

# Revolutionizing Drug Delivery: Future Perspectives, Challenges, Techniques and Applications of Nanosuspension

Ramprasad D. Kadam<sup>1</sup>, Amol S. Rakte<sup>1,\*</sup>, Sanjay R. Arote<sup>2</sup>, Mangesh M. Galbale<sup>1</sup>

<sup>1</sup>Department of Pharmaceutics, IVM'S Krishnarao Bhegade Institute of Pharmaceutical Education and Research, Talegaon Dabhade, Tal. Maval, Pune-410507, India

<sup>2</sup>IVM'S Krishnarao Bhegade Institute of Pharmaceutical Education and Research, Talegaon Dabhade, Tal. Maval Pune-410507, India

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**Abstract** Nanotechnology is changing how drugs are delivered. It offers new ways to tackle problems with drugs that don't dissolve well in water. This is especially true for certain types of drugs in BCS Classes II & IV. One exciting method in this field is called Nanosuspensions (NS). In this method, drug particles get really tiny down to the nanometer scale. They are mixed into a medium using surfactants to keep them stable. By doing this, we can boost the solubility and the rate of drug dissolution. It also helps the body absorb these drugs better because more surface area is available for interaction. Both targeted distribution and regulated medication release are made possible by NSs! They can be used in many ways: orally, in the eyes, through the lungs, or even through the skin. This review looks at new methods for making NSs. There are techniques like top-down, bottom-up, and even hybrid methods. Some cool approaches include HPH, SF Technology, and Emulsification Solvent Evaporation. Each of these aids in the creation of NSs with special qualities, such as improved stability and particle size distribution. There are problems like long-term stability and large-scale production. Regulatory challenges also make it hard. Researchers aim to overcome these hurdles by using new technologies like microfluidics and personalized medicine. NSs hold promise for solving big challenges in healthcare! By incorporating green chemistry

ideas & smart systems to provide long-term answers to pharmaceutical problems, NSs open the door for their wider use in therapeutic settings. This review bridges the gaps between cutting-edge research and real-world applications by offering a thorough grasp of NS technology. It is a useful tool for developing the field of drug delivery, emphasizing how NSs can be used to address important problems such as therapeutic inefficacy, bioavailability variability, and the rising need for effective drug delivery methods.

**Keywords** NSs, Poorly Water-Soluble Drugs, Bioavailability Enhancement, High-Pressure Homogenization (HPH), Precipitation Techniques, Nano Edge, Drug Solubility, Particle Size Reduction, Zeta Potential, Pharmaceutical Nanotechnology

## 1. Introduction

Modern drug delivery methods have drawn more attention in recent years, especially those based on nanotechnology, such as complex forms, solid dispersions, microemulsions, and liposomes. Nanotechnology, especially nanoparticles NPs and nanodrug delivery

systems, has attracted significant attention due to its potential in improving drug efficacy. NSs represent an advanced formulation where Active Pharmaceutical Ingredients (APIs) are micronized to the nanometer scale and dispersed in solvents with the help of surfactants. These surfactants form a stabilizing matrix around the API, ensuring that it remains in a suspended state for prolonged periods without altering its physicochemical properties. Based on their permeability and solubility, APIs are divided into four classes by the Biopharmaceutics Classification System (BCS). Low water solubility is a characteristic of BCS Class II and Class IV drugs, which results in decreased bioavailability and shorter shelf life. Historically, a number of tactics have been used to improve the solubility of these weakly water-soluble medications, including buffer systems and pH adjustment. However, nanotechnology, particularly NSs, offers a more promising solution for addressing these challenges [1-3]. The limited solubility of certain drug compounds presents a critical hurdle during the early stages of screening for pharmacological effectiveness and persists as a challenge throughout formulation development and clinical testing [4]. Before these substances can be considered for commercialization, it is essential to prepare them for preclinical trials and pharmacological assessments [5].

To guarantee smooth progress, this planning needs to be done well in advance. Consequently, it is evident that novel technical methods are required to enhance the bioavailability of medications with low solubility. The pharmaceutical industry's primary challenge is creating cutting-edge formulation and drug delivery strategies that can successfully get past solubility constraints. This challenge is often closely linked to poor oral bioavailability [6-8]. To enhance bioavailability, rapid absorption after oral administration must be prioritized. Alternatively, intravenous administration can be a feasible option for improving drug delivery and therapeutic effectiveness [9]. To address the challenges posed by medications that don't dissolve well in water, a number of formulation techniques have been developed. These techniques are sometimes referred to as "specific strategies" since they are intended to improve the treatment effectiveness and bioavailability of such drugs [10].

The molecules' special chemical characteristics, such as their solubility in different organic solvents and particulars pertaining to structure or molecular size, are crucial to the effectiveness of these techniques. For instance, some molecules are specially designed to fit within cyclodextrin ring structures, making these characteristics crucial for their effective application [11,12].

A more systematic strategy would be the adoption of a "universal formulation method" applicable across a broad spectrum of drug molecules. Micronation is a key technique that includes cutting drug particles down to a size of 1 to 10 $\mu$ m. This procedure is well known for its ability to increase the bioavailability of pharmaceutical compounds, hence increasing their efficacy.

Pharmaceutical formulations frequently employ this technique to increase the absorption through the mouth of medications. The aforementioned formulation method is frequently employed to increase the potential for bioavailability and gastrointestinal absorption of several medicinal substances [13]. Micronation techniques are often less effective due to the limited solubility of commonly used medications. According to the Biopharmaceutical Classification System (BCS), drugs in Class II are distinguished by their poor solubility, which makes them challenging to dissolve. Increasing surface area alone won't solve these problems in terms of bioavailability. Improved methods are necessary to address these outstanding problems and accomplish efficient medication administration [14]. The skin is an essential site for the pain-free and harmless delivery of medicinal drugs because it prevents first-pass metabolism and permits controlled drug release. Following skin absorption, these drugs may have systemic, localized, or regional effects at different target sites [15,16]. Despite its challenges, modern drug delivery systems have garnered significant attention due to their ability to enhance therapeutic efficacy and patient compliance. One of the key challenges in drug delivery is overcoming biological barriers such as the gastrointestinal tract, blood-brain barrier (BBB), and skin, which can limit drug absorption and bioavailability. For oral drug delivery, poor solubility and permeability often lead to low bioavailability [17,18].

