Review

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Advances in Nanosuspension Technology: Current Trends and Future Horizons

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Abstract

Advancements in contemporary technology have led to the discovery of numerous medications with improved efficacy; however, their limited water solubility restricts their clinical use. Approximately 40% of drugs in development and 60% of synthesized molecules have low water solubility, presenting a major challenge in drug formulation. Generally, low bioavailability is correlated with poor solubility. Nanosuspension offers a potential solution to this challenge. When materials are transformed into nanoscale dimensions, they undergo significant changes in their physical properties. This review describes the various medicinal benefits of nanonization, the industrial production processes currently available, and the different dosage forms created with nanocrystals. An overview of existing nanosuspension products is provided, highlighting their advantages over conventional products and offering an outlook for the future.

Keywords: nanosuspension; solubility; targeted drug delivery; transdermal; bioavailability

Introduction

Many medications face solubility challenges in both aqueous and nonaqueous environments, impacting their efficacy and resulting in poor bioavailability. This bioavailability issue is often due to inadequate permeability or solubility. With technological advancements, there is an increasing need for improved pharmaceutical technologies [1]. The solubility and stability of drugs at room temperature are crucial factors in developing novel formulations [2]. Hence, various strategies have been employed to enhance the solubility and bioavailability of pharmaceuticals. Developing medications with poor water solubility into standard dosage forms presents numerous challenges, with unpredictable absorption being a major challenge [3]. To address this, several methods have been devised to increase the dissolution rate of these medications. Consequently, the primary goal of drug development in recent decades has been to enhance the bioavailability of poorly soluble drugs. One common approach to increasing solubility is particle size reduction. Micronization, which creates particles ranging from 2 to 5 μm, increases the surface area of the drug particles. However, for poorly soluble drugs, micronization may not be sufficient to improve absorption and dissolution rates in the gastrointestinal system [4]. Other methods developed to optimize the dissolution rate of these poorly soluble drugs include solubilization, salt formation, and the creation of solid dispersion systems. Particle size reduction, in particular, can

deteriorate the wettability and flow characteristics of powders, promote the formation of electrostatic forces, and result in inconsistent formulations. Furthermore, the solubility of salts is highly dependent on the pH value, which varies greatly in the gastrointestinal tract, making the dissolution rate highly unpredictable. These methods require significant energy and have several drawbacks, including a wide particle size distribution, contamination of medications, variation in crystal structures, and uncontrollable particle morphology. Recently, extensive research has focused on the efficacy of bottom-up technologies in nanotechnology. These technologies, including the supercritical fluid (SCF) technique and liquid precipitation, are used to produce ultrafine drug particles, such as paclitaxel, olanzapine, and clarithromycin. Although advanced methods—such as cyclodextrin-based inclusion complexes, liposomes, microemulsions, and solid dispersion technology—are available to synthesize water-insoluble medications, there is no universal solution for creating these drugs. Therefore, specific approaches are needed to enhance clinical efficacy and address pharmacoeconomic concerns to overcome formulation-related issues [5]. The nanosuspension technique stands out owing to its simplicity and advantages over alternative formulations. It effectively addresses the problems associated with Biopharmaceutical Classification System (BCS) Class II medications by improving the dissolution rate and bioavailability while maintaining the necessary crystalline state. This method also helps reduce the dosage required for traditional oral administration forms [6, 7].

A nanosuspension is a biphasic, submicron, colloidal, stable aqueous drug dispersion [8]. The most common delivery methods for marketed nanosuspensions include oral, topical, parenteral, ophthalmic, and pulmonary routes. Nanosuspension is an appropriate formulation strategy for medications insoluble in both organic and aqueous media. Nanosuspensions can be formulated using top-down or other methods, with nanoprecipitation showing promise for creating nanosuspensions of drugs with limited water solubility [9]. To formulate a nanosuspension, the drug should have high dosage, high melting point, and high log*P* value. Medications with a log*P* value of 1−3 indicate good passive absorption through lipid membranes; however, log*P* values outside this range often indicate inadequate transport mechanisms. Over the past three decades, various approaches have been used to nanonize hydrophobic drugs to address solubility and bioavailability concerns. Nanosuspensions have extensive applications [10], including high drug loading and passive drug targeting. Methods such as high-pressure homogenization and media milling have been used to produce commercially stable nanosuspensions. Compared to other nanotechnology-based formulations, nanosuspension patents have a greater chance of commercial success. Currently, there is a push to expand their use in targeted drug delivery to specific sites.

