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Nanosuspensions for Enhancing Drug Solubility: Formulation Strategies and Stability Challenges

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Abstract: The poor solubility of several active pharmaceutical ingredients is a major challenge that compromises bioavailability and pharmacological responses. Nanosuspensions have emerged as an effective technology for enhancing drug solubility and the dissolution rate of the drug. This review critically explores the formulation strategies, including bottom-up, top-down, and combinative techniques, and solidification methods such as spray drying and lyophilization. A detailed evaluation of key stability challenges—aggregation, Ostwald ripening, and crystal growth—is provided, along with mechanistic insights into electrostatic, steric, and electrosteric stabilization. The manuscript emphasizes how stabilizer type and concentration significantly influence the physical stability and performance of nanosuspensions. Characterization parameters such as particle size, zeta potential, saturation solubility, and crystallinity transitions are discussed to ensure optimal formulation quality. Additionally, recent advancements in route-specific nanosuspension applications and selected clinical trial data underscore the evolving relevance of this approach. The review concludes by outlining future directions for enhancing long-term stability and expanding therapeutic applications.

Keywords: Solubility enhancement, nanosuspension, stabilization, crystal growth, bioavailability, formulation strategies

INTRODUCTION

The solubility of the medication is a critical factor in determining how quickly it dissolves and absorbs into the body (Das et al., 2022). According to the USFDA biopharmaceutics classification system-based biowaivers, approximately 54% of new drug entities and 33% of marketed drugs belong to BCS Class 2, characterized by poor water solubility (*The Innovation Makers: First-in-Class New Drug Approvals - DCAT Value Chain Insights*, 2022). These drugs often exhibit limited oral bioavailability and require higher doses. Factors influencing drug solubility include particle size, shape, solvent type, pH, pKa, log P value, and chemical structure. Various enhancement strategies aim to improve solubility and, in turn, the therapeutic efficacy of poorly soluble drugs (Khan et al., 2022).

In recent years, nanosuspensions have emerged as a versatile and effective nanotechnological platform to overcome solubility-related challenges. Numerous studies have explored different preparation techniques, stabilization mechanisms, and solidification approaches to optimize nanosuspension performance. Despite this, a comprehensive understanding of the intricate balance between formulation techniques, physical stability, and scalability remains underdeveloped (Jadhav et al., 2023a).

This review uniquely consolidates existing knowledge on nanosuspension technologies while placing a particular prominence on the

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physicochemical stability challenges that limit their practical application. Unlike existing literature, which often focuses either on preparation methods or clinical applications, this work systematically links formulation strategies with the underlying stabilization mechanisms and long-term performance. The novelty of this review lies in its combined approach—discussing not only how nanosuspensions are prepared and solidified but also critically examining the causes of instability such as aggregation, Ostwald ripening, and crystal growth. This complete viewpoint aims to provide researchers and formulators with practical insights for advancing nanosuspension-based drug delivery systems (Tian et al., 2022).

IMPORTANCE OF SOLUBILITY ENHANCEMENT

Low solubility of drugs significantly impacts bioavailability and reduces therapeutic effectiveness. When drugs are administered orally, high solubility is essential; otherwise, it becomes the rate-limiting step for absorption, limiting the drug's efficacy (Coltescu et al., 2020). Therefore, poorly water-soluble drugs exhibit a slow absorption rate, leading to reduced bioavailability and ultimately diminishing the pharmacological response. Solubility and dissolution rate are critical parameters that greatly influence the bioavailability and absorption of a drug. When these factors are insufficient, they compromise the attainment of the desired drug concentration in systemic circulation, reducing therapeutic effectiveness. Due to the lower solubility and bioavailability of hydrophobic drugs, they typically require high dosages and high dosing schedules to affect therapeutic plasma concentrations following administration (Rahman & Haider, 2023).

SUSPENSION

A suspension is a heterogeneous, biphasic system in which a solid drug is dispersed within a liquid (aqueous or non-aqueous) dosage form. In this system, the liquid vehicle acts as the external or continuous phase, also known as the dispersion medium, while the solid drug, which is insoluble in the liquid, forms the internal phase. The liquid phase may be aqueous or oil-based, depending on the formulation requirements. Additionally, a suspension is a type of coarse dispersion, where hydrophobic drugs are uniformly distributed within the dispersion medium (Arora et al., 2022).

NANOSUSPENSION

Nanosuspension is a nano-sized carrier-free dispersion of solid drug particles in an aqueous phase or sub-micron-sized colloidal dispersion within the range of 100–1000 nm. It is stabilized using a suitable polymer, surfactant or both (Ibrahim et al., 2019). Nanosuspensions are prone to agglomeration, Ostwald ripening, and crystal growth due to their increased surface area and high surface free energy, which result in thermodynamic instability. However, the desired quality of nanosuspensions can be achieved by carefully selecting and optimizing the type and concentration of stabilizers (Baumgartner et al., 2016). Nanosuspension can be administered by different routes such as dermal, pulmonary, nasal, oral, parenteral, transdermal, ophthalmic, etc. Currently, various commercial oral nanosuspension products are available, such as Tricor® (fenofibrate) by Abbott, Zanaflex® (tizanidine HCl capsules) of Acorda, and Emend® (aprepitant capsule) by Merck (Pınar et al., 2023a).

Potential Benefits of Nanosuspension

Nanosuspensions enhance drug dissolution, absorption, bioavailability, and onset of action by reducing particle size. This carrier-free nanonization approach improves the solubility of drugs, making them more effective in the gastrointestinal (GI) tract. Additionally, nanosuspensions can be lyophilized to solidify the formulation, reducing physical instability and improving suitability for oral administration. They can adhere to GI mucosa depending on the surface charge and the physicochemical properties of the active pharmaceutical ingredient (API) and surfactant used. By reducing the required dose, nanosuspensions make formulations more economical while minimizing the side effects of the API (Fathi-Karkan et al., 2024; Rani et al., 2023a).

