REVIEW ARTICLE

Nanosuspensions in Drug Delivery: Strategic Formulation, QbD Integration, and Overcoming Biopharmaceutical Barriers

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Abstract: Nanosuspensions offer a promising strategy to resolve solubility and bioavailability challenges often encountered with modern pharmaceutical actives. This review describes core formulation principles, highlights the mechanistic underpinnings of nanosuspension technology, and examines advances in stabilization and scalable manufacturing. The integration of Quality by Design (QbD) is explored, illustrating how systematic risk assessment and process control enhance product reliability and regulatory readiness. Overcoming key biopharmaceutical barriers—such as physical stability, dissolution rate, and patient compliance—is discussed using illustrative case studies from both oral and non-oral drug delivery applications. The synthesis of recent research trends provides guidance on how nanosuspensions can be strategically positioned to improve therapeutic outcomes and accelerate clinical translation.

KEYWORDS: Nanosuspension, drug delivery, solubility enhancement, bioavailability, quality by design

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1. INTRODUCTION

The lack of good aqueous solubility continues to pose one of the most critical obstacles in formulation and clinical development of many new chemical entities (NCEs). It is already estimated that almost 40% of drugs in the existing pharmaceutical pipeline and up to 60% of chemical molecules that are synthesized are low water soluble, and this is highly problematic to the drug delivery process, especially through the oral route (Mane et al., 2025, Lipinski, 2002). Its poor solubility may lead to unsatisfactory bioavailability, a variable absorption pattern and inconveniently end in therapeutic failure without proper resolution at the formulation step (Serajuddin, 2007).

Historically, formulation scientists have relied on conventional strategies to overcome poor aqueous solubility, including salt formation, the use of cosolvents, cyclodextrin complexation, and solid dispersions (Savjani et al., 2012). While these traditional methods can be effective, they often present distinct limitations. For example, salt formation is strictly limited to ionizable drug candidates and carries the risk of *in vivo* precipitation. The extensive use of cosolvents and surfactants can lead to systemic toxicity, tissue irritation, and strict dose-volume constraints, whereas solid dispersions frequently suffer from thermodynamic instability and unexpected recrystallisation during their shelf life (Brough & Williams, 2013; Kalepu & Nekkanti, 2015). In stark contrast, nano-formulations—specifically nanosuspensions—offer a versatile, carrier-free alternative. By relying solely on the physical reduction of drug particles to the nanometer scale, without the need for chemical modification or high

excipient ratios, nanosuspensions circumvent the toxicity and thermodynamic instability issues associated with conventional methods. Furthermore, they are uniquely capable of handling "brick dust" molecules that are simultaneously insoluble in both aqueous and organic media, providing higher drug loading capacities, superior physical stability, and a universal platform for multiple delivery routes (Khan et al., 2022; Müller et al., 2011).

Nanosuspension technology has been proven to be an effective formulation platform that can be applied to resolve many solubility-associated problems. Commonly, a nanosuspension is defined as a colloidal dispersion of pure drug particles in the nanometer scale that have been stabilized in an aqueous vehicle using either surfactants or polymers to prevent aggregation and maintain physical stability (Aldeeb et al., 2024; Patravale et al., 2004). Its technology is based upon the principles of the Noyes-Whitney equation such that shrinking the drug particle size has a major effect on increasing the surface area available to the drug to dissolve, thus increasing the rate of dissolution and improving the saturation solubility (Junghanns & Müller, 2008, Patravale et al., 2004). Enhanced drug absorption and high oral bioavailability have been achieved through the effect of increasing the dissolution rate of poorly soluble drugs using nanosuspension formulations, successfully demonstrated with several drugs in Classes II and IV of the Biopharmaceutical Classification System (BCS) (Keck & Müller, 2006). In addition, nanosuspensions can deliver drugs to specific sites (site-specific delivery) and have also been expanded to non-oral routes of administration including eye (ocular), injection (parenteral), lung (pulmonary), and skin (topical) routes, and thus, their application has increased to favor their therapeutic potential (Kumari et al., 2010). The modernization of production methods such as high-pressure homogenization and controlled precipitation has also increased the scope of this technology to molecules traditionally regarded hard-to-formulate (Verma et al., 2013). However, an area of concern is the physical stability, scalability and acceptance by regulatory agencies which need to be addressed to see to it that the full potential of nanosuspension-based drug delivery systems is ever achieved.

This review aims to provide an in-depth analysis of nanosuspension technology, its mechanistic foundations, and formulation strategies, with a special emphasis on key case studies, emerging trends, and the persistent hurdles that must be overcome for broader clinical adoption.

2. FUNDAMENTALS OF NANOSUSPENSION TECHNOLOGY

2.1. Historical Background

To align this historical context with the primary focus of this review, it is essential to first clarify the distinction between nanocrystals and nanosuspensions. Nanocrystals refer strictly to the pure, solid-state drug particles reduced to the nanometer scale. A nanosuspension, however, is the actual formulated colloidal delivery system in which these nanoparticles are suspended and stabilised within a liquid vehicle (Malamatari et al., 2018; Rabinow, 2004).

The formulation of low-solubility drug candidates into stabilised, nanometer-sized dispersions was first demonstrated in the early 1990s. The industrial breakthrough occurred with Elan's NanoCrystal® platform, which culminated in the FDA approval of Rapamune® (sirolimus) in 1999. Rapamune was formulated as an oral solution, effectively launching the first commercial liquid nanosuspension and proving that purely drug-based colloidal dispersions could successfully achieve large-scale production, sterilisation, and regulatory control (Merisko-Liversidge, 2015; Shen & Li, 2007).

Subsequent accelerations in nanosuspension technology allowed liquid nanosuspensions to be successfully post-processed into solid oral dosage forms. In 2003, Emend® (aprepitant) was approved, utilising wet-media milling to create a stabilised nanosuspension that successfully negated food effects and avoided solvent toxicities. Tricor® (fenofibrate) followed in 2004, leveraging a similar nanosuspension-based manufacturing pathway.

A major milestone for parenteral drug delivery was achieved in 2009 with the authorisation of Janssen's Invega Sustenna® (paliperidone palmitate). Formulated as a once-monthly intramuscular nanosuspension, it established colloidal particle engineering as a highly effective and commercially viable competitor to traditional polymeric depot technologies (Zhou et al., 2024).

Recently, research into nanosuspension-based drug delivery has extended beyond the typical oral and intramuscular routes to include inhaled, ocular, and

dermal delivery. In these non-invasive applications, nanosuspensions have been shown to successfully overcome physiological barriers, increasing the bioavailability and therapeutic efficacy of molecules that were previously considered too difficult to formulate (Aldeeb & Elkhodairy, 2024). Today, over twenty drugs originating from nanosuspension formulations are in global use, with more than sixty products currently in clinical testing. This robust pipeline is evidence of a quarter-century transformation from a laboratory proof-of-concept to an orthodox pharmaceutical modality (Kocbek et al., 2010).