NSs have emerged as a promising approach to enhance solubility, dissolution rate, and overall drug absorption by increasing the surface area of drug particles. In parenteral drug delivery, NSs offer advantages such as improved dispersion of hydrophobic drugs, controlled release, and targeted delivery, making them suitable for intravenous, intramuscular, and subcutaneous administration. Additionally, for pulmonary drug delivery, NSs can be formulated as inhalable aerosols, facilitating deep lung deposition and enhanced therapeutic effects in respiratory diseases. In ocular drug delivery, NSs help overcome issues related to poor drug penetration across the corneal barrier, enabling sustained drug release and improved bioavailability in treating ophthalmic disorders. While transdermal drug delivery remains a promising non-invasive route, the skin's barrier function poses a significant challenge [19]. However, NSs, with their ability to enhance drug solubility and permeability, offer potential solutions for overcoming this barrier and ensuring effective drug delivery [20].

## 2. Objective of the Review

This review aims to provide an overview of the current trends in NS technology, focusing on the recent advancements, challenges, and opportunities in their formulation and application. The review will discuss novel preparation techniques, stabilization methods, and the innovative applications of NSs in both pharmaceutical and

non-pharmaceutical sectors. Key trends such as the integration of smart delivery systems, advances in characterization technologies, and the increasing use of green chemistry in NS development will be highlighted. Additionally, the review will examine the challenges that hinder the widespread use of NSs, including issues related to scale-up, physical instability, and regulatory hurdles. Future perspectives will be discussed, emphasizing the potential of NSs in personalized medicine, sustainable drug delivery systems, and next-generation nanotechnologies [21].

### 3. NSs Provide Multiple Advantages over Alternative Drug Delivery Techniques

- The oral bioavailability of drugs is increased by NS through enhancing the active ingredient's saturation solubility, dissolution, and adherence to cell surface membranes.
- NSs can also enable targeting that is passive because of the particle's nanometer size.
- Their own production is straightforward, inexpensive, and results in quick and repeatable formulations.
- Because there are very few excipients needed for preparation, production costs are very low. They can expand the scope of their manufacturing as well.
- Whether a person is fed or fasting, they help to ensure more consistent absorption by mitigating the fluctuations in bioavailability caused by food intake.
- They lessen the variation in bioavailability between subjects.
- Because of their high drug content (recognized as 100%), the dosage used in therapy is decreased.
- Solidified NSs demonstrate improved physical stability, enabling their formulation into solid dosage forms like tablets or capsules for patient administration.

- In addition to the oral route, other routes such as parenteral, pulmonary, topical, and ocular can be created for NSs.
- These formulations can undergo sterilization through several techniques, including filtration, dry heat, steam, and radiation, ensuring their safety and effectiveness [22].

### 4. Preparation Techniques for NSs

Figure 1 is an illustration of the NS production processes. This visualization shows the transition from a basic suspension to a NS, highlighting the steps involved and the resulting enhanced bioavailability [23].

NSs are a very useful tool for improving the bioavailability and solubility of hydrophilic and hydrophobic bioactive substances. The polymers, co-surfactants, and surfactants stabilize the aqueous colloidal dispersion of NPs in which they are present. Because of their high dispersibility and solubility [24], these drug-loaded NPs made using NS techniques can get past physiological barriers in oral drug delivery. Additionally, they enhance stability and therapeutic results while facilitating targeted, controlled, and sustained drug release. Researchers and pharmaceutical experts have developed a number of strategies for creating NSs which can be broadly divided into three categories: top-down technology, bottom-up technology, and hybrid approaches that incorporate aspects of both. Innovative preparation techniques, such as melt emulsification, emulsification–solvent evaporation, and SF technology, have also surfaced in addition to these fundamental strategies. The successful development of these sophisticated methods through continued study shows how sophisticated NS formulation is becoming [25].

Top-down technology and bottom-up technology are the two main techniques used to prepare NS. Different approaches for the preparation of NS are mentioned in Figure 2 [26].

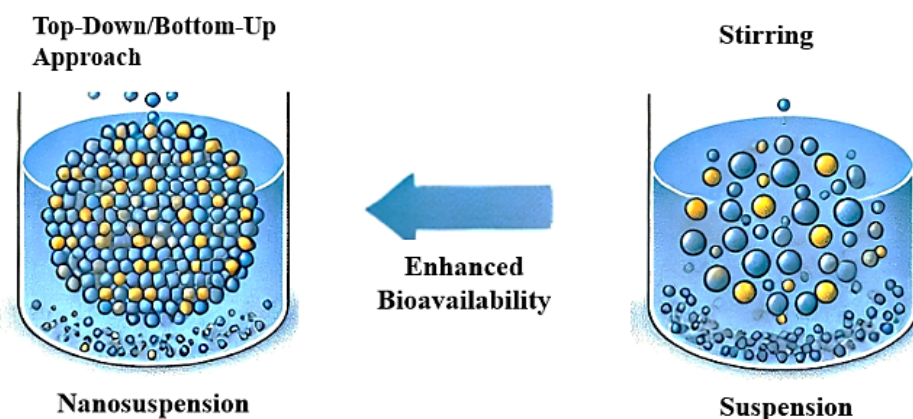
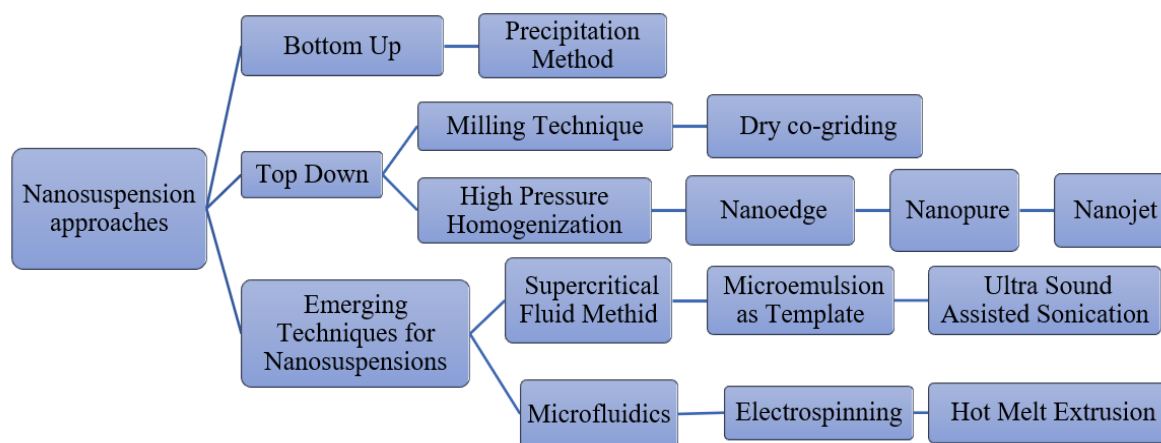


Figure 1. Manufacturing Process for NS



**Figure 2.** Different Approaches for the Preparation Of NS

#### 4.1. Bottom-up Technology

It uses methods including precipitation, microemulsion, and melt emulsification to create NPs. Atomically-level bioactive compounds are processed using a variety of chemical and physical techniques in Bottom-up (B-U) approaches. Among these methods are inclusion Complexation, Coacervation, Melt Emulsification, Liquid Antisolvent Precipitation, and SF Extraction. Each of these methods contributes to the regulated precipitation of particles from melts or solutions, which makes it easier to produce drug particles that are nanosized and have higher bioavailability. Effective NSs of poorly soluble drugs require the ability to accurately control particle size and dispersion in a controlled setting [27].