Stability Problems with Nanosuspension

Suspensions, as biphasic liquid formulations, are inherently unstable. Nanosuspensions, in particular, are prone to various stability challenges, including physical, chemical, and, to some extent, biological instability. For intravenous administration, it is crucial to evaluate plasma compatibility. Furthermore, chemical stability concerns, such as susceptibility to hydrolysis, oxidation, or reduction, must be carefully

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assessed to ensure the formulation's effectiveness and safety (Guan et al., 2022b).

Aggregation is a significant factor contributing to the instability of nanosuspension formulations, primarily caused by the Brownian motion of drug particles. As these particles move, they may stick together and coalesce due to attractive forces or strong interactions such as van der Waals forces, covalent bonds, or ionic interactions. This phenomenon is especially common in liquid nanosuspensions during storage, leading to the formation of tightly bound, strong, and often irreversible aggregates (Kovalchuk et al., 2019). Aggregation results in an increase in particle size and available surface area, which diminishes solubility and dissolution rates, ultimately delaying the bioavailability of the formulation. Additionally, insufficient concentrations of stabilizers in the nanosuspension can exacerbate aggregation, further compromising the formulation's stability and performance (Li et al., 2018). Agglomeration is another form of instability in nanosuspensions, characterized by the loose association of particles due to weak forces such as van der Waals forces, electrostatic interactions, capillary forces, or other physical forces. This process results in the rapid settling of particles, leading to a reduction in surface area and an increase in particle size due to the formation of agglomerates. The large surface area of nanoparticles contributes to high surface free energy, which drives thermodynamic instability. Agglomeration occurs as a way to reduce the system's free energy by decreasing the surface area. However, this process compromises the physicochemical stability of the nanosuspension, affecting its performance and effectiveness (Okada et al., 2021).

Aggregation and agglomeration in nanosuspensions can lead to rapid sedimentation of particles, a phenomenon known as sedimentation. The transition in size ranges, whether from molecular dispersions to colloids or from colloids to coarse dispersions, occurs gradually and without clear boundaries. Sedimentation becomes inevitable when the gravitational force acting on the particles exceeds the buoyancy force within the colloidal system. Particles of varying sizes, densities, and velocities tend to aggregate into floccules, which significantly accelerate particle settling (Shete et al., 2016). Sedimentation is one of the reasons for the instability of particles present in nanosuspension. In flocculated and unflocculated nanosuspension, sedimentation is directly proportional to particle size (nm), particle size distribution, charges present on particles, density of nanoparticles and viscosity of dispersion phase (Lokare et al., 2022).

Ostwald ripening is a process where smaller particles in a mixture dissolve, and their material moves through the medium to larger particles, causing the larger ones to grow due to accumulation on them. This process depends on two main factors: the diffusion of solute molecules through the medium and the attachment or detachment of these molecules at the particle surface (crystal growth or dissolution). If the solute attaches or detaches quickly at the surface, the movement of solute through the medium (diffusion) becomes the limiting factor, making the process diffusion-controlled. On the other hand, if solute molecules move quickly but take time to attach or detach from the surface, the rate is determined by the mechanisms of crystal growth, also known as interface-controlled growth (Prajapati et al., 2025). These mechanisms can occur in three ways: continuous growth (steady addition of molecules to the surface), surface nucleation (sporadic layer formation), or spiral growth (attachment along defects or steps) (Dong et al., 2022). The equation $\mathbf{dn - d_0^n = k \times t}$ explains how particle size changes over time during this process, where the difference between the current size and the initial size depends on the specific growth mechanism, the rate constant (k), and the time elapsed (t) (Hiemenz & Rajagopalan, 2016).

Agglomeration and aggregation of small nanoparticles present in nanosuspension cause the formation of larger particles, which compromises the physical stability of nanosuspension, which is also known as crystal growth (Okada et al., 2021). Amorphous particles are less stable than crystalline particles because they have higher energy and dissolve more readily. Their increased solubility leads to the formation of a supersaturated solution, where the concentration of the dissolved substance exceeds the solubility limit of the crystalline form. This triggers crystal formation, with the rate depending on the level of supersaturation. To slow down crystal formation, additives can be introduced to reduce the solubility of amorphous particles. However, for oral medications, minimizing the use of additives is essential to maintain high bioavailability (the body's ability to absorb the drug). Typically, the solubility of amorphous particles is about ten times greater than that of crystalline particles. Once crystals begin to form, they grow rapidly, drawing material from the amorphous particles. Additionally, crystalline particles may accidentally form during the preparation of amorphous particles, potentially compromising the stability and effectiveness of the final product (Hang et al., 2022).

CRYSTAL GROWTH

The milling process alters Gibbs free energy, leading to a thermodynamically unstable nanosuspension prone to crystal growth due to Ostwald ripening, which in turn negatively impacts dissolution rates and solubility. The selection of stabilizer and concentration of stabilizer highly affect the crystal growth (Patel, 2022). The amorphous drug dissolves in the solvent, creating an unstable supersaturated state relative to crystalline solubility, which triggers crystal nucleation. Controlling solubility can help reduce the nucleation rate, ensuring better stability (Guan et al., 2022a; Meng et al., 2021). Crystal growth occurs when dissolved drug molecules from a supersaturated solution precipitate and attach to existing crystals, leading to an increase in crystal size. This process is influenced by solubility differences between amorphous and crystalline forms, where amorphous nanoparticles dissolve faster, creating a supersaturated environment. If crystalline particles are present, they act as seeds, promoting further crystal growth while amorphous particles dissolve, a phenomenon similar to Ostwald ripening (Sutradhar et al., 2013; Zhang et al., 2024).

COMPONENTS OF NANOSUSPENSION

Nanosuspensions commonly contain excipients such as stabilizers, polymers, surfactants, osmotic agents, organic solvents, cryoprotectants, buffers, complexing agents, organoleptic agents, and preservatives. These excipients play crucial roles in ensuring stability, improving solubility, preventing aggregation, and enhancing the overall performance and shelf life of the formulation (Jacob et al., 2025).