2.2. Theory of Nanosuspensions

The foundational principle of nanosuspension technology is governed by the Noyes-Whitney equation, which establishes that dissolution velocity is directly proportional to the available surface area of the dissolving solid. Downsizing a drug particle from the micrometre to the nanometer scale induces an exponential increase in its surface area-to-volume ratio. Because the total volume (or mass) of the administered dose remains constant while the specific surface area multiplies massively, this extraordinarily high surface area-to-volume ratio becomes the primary biophysical driver for rapid dissolution in gastrointestinal or biological fluids. Consequently, this leads to a steep concentration gradient that facilitates much faster absorption across biological membranes (Kesisoglou et al., 2007; Peltonen & Hirvonen, 2010; Khan & Boateng, 2021).

Simultaneously, using the Ostwald-Freundlich relationship results in a direct correlation between decreases in the particle size and increases in saturation solubility related to a curvature change that causes an increase in the chemical potential of the system (Yu et al., 2010). Such properties are especially helpful in the case of Biopharmaceutics Classification System (BCS) Class II and IV drugs that are constrained by aqueous solubility and permeability, respectively.

Mechanistically, P-glycoprotein efflux and first-pass metabolism can also be circumvented by facilitating lymphatic absorption, or nose-to-brain transport in some classes of molecules (Shabir et al., 2021). It has been shown in several in vivo ocular, nasal, and pulmonary nanosuspension-based preparations that not only are their muco-adhesion characteristics improved, but also, they possess a greater residence time in the mucosal layers and enhanced penetration into tight epithelial junctions (Raval et al., 2021; Pattekari et al., 2020).

It is important to note that the stabilisation of the nanocrystalline structure is important in ensuring that the particle does not grow, nor does it undergo Ostwald ripening or aggregation; this eliminates the performance of the formulation and limits the shelf-life of the product. To keep the colloidal stability, zeta potential modulation and yet steric stabilisation by polymers such as poloxamers, PEGs, or polysorbates (Alshora et al., 2022) are used.

Beyond surface area and stabilisation mechanics, the overall *in vitro* and *in vivo* performance of a nanosuspension is profoundly governed by several key physicochemical and formulation variables:

Viscosity: Governed by the principles of the Stokes-Einstein equation, the viscosity of the dispersion medium inversely affects the diffusion coefficient of the drug. While increasing the viscosity (often via polymeric stabilisers) reduces particle sedimentation and enhances kinetic stability during storage, it can concurrently retard the drug's dissolution velocity upon administration (Tuomela et al., 2016).

Drug Concentration (Solid Loading): The concentration of the active ingredient dictates the frequency of inter-particle collisions. High drug concentrations escalate the thermodynamic drive for aggregation and Ostwald ripening. Therefore, higher solid loading requires carefully optimised stabiliser-to-drug ratios to prevent spontaneous crystal growth and maintain a narrow polydispersity index (Jacob, 2020).

Drug Variation in Molecular Weight: The intrinsic molecular weight and lattice energy of the active pharmaceutical ingredient (API) influence its comminution efficiency and diffusion kinetics. High-molecular-weight drugs generally exhibit lower diffusion coefficients, which alter both the supersaturation kinetics during bottom-up formulation and the final dissolution velocity in biological fluids (Verma et al., 2013).

Mode of Suspensions: The physical state in which the nanosuspension is presented—whether maintained as an aqueous liquid dispersion, incorporated into a rheologically modified hydrogel for topical use, or lyophilised into a solid matrix for reconstitution—directly dictates its long-term kinetic stability, redispersibility, and route-specific

release profile (Tuomela et al., 2016; Malamatari et al., 2018).

2.3. Formulation Strategies

Three major methodologies (top-down, bottom-up and combination/hybrid technologies) have been developed to build nanosuspensions. Method selection is influenced by aspects of drug solubility, the required particle size distribution, the ability to scale up, the sensitivity of the drug to heat and the route of administration that is desired (Figures 1, 2).

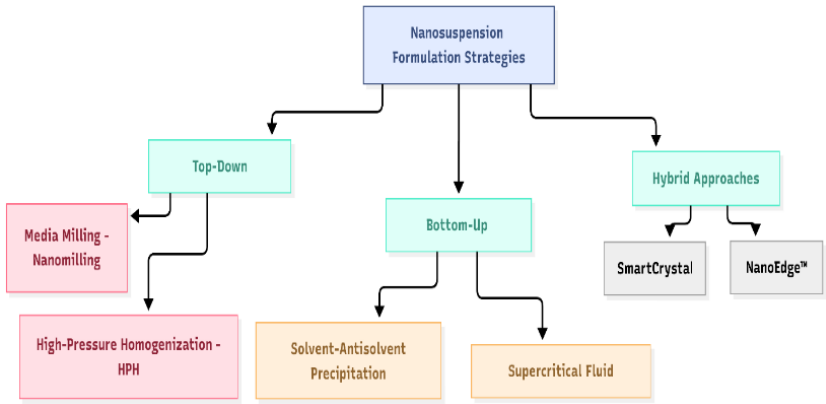


Figure 1. Formulation strategies

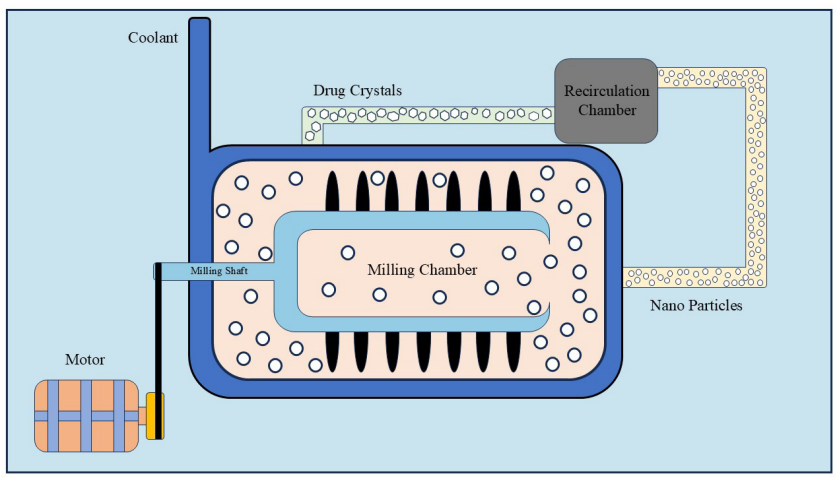


Figure 2. Schematic representation of approaches to prepare nano-particles (Rampurawala M. et.al. 2024)

2.3.1. Top-down Approaches

Top-down methodologies are the most firmly established industrial techniques, relying on the mechanical comminution of macroscopic bulk drug crystals into nanometer-sized particles through the application of high-energy forces.