Advantages of Nanosuspension over Conventional Formulations

Advantages of nanosuspension

Over 40% of medications exhibit poor water solubility, posing significant formulation challenges. This issue is particularly complex for BCS Class II medications, which have poor solubility in both organic and aqueous media. For molecules with a high log*P* value that are soluble in oil but insoluble in water, creating a nanosuspension is recommended. There are several methods for addressing issues related to low solubility and bioavailability, including liposomes, emulsions, microemulsions, solid dispersions, β-cyclodextrin inclusion complexes, micronization, co-solvency, oily solutions, and salt formation. However, these methods are not always applicable to every drug. Instead of using lipidic systems for drugs insoluble in both water and inorganic media, nanosuspensions are employed for formulating drugs [11, 12]. Nanosuspensions can improve the solubility of drugs that are poorly soluble in both lipid and aqueous media by allowing the active component to reach the maximal plasma level more quickly when administered orally or intravenously. This method is beneficial for compounds that are poorly soluble, poorly permeable, or both, addressing the challenges associated with inadequately soluble chemicals in water [13].

Nanosuspensions, a cutting-edge formulation approach, have garnered significant attention in pharmaceutical research and development due to their remarkable advantages over conventional formulations. By reducing drug particle size to the

nanometer range and dispersing them in a suitable carrier medium, nanosuspensions offer a promising strategy for addressing various challenges in drug delivery. Table 1 shows the advantages of nanosuspensions over conventional formulations.

Properties of nanosuspensions

Physical long-term stability

The lack of Ostwald ripening in nanosuspensions is a unique characteristic that contributes to their long-term physical stability. Ostwald ripening, which leads to the formation of crystals and microparticles, is driven by differences in dissolving pressure and saturation solubility between small and large particles. Molecules diffuse from the more concentrated regions around small particles (with higher saturation solubility) to the regions around larger particles (with lower drug concentrations). This creates a supersaturated solution around the larger particles, leading to the crystallization and growth of these particles. Consequently, the small particles dissolve, eventually disappearing as the region around them becomes unsaturated [14].

Internal structure of nanosuspensions

The high-energy input during the disintegration process causes structural alterations in the drug particles. Under high-pressure homogenization, drug particles can transform from crystalline to amorphous states. Factors influencing these state changes include the drug's chemical composition, hardness, number of homogenization cycles, and the power density of the homogenizer. These chemical structure changes provided an interesting strategy for low-soluble compounds [15].

Adhesiveness

Ultrafine powders exhibit a noticeable increase in adhesiveness compared to coarse particles. This property can be leveraged to improve the oral administration of poorly soluble medications. For example, the bioavailability of danazol increased from 5% as a macrosuspension to 8% as a nanosuspension, demonstrating the potential benefits of using tiny drug nanoparticles for oral delivery [15].

Crystalline state and morphology

When developing nanosuspensions, one important consideration is the potential shift in the crystalline structure, which can include an increase in the particle's amorphous fraction or even the formation of entirely amorphous particles. Applying high pressures during nanosuspension creation promotes the amorphous form [15].

Increase in the saturation solubility and dissolution velocity of the drug

The increase in drug dissolution can be attributed to the surface area of the drug particles as they transition from micrometer- to nanometer-sized particles. According to the Noyes–Whitney equation (Eq. 1), an increase in surface area from micron-sized to nanometer-sized particles results in a higher dissolution velocity:

$$\mathrm{d}x/\mathrm{d}t = [(DA)/h][C_s - X/V] \quad (1)$$

where V is the volume of the dissolution medium, A is the surface area of the particle, D is the diffusion coefficient, h is the thickness of the diffusion layer, C_s is the solubility of the substance, and X is the concentration in the surrounding liquid [15].

Synthesis of Nanosuspensions

Nanosuspensions are prepared using bottom-up (e.g., antisolvent precipitation, liquid emulsion, and SCF techniques) and top-down (e.g., wet milling, dry milling, high-pressure homogenization, and co-grinding) methods (Fig. 1). Nowadays, techniques that combine these two methods are also frequently employed.