Stabilizers

Stabilizers are crucial for preventing particle agglomeration or aggregation formation, which further hinders sedimentation and helps in dispersing solid particles in nanosuspensions and enhances the physical appearance of the formulation. The primary stabilization techniques are electrostatic and steric stabilization. Electrostatic stabilization occurs when ionic surfactants, such as soya lecithin or sodium lauryl sulfate (SLS), adsorb onto the particle surface. This adsorption imparts a surface charge, generating electrostatic repulsion that prevents the aggregation of nanosized particles (Soroushnia et al., 2022). Steric stabilization or entropic steric interactions involve the adsorption or attachment of non-ionic amphipathic polymers to the particle surface, preventing aggregation. These stabilizing moieties are mutually repulsive, maintaining adequate particle separation. To be effective, the polymers must be adsorbed, partially absorbed, or firmly attached to the surface, ensuring stability against Brownian collisions. Complete surface coverage is crucial to prevent particle escape. Polymers with a specific affinity for the particle surface are typically used, adsorbing in a manner that allows their chain segments to extend into the dispersion medium. When particles approach each other, the adsorbed polymer layers interact, leading to interpenetration of the hydrophilic chains (Pryazhnikov et al., 2025).

Flocculation may occur with heating, cooling, or both, but it is usually reversible. The most commonly used steric stabilizers include povidone (PVP), hydroxypropylmethylcellulose (HPMC), and hydroxypropyl cellulose (HPC). This technique is crucial for improving the stability of nanosuspensions by preventing particle aggregation through the formation of a protective layer surrounding the particles (Patel et al., 2016). Sterically stabilized dispersions are generally sensitive to temperature changes as compared to electrostatic stabilization. Hence, combining electrostatic and steric stabilizers is recommended for better stabilization of nanosuspensions, known as electrosteric stabilization. A neutral polymer enhances ionic surfactant coverage by reducing self-repulsion between charged surfactant molecules, enabling closer packing (Smith et al., 2021). Nanosuspensions consist of solid drug particles enveloped by a stabilizer layer, making their preparation relatively simple. However, determining the optimal stabilizer concentration is crucial for maintaining product stability (Elmowafy et al., 2021a). The selection of a stabilizer is especially critical for certain routes of administration, such as parenteral delivery, where the risk of toxicity and infection must be minimized (Ahire et al., 2018). Lecithin is widely recommended as a stabilizer for both parenteral and autoclavable formulations. The concentration of surfactants and polymers plays a crucial role in determining key parameters such as critical micelle concentration (CMC) and critical flocculation concentration (CFC). While higher stabilizer concentrations typically enhance adsorption and improve nanosuspension stability, exceeding the CMC or CFC can result in micellar solubilization, which may promote Ostwald ripening and ultimately compromise system stability (Elsebay et al., 2023). Therefore, choosing the appropriate type and optimal concentration of a surfactant or stabilizer is crucial. Stabilizers help maintain the system's integrity by preventing or slowing undesirable

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physical and chemical changes, thereby enhancing overall performance. In addition to stabilizing newly formed nanocrystals, they influence the formulation process and may affect drug bioavailability. Thus, selecting the right stabilizer for nanosuspension formulations requires careful evaluation. Depending on the formulation requirements, stabilizers can be either polymers or surfactants (Guan et al., 2017).

Surfactants

Surfactants are helpful to reduce the interfacial tension between the dispersed phase and the continuous phase. It also helps in maintaining the surface charges by which enhances the stability of the drug. Surfactant can act as a stabilizers as its role is to prevent the clumping of particles, which inhibits the growth of particle size. The mechanism of action of nonionic surfactant and polymeric stabilizer is based on the steric layer. Surface-active agents, or surfactants, are amphiphilic molecules, meaning that part of the molecule is hydrophilic (water-loving) and part is lipophilic (oil-loving). This dual nature causes the surfactants to orient themselves at interfaces, such as between water and oil, reducing the interfacial tension between the continuous and dispersed phases. This property is crucial in processes like emulsions and suspensions (Pryazhnikov et al., 2025).

The Hydrophilic-Lipophilic Balance (HLB) scale, developed by Griffin, classifies nonionic surfactants and aids in selecting suitable emulsifiers and surfactants. Surfactants with lower HLB values (0–10) are lipophilic, used for antifoaming, water-in-oil emulsification, and wetting, while those with higher values (10–20) are hydrophilic, suited for oil-in-water emulsification and solubilization. As surfactants are often complex mixtures, their properties may vary across manufacturers. They are widely valued for enhancing the solubility of poorly water-soluble substances and their relatively low toxicity (Gong et al., 2021).

A screening study suggests that results indicate that for anionic surfactants, concentrations above the critical micelle concentration (CMC) are beneficial for producing nanosuspensions with particle sizes <250 nm. Below the CMC, only half of the surfactant binds to the drug molecule, while the rest provides repulsion, leading to incomplete surface coverage and insufficient surface stabilization. At or above the CMC, the surfactant fully saturates the surface, and micelles form, enhancing repulsion and improving nanosuspension stability. However, as the ion concentration increases, the electrical double layer thins, reducing the zeta potential and stability, causing particle agglomeration. In general, combining both electrostatic and steric stabilizers is recommended for better stabilizing a nanosuspension. A neutral polymer can improve the coverage provided by an ionic surfactant by reducing the self-repulsion of the charged surfactant molecules. This allows the surfactant molecules to pack more closely together, enhancing the overall stability of the suspension (Tok et al., 2023). Table 1 presents the suitable materials commonly used in nanosuspension formulation.