##### 4.1.1. Precipitation Method

This technique, also known as the Solvent-Antisolvent method, uses an antisolvent to precipitate the solute. A suitable solvent, usually water, is used to dissolve the drug ingredient in order to create a solution. Next, an antisolvent that is miscible with the primary solvent but insoluble in the drug itself is mixed with the drug, often with some surfactant still present. The drug becomes instantly supersaturated in the mixture due to the quick blending of the antisolvent with the drug solution. This fast process triggers the immediate formation of a supersaturated state. API that are either amorphous or crystalline are produced as a result of this process. The first stage of nucleation and the subsequent phase of crystal growth are the two main stages of the process. In order to minimize crystal growth and maximize nucleation, NS must be achieved. Temperature affects both phases, so temperature optimization is essential for a successful formulation of the NS. The technique has a number of advantages, such as being straightforward, easily implementable, scalable, and economical. It does, however, have certain disadvantages, including the need that the medication dissolve in at least

one solvent and that crystal growth be regulated to avoid going beyond the nanoscale, which necessitates the use of the proper solvent [6].

#### 4.2. Top-down (T-D) Technology

It includes reducing larger particles to NPs; milling methods and HPH are two examples of this procedure.

##### 4.2.1. Media Milling

Usually, high-shear media mills or pearl ball mills which are made up of a milling chamber, a recirculating chamber, and a milling shaft are used in this process. In this process, the drug, dispersed in an aqueous solution, is introduced into a milling device. Inside the mill, tiny grinding beads or balls are employed to aid in the reduction of particle size. These beads help break down the drug particles, leading to their size being diminished [28]. As the milling process progresses, these grinding balls move rapidly within the mill, striking the sample with high shear force. The combined effects of impact and friction cause a substantial particle size reduction, while maintaining temperature control [29]. For exceptional abrasion resistance, the balls are composed of sturdy materials such as strongly cross-linked polystyrene resin, zirconium oxide, or aluminium oxide sintered ceramic. The planetary ball mill is one piece of specialized equipment that can create particles as fine as 0.1 $\mu$ m. Using wet milling, for instance, Zn-Insulin NSs with an average particle size of roughly 150 nm have been created. In order to achieve the required particle size, this method involves continuously passing the medication and stabilizer through the grinding chamber in a coarse suspension [30].

##### 4.2.2. Dry-Co-Grinding

Without a liquid medium, dry-co-grinding is a top-down method that effectively reduces the size of drug particles by using mechanical forces to create NSs. The drug is physically mixed with a stabilizer (like a polymer,

surfactant, or lipid-based carrier) and then put through a lot of impact, shear, and frictional forces in milling machines like a ball mill, jet mill, high-energy planetary mill, or other sophisticated grinding systems. Through the breakdown of bigger drug particles into finer NPs, which frequently reach the nanoscale, these mechanical forces cause particle size decrease. A stabilizer is essential to this process because it adsorbs onto the surfaces of the freshly formed NPs, preventing recrystallization, Ostwald ripening, and aggregation because of their high surface energy. Lipids, surfactants, and hydrophilic polymers (eg. sodium lauryl sulfate, poloxamers, and hydroxypropyl methylcellulose) are examples of common stabilizers. The stability, dissolving behavior, and particle size of the NS are all influenced by the stabilizer selection. Advantages: Solvent-free processing, making it an environmentally friendly method. Lower production costs due to the elimination of organic solvents and drying steps. Improved drug wettability and solubility, as surface-modified NPs exhibit enhanced dissolution properties [31].

#### 4.2.3. High-Pressure Homogenization

HPH which makes use of strong shear forces and cavitation, is a crucial method for preparing NSs. This procedure disperses the drug crystals by forcing a suspension through small openings and exerting pressure on them. Micro fluidization and piston-gap homogenization are the two main homogenization techniques used in this procedure. Using a jet-stream mechanism, Micro fluidization reduces particle size by speeding the coarse suspension through a homogenizing chamber where it is exposed to cavitation, shear forces, and high-speed collisions [32]. 'Z' and 'Y' type chambers are the two ways in which this principle is implemented. Whereas the suspension in the 'Y'-type splits into two streams that collide head-on, the suspension in the 'Z'-type chamber experiences multiple directional changes that result in particle collisions and shear forces. The piston-gap homogenizer is a further method that uses pressures ranging from 500 bar to 350 MPa to force the coarse suspension through an ultra-fine gap at extremely high speeds. Particle size can be controlled by varying the cycle number and pressure; generally speaking, higher values produce finer particles. A freshly prepared coarse suspension containing the API and a stabilizer is shaken to begin the process. The particle size of this combination is directly impacted by the different processing factors, such as cycle count and pressure, as it passes through a tight gap at high pressure, creating a stable NS [33].

#### Advantages

Scaling up the process is straightforward and highly efficient, ensuring ease of production even on a larger scale. The reproducibility of results is consistent, allowing for uniform outcomes across multiple batches. Achieving homogeneous particle size distribution is relatively simple, and by making specific adjustments to the process, the

appropriate particle size is achievable. Additionally, the approach effectively reduces the likelihood of recrystallization, enhancing product stability [34].

#### 4.2.4. Nano Edge

In a novel way, the Nano edge Technique combines homogenization techniques with microprecipitation of the API in water, improving stability and particle size distribution. Precipitation usually produces an amorphous precipitate and requires water-miscible solvents like methanol, ethanol, or isopropanol. A step for solvent evaporation is incorporated in Nano edge technology, resulting in a solvent-free substance that is then treated by Sonication or HPH with piston-gap homogenizers. This homogenization stage efficiently produces nanosized particles (ranging from 80–700 nm) with high stability and prevents further crystal growth in a short period. Like Nano Edge, the Smart Crystal® group's H 69 Technology applies instantaneous cavitation, particle collision, and shear forces to the micro precipitate to create extremely stable drug nanocrystals in the 20–900 nm size range [24,25].