Table 1 Advantages of nanosuspension over conventional formulations

Route of administration	Advantages of nanosupension	Limitations of conventional formulation
Intravenous	Quick dissolution;tissue intended for extended retention	Nonspecific action;ineffective dissolution
Inhalation	Dose regulation;rapid dissolution	Reduced solubility, resulting in reduced bioavailability
Oral	Quick onset of action; enhanced solubility, resulting in enhanced bioavailability	Gradual start of action; insufficient solubility
Intramuscular	Decreased tissue inflammation; quick single-set of action	Low patient adherence due to pain
Ocular	Increased bioavailability; dose uniformity	Insufficient bioavailability

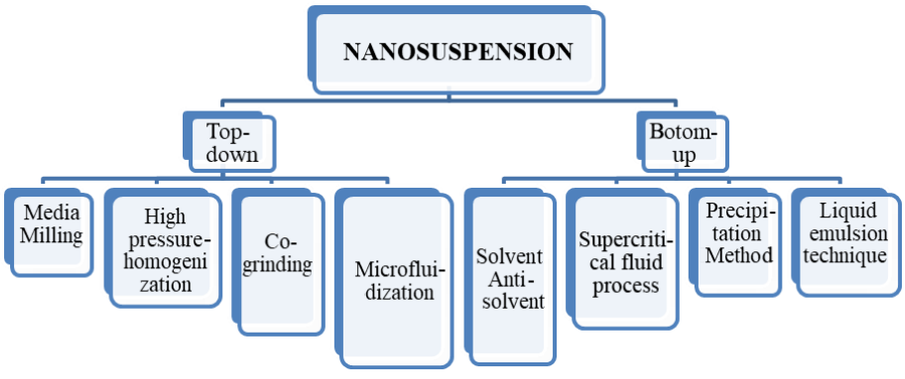

Fig. 1 Methods of nanosuspension preparation.

Bottom-up methods

In 1987, List and Sucker [15] introduced a bottom-up method, commonly known as "nanoprecipitation". This method is based on the principle that dissolved molecules can be precipitated by adding an insoluble material, resulting in nanosized particles [16–18]. For the successful implementation of this method, the active ingredient must be soluble in at least one solvent and appropriate stabilizers must be added to prevent particle growth after precipitation [19]. Bottom-up methods include antisolvent precipitation, precipitation technique, liquid emulsion, and SCF techniques.

Precipitation technique

In the past decade, the precipitation technique has been extensively used to generate submicron particles, particularly for poorly soluble medications. Initially, the drug is dissolved in a solvent [20]. This solution is then combined with a miscible antisolvent in the presence of surfactants. When the drug solution is quickly added to the antisolvent, typically water, the drug becomes supersaturated in the mixed solution, resulting in the formation of ultrafine crystalline or amorphous drug solids. This process involves two stages: nucleation and crystal growth [21]. A high nucleation rate combined with a low growth rate is essential to prepare a stable solution with the smallest possible particle size. Temperature influences both nucleation and crystal growth rates; the optimal temperature for nucleation may be lower than that for crystal growth, allowing for temperature adjustment [22]. The precipitation technique is simple, cost-effective, and easy to scale up for production. However, surfactants are necessary to control crystal growth, and the drug must dissolve in at least one solvent.

Supercritical fluid process

SCF techniques, combined with solubilization and nanosizing technologies, further reduce particle size. SCFs are noncondensable dense fluids with temperatures and pressures exceeding their critical temperature (T_c) and critical pressure (T_p) [23]. This method allows drug particles to be micronized to the submicron level. Recent advancements in SCF techniques have enabled the production of nanoparticulate suspensions with diameters ranging from 5 to 2 000 nm. However, the low solubility of surfactants and poorly water-soluble drugs in supercritical CO_2, along with the high pressure required for these operations, limits the application of this technology in the pharmaceutical sector [24].

Moreover, newly developed bottom-up methods, such as liquid antisolvent precipitation, precipitation assisted by the acid–base method, and the emulsion polymerization method—offer flexibility in controlling particle size and distribution.