Table 1: Excipients for Nanosuspension

Type of excipients	Sub types	Examples	Role in nanosuspension formulation	References
Continuous Phase or Dispersion Phase	Aqueous Phase	Double Distilled Water	Act as a continuous phase for nanosuspension	(Jadhav et al., 2023a)
	Non-aqueous Phase			
Organic Phase		Ethanol Methanol DMSO	It is one of the methods which is used for the Nanosuspension formulation to precipitate the drug out.	(Geetha et al., 2014)
Stabilizer	Polymer or nonionic surfactants	Poloxamers 188 Poloxamers 407 Polyvinyl Alcohol	To enhance the stability of the Drug & Prevent agglomeration of drug and inhibit larger particle size	(Purkayastha & Hossian SKI, 2019)
	Ionic surfactant (Anionic and cationic)	Sodium Lauryl Sulphate & Sodium dodecyl sulfate (SDS), Docusate sodium (dioctyl sodium sulfosuccinate), Sodium stearate, Cetyltrimethylammonium bromide (CTAB), Cetylpyridinium chloride		(Purkayastha & Hossian SKI, 2019)

Organic Solvent

In some bottom-up methods of nanosuspension preparation, such as emulsion diffusion or solvent evaporation, the use of organic solvents is necessary. The primary concerns with these methods are the potential toxicity of the solvents and the challenge of completely removing them from the final formulation (Ravi et al., 2021). Commonly used water-miscible and partially water-miscible ICH-listed solvents include ethanol, isopropanol, ethyl acetate, propylene carbonate, ethyl formate, triacetin, and benzyl alcohol (Aldeeb et al., 2024). When preparing nanosuspensions using emulsion or microemulsion models, the use of organic solvents may be necessary. The acceptance of organic solvents in pharmaceuticals requires careful consideration of their potential toxicity and the effectiveness of their removal from the final product. These factors must be carefully evaluated when developing nanosuspensions(Patel et al., 2016).

Co-Surfactants

When using microemulsions to prepare nanosuspensions, selecting the appropriate cosurfactant is essential. The influence of the co-surfactant on the acquisition of the inner phase and drug loading, particularly in microemulsion formulations, should be thoroughly investigated, as it significantly affects the phase characteristics. Bile salts and dipotassium glycyrrhizinate are frequently mentioned as co-surfactants in the literature, while other solubilizers like transcutol, glycofurol, ethanol, and isopropanol are also suitable for safe use in microemulsion and nanosuspension formulations (Pawar et al., 2017).

METHODS FOR PREPARING NANOSUSPENSION

Nanosuspensions are created by reducing particle size to achieve a physically stable formulation. Two primary methods are used in their preparation: bottom-up technology and top-down technology. In the bottom-up approach, molecules come together and gradually form nanosized particles, while in the top-down approach, larger macromolecules are broken down into nano-sized particles through techniques like milling or high-pressure homogenization. Both methods are aimed at achieving stability, enhancing solubility, and improving bioavailability of the nanosuspension formulation (Pawar et al., 2017).

Bottom-up Method

It includes precipitation of a saturated solution of the drug in which some methods, such as the solvent-antisolvent method, spray drying, supercritical fluid and emulsion-solvent evaporation method. A series of processes includes supersaturation, nucleation of molecules, and diffusion across the solute and nanoparticle growth in nanosuspension. It produces nanoparticles with a narrow particle size distribution or PDI. However, this method forms various unstable polymorphs, hydrates and solvates which are needle-shaped crystals. The organic solvent can be removed by evaporation (by applying temperature) and high pressure (Ahmadi Tehrani et al., 2019).

Precipitation Method or Anti-solvent Method

This technique is simple and cost-effective, particularly for formulating small-scale nanosuspensions in the laboratory. The process begins by dissolving the drug in an organic solvent (acetone, acetyl nitrile, methanol, ethanol, chloroform, or DMSO) to create a highly saturated solution. This saturated solution is then mixed with an aqueous solution with surfactant, leading to the precipitation of the drug molecules in an amorphous form, which significantly enhances the solubility of the medicinal compound. However, a major challenge lies in preventing crystal growth due to Ostwald ripening, which occurs because of the varying saturation solubilities among the nano-sized particles; other top-down techniques are more preferred over the precipitation method (Jadhav et al., 2023b; Shinkar et al., 2022).

Micro-emulsification Method or Solvent-emulsification Method

In this method, the drug is dissolved in an appropriate amount of organic solvent and then dispersed in an aqueous medium containing a stabilizer to prevent particle aggregation and agglomeration. The mixture is stirred continuously using a magnetic stirrer. The organic solvent is subsequently evaporated by maintaining a suitable temperature,

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considering the boiling point of the solvent (Aher et al., 2017).

Melt Emulsification Method

In this method, a lipophilic or poorly water-soluble drug is dispersed in water or an aqueous medium containing a surfactant and heated above its melting point to create molten drug droplets. This emulsified mixture is then subjected to high-shear mixing or high-pressure homogenization, where intense mechanical forces reduce the droplet size to the nanoscale. The homogenized emulsion is rapidly cooled (quenched), solidifying the molten droplets into stabilized nanoparticles, resulting in a nanosuspension. The surfactant prevents aggregation by stabilizing the nanoparticles in the aqueous medium, ensuring a uniform dispersion. This technique is solvent-free, scalable, and suitable for improving the solubility and bioavailability of poorly water-soluble drugs, although it may not be ideal for thermosensitive compounds (Pan et al., 2015; Yadollahi et al., 2015).

Supercritical fluid method

Conventional techniques like solvent extraction-evaporation, solvent diffusion, and organic phase separation rely on organic solvents, posing environmental and biological risks. Supercritical carbon dioxide (SC-CO_2) presents a sustainable alternative for nanosuspension preparation, offering a low critical temperature, optimal density, and viscosity near the critical point, along with environmental benefits. A fluid becomes supercritical when its temperature and pressure exceed critical values, eliminating distinct liquid and gas phases. In this state, it exhibits unique properties, blending characteristics of both liquids and gases (Ikeda et al., 2023). Among the most commonly employed methods utilizing supercritical fluids are supercritical assisted atomization (SAA), supercritical anti-solvent precipitation (SAS), supercritical emulsion extraction (SEE) and rapid expansion of supercritical solvent (RESS) techniques. Expanded fluid for the nanosuspension formulation is a mixture of SC-CO_2 and an organic solvent to dissolve the drug amount. The mixture is depressurized in surfactant-containing water or aqueous phase (Campardelli & Reverchon, 2015). In the RESS process, SC-CO_2 was generated via solvent fluid extraction (SFE), operating at a maximum pressure of 390 bar. A syringe pump maintained precise CO_2 flow control at 0°C, ensuring accuracy in extraction and expansion. For drugs with poor solubility in supercritical fluids, the supercritical anti-solvent (SAS) process is used. Here, the drug is first dissolved in a solvent miscible with the supercritical fluid. Upon injection into the supercritical medium, the solvent is extracted, leading to drug supersaturation and precipitation as fine particles (Esfandiari & Sajadian, 2022).