#### Advantages

This technique makes use of basic, inexpensive equipment.

Higher solubility at saturation can be achieved, which is an added advantage over other methods of NS preparation [22,24].

#### Disadvantages

The requirement that the medication be soluble in at least one solvent is a significant disadvantage.

A minimum of one non-solvent and the chosen solvent should mix well together.

Solvent residues must be removed during the process, which could increase production costs.

It can also be difficult to maintain the particle's characteristics, especially its size and amorphous fraction [35].

#### 4.2.5. Homogenization in Non-Aqueous Media

Also known as Nano pure technique, this is a method where suspensions undergo homogenization in non-aqueous or water-mixed media, such as polyethylene glycol (PEG 400 or PEG 1000). The process operates at controlled temperatures, which can range from room temperature down to 0°C or even below, often reaching freezing points. Due to these low temperatures, this technique is sometimes referred to as deep-freeze homogenization. It's particularly well-suited for thermolabile substances, as the mild processing conditions help maintain the stability of these sensitive drugs. Drug nanocrystals are usually dissolved in liquid PEG or other oils using this technique, and the resulting material can be readily encapsulated into gelatine or hydroxypropyl methylcellulose (HPMC) capsules for delivery [36].

#### 4.2.6. Nano Jet Technique

The Nano Jet Technique is a sophisticated HPH technique used to create NSs. It is sometimes referred to as opposing stream technology. This method entails splitting a suspension stream into two or more segments inside a customized chamber. The streams are then driven in opposite directions at incredibly high speeds while being subjected to pressures of up to 4000 bar. When the opposing streams contact at speeds of around 1000 meters per second, powerful particle-particle interactions, cavitation phenomena, and intense shear forces are produced. The main force reducing particle size in this method is the collision process. The cohesive forces holding drug particles together are broken down by the strong collision between the opposing liquid streams, causing the particles to break down into fractions the size of a nanometer. This non-thermal method works very well for processing heat-sensitive medications because it produces consistent NPs without the possibility of thermal deterioration. Advantages: A narrow size distribution with particles less than 100 nm is the result of effective particle size reduction. Preserving Drug Stability: This approach stops the API from degrading chemically and thermally, in contrast to high-temperature or grinding operations. Reproducibility and Scalability: Easily modified for large-scale pharmaceutical manufacturing, guaranteeing uniformity from batch to batch. Better Bioavailability: Drug solubility, absorption, and dissolution rate are all improved by decreasing particle size, which results in increased bioavailability [37].

### 4.3. Emerging Techniques for NSs

The field of NSs is rapidly evolving, with several innovative techniques being developed to improve formulation, stability, and therapeutic efficacy. Here are some of the most promising emerging techniques:

#### 4.3.1. Supercritical Fluid (SF)

Through the use of advanced techniques, drug NPs can be produced from drug solutions. Several approaches have been explored, including the Rapid Expansion of Supercritical Solution (RESS), supercritical anti-solvent (SAS) processes, and precipitation using compressed anti-solvent (PCA) techniques [38]. In the RESS method, a drug solution is expanded through a nozzle into a SF, which significantly weakens the solvent's ability to hold the drug, leading to the formation of fine drug particles. The PCA procedure involves atomizing the medication solution in a container that contains pressurized CO<sub>2</sub>. Fine crystals precipitate as a result of the drug solution being supersaturated due to solvent extraction. This method allows the SF to function as an anti-solvent because the drug shows little solubility in it while the solvent is still miscible. Upon injecting the drug solution into the SF, the solvent is eliminated, resulting in the precipitation of fine drug crystals [39].

#### 4.3.2. Ultrasound Sonication

The high-energy, non-mechanical process of ultrasound-assisted sonication is frequently used to create NSs. The breakdown of bigger drug particles into nanometer-sized suspensions is facilitated by the acoustic cavitation forces created by the use of ultrasonic waves in the frequency range of 20–100 MHz. This approach works on the basis of the application of ultrasonic energy, which causes small bubbles to develop, grow, and collapse in the liquid medium. These bubbles implode, producing strong localized pressure and temperature changes that reduce particle size, increase dispersibility, and stabilize the NS. The capacity of ultrasound-assisted sonication to accurately regulate the size distribution of medication particles is one of its main advantages. This method minimizes undue mechanical stress on the system while permitting the selective fragmentation of bigger particles, in contrast to traditional milling or HPH. The method guarantees the creation of a consistent and stable NS, which is essential for improving the solubility, rate of dissolution, and bioavailability of medications that are not very soluble in water. Furthermore, this technique efficiently inhibits aggregation and improves long-term colloidal stability by lowering the particle surface energy. When it comes to preparing NSs, ultrasound-assisted sonication is a straightforward, affordable, and scalable method. This method is appealing for enhancing the pharmacokinetic performance of poorly soluble pharmaceuticals because of its capacity to efficiently decrease particle size, regulate crystallization, and improve drug solubility. As ultrasonic technology and process optimization continue to progress, this technique has enormous potential for producing stable and potent NSs on a large scale for use in pharmaceutical applications [40].

#### 4.3.3. Micro Emulsions as Templates

The microemulsion technique is a popular and successful method for creating NSs, especially for medications that are poorly soluble in water. Oil, water, surfactants, and co-surfactants combine to form a thermodynamically stable, transparent, or translucent solution known as a microemulsion. When the medicine is distributed within the aqueous phase using a suitable organic solvent or solvent mixture, these microemulsions serve as templates for the NS formulation process. In order to stabilize the medicine within the microemulsion, stop aggregation, and guarantee a consistent particle size distribution, surfactants and co-surfactants are essential. Particle size control is a key advantage of using microemulsions as templates for the creation of NSs. By varying the size of the emulsion droplets, the final particle size may be controlled because the medicine is first dissolved in a clearly defined dispersion phase. This is especially helpful for medications whose particle sizes need to be precisely controlled in order to obtain the best possible bioavailability and dissolution. A very easy and

economical way to produce NSs, the microemulsion approach also eliminates the need for specialized high-energy equipment such as high-pressure homogenizers or milling systems. Usually, there are two steps involved in creating NSs using microemulsion templates:

1. The process of creating a microemulsion involves surfactants that help dissolve the medication in an aqueous or oil phase.
2. The process of precipitation or solvent removal involves exposing the microemulsion to circumstances that result in the creation of drug NPs, and then stabilizing it to stop agglomeration [41].