Top-down methods

Top-down methods focus on reducing the size of larger particles to obtain various particles in the nanometer range [25]. The primary techniques used were media milling and high-pressure homogenization. These methods are generally more suitable for industrial production compared to bottom-up technologies and apply to currently marketed products.

Media milling

Nanosuspensions are created using pearl or high-shear media mills. The key components of these mills include the milling shaft, recirculation chamber, and milling chamber. The milling medium typically consists of balls or pearls made from ceramic-sintered

aluminum oxide or zirconium oxide [26]. The milling chamber contains a stabilizer, drug, water, and milling media. As the balls rotate at a high shear rate under controlled temperatures, they exert friction and impact on the sample, leading to particle size reduction and the formation of nanosized particles [27]. Media milling offers several advantages: it allows for the production of both highly concentrated and extremely dilute nanosuspensions, with drug concentrations ranging from 1 to 400 mg/mL while ensuring a nanoscale distribution of the final product. However, a common challenge with this method is the risk of corrosion of the beads and the milling chamber.

High-pressure homogenization

This technique involves three phases. First, a presuspension is created by dispersing drug powders in a stabilizing solution. Next, the presuspension is homogenized using a high-pressure homogenizer at low pressure, occasionally for premilling [28]. Finally, it is homogenized at high pressure for 10–25 cycles until the nanosuspensions of desired size are achieved [29].

Other methods

In addition to bottom-up and top-down methods, other preparation techniques, such as the solvent evaporation and melt emulsification methods, have been successfully developed. The solvent evaporation method involves creating polymer solutions in volatile solvents and emulsions. In recent years, ethyl acetate has replaced dichloromethane and chloroform due to its superior toxicological profile [30]. During this process, as the solvent for the polymer evaporates and the emulsion disperses through its continuous phase, it transforms into a suspension of nanoparticles. Traditional methods utilize two primary approaches to generate emulsions: single emulsions (e.g., oil-in-water) and double emulsions (e.g., water-in-oil). These techniques require rapid homogenization or ultrasonication, followed by continuous magnetic stirring at ambient temperature or low pressure to evaporate the solvent. The solidified nanoparticles are then recovered through ultracentrifugation and lyophilized after being cleaned of additives (e.g., surfactants) using distilled water. The size of the particles is influenced by several factors, including the stabilizer, homogenizer speed, and polymer concentration [31].

Advancements in Nanosuspension Technology

Recently, nanosuspensions have emerged as a promising substance in nanopharmaceuticals, showing high commercial potential [32]. The latest application of nanopowders as a delivery mechanism for oral drug administration aims to enhance the dissolution rates of poorly soluble medications. For instance, a hydrophobic antiretroviral drug, loviride, was stabilized in a Tween 80/poloxamer 188 nanosuspension in a laboratory setting through media milling, resulting in a sucrose co-freeze-dried nanopowder [33]. Generally, there is potential for pulmonary products. Although commercial nebulizers can aerosolize nanosuspensions, no products have been developed to date. Improving pulmonary deposition could make nanosuspensions popular products in the future [34].

Moreover, the injection of weakly water-soluble nanosuspension medications is a rapidly expanding field due to its advantages in reducing toxicity and enhancing therapeutic efficacy by eliminating the need for cosolvents in formulations. Current parenteral administration methods include complexation with cyclodextrins, micellar solutions, salt formation, solubilization with cosolvents, and, more recently, liposomes. However, these methods often have limited applications due to their limited solubilization capabilities and parenteral tolerability. In contrast, liposomes are generally more palatable and versatile for parenteral administration, but they frequently encounter issues such as physical instability, high manufacturing costs, and challenges in scaling up. Nanosuspensions may provide solutions to these challenges.

Recent stability-based research has demonstrated that quercetin's chemical and optical stability can be significantly enhanced by nanosuspension compared to a solution stored under identical conditions. The application of nanosuspension technology may optimize the stability of chemically labile pharmaceuticals. Engstrom et al. [34] attempted to create stable nanosuspensions using a unique floc structure design known as "open flocs". Through thin film freezing, bovine serum albumin (BSA) nanorods

with an aspect ratio of approximately 24 were produced. When mixed with hydrofluoroalkane (HFA) propellants, these BSA nanorods exhibited remarkable stability, with no sedimentation observed after a year. The high aspect ratio of the BSA nanorods, combined with the relatively strong attractive van der Waals forces at the particle contact sites, allowed the main nanorods to quickly lock together in an open structure when HFA was added, preventing the flocs from collapsing [35].