Top-down Technology

Top-down technologies involve reducing large particles to the nanoscale. The primary techniques used are high-pressure homogenization and media milling (Pınar et al., 2023b). These methods are more scalable at industrial-scale production than bottom-up technologies and are already utilized in commercially available products. It does not involve the use of organic solvent. These technologies involve suspending either micronized or nanonized drug particles in a dispersion medium, which can be aqueous or non-aqueous. The medium is further enhanced and stabilized using the addition of surfactants or polymeric stabilizers (Sharma et al., 2022).

High-Pressure Homogenization

The high-pressure homogenization (HPH) technique utilizes intense shear forces and potentially cavitation to break down drug crystals. This is achieved by forcing a suspension through voids or crevices, dispersing the particles. The drug in powder form is initially dispersed in a dispersion medium to create a pre-suspension, which is then pressurized for pre-milling. This process reduces particle size and facilitates the formation of advanced nanosuspension systems such as (Sharma et al., 2022). Two main homogenization principles are employed, along with specific homogenizer types: microfluidization and piston-gap homogenization. Microfluidization operates on the jet-stream principle, where a coarse suspension is accelerated and forced through a homogenizing chamber. Under the influence of high-speed collisions, shear forces, and cavitation, the particle size is effectively reduced (Pınar et al., 2023b). In a

piston-gap homogenizer, the coarse suspension with big sized particles is pressurized at 500 bar to 350 MPa through a narrow gap or orifice at extremely high speeds. Increasing the pressure and number of cycles enhances particle size reduction, leading to the formation of a nanosuspension with small sized particles (Tashan et al., 2019). The process can be categorized based on the liquid medium used: homogenization in water (DissoCubes), in non-aqueous media, or in water mixtures (Nanopure). The particle size of the nanosuspension produced by this method is primarily influenced by factors such as temperature, the number of homogenization cycles, energy density, and homogenization pressure (Rani et al., 2023b).

Wet Media Milling Method

This method is the most commonly used nanosuspension formulation method, also known by various terms, including bead milling, wet media milling, and pearl milling. In this process, the drug and stabilizer solution are placed in a chamber, where mechanical grinding occurs as the balls (or beads) collide with the mixture, reducing particle size effectively. Various process parameters can affect the particle size of the nanosuspension, for instance, the size of the milling chamber, milling bead type and diameter, the type of beads (zirconium or stainless steel), the concentration of the milling beads, the speed of the mechanical stirrer or homogenizer, etc. (Karakucuk et al., 2021). The milling chamber can be filled one-third using beads and pre-suspension to avoid overfilling, wastage and facilitate proper homogenization of the suspension (Gülbağ Pınar et al., 2022). The device's rotation speed is then set, and the milling process begins, lasting for a specified time. A common issue with this method is wear and tear caused by the milling chamber or the beads' impact. To minimize this, it's essential to use a chamber made from durable materials like stainless steel or porcelain and beads made from materials such as porcelain, glass, agate, or zirconium oxide. A particle size of less than 200 nm is achieved by milling the sample for 30 to 120 minutes. The ratio of drug to polymer and the milling speed significantly affect the zeta potential, while the particle size range of a nanosuspension is influenced by the total milling time and milling speed. However, this technique has certain drawbacks. During grinding, shear forces exerted by the milling media can disrupt the crystal surface, leading to defects and the formation of amorphous regions. These structural changes increase the surface energy of the particles, potentially affecting their stability and performance (Tian et al., 2022).

Dry Co-grinding

Stabilizers and surfactants can be incorporated into poorly water-soluble drugs to enhance surfactant polarity and facilitate the transformation of crystalline structures into a stable amorphous form. Dry co-grinding offers a simple, cost-effective, and eco-friendly approach, eliminating the need for organic solvents (Bartos et al., 2024).

Combination Methods

Various combinational methods are used for nanosuspension preparation, including the bottom-up approach combined with the top-down method. Additionally, two top-down techniques, such as high-pressure homogenization and wet media milling, can be integrated, where a pre-suspension is further processed to produce nano-sized particles. In some cases, high-energy methods, such as media milling, high-pressure homogenization, or microfluidization, are followed by ultrasonication or probe sonication to further refine particle size and enhance nanosuspension stability (Attari et al., 2016).

BENEFITS AND DRAWBACKS OF VARIOUS MANUFACTURING METHODS FOR NANOSUSPENSIONS

The different production procedure is discussed in Table 2 for a better understanding of the advantage and limitations, highlighting critical considerations such as scalability, energy requirements, particle size control, solvent use, and formulation stability. This comparative overview serves as a valuable guide for selecting the most appropriate method based on the physicochemical properties of the drug and the intended therapeutic application.