#### 4.3.4. Microfluidics

Modern technology known as microfluidics makes it possible to precisely control tiny fluid volumes, which makes it a very effective way to create NSs. Based on the regulated mixing of fluids in microchannels, this method produces homogenous NPs with narrow size distributions. Microfluidics provides more control over particle size and shape than traditional high-energy methods like HPH or milling, guaranteeing increased scalability and repeatability in the formulation of NSs. The fundamental idea behind microfluidics is the application of micro-scale flow channels, which are places where two or more liquid streams converge under specified flow circumstances. The drug precipitates in nanocrystalline form when an anti-solvent and drug solution are added to the microfluidic device and mixed quickly. Stabilizers and surfactants help to stabilize these NPs instantly, preventing aggregation and guaranteeing colloidal stability. Through careful adjustment of temperature, flow rates, and reagent concentrations, scientists can produce reliable particle size distributions that range from a few nanometers to sub-micron levels. Additionally, improved bioavailability and dissolution rates are provided by microfluidics-based NSs, which are essential for medications that are poorly soluble in water. It is appropriate for oral, injectable, pulmonary, and ophthalmic drug delivery systems because the creation of very homogenous NPs guarantees improved absorption and regulates drug release. Additionally, by using fewer organic solvents, this approach improves regulatory compliance in pharmaceutical applications and is consistent with green chemistry principles [41].

#### 4.3.5. Electrospinning

With its great potential for creating NSs, electrospinning is a creative and adaptable method for creating nanofibers from polymer solutions. By drawing ultrafine polymer fibers from a liquid droplet using a high-voltage electric field, this technique creates a continuous network of nanofibers. Electrospinning can efficiently integrate APIs into polymeric nanofibers when paired with NS technology, improving the solubility, stability, and controlled drug release characteristics of the resulting fibers. A strong electric field is applied to a polymeric solution or melt that

has been loaded with a drug NS to start the procedure. The supplied voltage causes charge repulsion as the solution is extruded via a fine nozzle, stretching the polymer into thin fibers. As the solvent evaporates, these threads harden, trapping drug particles at the nanoscale inside the matrix. Electrospinning is a useful technique for medications that are poorly soluble in water because the resultant nanofibers have a high surface area-to-volume ratio, which enhances drug solubility and bioavailability. Controlling the medication release profile is one of the main advantages of electrospinning when creating NSs. Researchers can create controlled-release, sustained, or immediate drug delivery systems by choosing appropriate polymeric carriers. Electrospun nanofibers have also been used for purposes other than traditional medication delivery. They are being utilized more and more in bioactive coatings, scaffolds for tissue engineering, and wound dressings, where they improve therapeutic efficacy by facilitating localized drug delivery. Electrospinning has many advantages, but there are disadvantages as well. The physicochemical characteristics of the finished formulation are greatly influenced by the kind of polymer, solvent systems, and processing parameters chosen [42].

#### 4.3.6. Hot Melt Extrusion

By combining poorly water-soluble medications into a polymeric matrix at high temperatures, Hot Melt Extrusion (HME), a commonly used process in pharmaceutical manufacture, makes it easier to create NSs. Through dispersion in a suitable liquid medium, the solid dispersion system produced by this technique can then be transformed into NSs. HME has attracted attention due to its capacity to enhance drug solubility, stability, and bioavailability, making it particularly ideal for the formulation of BCS Class II and IV medicines that demonstrate low water solubility. A drug-polymer mixture is continuously fed into an extruder as part of the HME process, where it is mechanically sheared, heated, and compressed under controlled conditions. A uniform solid dispersion is created when the medication molecules dissolve or disperse inside the polymeric carrier. Amorphous or crystalline drug-polymer matrices are created when the material cools and solidifies after leaving the extruder. The hardened matrix is then broken down into nanosized drug particles using milling, sonication, or dispersion procedures to create NSs from the resultant extrudates. The fact that HME is solvent-free, removing the requirement for organic solvents that could be hazardous or environmentally harmful, is one of its main advantages. Large-scale pharmaceutical manufacture is a great fit for the technique because it is scalable and continuous. The heat sensitivity of some APIs is one of the difficulties that HME poses despite its many advantages. For poorly soluble medications, Hot Melt Extrusion provides improved solubility, stability, and bioavailability, making it an effective and scalable method for producing NSs [43].

## 5. Evaluation of NSs Characteristics

As these factors significantly affect the stability, safety, and efficacy of the formulation, zeta potential, size distribution, and particle size evaluation are essential components of NS characterization [28].

### 5.1. Particle Size and Its Distribution

The distribution of particle sizes greatly influences the physicochemical characteristics of formulations, such as saturation solubility, dissolution and physical stability. Many techniques are used to evaluate particle size distribution, including Dynamic Light Scattering (DLS), Laser Diffraction (LD), Photon Correlation Spectroscopy (PCS), and the Coulter Counter Multi-sizer. Particle sizes measured by PCS range from 3 nm to 3  $\mu\text{m}$ , while those measured by LD range from 0.05  $\mu\text{m}$  to 80  $\mu\text{m}$ . In contrast to LD, which provides a relative size distribution, Coulter Counter Multi-sizer produces an absolute particle count. The particle size and the polydispersity index (PI) are important factors in NSs. The particle size and PI of NSs, which indicate their physical stability, are one of the most crucial variables in defining their characteristics. A low PI is necessary to guarantee stability over the long run. A narrow size distribution is indicated by a PI between 0.1 and 0.25, and a broad distribution is suggested by values greater than 0.5. Because capillaries range in diameter from 5 to 6  $\mu\text{m}$ , larger particles have the potential to cause embolism and obstruction; hence particle sizes for intravenous delivery should not be greater than 5  $\mu\text{m}$  [44].

### 5.2. Dynamic Light Scattering (DLS) and Scanning Electron Microscopy (SEM)

The size distribution of tiny particles in suspension or polymers in solution is commonly ascertained using the physical method known as DLS. A common method for analysing temporal fluctuations in DLS observations is PCS, sometimes referred to as quasi-elastic light scattering or photon self-correlation. Condensed polymer solutions and other fluids are also treated with DLS. This technology detects light that is reflected from a flow stream that carries a sample inside a cylindrical capillary. The apparatus is powered by a laser beam that is directed in the opposite direction. Both the laser beam and detectors are co-planar, and the sample stream and laser beam are coaxially aligned. Measurement of scattering at smaller angles is greatly improved by the setup's circular design, which offers a scattering angle range of 0° to 180°. DLS simultaneously measures scattering at distinct angles using multiple detectors, which forms the basis for commercial light-scattering systems and the concept of simultaneous DLS detection [45,46]. The high-resolution imaging method known as SEM is frequently used to examine the microstructure, shape, and surface morphology of NSs. In

order to produce a variety of signals that offer comprehensive information on the sample's topography and composition, it focuses an electron beam onto the surface. Because SEM has a resolution of up to 1 nanometer, it can precisely examine NPs and how they aggregate. SEM's analytical capabilities are improved by a number of cutting-edge methods, including Auger electron spectroscopy, X-ray mapping, backscattered electron imaging (BEI), and secondary electron imaging (SEI). Additionally, the method offers a broader field of view, which makes it very helpful for studying the structures of three-dimensional NPs. SEM is essential for comprehending and refining NS formulations for better medication delivery because it evaluates particle size, shape uniformity, and surface changes [47].