In a separate study, humanized mice infected with HIV-1 received an injection of an indinavir nanosuspension loaded into macrophages derived from bone marrow. This targeted administration method provided $CD4^+$ T-cell protection and markedly reduced the number of virus-infected cells in the lung, spleen, liver, lymph nodes, and plasma. Spironolactone (SP), a common mineralocorticoid prescribed to pediatric patients, is a poorly soluble medication with a bitter taste, low oral bioavailability, and a tendency to destabilize in aqueous environments. Lipid nanoparticles appear to be an effective method for overcoming the solubility issues associated with SP in lipid materials. Various approaches have been utilized to address challenges related to oral absorption and bioavailability [36]. One emerging strategy that shows promise for the effective administration of hydrophobic medications is nanosuspension.

Additionally, nanosuspensions can be incorporated into other forms using various methods, such as nanosuspension-loaded oral thin films (OTFs), nanosuspension-loaded *in situ* gels for ophthalmic administration, and nanoedge.

Nanosuspension-loaded OTFs

The oral route is the most practical, affordable, and widely used method of drug delivery due to its high patient compliance and versatility in dosage form formulation [37]. However, many medications suffer from low oral bioavailability and water solubility [38]. OTFs, a novel dosage form, resemble a postage stamp in dimensions, shape, and thickness (Fig. 2). When placed in the mouth without the need for water or chewing, OTFs quickly disintegrate, thereby protecting the formulation from instability caused by pH changes and gastrointestinal enzymes [39]. OTFs can stabilize nanosuspensions and enhance drug delivery. The drying process improves stability,

Fig. 2 Advantages of nanosuspension-loaded oral thin films.

whereas the film's high viscosity helps limit nanoparticle agglomeration. Such a tailored formulation is crucial for achieving a rapid onset of effect in emergencies without altering the drug's chemical composition. Advantages of nanosuspension-loaded oral thin films were shown in Fig. 2.

Nanosuspension-loaded *in situ* gel for ophthalmic administration

The eye is often recognized for its complex structure and resistance to external substances, including medications. While the anatomy and physiology of the anterior and posterior segments of the eye differ, both work together to impede the administration of drugs. When using topical medications to treat ocular infections, the main challenges typically include drug loss from the precorneal surface, limited absorption in the conjunctiva, and rapid drainage through the nasolacrimal system. Corneal impermeability and brief precorneal contact time lead to poor absorption, necessitating repeated dosing [40]. One significant cause of medication loss is the eye's defense mechanisms. Due to nasolacrimal drainage, tear turnover, lacrimation, and eye blinking, drugs can be removed quickly and easily from the eye's surface [41]. Developing a drug delivery system that addresses the shortcomings of existing methods and provides the benefits of targeted drug delivery over extended periods is a promising approach. Nanosuspensions can offer enhanced drug absorption due to longer residence time of nanoparticles on the corneal surface, higher drug concentrations in the infected tissue, maintenance of drug release over a prolonged period of time, reduction in the amount of dose, etc. [42].

Combination technology (nanoedge)

The American Association of Pharmaceutical Scientists held its annual meeting in Denver in 2001, where Baxter Healthcare Company introduced its nanoedge technology. Nanoedge is an aqueous dispersion of medication nanoparticles suitable for intravenous administration. Nanosuspension of itraconazole is an example of nanoedge technology. The particles are primarily produced using a high-pressure homogenization process, which can be achieved through piston-gap homogenizers for microfluidization or conventional homogenization in water. Alternatively, a new production method developed by Ghosh et al. can be used [43]. This method, known as the "microprecipitation method" combines precipitation with a high-energy input process, such as homogenization. Their process comprises three steps: (1) Creating a solution by dissolving the organic molecule in a first solvent that is water soluble; (2) Combining this solution with a second solvent to create a precipitate or "presuspension"; (3) introducing energy to the "presuspension" to create particles with an average effective particle size ranging from 400 nm to 2.0 µm.