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Table 2: Merits and Demerits of preparation methods of nanosuspension

Methods	Advantages	Disadvantages	Reference
High pressure homogenization	Limited size spectrum of particle size, ease of scaling up, minimal batch-to-batch variation, and aseptic creation of nanosuspensions for parenteral administration	Prior to homogenization, materials should be presuspended and medication particles should be micronized.	(Kodipyaka & Govindu, 2025)
Media milling method	The same as those for homogenization under high pressure.	Possible material erosion from the pearl milling process	(Patel et al., 2018)
Precipitation method	Low energy consumption, an easy procedure	High size distribution, possible toxicity of non-aqueous solvents	(Papdiwal et al., 2014)
Melt Emulsification Method	Avoiding organic solvents as opposed to the diffusion of solvents, less surfactant needed.	Larger particles from it than solvent diffusion, less suitable for drugs with a lower melting point and thermolabile drugs, require high energy consumption.	(Pan et al., 2015)
Micro-emulsification method	Minimal energy consumption, consistent outcomes, straightforward procedure, tiny particle size, and even dispersion of particles	High levels of leftover solvents and undesirable surfactants	(Li et al., 2015)
Microprecipitation-high pressure homogenization	Much smaller, more homogeneous, and more stable than that produced by microprecipitation; requires less energy and mechanical effort than high-pressure homogenization.	The process of production is intricate.	(Kodipyaka & Govindu, 2025)
Dry co-grinding method	Easy, simple, economical, solvent free system	High energy consumption and poor flow property, can cause thermal degradation and may cause aggregation	(Kodipyaka & Govindu, 2025)

SOLIDIFICATION OF NANOSUSPENSION

Spray Drying

Spray drying is a widely used method for particle and crystal engineering to change the physico-chemical properties. It is a one-step, continuous process in which a liquid feed is transformed into a dry powder form. The process involves four key stages: preparation of the liquid feed, atomizing the feed into a spray using a nozzle and exposing it to hot drying gas, formation of particles as the solvent evaporates, and finally, separating the dried product from the gas (Vehring et al., 2020). Spray drying is reported to be one of the best drying methods to convert directly the fluid materials into solid or semi-solid drug delivery systems (Rezvankhah et al., 2020). This unit operation involves atomizing a liquid product into a hot gas stream (air or, rarely, a nitrogen stream as an inert gas) to rapidly produce a powder (Gajera et al., 2024).

The liquid feed (suspension, emulsion, or solution) may be affected by various process parameters such as feed flow rate, feed temperature, viscosity of feed, feed composition or components, feed concentration, atomization method or rate, and type of feed. This technique can produce a high-quality product with low water activity, making it easier to store and

transport due to its reduced weight (Jakubowska et al., 2022). One of the main advantages of spray drying is its versatility, as it is suitable for both heat-resistant and heat-sensitive materials. Additionally, the process is fast and allows for a controlled particle size distribution (Haghighi et al., 2022).

Freeze Drying (lyophilization)

Freeze drying, also known as lyophilization, is a widely used method for removing solvents, primarily water, from pharmaceutical products and making powder free of water. The process consists of three main stages: freezing the product, primary drying to remove the majority of the solvent, and secondary drying to eliminate any remaining traces of solvent. The final freeze-dried product typically exhibits a highly porous structure with low moisture content (Machamasi et al., 2024). Freeze drying improves the stability of moisture-sensitive, heat-labile drugs, particularly for long-term storage, and minimizes damage to the compounds during processing. Additionally, this method allows for the production of nanosuspensions in a dry form, which are easy to handle and can be reconstituted with water or other aqueous solutions before use. Lyophilization of pharmaceuticals enhances their stability, ensuring they remain effective during long-term storage (Jakubowska & Lulek J, 2021).

Lyophilization Process

The initial stage of freeze-drying is freezing, where water is frozen to isolate solutes, and the degree of supercooling, influenced by the freezing rate, may occur, with freezing typically taking several hours to complete. In the freezing process, the formulation must be cooled to the temperature at which ice nucleation occurs (Abla & Mehanna, 2025). Secondary drying typically takes place once the product is heated past its eutectic point. At this stage, the vacuum pump creates the low-pressure environment required for the removal of remaining solvents, resulting in a product with a drier appearance (Mehanna & Abla, 2022). The frozen ice undergoes sublimation, yielding a dry and structurally stable product. This phase is the most time-consuming in the process. To ensure optimal product quality, both the chamber pressure and shelf temperature must be carefully controlled. After freeze-drying, some bound moisture remains, requiring higher-temperature drying to reach acceptable levels. “Isothermal Desorption” removes this residual water. Secondary drying, performed at a safe temperature above room temperature, is easier than primary drying but requires careful temperature control to prevent protein polymerization or biodegradation (Joshi et al., 2025). Secondary drying requires almost 30–50% of total drying time; the shelf temperature and chamber pressure are gradually adjusted to their lowest points. On removal of ice, the “melt track” is no longer a concern, allowing higher temperatures without harming the product. However, some tightly bound water remains, requiring more energy to remove. To enhance water desorption, chamber pressure is further reduced (Silambarasan et al., 2022).

Spray Freeze Drying

Spray freeze drying (SFD) combines spray drying and freeze-drying by atomizing a liquid into droplets, freezing them under cryogenic conditions, and lyophilizing to remove the solvent via sublimation. This produces a porous, high-surface-area dry powder, ideal for stabilizing thermosensitive drug nanosuspensions. SFD is commonly used for solidifying thermosensitive drug nanosuspensions, converting them into dry powders (Wanning et al., 2015).

CHARACTERIZATION OF NANOSUSPENSION

Comprehensive characterization of nanosuspensions is essential to ensure their quality, stability, and performance. Several analytical parameters are employed to evaluate critical aspects such as particle size, surface charge, crystallinity, and dissolution behavior.

Particle Size (nm) and Particle Size Distribution

In nanosuspensions, particle size is a critical quality attribute to ensure the formulation’s size range, solubility, stability, and absorption. The particle size measurement is typically conducted using a Zetasizer, an instrument that employs dynamic light scattering (DLS), quasi-elastic light scattering (QELS) or photon correlation spectroscopy (PCS) (Bhattacharjee, 2016). This technique evaluates both particle size and particle size distribution (PDI) within the nanosuspension, covering a submicron size range

from below 1 nm to above 1 µm. DLS or PCS is a technique for measuring particle size by analyzing their Brownian motion (Willmann et al., n.d.). The process begins by irradiating particles suspended in a liquid with a laser. As light hits these particles, it scatters in all directions. If a screen is placed near a single illuminated particle, the scattered light will create a bright spot on the screen. The stability of a nanosuspension is influenced by its PDI; a lower PDI generally indicates better long-term stability. A PDI of 0.1–0.25 indicates a narrow particle size distribution, while a PDI above 0.5 suggests a broad distribution (Sun et al., 2022). Laser Diffraction (LD) analyzers operate on the principle of light diffraction as it passes through particles. The angle of diffracted light is inversely proportional to the particle size. Common characterization parameters in LD analysis include D50, D90, and D99, which represent the particle diameters at which 50%, 90%, and 99% of the particle volume is below a given size, respectively (Sun et al., 2022).