Media Milling (Nano-milling)

Principle: The macroscopic powder of the drug is suspended in a solution of polymeric and/or surfactants in aqueous solution. This macro-suspension is forced into a milling chamber that contains milling media (usually yttrium-stabilised zirconium oxide or highly cross-linked polystyrene beads). The high speed of the milling shaft produces high mechanical forces, namely impaction, shear, and attrition, and physically breaks the drug crystals on their weakest lattice planes.

Critical Process Parameters (CPPs): The milling speed, milling duration, bead size (usually 0.1 1

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mm), ratio of the drug and the beads, and the cooling jacket temperature to remove heat generated.

Advantages and Limitations: Media milling is very repeatable, can be easily scaled between laboratory and commercial quantities and has been proven by hundreds of FDA-approved formulations, including Emend and Tricor. The process is however, infamously time-consuming (it may take hours to days). In addition, there is a unique risk of contaminated products due to the gradual deterioration of the milling media, and the heat produced can cause undesirable polymorphic changes or amorphous transformations in thermolabile drugs (Peltonen and Hirvonen, 2010).

High-Pressure Homogenization (HPH)

Principle: An already prepared macroscopic suspension is pushed through a very small micro-gap valve (or interaction chamber) at very high pressures, usually between 500 and 1500 bar. The principle of Bernoulli states that the pressure of the fluid decreases and becomes lower than the pressure of water in the air at room temperature when the fluid velocity rapidly rises due to the narrow gap. This causes local boiling and the development of bubbles of cavitation. The following violent bursting of these bubbles, along with the strong shear stress and turbulent collisions, breaks the drug particles. Technologies can be broadly classified into piston-gap homogenisers (e.g., Disso Cubes) and microfluidisers.

Critical Process Parameters (CPPs): The homogenization pressure, number of homogenization cycles, and exact control of the temperature of the pre-suspension.

Advantages and Limitations: HPH is a solvent-free continuous method that does not suffer erosion problems of the media as in nanomilling. It can be subjected to continuous large-scale production. On the other hand, it is extremely energy-consuming, and the strong mechanical force may lead to crystal lattice defects. In the absence of active and effective cooling, the amount of heat produced may jeopardise physical stability (Rohani et al., 2023) (Figure 3).

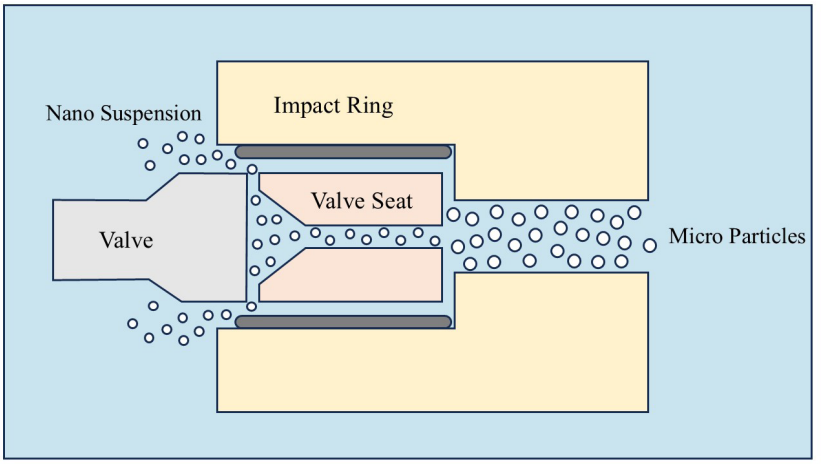


Figure 3. Schematic representation of high pressure homogenization process

2.3.2. Bottom-Up Approaches

Bottom-up strategies rely on the controlled precipitation of dissolved molecules, effectively building nanoparticles from the molecular level upward by manipulating thermodynamic solubility and supersaturation kinetics.

Solvent-Antisolvent Precipitation:

Principle: The active pharmaceutical ingredient is completely dissolved in an organic solvent that is water-soluble (e.g., ethanol, methanol, or N-methyl-2-pyrrolidone). This organic solution is quickly added to an aqueous antisolvent in which the stabilisers are dissolved. The high level of supersaturation is instant and the phases are rapidly micromixed. This provides the thermodynamic impetus of a giant burst of spontaneous nucleation, then the growth of nanometer-sized crystals. The dissolved stabilisers quickly adsorb onto the newly created high-energy surfaces in order to stop further crystal growth (Sinha et al., 2013).

Critical Process Parameters (CPPs): Volumetric ratio of solvent-antisolvent, intensity of mixing (impeller speed or microfluidic flow rates), rate of addition, and particular affinity and concentration of the selected stabilisers (Tehrani et al., 2019).

Advantages and Limitations: Precipitation needs a much lower input of mechanical energy as compared to top-down techniques and requires relatively cheap, simple equipment. The use of organic solvents, however, presents toxicity concerns, requiring stringent and frequently costly downstream purification steps (e.g., lyophilisation or ultrafiltration). Moreover, the newly formed particles are highly energetic and therefore the system is very vulnerable to Ostwald ripening, aggregation and undesired solvate formation or polymorphic changes (Sinha et al., 2013; Zhang et al., 2020).

Supercritical Fluid (SCF) Technology

Principle: This process involves the control of the solvating power of supercritical fluids, which is most often supercritical carbon dioxide (scCO2). Techniques can broadly be categorised into two: Rapid Expansion of Supercritical Solutions (RESS), in which the drug is dissolved in scCO2 and precipitated by means of a nozzle and rapid depression and Supercritical Antisolvent (SAS), in which the scCO2 serves as an antisolvent to precipitate the drug out of an organic solution (Figure 4).

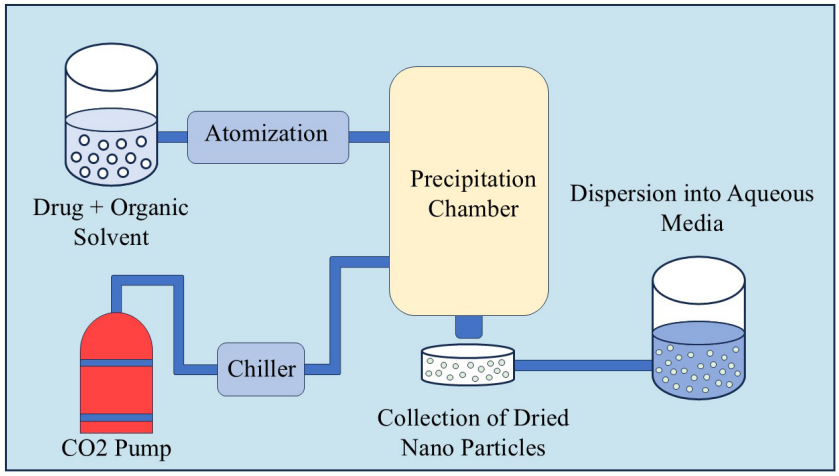


Figure 4. Schematic representation of super critical antisolvent process

Critical Process Parameters (CPPs): The pressure, temperature, nozzle shape, and the velocity of the supercritical fluid and the drug solution.