### 5.3. Particle Charge (Zeta Potential) and Viscosity

In order to ascertain how dispersed NPs in NSs interact with biological environments and behave electrostatically with bioactive substances, zeta potential is a critical indicator of the type and strength of surface charge on these particles. This potential difference, which is expressed in volts (V) or millivolts (mV), lies between the surface of solid particles submerged in a conductive liquid and the bulk of that liquid. The colloidal or storage stability of dispersed NPs can be predicted using zeta potential, which can also reveal information about the type of substance coated or encapsulated on the particle surface. It also indicates the stability of suspension: a zeta potential of about 30 mV is required if the stability is due to electrostatic repulsion alone, while a zeta potential of  $\pm 20$  mV is sufficient for stability arising from a mix of steric and electrostatic stabilization [12,48]. Viscosity is a crucial physical characteristic of NSs that has an immediate effect on their stability, bioavailability, and production process. It affects the homogeneity of drug dispersion, the ease of administration, and the drug release profile, making it especially significant in formulations meant for parenteral, oral, or topical distribution. The viscosity of lipid-based and non-lipid-based NSs is frequently measured using a Brookfield-type rotating viscometer under various temperature and shear rate settings. This instrument is necessary to get precise viscosity measurements, which are necessary to guarantee the NS's injectability and flowability. In order to accurately determine viscosity, samples must be kept in a thermal bath that simulates physiological circumstances at a constant temperature of about 37°C. It should be noted that non-lipid stabilizers, such as polymers and surfactants, can also be utilized in NSs; however, their effects on viscosity may differ from those of lipid-based systems. For medication delivery applications, stable formulations with desired properties are ensured by accurate viscosity testing and adjustment [13,17].

#### 5.4. Crystalline State, Particle Morphology and X-Ray Diffraction (XRD)

The physicochemical stability, solubility, and bioavailability of NSs are significantly influenced by their crystalline state and particle shape. Because of the extreme mechanical stress and shear forces used during the process, HPH, a popular method for creating NSs can cause polymorphic changes in drug particles. These pressures have the power to change the crystal lattice, decrease crystallinity, or encourage the development of amorphous structures, all of which can speed up drug breakdown but also raise stability issues [7]. Techniques like differential scanning calorimetry (DSC), differential thermal analysis (DTA), and XRD are used to examine these structural alterations. While DSC and DTA offer information on thermal behavior, phase transitions, and polymorphic changes, XRD aids in determining if a material is crystalline or amorphous. Optimizing NS formulations to guarantee desirable drug release profiles and long-term stability requires an understanding of how processing factors affect crystal structure and shape [8,19,29]. Materials whose structural characteristics are between 1 and 100 nm in at least one dimension can be studied with the aid of XRD. The intensity data generated from XRD offers precise and quantitative insights into atomic arrangements at interfaces. The microstructures of nanomaterials provide them unique mechanical, optical, and electrical capabilities because they fit well with the critical length scales of many physical processes. Phase composition, crystallite size, lattice strain, and crystallographic orientation are just a few of the many details regarding nanomaterials that may be found using XRD. Analyzing native maize starches and starch hydrolysates using XRD with an X-diffractometer running at 40 kV and 30 mA of current. Different crystalline structural patterns A, B, and C that are typical of native starches were visible in the ensuing X-ray diffractograms. Diffraction peaks at Bragg angles ( $2\theta$ ) of  $15^\circ$ ,  $17^\circ$ ,  $18^\circ$ , and  $23^\circ$  in waxy and regular maize starches specifically indicated the A-type crystalline structure. B-type crystals were found at  $5.68^\circ$ ,  $15^\circ$ ,  $20^\circ$ ,  $22^\circ$ , and  $24^\circ$  for high-amylose maize and potato starches, but a noticeable peak emerged at  $17^\circ$  [49].

#### 5.5. Solubility and Dissolution Rate

By decreasing particle size to the nanoscale and raising the surface area-to-volume ratio, NSs dramatically increase the solubility and dissolution rate of poorly water-soluble medications. The Noyes-Whitney equation states that a smaller particle size promotes improved medication absorption by increasing the dissolving pressure and decreasing the thickness of the diffusion layer, which results in a quicker dissolution rate. Additionally, by changing the drug's thermodynamic equilibrium in solution, NSs can improve saturation solubility [50]. In order to

assess these characteristics, solubility and dissolution tests are performed on NSs in a range of physiological media, such as buffer solutions, simulated intestinal fluid, and simulated stomach fluid. These investigations aid in the prediction of *In Vitro* drug performance and establish a relationship between dissolution behavior and increased bioavailability. For poorly soluble Biopharmaceutics Classification System (BCS) Class II and IV medications, NSs are a better formulation approach due to their increased dissolution rate, which not only speeds up drug onset but also guarantees more consistent absorption [51].

#### 5.6. Density

A crucial factor that might affect the formulation's processing properties and physical stability is the density of NSs, sometimes referred to as specific gravity. Air pockets or gas entrapment may be present in a NS if its density decreases, which could compromise the stability and functionality of the formulation. The homogeneity and drug release profile of the suspension are compromised by trapped air, which might eventually cause problems like flocculation or sedimentation. Precision hydrometers or pycnometers that can detect the specific gravity at regulated temperatures are crucial for precisely determining the density of NSs. The formulation needs to be well mixed to ensure that no air is trapped during the procedure in order to produce accurate results. Density monitoring during formulation creation contributes to the efficacy and shelf-life of the NS by ensuring that the dispersion stability is maintained. Frequent density assessments are essential for anticipating the formulation's long-term behavior and improving production conditions [4,44].