One advantage of this approach is that the particles are intermediate products that will undergo further reduction through annealing, which addresses the issue of continued crystal growth after precipitation [44, 45]. By optimizing the precipitation conditions, more friable particles (semicrystalline or amorphous) can be created, allowing for more effective reduction during the subsequent high-pressure homogenization stage. This is particularly important for jet-milled medications already on the market, which may have highly crystalline and hard crystal structures (high Mohs hardness). In some cases, more homogenization cycles may be necessary for the direct homogenization of the jet-milled powder, leading to longer production times. Additionally, when producing tough crystals, the highest homogenization pressures (e.g., 2 000 bar) may yield maximum dispersity closer to 1 µm instead of the desired nanometer range [46–48].

Petersen [49] developed another combination process of nanosuspension that involves ball milling, followed by high-pressure homogenization. The performance of nanocrystals (e.g., their physical stability) can be significantly enhanced using controlled technology. For example, in dermal applications, poorly soluble pharmaceutical and cosmetic actives can penetrate the skin more effectively when coated with nanocrystals [50]. This enhanced penetration is facilitated by the increased concentration resulting from improved saturation solubility. New molecules that dissolve from the cream's nanocrystal depot quickly replace those that have entered the skin [51–55]. The use of nanosuspension for topical applications is protected by a patent application under the US Patent Cooperation Treaty [56 , 57]. Figure 3 gives brief procedure for combination technology.

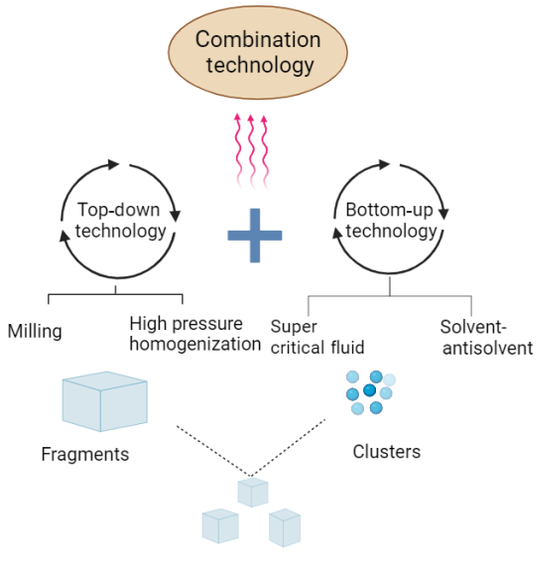

Fig. 3 The procedure for combination technology.

Table 2 highlights the applications of nanosuspensions in the treatment of various diseases and the corresponding drugs utilized. Nanosuspensions provide unique advantages tailored to each condition, including enhanced solubility, targeted delivery, improved therapeutic efficacy, and reduced systemic side effects.

Characterization of Nanosuspensions

Particle size distribution

The primary parameters that determine the physicochemical properties of a nanosuspension—such as saturation solubility, dissolution velocity, physical stability, and biological performance—are mean particle size and width of the particle size distribution, also known as the polydispersity index. Variations in particle size affect both saturation solubility and dissolution velocity. Particle size

Table 2 Applications of nanosuspensions for disease treatment

Drug	Category	Year	Method of preparation	Author	Outcome	Ref.
Methylprednisolone acetate	Anti-inflammatory	2007	Quasiemulsion solvent diffusion	Adibkia et al.	Prevention of ocular disease–related inflammatory symptoms	[58]
1,3-Dicyclohexylurea	Antihypertensive	2008	Wet milling	Ghosh et al.	Through oral delivery, a low-solubility substance can achieve significantly higher exposure levels.	[59]
Candesartan cilexetil	Antihypertensive	2011	Media milling	Detroja et al.	Candesartan's antihypertensive efficacy significantly increases when it is prepared as a nanosuspension.	[60]
Puerarin	Anticancer	2013	High-pressure homogenization	Wang et al.	Increased antiproliferative action is achieved by inducing morphological alterations and reducing cell viability.	[61]
Rifaximin	Anti-inflammatory	2016	Nanoprecipitation	Kumar et al.	Nanoformulations target the inflammation site, making them more effective than traditional tablets in reducing dosage and minimizing side effects.	[62]
Curcumin-docetaxel	Anticancer	2016	Precipitation	Sahu et al.	The co-administration of docetaxel and curcumin, a P-glycoprotein inhibitor, may enhance their efficacy against breast cancer.	[63]
Azoxystrobin	Antifungal	2018	Wet media milling	Yao et al.	Increased biological activity with reduced adverse environmental effects	[64]
Fluconazole	Antifungal	2021	Ultrasonication	Morteza-Semnani et al.	They have a suitable antifungal impact on *C. albicans* strains that show resistance.	[65]
Doxazosin	Antihypertensive	2021	Emulsification solvent diffusion	Al Ashmawy et al.	Hypertensive rats showed a significant and rapid decrease in mean arterial pressure.	[66]

