants is crucial when utilizing micro-emulsions for the formulation of Nano-suspensions. Co-surfactants can significantly influence the phase behaviour, and their effect on the uptake of the internal phase in a given micro-emulsion composition, as well as on drug loading, should be thoroughly evaluated. Examples of commonly used co-surfactants include Transcutol, glycerol, ethanol, isopropanol, bile salts, and dipotassium glycyrrhizinate.⁹

- **Other Additives:**

Nano-suspensions may contain various excipients, including buffers, salts, polyols, co-solvents and cryoprotectants, which are selected based on the route of administration and the physicochemical properties of the active pharmaceutical ingredient.¹⁰

TECHNIQUES FOR PREPARATION OF NANOSUSPENSION:

There are primarily two converse methods for preparing Nano-suspensions. The traditional precipitation method is referred to as ‘Bottom-up technology’ and ‘Top down method’.¹¹

In the **Bottom-up technology**, the drug is initially dissolved in a solvent, which is subsequently added to a non-solvent to induce crystallization. During this process, the growth of drug crystals must be carefully controlled by the addition of surfactants to prevent the formation of micro-particles. In contrast, Top-down technologies, which involve disintegration methods, are often favoured over precipitation techniques due to their ability to produce more uniform particle sizes.¹²

Top-down technologies are methods used to reduce the size of larger particles or bulk materials into nanoscale dimensions through mechanical processes, such as milling, grinding, or high-pressure homogenization. These techniques are commonly employed in the preparation of Nano-suspensions and offer advantages in producing more uniform particle sizes compared to traditional precipitation methods.

Different method of Top-down technique:

MEDIA MILLING¹³

Nano-suspensions are mostly prepared by using high shear media mills, which contains of a milling chamber, recirculation chamber, and milling shaft. The milling media, typically composed of ceramic materials such as sintered aluminium oxide or zirconium oxide, are in the form of balls or pearls. The milling chamber is charged with a mixture of milling media, water, the active pharmaceutical ingredient (API), and stabilizers. The balls are rotated at high shear rates under controlled temperature conditions, generating both friction and impact forces. These forces facilitate the reduction of particle size, leading to the formation of nanosized particles. Methods for Nano-suspension preparation also include media milling, high-pressure homogenization in aqueous or non-aqueous media, as well as a combination of precipitation and high-pressure homogenization.

HOMOGENIZATION: (High pressure homogenization (dissocubes))

"This technique involves forcing the suspension through a narrow valve under high pressure using a plunger-type pump".¹⁴ When the suspension is forced through an orifice, the static pressure drops below the boiling point of water, leading to the formation of gas bubbles due to localized boiling. As the suspension exits the orifice, the pressure returns to normal, causing these bubbles to collapse or implode. This implosion generates intense shear forces that drive surrounding particles toward each other, resulting in particle size reduction. This principle is utilized in the APV Gaulin Micron Lab 40 homogenizer.

In non-aqueous homogenization (NanoPure), the process is carried out in a water-free medium or a water-based mixture at temperatures as low as 0°C or even at the freezing point. This approach, known as deep-freeze homogenization, is particularly suitable for thermolabile (heat-sensitive) substances, as it minimizes thermal degradation during processing.¹⁵

NANOEDGE TECHNOLOGY:

Combines elements of both homogenization and precipitation methods, offering improved stability and enhanced bioavailability of drug formulations. The initial suspension produced through this technique is further homogenized to reduce particle size and inhibit crystal growth. While the precipitation method alone may lead to issues such as crystal growth and poor long-term stability, the integration of nanotechnology in the NanoEdge approach helps to overcome these limitations. Additionally, an evaporation step is included in the NanoEdge process, resulting in a solvent-free, modified starting material that enhances the quality and consistency of the nanosuspension.

PRECIPITATION TECHNIQUE (SOLVENT ANTISOLVENT METHOD):

The precipitation method has long been employed to prepare submicron particles, particularly for drugs with poor solubility. Initially, the drug is dissolved in an appropriate solvent. This solution is then introduced into a miscible anti-solvent system, accompanied by surfactants. The rapid introduction of the drug solution into the anti-solvent results in a sudden super saturation of the drug, leading to the formation of ultrafine drug particles. The precipitation process involves two key stages: nucleus formation and crystal growth. To achieve a stable suspension with minimal particle size, a high nucleation rate coupled with a low growth rate is essential. Both of these rates are influenced by temperature. In this approach, the drug must be soluble in at least one solvent that is compatible with the anti-solvent¹⁶.