#### 5.7. pH Value

One crucial factor that affects the stability, solubility, and release profile of the medication in the formulation is the pH level of a NS. Following sedimentation, it is essential to allow the formulation to reach equilibrium before measuring the pH to make sure the system is in a stable state. Temperature variations can impact the drug's ionization state and stabilizer activity, and thus it's critical to do pH tests at the right temperature. Furthermore, cautious handling is required to prevent pH drift, which may happen as a result of interactions between the suspended particles and the measuring electrode. Additionally, it is best to avoid adding electrolytes to the Formulation's External Phase since this could change the zeta potential and perhaps destabilize the NS by changing the pH or producing aggregation. In formulations containing pH-sensitive medications, pH monitoring is especially crucial since even small changes in pH can have a big impact on the solubility, stability, and therapeutic efficacy of the medicine [33].

## 6. Recent Advances and Innovations in NSs

Recent advances in NS formulation have focused on enhancing stability, bioavailability, and targeted delivery. Some innovative strategies include:

### 6.1. Surface Modification

When it comes to stabilizing NSs and improving the solubility and bioavailability of poorly soluble medications, surface modification is essential. In order to keep the suspension stable over time and avoid particle agglomeration, surfactants and polymers are essential. Polyvinyl alcohol (PVA) and polysorbates, two of the most widely used stabilizers, have drawn a lot of interest because of how well they regulate particle size distribution and improve dispersion stability. In order to keep the drug particles from clumping together or creating big crystals, these polymers construct a protective barrier around them. By enhancing the drug's interaction with its surroundings, surface modification also aids in managing the drug release profile and promotes more consistent and long-lasting drug release. By boosting the medication particles' surface area, polymers like PVA also help them become more soluble, which is important for oral bioavailability. The creation of more stable and efficient NSs that are also tailored for targeted drug delivery depends on advancements in surface modification. Example: The stabilization of nanosuspensions using polyvinyl alcohol (PVA) is a typical instance of surface modification. PVA is a polymer that creates a protective coating by adhering to the surface of medication particles. This layer keeps the medicine in a stable, nanosized form by preventing the particles from clumping together (agglomeration). Furthermore, PVA improves the wettability of medications that are poorly soluble in water, which increases their solubility and, consequently, their bioavailability [52].

### 6.2. Self-Emulsifying Drug Delivery

Drug delivery systems that self-emulsify (SEDDS) have become a novel way to improve the solubility and absorption of medications that are not particularly soluble in water. A dual strategy that tackles the issues of solubility and bioavailability has been developed recently by fusing self-emulsifying systems with NSs. The lipid-based excipients and surfactants used in SEDDS combine to generate fine emulsions on their own when they come into contact with aqueous environments. This emulsion makes hydrophobic medications more soluble, which improves absorption throughout the digestive system. Drug dissolving rates are further enhanced when this system is combined with NSs, which have a large surface area and small particle size. Faster absorption and increased therapeutic efficacy are among the better pharmacokinetics

that come from this combination. In addition to increasing the bioavailability of poorly soluble medications, the dual strategy maximizes drug delivery by guaranteeing better regulated and prolonged release patterns. There is great potential for this novel combination to enhance the clinical efficacy of numerous medicinal substances. An example of this strategy in action is the use of self-emulsifying drug delivery systems (SEDDS) in conjunction with nanosuspensions of medications that are not highly soluble in water, such as the antiviral agent ritonavir. Ritonavir is much more soluble and absorbable when prepared as a nanosuspension and combined with SEDDS. In order to improve drug release and absorption, the self-emulsifying technology makes sure that the ritonavir nanosuspension creates a fine emulsion when it comes into touch with the gastrointestinal fluids [53].

### 6.3. Lyophilization Techniques

The preservation of NSs using lyophilization, also known as freeze-drying, has become essential for increasing their stability and prolonging their shelf life. By first freezing the NS and then lowering the pressure to permit solvent sublimation, the liquid is essentially reduced to a dry powder without undergoing a liquid phase. Because it preserves the integrity of the NPs and inhibits aggregation, a frequent problem with aqueous formulations, this method is especially advantageous for NSs. In order to maintain the particle size and distribution of NSs, recent developments have concentrated on optimizing lyophilization parameters, such as freezing rates, sublimation settings, and the application of cryoprotectants. More stable formulations with improved handling and storage stability are the outcome of these advancements. Additionally, lyophilized NSs are convenient and less expensive to transport because they are simply reconstituted for usage. Example: An example of lyophilization in nanosuspension applications is the preparation of indomethacin nanosuspensions. Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), suffers from poor solubility, and nanosuspension formulations are used to enhance its bioavailability. To further improve the stability of the formulation, the nanosuspension of indomethacin is subjected to lyophilization [54].

### 6.4. Use of Nanotechnology in Combination Therapies

One possible tactic to increase the efficacy of medication treatments while lowering adverse effects is the combination of NSs with other therapeutic techniques. By integrating NSs with immunotherapy, gene therapy, or chemotherapy, more specialized drug delivery methods can be developed. Enhancing therapeutic results, NSs allow for precise control over drug release and the targeted distribution of APIs to particular tissues.

### 6.5. Synergistic Drug Delivery

One innovative method in the field of nanomedicine that aims to improve the therapeutic advantages of medications is the idea of synergistic drug delivery utilizing NSs. Through the co-formulation of NSs with other NPs, like liposomes or micelles, scientists have created multipurpose systems that enable the targeted and simultaneous delivery of several medications. When working with medications that have distinct solubility profiles or modes of action, this tactic is especially helpful. For instance, mixing hydrophilic and hydrophobic medications in the same NS improves each compound's stability and bioavailability, which in turn improves its therapeutic effects. In addition to improving overall efficacy by facilitating controlled distribution and increasing drug release, these synergistic systems also enable lower dosage and frequency of administration, which improve patient compliance. The use of doxorubicin, an anticancer medication, in conjunction with paclitaxel, another chemotherapeutic agent, to treat cancer, is an illustration of synergistic drug delivery in nanosuspensions. Despite their effectiveness, both medications have serious negative effects when taken by themselves. By combining both medications into a nanosuspension, the risk of damage to healthy tissues is decreased and the medications can be administered more precisely to the target region [55].