Advantages and Limitations: SCF technologies provide a green, essentially solvent-free, alternative that produces very pure nanoparticles with very narrow and controlled particle size distributions. The main constraint of wide-scale industrial implementation is the need for highly specialised, costly high-pressure equipment, complicated phase-behaviour thermodynamics, and substantial engineering challenges in scaling-up. (Chauhan et al., 2022).

Bottom-up approaches tend to consume less energy and result in less controlled crystal growth, and are prone to particle aggregation or unwanted polymorphism unless subject to careful stabilisation measures.

2.3.3. Combination Approaches (e.g., SmartCrystal®, NanoEdge™)

These hybrid strategies integrate bottom-up and top-down processes to minimise energy input while achieving narrow particle size distributions. For example, precipitation followed by homogenization reduces processing time and drug loss. SmartCrystal® technology offers improved reproducibility and industrial scalability for drugs like glibenclamide and celecoxib (Möschwitzer, 2013).

SmartCrystal® technologies are a range of second-generation drug nanocrystal strategies where a bottom-up step (e.g., precipitation or emulsion diffusion) is purposely paired with a subsequent top-down high-energy step, such as high-pressure homogenization or wet bead milling (Al Shaal et al., 2010; Joshi, 2019; Möschwitzer). The reason behind this combinative design was to address

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practical shortcomings of classical first-generation nanocrystals, such as excessive milling durations, equipment wear, and less efficient control of particle-size distribution, especially in the case of very poorly soluble compounds (Joshi, 2019; Möschwitzer, 2013). The first bottom-up process in the SmartCrystal® concept forms drug micro- or nanocrystals at controlled supersaturation, and the second homogenization/milling step homogenizes the size distribution and eliminates larger particles, which results in a high level of size reduction at minimum total energy input relative to purely top-down processes (Al Shaal et al., 2010; Bhaskar et al., 2024; Joshi, 2019) (Figure 5).

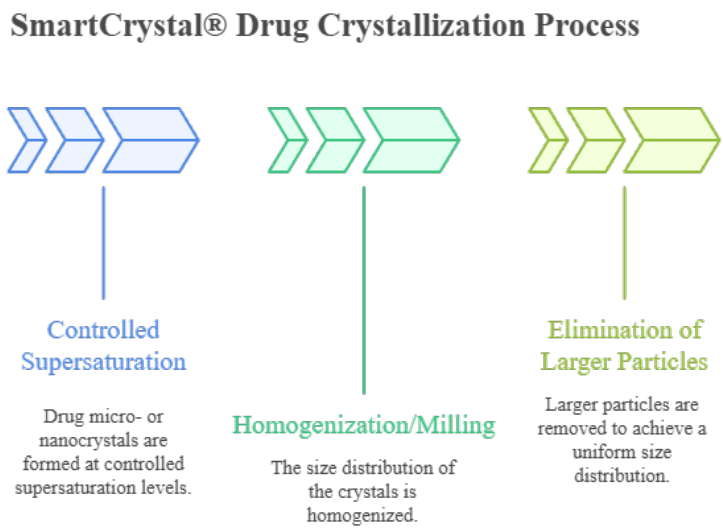


Figure 5. Flow diagram of formation of NanoCrystal®

In pharmaceutical terms, SmartCrystal® systems are intended to maintain the desirable crystalline structure of the drug and optimise the growth in the surface area to maximise the rate of dissolution and apparent solubility at saturation (Joshi, 2019; Li et al., 2015). Many nanocrystal reviews repeatedly demonstrate that the oral bioavailability of Biopharmaceutics Classification System (BCS) class II and IV drugs is enhanced by reducing the size to the nanometer scale, which also accelerates dissolution (Joshi, 2019; Li et al., 2015; Moechswitzer, 2013). In SmartCrystal® platforms, this dissolution enhancement is typically achieved with shorter processing times and reduced stress on the drug substance and equipment, because the high-energy step only needs to refine a pre-formed population of small particles rather than comminute bulk crystals from the outset (Al Shaal et al., 2010; Bhaskar et al., 2024).

Mechanistically, critical material and process parameters in SmartCrystal® production include the stabiliser type and concentration, drug load, precipitation conditions (e.g., solvent–antisolvent ratio, mixing intensity) and the subsequent homogenization pressure, cycle number and milling speed (Al Shaal et al., 2010; Ambrus et al., 2019). The combination of these variables controls the most important quality parameters like mean particle size, polydispersity index and zeta potential, which subsequently affect physical stability, redispersibility after drying, and in vivo performance (Ambrus et al., 2019; Joshi, 2019). Due to this close process-quality connection, SmartCrystal® technologies can be easily integrated into a Quality by Design framework, where design-of-experiments and risk assessment are employed to establish a robust design space in which nanocrystals can be manufactured (Bhaskar et al., 2024; Joshi, 2019).

Combination approaches using SmartCrystal-type nanocrystals have been investigated with a range of poorly soluble drugs, such as non-steroidal anti-inflammatory drugs like meloxicam and niflumic acid, where the nanocrystals obtained through combined bead milling and high-pressure homogenization exhibit significantly enhanced dissolution characteristics relative to the respective coarse drugs (Ambrus et al., 2019; Joshi, 2019). In a broader sense, second-generation and smarter nanocrystal systems with polymeric carriers or functional excipients have been reported to further increase solubility, control release, and

improve bioavailability in preclinical models, which justifies the overall utility of combinative nanocrystal approaches to challenging drug candidates (Bhattacharya et al., 2019; Li et al., 2015; Möschwitzer, 2013). In this continuum, SmartCrystal platforms can be considered as practical, process-based systems that are a bridge between classical nanocrystals and more sophisticated hybrid systems, which offer a scalable pathway to high-performance nanosuspensions that can be incorporated into oral, parenteral and topical dosage forms (Bhaskar et al., 2024; Joshi, 2019; Möschwitzer, 2013).