NANO SUSPENSION CHARACTERIZATION TECHNIQUES:

In-vitro Evaluations:

• Organoleptic properties:

These properties must be carefully evaluated in the formulation of oral dosage forms. Variations in particle size, crystal morphology, and subsequent disintegration of particles can significantly influence taste, particularly for active pharmaceutical ingredients (APIs). Furthermore, alterations in taste, aroma, and colour may serve as indicators of chemical instability in the formulation.

• Particle size distribution:

Particle size significantly influences various physicochemical properties, including dissolution rate, saturation solubility, and physical stability. Several analytical techniques, such as the Coulter counter multi-sizer, laser diffraction (LD), and photon correlation spectroscopy (PCS), are commonly employed to assess particle size distribution. Unlike LD, which has a measurement range of 0.05–80 μm , PCS can detect particles ranging from 3 nm to 3 μm . Additionally, while LD provides a relative particle size distribution, the Coulter counter multi-sizer offers a precise count of individual particles. For intravenous (IV) applications, it is critical to ensure that particles are smaller than 5 μm to prevent complications such as capillary obstruction or embolism, as the smallest capillaries typically measure between 5–6 μm .

• Zeta potential:

The stability of a suspension can be assessed by measuring its zeta potential. A suspension that is stabilized solely by electrostatic forces requires a minimum zeta potential of 30 mV to maintain stability. However, when both steric and electrostatic stabilization mechanisms are present, a zeta potential as low as 20 mV may suffice.

• Crystal morphology:

Techniques such as X-ray diffraction (XRD) analysis, coupled with differential thermal analysis (DTA) or differential scanning calorimetry (DSC), can be employed to evaluate the effects of high-pressure homogenization on the drug's crystalline structure. High-pressure homogenization in Nano-suspensions may lead to modifications in the crystalline structure, potentially resulting in the formation of amorphous forms or alternative polymorphic morphologies.

• Dissolution velocity and saturation solubility:

Compared to other techniques, Nano-suspensions offer a distinct advantage due to their ability to enhance saturation solubility and dissolution rate. To fully understand the in vitro behaviour of these formulations, it is essential to assess these properties in various physiological solutions. According to Bohm et al., reducing particle size to the nanoscale can increase both the pressure and rate of dissolution. Furthermore, studies have shown that as particle size decreases, the dissolution pressure tends to increase.

• Density:

An important parameter to consider is the formulation's specific gravity, also referred to as its density. A decrease in density may be attributed to the entrapment of air within the formulation matrix. To accurately determine density at a given temperature, it is recommended to use a homogeneous, thoroughly mixed sample. Precision hydrometers are commonly employed for measuring density.

• **pH Value:**

The pH of an aqueous formulation should be measured at a specific temperature to prevent "pH drift" and electrode surface fouling caused by suspended particles, as well as to confirm that equilibrium has been reached. To maintain pH stability, it is recommended to avoid the inclusion of electrolytes in the external phase of the formulation.

• **Droplet size:**

Electron microscopy is commonly employed to analyse the distribution of droplet sizes within micro-emulsion vesicles. Alternatively, a dynamic light scattering (DLS) spectrophotometer, utilizing a neon laser, can also be used to measure this distribution.

• **Measurement of viscosity:**

The viscosity of lipid-based formulations with varying compositions can be evaluated using a Brookfield rotational viscometer at different shear rates and temperatures. The samples should be placed in the instrument's thermobath-controlled sample chamber, which must be maintained at 37°C during measurement.

• **Stability of Nano-suspension:**

Nano-suspensions, due to their small particle sizes, exhibit high surface energies, which can lead to the aggregation of drug crystals. Stabilizers play a crucial role by creating steric or ionic barriers that ensure effective wetting of the drug particles, preventing agglomeration and Ostwald ripening, and promoting the formation of a physically stable formulation. Common stabilizers used in Nano-suspensions include cellulose, poloxamers, polysorbates, lecithin, polyoleate, and povidones. Among these, lecithin is often the stabilizer of choice when formulating parenteral nanosuspensions.¹⁷⁻²⁰

APPLICATION OF NANO-SUSPENSION:

Nano-suspensions have diverse applications, particularly for drugs with low solubility and poor bioavailability. These applications are outlined below.