distribution can be measured using various techniques, including the Coulter counter multisizer, laser diffraction, and photon correlation spectroscopy [67]. Laser diffraction measures the volume size distribution and counts particles ranging from 0.05 to 2 000 μm. Atomic force microscopy is used to visualize particle shape [68].

Particle charge (zeta potential)

Determining the zeta potential of a nanosuspension is essential, as it provides insights into the material's physical stability. The zeta potential is influenced by both the stabilizer and the drug itself. An electrostatically stabilized nanosuspension requires a minimum zeta potential of 30 mV to ensure high stability [69]. In cases of combined electrostatic and steric stabilization, a minimum zeta potential of 20 mV is preferred [70]. Electrophoretic mobility is commonly used to measure particle charge in the presence of an electric field, and the Helmholtz–Smoluchowski equation is then utilized to convert electrophoretic mobility to zeta potential [71].

Crystalline state and particle morphology

Evaluating both particle morphology and crystalline state is crucial for understanding any polymorphism or morphological changes of a drug may undergo during the nanosizing process. Nanosuspensions can exhibit varying crystalline structures due to high-pressure homogenization, potentially adopting amorphous shapes or other polymorphic forms [72].

Saturation solubility and dissolution velocity

The saturation solubility and dissolution velocity are critical parameters for analyzing changes in the *in vivo* performance of drugs, including bioavailability, plasma peak concentration, and blood profile. A significant advantage of nanosuspensions is their ability to enhance both saturation solubility and dissolution velocity compared to other methods. The saturation solubility of the drug should be evaluated using procedures outlined in the literature for various physiological buffers and temperatures. Research on the dissolution velocity of nanosuspensions highlights the benefits of developing sustained-release dosage forms based on nanoparticulate medicines. Dissolution velocity and saturation solubility should be evaluated under different conditions, including various physiological buffers and temperatures [73].

pH

To minimize "pH drift" and prevent electrode surface coating with suspended particles, the pH value of the aqueous formulation should be measured at a specific temperature and only after achieving settling equilibrium. Electrolytes should not be added to the external phase of the formulation to stabilize the pH. The pH of the prepared nanosuspension can be measured using a pH meter and transferred into a 10-mL beaker for accurate measurement [73].

Stability of nanosuspensions

Due to the high surface energy of nanoparticles, drug

crystals may aggregate. The primary role of the stabilizer is to fully wet the drug particles, creating an ionic or steric barrier that prevents Ostwald ripening and agglomeration, thereby forming a physically stable formulation. Common stabilizers used in nanosuspensions include cellulosics, poloxamer, polysorbates, lecithin, polyoleate, and povidones. Lecithin is often preferred in the preparation of parenteral nanosuspensions [74–78].

Drug content

To determine drug content, a necessary aliquot (0.5 mL) is removed from the nanosuspension and allowed to evaporate. After dissolving the residue in an appropriate organic solvent, the mixture is filtered using a 0.45-μm filter [79]. The total drug content is calculated using the following formula [80]:

Total drug content = (total volume of nanosuspension × amount of drug in aliquot)/volume of aliquot

Drug Delivery Application of Nanosuspensions

Due to particle size reduction and increased surface area, nanosuspensions have broad applications in oral, ocular, parenteral, and pulmonary drug delivery (Fig. 4), offering significant advantages over traditional treatments.