2.4. Stabilisation Techniques

Because nanosuspensions have a very high surface-area-volume ratio, the system is very energetic and thermodynamically unstable. The bare drug particles are naturally inclined to reduce their surface free energy by agglomerating, flocculating, or by Ostwald ripening (dissolution of small crystals and simultaneous growth of larger ones). Thus, stabilisers should be chosen and optimised to ensure crystal growth is stopped and a homogenous colloidal suspension is obtained. The two main biophysical processes, or a mixture of them, promote stabilisation (Peltonen and Hirvonen, 2010; Wang et al., 2013).

Steric Stabilisation: Steric stabilisation is based on physical adsorption of the amphiphilic polymers or non-ionic surfactants on the drug nanocrystal surface. These molecules anchor to the drug with the hydrophobic parts and carry on their hydrophilic chains to the aqueous vehicle. This forms a large, physical barrier that causes approaching particles not to move too close to each other to combine into a larger particle through attractive van der Waals forces.

Examples: Hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP K30), and polyethene glycol (PEG 6000) are common polymeric stabilisers. Others that are in wide use include the non-ionic surfactants, Poloxamer 188, Tween 80, and Vitamin E TPGS (D-alpha-Tocopheryl polyethene glycol 1000 succinate). Remarkably, TPGS not only sterically stabilises the particles but also serves as an efflux pump inhibitor, which further increases the bioavailability in vivo (Tuomela et al., 2016). Steric stabilisation has been especially beneficial in oral preparations since it is not strongly affected by the changing pH and high ionic strength of the gastrointestinal tract.

Electrostatic Stabilisation: Ionic surfactants are used to stabilise the particle electrostatically by adsorbing onto the particle, and giving the particle a strong net electrical charge on the surface. The uniform charge, according to the DLVO (Derjaguin, Landau, Verwey, and Overbeek) theory, forms a repulsive electrostatic barrier between the neighbouring particles.

Examples: Sodium lauryl sulfate (SLS) and sodium deoxycholate are typical anionic stabilisers. The zeta potential is the measure of the efficiency of this repulsion. A pure electrostatically stabilised suspension needs an absolute zeta potential of at least 30 mV to prevent aggregation (Kargar et al., 2021). Nevertheless, the repulsion of ions by electric charges is easily neutralised by the action of the environment, including a high concentration of electrolytes in biological fluids.

Electrosteric Stabilisation: Formulation scientists often use electrosteric stabilisation, a combination of these two mechanisms, in practice. This dual-barrier technique is attained by either the use of charged polymers or, more often, by the formulation of a specific combination of a steric polymer (e.g., HPMC) and an electrostatic surfactant (e.g., SLS). This composite solution averts the growth of particles in the manufacturing processes of high energy (such as homogenization) and offers the highest resistance to agglomeration in the long-term shelf life and transit in the body (Jacob, 2020; Wang et al., 2013).

2.5. Post-processing and Solidification

Nanosuspensions can be transformed into solid forms such as granules, tablets, or capsules using spray drying, freeze-drying, or fluidised bed drying. These strategies improve storage stability, ease of transport, and patient compliance. Re-dispersibility of dried nanosuspensions in aqueous media is often optimised using cryoprotectants or bulking agents (Malamatari et al., 2018).

3. QUALITY BY DESIGN AND ITS APPLICATIONS IN NANOSUSPENSIONS

The past few decades have witnessed the evolution of Quality by Design (QbD) from a regulatory aspiration to an actual, data-based methodology that directs formulation scientists through the entirety of development, from initial idea to commercial

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production. This report is an introductory report that explains the concepts and various terminologies of QbD before going ahead to explain the current implementation of the paradigm being exploited to develop robust nanosuspension drug products to overcome the challenges of solubility and bioavailability issues of modern therapeutics.

QbD incorporates process knowledge, risk identification and reduction, as well as perpetual improvement in a lifecycle context; nanosuspension technology is one such example where the same principles are strictly enforced

3.1. Historical Context

The pharmaceutical industry has long been based on a "Quality by Testing" (QbT) paradigm. In QbT, the quality of the products was guaranteed by strict production procedures and the vast testing of the end products. Nevertheless, with the advent of even more complex drug formulations, especially nanomedicines, it became clear that quality could not just be put into a product after its production; it needed to be designed into it (Zhang and Mao, 2017).

In 2002, the FDA stimulated the modern QbD paradigm with the initiative, Pharmaceutical cGMI of the 21st Century: A Risk-Based Approach. This movement aimed at replacing trial-and-error formulation with empirically formulated science-based, managed-risk development strategies. This philosophy was formally integrated into international pharmaceutical standards as part of the International Council for Harmonisation (ICH) guidelines, namely ICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) (Yu et al., 2014). This change in history is especially crucial to nanosuspensions. Since nanoscale thermodynamics and the stability of particle depend on small variations in processes, an empirical approach often results in batch failures. QbD requires an active knowledge of these factors, where medicines exhibit consistent clinical performance throughout each batch to the final one.

3.2. Core Terminology

Quality Target Product Profile (QTPP) - prospective summary of the drug product's quality characteristics that ensure desired safety and efficacy.

Critical Quality Attributes (CQAs) - measurable physical, chemical or microbiological properties that must remain within limits to meet QTPP goals.

Critical Material Attributes (CMAs) - raw-material properties that influence CQAs.

Critical Process Parameters (CPPs) - operational variables that impact CQAs.

Design Space - multidimensional combination of CMAs and CPPs that consistently delivers CQAs; movement within this space is not a regulatory change.

Control Strategy - planned set of controls that assures operation within the design space throughout the lifecycle.

3.3. Risk Assessment and Design of Experiments

The key driver of the QbD model is risk assessment. It fills the difference between the Quality Target Product Profile (QTPP) and the real manufacturing parameters by quantifying the risk of certain variables to the quality of the product systematically.

This is normally initiated by qualitative brainstorming tools, e.g. the Ishikawa (Fishbone) diagram, that plots out all the possible Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) that may theoretically influence the Critical Quality Attributes (CQAs) of the nanosuspension (e.g. equipment type, milling speed, stabiliser concentration). A quantitative tool, such as Failure Mode and Effects Analysis (FMEA), will be used after this qualitative mapping. FMEA is used to provide a numerical value to each variable according to three criteria, which include the Severity of the effect on the CQA, it is Likely to Occur, and it is Detectable. The product of these factors results in a Risk Priority Number (RPN) (Zhang and Mao, 2017; Sharma et al., 2022).

Variables with a high RPN are considered high-risk and are then input into statistically designed experiments (Design of Experiments, or DOE). DoE substitutes the old approach of One Factor at a Time (OFAT) testing with multivariate statistical models. Non-essential variables have been filtered out in most cases by first using screening designs (like Plackett-Burman). The optimisation designs (e.g., Box-Behnken design, Central Composite design) are then applied to test the exact mathematical interactions between the remaining high-risk CPPs and CQAs.