### 6.6. Targeted Delivery Systems

In order to improve the precision of drug administration, recent developments in NSs have concentrated on functionalizing these particles with particular targeting ligands, such as aptamers, peptides, or antibodies. By affixing these ligands to the NS's surface, tailored therapy can be accomplished by guiding the NPs to specific tissues or cells, including malignant cells. By ensuring that the medicine operates exclusively on the intended site, this strategy minimizes systemic toxicity and drastically eliminates off-target effects, which are frequent with standard drug delivery methods. The direct delivery of chemotherapeutic drugs or other therapeutic compounds to the tumor site is made possible by the ability of antibody-functionalized NSs to bind to particular antigens that are overexpressed on the surface of cancer cells. This enhances patient safety by allowing for lower dosages while also improving therapeutic outcomes. Additionally, pharmacokinetics can be improved by targeting particular cells or tissues, which increases absorption and decreases adverse effects. For instance, the use of Herceptin-coated nanosuspensions to treat HER2-positive breast cancer is a well-known instance of targeted drug delivery utilizing nanosuspensions. A monoclonal antibody called Herceptin (Trastuzumab) selectively binds to the HER2 receptor, which is overexpressed in certain breast cancer cells [56].

## 7. Perspectives and Challenges for the Future

NS has a promising future since it can assist researchers in product development in overcoming challenges associated with drug formulation and delivery, particularly when working with drugs that are challenging to handle. The crucial aspects of the stability problem related to NS remain unresolved, despite the numerous published studies in the field. The critical elements that influence the electrostatic and steric stabilizers' capacity to stabilize, as well as the relationship between these stabilizers and the characteristics of APIs, the largest particle size achievable, and the ensuing physical stability, need to be further investigated. It is anticipated that high concentration monoclonal antibodies (mAB) and biosimilar goods given subcutaneously will have better safety and biopharmaceutical qualities, thanks to modification tools such as conjugates of antibody-drug and small bodies as well as developments in biotechnology. Future developments in enabling technologies such as NS will provide technological solutions for many of the formulation issues currently faced by protein- and peptide-based drugs using carbohydrate stabilizers like trehalose [5]. Numerous research groups have used NS technology to investigate a range of formulations thus far. Particularly for oral delivery, very few of these formulations have been successfully brought to market. The fundamental causes of this predicament go beyond technical difficulties; replacing a well-known product with a NS is challenging due to high market entry costs. Additionally, when introducing a novel chemical, established and tried-and-true administration techniques are frequently chosen. For active compounds with low solubility, NS technology offers a flexible framework for creating safe and efficient formulations [11]. The use of surface-modified NSs to create customized formulations has become more and more common in recent years. Using drug nanocrystals to provide targeted drug delivery to specific sick tissues, such as infected macrophages, and tumors, may improve pharmacological efficacy. Nowadays, scientists are looking into using NSs to transport NPs to specific cells and enhance their uptake in the cellular milieu. Therefore, issues with the currently used dose formulations may be resolved by nanocrystals [32,57].

## 8. Applications of NS in Drug Delivery

### 8.1. Improving Bioavailability

Examples of Drugs with Poor Water Solubility:

- Curcumin: Its solubility and bioavailability have been greatly increased using NSs, enabling more potent therapeutic effects.

- Rifampicin: Formulating rifampicin in NS form has been shown to enhance its absorption, improving treatment outcomes in tuberculosis [32].

#### Impact on Pharmacokinetics and Pharmacodynamics:

- NSs often lead to faster absorption and higher peak plasma concentrations, thus enhancing the overall therapeutic effect of poorly soluble drugs.
- Studies have indicated that NSs can reduce the time to reach maximum concentration (T<sub>max</sub>), improving the onset of action [58].

## 8.2. Targeted Drug Delivery

#### NSs for Cancer Therapy:

- Chemotherapeutic drugs can now be delivered precisely with NSs, increasing their effectiveness while reducing adverse effects [2].
- CNS Delivery:
- In order to deliver medications straight to the central nervous system (CNS), NSs can more efficiently traverse the blood-brain barrier.

#### Mechanisms of Targeting:

- EPR Effect: The accumulation of NSs in tumor tissues is made possible by the increased permeability as well as retention (EPR) effect.
- Ligand-Receptor Interactions: Functionalizing NSs with ligands can facilitate targeted delivery by binding to specific receptors on diseased cells [59].

## 8.3. Pulmonary and Ocular Delivery

#### Advantages in Non-Oral Routes of Administration:

- NSs can improve drug deposition in the lungs or eyes, enhancing local therapeutic effects while reducing systemic side effects.
- Improved absorption characteristics and sustained release profiles make them suitable for chronic conditions [2].
- Challenges and Recent Developments:
- Challenges: Stability and aggregation of NSs can hinder their effectiveness. Other major challenges include maintaining consistent quality and scaling up production.
- Recent Developments: New developments in stabilizing agents and production methods, like milling and HPH, have shown promise in resolving these issues [60].

## 9. Conclusions

In conclusion, an important technique for improving the solubility and bioavailability of medications that are poorly soluble is NSs. Effective drug delivery systems are made possible by their special qualities, which also solve

important problems with pharmaceutical formulations. This review has highlighted the diverse preparation methods, characterization techniques, and broad applications of NSs, underscoring their potential in both pharmaceutical and non-pharmaceutical sectors. Despite their advantages, challenges, future research should focus on innovative formulation strategies, improved stabilization techniques, and a deeper understanding of the long-term safety and efficacy of NSs. All things considered, the development of NS technology has enormous potential for the future of medication delivery, opening the door to more potent treatments and better patient outcomes. As research continues to evolve, interdisciplinary collaboration will be vital in unlocking the full potential of NSs in various applications. While NSs present a transformative approach to drug delivery, ongoing efforts in research and development will be essential to fully realize their potential in improving patient outcomes and addressing unmet medical needs.

## Abbreviations

NS- Nanosuspension  
 NSs- Nanosuspensions  
 BCS- Biopharmaceutical Classification System  
 API- Active Pharmaceutical Ingredients  
 pH- Potential of Hydrogen  
 SC- Stratum Corneum  
 NPs- Nanoparticles  
 BU- Bottom-Up  
 TD- Top-Down  
 Zn- Zinc  
 HPH- High-Pressure Homogenization  
 PEG- Polyethylene Glycol  
 HPMC- Hydroxypropyl Methylcellulose  
 RESS- Rapid Expansion of Supercritical Solution  
 SAS- Supercritical Anti-Solvent  
 SF- Supercritical Fluid  
 PCA- Precipitation using Compressed Anti-Solvent  
 DLS- Dynamic Light Scattering  
 LD- Laser Diffraction  
 PCS- Photon Correlation Spectroscopy  
 PI- Polydispersity Index  
 SEM- Scanning Electron Microscopy  
 XRD- X-Ray Diffraction  
 PVA- Polyvinyl Alcohol  
 mAB- Monoclonal Antibody  
 CNS- Central Nervous System  
 EPR- Increased Permeability as Well as Retention

## Ethics Statement

The authors confirm that this review work is their original work, and that references are given in this article.

## Competing Interests

The authors declare no competing interests.

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