X-Ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC)

Polymorphic and morphological changes in a drug during nanosuspension preparation can be analyzed using XRD. XRD also helps estimate amorphous particle transformation during formulation. The high-energy amorphous form of a drug is thermodynamically unstable and tends to convert into a crystalline form over time during storage. However, the amorphous form is often preferred because it offers better dissolution properties, leading to enhanced bioavailability of the drug. DSC can also be combined with XRPD for a more comprehensive analysis (Jain, n.d.).

DSC is an additional method for determining the crystallinity and amorphousness of produced nanoparticles. It is founded on the idea of measuring a material's thermal characteristics in order to determine a relationship between temperature and particular physical characteristics of substances. More significantly, it is the sole technique for directly determining process enthalpy that has been documented (Kolipaka et al., 2023a). The primary characteristics of an amorphous or crystalline material are the glass transition endotherm (Tg), crystallization exotherm, and endotherm peaks for the nanosuspension. These are evaluated when the sample is being analyzed for DSC. The existence of an amorphous phase produces the Tg, while the recrystallization of the amorphous content produces the crystallization exotherm. A melting endotherm is created when the preexisting crystalline content and the acquired crystalline state combine (Jadhav et al., 2024; Kolipaka et al., 2023a).

Zeta Potential

Zeta potential (ZP), or electrokinetic potential, is the charge at the shear plane of a colloidal particle in an electric field. It determines nanosuspension stability by reflecting the charge difference between the dispersed solid and liquid phases, measured in millivolts (mV). A minimum ZP of ±30 mV is required to ensure particle repulsion, preventing agglomeration and maintaining stability (Serrano-Lotina et al., 2023). Electrostatic stabilization can reduce the zeta potential by ± 20 mV, which is sufficient to prevent nanoparticle aggregation. "Zeta-sizer" is a tool used to quantify the nanosuspension's zeta potential value that utilizes the ELS principle for measurement (Elmowafy et al., 2021b).

Saturation Solubility & Dissolution Studies

The investigation of the dissolution rate and saturation solubility is essential to ascertain the in-vitro behavior of nanosuspension. Dissolution rate can be used to predict drug release, which is important when using sustained-release dose forms of nanoparticles (Aghrbi et al., 2021). Drug release study of the nanosuspension is a significant characteristic to determine the influence of dissolution rate, bioavailability, and therapeutic efficacy of poorly water-soluble drugs. Nanosuspension dissolution and drug release are assessed using a dissolution apparatus or dialysis membrane method, with a dissolution medium of 900 mL or 40-50 mL (dialysis membrane method) maintained at 37°C. The medium typically includes 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.0–6.5) to simulate gastrointestinal conditions, or biorelevant media given in the pharmacopeia or FDA website is utilized with the mentioned conditions. Finally, almost 1–5 mL of the sample is analyzed at the predetermined intervals to evaluate the dissolution rate of liquid or lyophilized nanosuspension (Shaikh et al., 2022).

Stability

Reducing particle size increases surface energy due to more unstable surface atoms, which can destabilize colloidal suspensions. Stabilizers are often needed to prevent agglomeration and reduce the risk of Ostwald ripening (Guan et al., 2022b). A combination of surfactants and polymers has been shown to be effective for the long-term stabilization of nanosuspensions. The stability of a nanosuspension system can be improved by enhancing the uniformity of particle sizes, which can be achieved through centrifugation or other methods to remove larger particles. Stability studies for both nanosuspension and lyophilized nanosuspension are conducted under two storage conditions: room temperature and refrigerated conditions (2–8°C) for a long-term stability study (12 months) and an accelerated stability study (6 months). At specified time intervals, samples are collected and examined for particle size (nm), PDI, zeta potential and drug content, etc. (Jawahar et al., n.d.). Table 3 summarizes the recent advancements in the development of nanosuspensions for effective drug delivery.

Table 3: Advancement in the nanosuspension in the delivery of drugs

Title	Route	Description	References
Biomimetic nanosuspension for cancer cell membrane based on homology and active targeting for the treatment of glioma	Intravascular (targeted delivery)	Paclitaxel nanosuspension was coated with C6 glioma cell membranes that actively target the glioma tumor cell. Then, a BBB-penetrating and tumor-targeting peptide called WSW (or PhrCACET1), derived from *Clostridium acetobutylicum,* was attached to the membrane surface using the lipid insertion method. The final formulation was able to cross the blood-brain barrier (BBB) and accumulate at the tumor site in glioma-bearing mice.	(Fan et al., 2021)
Artemisia absinthium extract containing nanosuspension as a novel drug delivery system to enhance its bioavailability and hepatoprotective potential	Oral	The nanosuspension of *Artemisia absinthium* extract significantly enhanced oral bioavailability, antioxidant activity, and hepatoprotective efficacy, demonstrating its potential as an effective drug delivery system.	(Jahan et al., 2023)
Novel albumin wrapped nanosuspension of meloxicam to improve inflammation-targeting effects	Intravenous	Bovine Serum Albumin (BSA)-coated meloxicam nanosuspension was formulated to enhance targeted delivery to inflamed tissues, leveraging albumin's natural accumulation and uptake at inflammation sites.	(Li et al., 2018)
Novel nose-to-brain delivery of Donepezil Nanosuspension	Intranasal	Donepezil gives targeted delivery of Alzheimer's disease in brain delivery drug with safety; no hematological changes and toxicity were shown.	(Md et al., 2014)
Posaconazole nanosuspension via wet milling	Oral	QbD-based wet-milled posaconazole nanosuspension improved solubility, dissolution, and bioavailability.	(Kolipaka et al., 2023b)
Voriconazole-loaded ophthalmic nanosuspension	Topical ocular	Voriconazole nanosuspension (1%) with Pharmasolve® improved corneal permeability, antifungal activity, and safety.	(Qin et al., 2020)
Spray-dried nanosuspension of Rutin	Oral	Media-milled rutin nanosuspension using Box-Behnken design showed enhanced dissolution (7.5×) and permeability (5.4×) with non-toxic profile. Stable under accelerated conditions.	(Chary et al., 2024)
Nanosuspension of Sonchus arvensis L. folium (NS-Sa-4:1)	Oral	Antisolvent-prepared nanosuspension (12.9 nm, −12.5 mV) enhanced antioxidant and lipid-lowering effects versus simvastatin, with stable sustained release and 28-day stability.	(Aldeeb et al., 2025)