• **Oral Drug Delivery:**

Due to its numerous advantages, the oral route is often the preferred method for administering various drugs, including antibiotics like atovaquone and buparvaquone. When formulated as Nano-suspensions, these drugs exhibit enhanced solubility and bioavailability. For instance, the oral administration of naproxen nanoparticles results in an area under the curve (AUC) (0-24 h) of 97.5 mg-h/L, significantly higher than that observed for

naproxen Nano-suspension and tablet formulations. Similarly, the bioavailability of danazol (a gonadotrophin inhibitor) in Nano-suspension form is 82.3%, compared to just 5.2% for its conventional dispersion.²¹

- **Parenteral Drug Delivery:**

Nanotechnology is increasingly utilized in parenteral drug delivery systems. One of the key advantages of this approach is the reduced requirement for toxic co-solvents in the formulation of poorly soluble drugs. This can significantly enhance the therapeutic efficacy of the drug compared to conventional oral formulations, as well as enable targeted delivery to specific cells, such as macrophages. For example, when clofazimine is administered intravenously, its concentration in the liver, spleen, and lungs reaches levels that are well above the minimum inhibitory concentration (MIC) required to combat most *Mycobacterium avium* strains. Additionally, tarazepide is formulated as a Nano-suspension to minimize the need for surfactants and cyclodextrins, thereby improving bioavailability.²²

- **Pulmonary Drug Delivery:**

In pulmonary drug delivery, Nano-suspensions are utilized for drugs that exhibit poor solubility in pulmonary secretions. The formulation is nebulized using either a mechanical or ultrasonic nebulizer to achieve efficient lung delivery. This process ensures uniform distribution of the drug, with each droplet containing at least one drug particle. Nanosizing improves both the diffusion and dissolution rates of the drug, enhancing its adhesiveness to the mucosal surface and prolonging its residence time at the site of absorption. Pulmonary Nano-suspensions are characterized by a rapid onset of action followed by a controlled release of the active ingredient, which is essential for treating various pulmonary diseases.²⁴ e.g. budesonide

- **Ocular Drug Delivery:**

Some drugs exhibit limited solubility in lachrymal fluid, which can hinder their efficacy in ocular applications. However, when formulated as nanoparticles, their saturation solubility and bioavailability are significantly enhanced. This approach is particularly beneficial for hydrophobic drugs. Nano-suspensions also prolong the drug's residence time in the cul-de-sac, improving the therapeutic effect. A prominent example is ibuprofen, where the anti-inflammatory activity is notably enhanced in the Nano-suspension form compared to conventional aqueous formulations.²³

- **Targeted Drug Delivery:**

Nano-suspensions can also be engineered to target specific tissues by modifying their surface properties and stabilizer composition, which in turn can influence their in vivo behaviour. Through this approach, drugs are efficiently taken up by the mononuclear phagocytic system (MPS), enabling targeted drug delivery to specific regions. This strategy is particularly useful for directing anti-microbial and antifungal drugs to macrophages. An example of this is the use of atovaquone in Nano-suspension form for targeted delivery to the brain.²⁵

• **Mucoadhesion of Nanoparticle:**

When administered orally, Nano-suspensions diffuse into the gastrointestinal (GI) fluid and adhere to the mucosal surface, facilitating absorption. This enhances both bioavailability and targeted delivery to pathogens residing in the GI tract. An example of this is buparvaquone, which targets *Cryptosporidium parvum*, a parasite that persists in the gastrointestinal system.²⁶

Conclusion:

Nanosuspension formulations have significantly addressed the challenges of poor solubility and dissolution, thereby enhancing drug absorption. They offer several therapeutic advantages, including a straightforward preparation process, minimal use of excipients, and increased saturation solubility and dissolution rate of the drug. Although many drug candidates discovered during pharmaceutical research exhibit poor solubility, nanosuspensions present a promising solution. These formulations are a commercially viable approach for improving both the solubility and bioavailability of poorly soluble drugs. Among the various techniques, high-pressure homogenization is commonly employed for large-scale production. Beyond solving solubility issues, nanosuspensions also contribute to enhanced drug efficacy.

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