This risk-to-optimisation pipeline systematically will result in the Design Space, the defined operating space within which stability and functions of the nanosuspension are assured (Peltonen, 2018; Politis et al., 2017).

3.4. QbD in Nanosuspensions

The development pathway in QbD terms begins by translating the intended clinical uses of a nanosuspension product into a Quality Target Product Profile (QTPP), which states parameter values, e.g. mean particle size, polydispersity index (PDI), zeta potential, solid-state form, and dissolution characteristics. (Kuk et al., 2019)

In this context, Critical Quality Attributes (CQAs) are assigned, the variables, the exact control of which is crucial to patient safety and efficacy. Particle size (within a range of about 100-300 nm), and PDI (<0.25) are particularly typical, to facilitate fast dissolution and avoid capillary clogging, and zeta potential values outside of the range of +/-20 mV to assure long-term colloidal stability. (Gogoll et al., 2023) Each CQA is then mapped to its controlling Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) through a structured risk assessment, often including Ishikawa diagrams and Failure Mode and Effects Analysis, and the three most important levers turn out to be stabiliser chemistry, the energy input in milling, and drug load. (Sharma et al., 2022) (Figure 6).

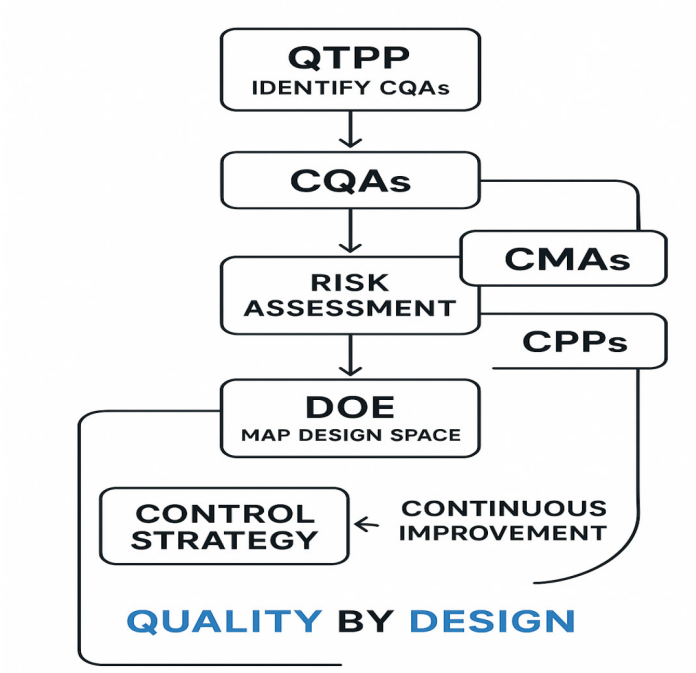


Figure 6. Quality by design workflow from QTPP to continuous improvement

At this point, an experimental design is called upon, which in most cases is a Design of Experiments (DoE) strategy to measure the interaction between the identified inputs. In top-down wet media milling, Box Behnken or central-composite designs have been shown to produce second-order models that correlate bead size, milling speed, and stabiliser concentration with particle-size outcome, often with R 2 values of 0.90 or greater. (Box & Behnken, 1960).

Bottom-up antisolvent precipitation shows comparable reliance on supersaturation ratio, mixing intensity and stabiliser blend, though it generally achieves smaller primary particles at the cost of scale-up complexity (Tehrani et al., 2019). After pilot-scale confirmation has been achieved, the resulting design space, which is the multi-dimensional space in which all batches satisfy the specified CQAs, gives manufacturers the flexibility to vary operating conditions without initiating a regulatory inquiry into variation requests. (International Council for Harmonisation, 2009).

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Recent studies confirm the effect of Quality by Design (QbD) on the performance of nanocrystals. A resveratrol nanosuspension using a three-factor Box Behnken design provided particles with an average diameter of 46 nm and a negative zeta potential of -38 mV with 1.6-fold increased bioavailability in rats (Kuk et al., 2019). A wet-milled imiquimod dispersion was optimised with a central-composite design based on milling time and speed, and the process had an ability to keep particle sizes between 350 and 400 nm in 13 Good Manufacturing Practice (GMP) batches, which confirmed scalability under actual operating conditions (Sharma et al., 2022). Simultaneous observations using high-pressure homogenization corroborate that the relative energy levels and not the absolute pressure levels are used in maintaining the size of the particles, when scaling-up from laboratory-scale (40 mL) to a commercial-scale (100 L) apparatus (Bhakay et al., 2022).

4. CASE STUDIES IN NANOSUSPENSION-BASED DRUG DELIVERY

The recent uses of nanosuspension technology are good examples that give a good experimental and clinical support to the effectiveness of nanosuspension technology to improve solubility, oral bioavailability, and therapeutic efficacy of poorly water-soluble drugs. Table 1 provides comprehensive case studies of some successful examples of small drugs transformed into nanosuspension formulations.

Table 1. Drug-specific nanosuspension case studies

Drug	Stabilizers	Preparation Method	Pharmacokinetic Improvements	*In Vivo* Model	Relative Bio-availability	Ref.
Valsartan	Poloxamer 188	High-pressure homogenization (HPH)	↑Cmax (2.3x), Faster Tmax, ↑AUC, Enhanced antihypertensive effect	Wistar rats	2.3 fold increase	(Gora et al., 2016)
Aceclofenac	HPMC, PVP-K30, SLS	Ultrasonication nanosuspension as granulating fluid	↑Cmax (1.74x), ↑AUC (2.3x), Higher dissolution rate	Rabbits	Increased vs marketed formulation	(Rahim et al., 2020, Patnaik et al., 2015)
Diacerein	Poloxamer 407, sodium deoxycholate	High-speed homogenization + media milling (top-down combo)	~400-fold ↑ saturation solubility, ~98% drug release at 2min, ↑Cmax, ↑AUC	Healthy human volunteers	131.4% relative to commercial product	(Parekh & Kanabar, 2017, Nanavati et al., 2019)
Celecoxib	TPGS (D-α Tocopheryl polyethylene glycol 1000 succinate)	HPH, Nano-precipitation	↑Dissolution rate (90.8% vs 47.9%), ↑Bioavailability (245.8%)	Rats	2.46-fold increase	(He et al., 2017)
Ezetimibe	Tween 80	Solvent-anti-solvent precipitation	~4-fold ↑ saturation solubility, ↑Cmax (3.1x), ↑AUC	-	3.1 fold increase	(Thadkala et al., 2014)
Metformin	MOF (nanoMIL-89)	Loading into MOF nanoparticles	Sustained release over 96h, reduced dosing frequency	-	Not applicable (extended-release profile)	(El-Tanani et al., 2024, Zare et al., 2016)
Tinidazole	Bacterial minicells, nanoprecipitation	Encapsulation in minicells, nano precipitation	↑Absorption and bioavailability compared to free drug	Mice, Ex vivo rat intestine	Improved absorption	(Vu et al., 2019, Pawar et al., 2016)
Itraconazole	Sodium lauryl sulfate, HPMC	High-pressure homogenization	↑Cmax (3.6x), ↑AUC (4.2x), >90% dissolution in 30min vs <20%	Rats	3.6-4.2-fold increase	(Mahmoud et al., 2022)