 https://doi.org/10.37819/nanofab.10.2085

Clinical Trials

As summarized in Table 4, multiple nanosuspension-based drug formulations have been evaluated in recent clinical trials for their therapeutic potential, safety, and pharmacokinetic advantages. These include formulations for cancer (BPM31510), viral infections (ivermectin, rilpivirine), and nutraceuticals (BIO 300), highlighting the versatility and growing clinical relevance of nanosuspensions in modern drug delivery.

Table 4: Recent Clinical Trials Involving Nanosuspension-Based Drug Formulations (clinicaltrials.gov)

Drug	Phase	Year	Route	Formulation	Study Design	Primary Outcome
NYR-BI03	Phase I	2023	Intravenous	NYR-BI03 nanosuspension	Randomized, placebo-controlled, double-blind, 6 ascending dose cohorts with sentinel dosing	Safety, tolerability, and pharmacokinetics (6 h infusion)
BIO 300	Phase I	2021	Oral	Genistein nanosuspension	Single-arm multiple ascending dose + 2 crossover food-effect arms	Adverse event profile (14-day repeat dose & food effect)
Ivermectin *(anosmia)*	Phase II*	2022	Intranasal	Ivermectin nanosuspension	Comparative 2-arm trial: ivermectin nasal spray vs placebo in post-COVID anosmia patients	Improvement in olfactory function post-treatment
Ivermectin *(early COVID)*	Phase II*	2021	Intranasal	Mucoadhesive ivermectin nanosuspension	Comparative trial: ivermectin nasal spray + standard therapy vs. standard therapy alone	Reduction in early viral symptoms and disease progression
Rilpivirine (RPV LA)	Phase I	2020	Intramuscular	Rilpivirine nanosuspension (varied PSDs)	Open-label, randomized, parallel-group trial: 5 IM formulations with different particle size distributions	Single-dose pharmacokinetics across PSD variants
RPV-LA vs Aged RPV-LA	Phase I	2023	Intramuscular	Standard vs aged rilpivirine nanosuspension	Open-label, randomized, parallel-group study evaluating storage condition effects on PK	Single-dose plasma pharmacokinetics under different storage conditions
BPM31510 *(glioma)*	Phase I	2022	Intravenous	Ubidecarenone (CoQ10) nanosuspension	Open-label trial in recurrent high-grade glioma; 72-hour IV infusions twice weekly + vitamin K; repeated every 28 days	Safety, tolerability, PK, and imaging-based tumor response
BPM31510 + Gemcitabine *(pancreatic cancer)*	Phase II	2023	Intravenous	Ubidecarenone (CoQ10) nanosuspension	Open-label, non-randomized, multicenter study in advanced pancreatic cancer; BPM31510 (144 h/week IV) + weekly gemcitabine	Safety and clinical benefit in 2nd/3rd-line pancreatic cancer therapy

CONCLUSION

Nanosuspensions have emerged as a promising approach for enhancing the solubility and bioavailability of poorly water-soluble drugs, addressing a critical challenge in pharmaceutical formulation. By reducing particle size to the nanometer scale, nanosuspensions significantly improve dissolution rates, leading to better drug absorption and therapeutic efficacy. However, stability remains a major concern, as factors such as aggregation, flocculation, Ostwald ripening, and crystal growth can compromise formulation integrity. The selection of appropriate stabilizers, surfactants, and optimization of formulation parameters play a crucial role in overcoming these challenges. With continuous advancements in nanosuspension technology, including novel stabilization techniques and solidification methods, this approach holds great potential for improving drug delivery across various routes of administration. Future research should focus on refining formulation strategies and exploring innovative drug delivery applications to maximize the therapeutic benefits of nanosuspensions.

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Authors' Contributions

A. Mishra was involved in the comprehensive literature survey, and initial drafting of the manuscript. M. B. Patel contributed to content review and preparation of tables. L. Lata Jha participated in critical review and editing of the content. M. Upadhyay was involved in the conceptualization, supervised the overall work, provided substantial revisions, and finalized the manuscript for submission.

Abbreviations

Biopharmaceutical classification system: BCS, gastrointestinal: GI, active pharmaceutical ingredient: API, sodium lauryl sulfate: SLS, polyvinyl pyrrolidone: PVP, Hydroxy propyl methyl cellulose: HPMC, Hydroxypropyl cellulose: HPC, Critical micelle concentration: CMC, Critical flocculation concentration: CFC, Hydrophilic-Lipophilic Balance: HLB, Supercritical carbon dioxide: SC-CO_2, Supercritical assisted atomization: SAA, Supercritical emulsion extraction: SEE, Rapid expansion of supercritical solvent: RESS, High-pressure homogenization: HPH, Spray freeze drying: SFD, Dynamic light scattering: DLS, Quasi-elastic light scattering: QELS, particle size distribution: PDI, Photon correlation spectroscopy: PCS, Laser Diffraction: LD, X-ray diffraction: XRD, Differential scanning calorimetry: DSC, Zeta potential: ZP.

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