Table 1. Continued

Drug	Stabilizers	Preparation Method	Pharmacokinetic Improvements	*In Vivo* Model	Relative Bioavailability	Ref.
Nifedipine	PVP-K30, Tween 80	Bottom-up nanoprecipitation	↑Cmax (2.4x), ↑AUC (2.8x), ~85% dissolution in 20min vs 28%	Rabbits	~2.4-2.8-fold increase	(Zainal Abidin et al., 2023)
Curcumin	Poloxamer 188, Lecithin	Media milling	↑Bioavailability (6.1x), Enhanced anti-inflammatory efficacy	Rats	6.1-fold increase	(Shrivastava & Mishra, 2023)
Apigenin	HPMC, Sodium cholate	High-speed homogenization and precipitation	↑Cmax (8.2x), ↑AUC (7.6x), >90% release in 30min, Tumor volume reduction	Wistar rats, Xenograft breast cancer models	~7.6-8.2-fold increase	(Khan et al., 2022)
Raloxifene	Tween 20, PVP	Ultrasonic-assisted precipitation	↑Cmax (3.5x), ↑AUC (3.2x), 95% dissolution in 20min	-	~3.2-3.5-fold increase	(Rai et al., 2021)
Rifampicin	-	Antisolvent precipitation followed by sonication	↑Cmax (2.9x), ↑AUC, Enhanced anti-TB efficacy	Rats, Infected mice models	~2.9-fold increase	(Umerska et al., 2023)
Olmesartan Medoxomil	Sodium deoxycholate, Lecithin	Nanoprecipitation	↑Cmax (2.1x), ↑AUC (2.6x), Enhanced antihypertensive action	Wistar rats	~2.1-2.6-fold increase	(Nanda et al., 2024)

5. ADVANCES IN NANOSUSPENSION

In the modern scenario of nanomedicine, nanosuspension technology has developed significantly to find the best formulation stability, targeted and regulated drug delivery, and at the same time has introduced novel manufacturing practices, namely systematic screening of stabilisers, design-of-experiments (DoE), and additive manufacturing to enhance solubility, bioavailability, and patient adherence.

One of the more recent developments that is very relevant is the methodical selection of stabilisers through wet milling. In a recent 2023 study, researchers have optimised nanosuspensions of canagliflozin with an assessment of different polymer-surfactant combinations like HPMC with Tween 80 or Soluplus with PVP. The optimised formulation had a zeta potential of -14 mV and a mean particle size of 204.5 nm. The nanosuspension had a 3.05- and 3.51-fold increase in the rate of dissolution at pH 4.5 and pH 6.8, respectively, compared to a marketed tablet during non-sink dissolution testing. In addition, the formulation was physically stable at room temperature and 4 C over three months (Birari & Garnaik, 2023).

The use of Design-of-Experiments (DoE) to have a specific control of release kinetics and therapeutic performance is equally important. Researchers optimised a nanosuspension of the new wound-healing agent NDH-4338 using a Box-Behnken design. The evaporative-ultrasonication time, concentration of the stabilizer and sonication power were tuned systematically to produce particles of around 180 nm with a low polydispersity index (PDI < 0.2) and high encapsulation efficiency (>85 %). The improved formulation had a sustained release of more than 24 h and remarkably enhanced wound healing in a mouse burn model, highlighting the value of statistical design in producing a precision-controlled drug delivery (Thompson et al., 2024).

In the context of personalised medicine, additive manufacturing has gained a central position in the wider debate. An example of such a study is a 2022 study that shows how to prepare ink-jet-printable naproxen nanosuspensions through resonant acoustic mixing. In this system, the volumes of drops (150 pL) were still within the commercial range of ink-

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jet nozzles without affecting viscosity or surface tension. Drug and particle size (D50 200 nm) were maintained after printing, enabling precise on-demand dosing and shortening prototyping time of patient-specific dosage forms. (Nguyen et al., 2022)

In the context of the highly developed pharmaceutical production, a shift in paradigm between traditional batch production and continuous flow chemistry in microfluidic devices is an important step in the right direction. In contrast to classical bulk-precipitation methods, which frequently have the disadvantage of poorly-controlled fluid dynamics and batch-to-batch variation, in microfluidic reactors, the rapid, controlled micromixing of streams of solvent and antisolvent can be achieved over the millisecond time scale. The resulting high homogenization of the mixing interface due to this tight spatiotemporal control provides a highly homogenous nucleation environment, resulting in nanosuspensions with very narrow particle size distributions and high reproducibility (Hamdallah et al., 2020).

Moreover, the application of Artificial Intelligence (AI) and Machine Learning (ML) is changing the pre-formulation landscape in essence. Instead of fully utilising the empirical trial-and-error, scientists now turn more to the ML algorithms to perform virtual formulation iterations. These predictive computational models can be used to analyse large datasets of physicochemical properties to pre-screen the best combinations of stabilisers, ratio of drug and polymer, and determine the long-term physical stability of the nanosuspension before going to the physical laboratory (Warke et al., 2026).

This data-driven, computational process is also enhanced with the implementation of digital twin technologies. By developing a realistic in silico model of the manufacturing equipment, including a digital twin of a microfluidic lamination mixer or a high-pressure homogeniser, researchers can recreate the complex fluid dynamics, mathematically predict important quality characteristics (such as particle size and polydispersity), and even perform real-time monitoring of the process. The potent combination of AI-based virtual formulation, monitoring digital twins process, and continuous microfluidic production can cut down drug development times by a factor of orders of magnitude and provide a seamless and highly controlled scale-up between the bench and commercial production (Hao et al., 2022).

Transdermal drug delivery has come a long way over the past few years with the strategic application of drug-loaded nanoparticles. One of the most promising methods is to incorporate nanosuspension into dissolving micro needles. In a typical study, investigators incorporated a diclofenac nanosuspension (made by bead milling to ensure that the particles were less than 300 nm in size) into poly(vinyl pyrrolidone) micro needle arrays. The micro needles allowed increased skin permeation by a factor of about four over that of conventional patches by offering not only micro-permeation routes but also a polymeric matrix with the ability to sustain release. It is therefore an effective and less invasive alternative to the oral route of administration and is effective in minimising the gastrointestinal side effects. (Rossi et al., 2023)

Future trends also emphasise the production of stimuli-sensitive and smart nanosuspensions. pH, temperature-, or enzyme-sensitive polymers are used to enable these systems to release drugs at a specific site, and the targeted characteristics of these systems are optimised by the addition of ligands like folate or biocompatible peptides to tumour cells. The combination of imaging agents permits theranostic use, and supercritical fluid (SCF) micronisation produces narrow particle size distributions (<150 nm) and sensitive release patterns in tumour microenvironments. Such formulations yielded highly superior therapeutic indices in preclinical studies, and they have considerable clinical potential. (Lee et al., 2025)

6. FUTURE PHARMACEUTICAL PERSPECTIVES AND INSIGHTS

The second generation of nanosuspension and nanocrystal products will likely go beyond mere improvement of solubility to platform technologies that can be adapted in individual therapeutic situations and patient requirements. Recent reviews highlight that drug nanocrystals are increasingly being positioned as versatile, carrier-free systems that can support targeted delivery, controlled release and improved pharmacokinetics across diverse indications, including oncology, anti-infective therapy and CNS disorders (Jacob, 2020; Khan & Boateng, 2021; Sivanathan et al., 2024). In this regard, further drug development is expected to involve the consideration of nanocrystal design at early stages of candidate selection and lifecycle

management to salvage so-called undruggable molecules and in order to prolong market life cycles.

One key opportunity is patient-centric and personalised dosage forms, which take advantage of the aqueous, high-drug-load character of nanosuspensions. As an illustration, nanosuspensions of naproxen that can be inkjet-printed have been created, allowing the on-demand dosing of this drug and maintained at sub-200 nm particle size after printing, which is especially appealing to pediatric, geriatric and personalised medicine (Nguyen et al., 2022). The same ideas can be applied to three-dimensional printed dosage forms and modular combination products, where nanocrystal feeds or inks are tailored to single pharmacokinetic profiles and pharmacogenomic profiles (Sivanathan et al., 2024). These methods are consistent with the wider trend of flexible, patient-specific solid oral dosage forms projected in future regulatory and industry roadmaps of precision pharmaceutics.

The development of stimuli-responsive and theranostic nanosuspensions is another critical direction whereby nanocrystals can be incorporated with smart polymers or hybrid carriers to realise microenvironment-triggered drug delivery. Nanosystems capable of responding to either tumour/inflamed tissue or non-tumour conditions by using pH-, enzyme-, or redox-sensitive polymers have been utilised to boost on-site drug liberation and reduce systemic exposure (Liu et al., 2024; Liu et al., 2020). In parallel, smart nanotheranostic platforms that integrate diagnostic imaging agents with drug-loaded nanocrystals are being investigated to enable response-guided dosing and real-time treatment monitoring (Montanari et al., 2020; Lee et al., 2025). These principles indicate that the products of nanosuspensions in the future could be more of a see-and-treat nature, especially in oncology and cardiovascular disease, where space and time of therapy are highly important.

From a manufacturing and regulatory standpoint, the incorporation of Quality by Design (QbD), process analytical technology (PAT) and digital process control is likely to be at the heart of the pharmaceutical future of nanosuspensions. QbD studies have already shown the ability to define robust design spaces of nanocrystal formulations using design-of-experiments and risk assessment, as has been done with resveratrol and NDH-4338 nanosuspensions (Peltonen, 2018; Kuk et al., 2019; Roldan et al., 2024). This is likely to be extended to continuous and semi-continuous manufacturing platforms in the future, where wet milling or high-pressure homogenization is paired with real-time particle-size measurements and model-predictive control (Jacob, 2020; Mane et al., 2025). These developments must enable real-time release testing, lessen the variability between batches, and enable international regulatory acceptance of sophisticated nanosuspension products.

7. CONCLUSION

Nanosuspension technology has moved undeniably out of the niche, last-resort approach to rescuing brick-dust molecules into a broad and flexible platform to build the new pharmaceutical development industry. Using the principle of biophysical mechanics, principally the geometric expansion of the ratio of surface area to volume, nanosuspensions readily overcome the solubility and bioavailability obstacles that historically have wreaked havoc on formulation science.

Nevertheless, even with huge commercial achievements, several critical risk factors need to be kept under close eye. These systems are thermodynamically metastable because of their large surface free energy, which makes them acutely susceptible to Ostwald ripening, irreversible agglomeration, and unwanted polymorphic transitions upon long-term storage or downstream processing (e.g., lyophilisation). Moreover, scale-up of high-energy processes (such as HPH and media milling) poses serious threats of thermal degradation and shear-induced crystal lattice defects. From a regulatory and clinical perspective, the possible in vivo nanotoxicology of the carrier-free particles and the long-term biology of the high-dose stabilising polymers should be strictly tested in the clinical trials in the future (Muller et al., 2011; Wang et al., 2013).

In the future, it can be expected that the interplay of material science, continuous manufacturing, and digital engineering will shape the future of this exciting field. The second breakthrough in nanomedicine will not be just the ability to make smaller particles, but to make smarter formulations. The paradigm has to change completely to non-empirical trial and error. Virtual formulation screening with artificial intelligence integration and microfluidic continuous manufacturing and monitoring of the digital twin process will enable unprecedented control of Critical

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Quality Attributes (CQAs) in real-time (Hamdallah et al., 2020; Warke et al., 2026). And, the conjugation of stable nanosuspensions with state-of-the-art additive manufacturing, including the 3D printing of nanocrystal ink-like materials, has an enormous potential in achieving the actual patient-centric, personalised dosing.

Finally, nanosuspensions should stop being thought of as a mere particle size reduction method, but as a versatile, adjustable delivery motor. Researchers can reduce the risks of thermodynamic limitations by actively implementing computationally-based Quality by Design (QbD) models to enable the full therapeutic potential of the next generation of complex pharmaceutical active ingredients to be unlocked.

Author Contributions

RC, SB: Conceptualization; Supervision; Formal analysis.

BT, YB, SK: Investigation; Methodology; Writing – original draft; Visualization.

SB, BP: Writing – original draft; Writing – review & editing; Data curation.

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Human Ethics

Not applicable.

List of Abbreviations

BCS: Biopharmaceutical Classification System

QbD: Quality by Design

API: Active Pharmaceutical Ingredient

NCE: New Chemical Entity

CQA: Critical Quality Attribute

CMA: Critical Material Attribute

CPP: Critical Process Parameter

QTPP: Quality Target Product Profile

PDI: Polydispersity Index

SLS: Sodium Lauryl Sulfate

FMEA: Failure Mode and Effects Analysis

DoE: Design of Experiments

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