Oral drug delivery

Traditional oral drug administration often faces issues such as poor solubility, inadequate absorption, and insufficient effectiveness. Oral nanosuspensions have been developed to address these challenges. The increased surface area and small particle size of oral nanosuspensions enhance the bioavailability and solubility of poorly soluble drugs (BCS Class II) [81]. For example, danazol, a gonadotropin inhibitor with low bioavailability, showed significantly higher bioavailability when administered as a nanosuspension than the marketed danazol macrosuspension Danocrine. The danazol nanosuspension yielded an absolute bioavailability of 82.3%, compared to just 5.2% for Danocrine [82].

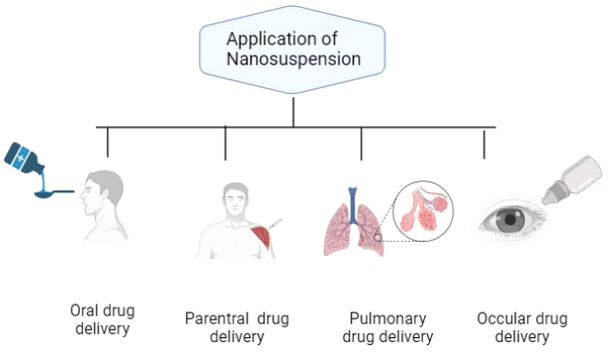

Fig. 4 Application of nanosuspension in a drug-delivery systems [81–84].

Ocular drug delivery

Nanosuspensions are also effective for drugs with low solubility in lachrymal secretions. Combining nanosuspensions with a suitable hydrogel, mucoadhesive base, or ocular inserts can sustain the medication's release over a predetermined period. Polymeric nanosuspensions have been shown to maintain drug release for 24 h and demonstrate better *in vivo* activity than currently available commercial formulations. For instance, the anti-inflammatory properties of ibuprofen improved significantly in a nanosuspension compared to its aqueous formulation [83].

Parenteral drug delivery

Drugs that are not injectable and are poorly soluble can be transformed into forms suitable for intravenous administration using nanosuspensions. Recent advancements have demonstrated the effectiveness of nanosuspensions as injectable formulations [83]. One major application of nanosuspension technology is the formulation of items for intravenous delivery. Intravenous administration offers several benefits, including delivering poorly soluble drugs without the need for more toxic cosolvents, enhancing the therapeutic effect of drugs available in conventional oral formulations, and targeting specific pathogens residing in macrophages. For instance, Peters et al. showed that when clofazimine nanosuspensions were developed for intravenous use, drug concentrations in the lungs, spleen, and liver were significantly higher, well above the minimal inhibitory concentration for most *Mycobacterium avium* strains [84].

Pulmonary drug delivery

Nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for pulmonary administration. Drug nanoparticles in aerosol droplets can reach deep into the lungs due to their small particle size. This small particle size also makes it possible to nebulize

aqueous medication solutions easily for pulmonary delivery. Medications successfully administered through the pulmonary route include itraconazole, budesonide, ketotifen, ibuprofen, indomethacin, and nifedipine [85].

Transdermal delivery of nanosuspension

Diclofenac sodium nanosuspension has been used for transdermal administration. The fundamental transdermal properties of the nanosuspension were assessed using a Yucatan micropig skin model. Through complex formation with sucrose erucate, the diclofenac sodium nanosuspension was successfully dispersed into isopropylmyristate as a nanosized suspension. Compared to the control, the nanosuspension enhanced the permeability flux of diclofenac sodium across the skin by up to 3–8 times. The optimal weight ratio for maximum diclofenac sodium penetration was 8:8, with a mean diameter of 14.4 nm for the nanosuspension [85].

Marketed formulations and patented formulations

Nanosuspension-based formulations are widely used to treat cancers, asthma, hypertension,inflammatory diseases, pains, nausea, cardiovascular diseases,and other diseases. Some nanosuspension-based formulations available on the market are shown in Table 3.

Patented nanosuspension formulations have emerged as a key area of innovation, driving the development of novel drug-delivery systems with diverse applications across various therapeutic domains. Table 4 presents some patented nanosuspension formulations.

Future Perspectives

BCS Class II includes many recently identified pharmacological compounds with extremely low water solubility [94]. The number of low-soluble medications that cannot be manufactured using conventional methods has been increasing, making nanosuspensions increasingly significant. The extensive use of nanosuspensions in drug formulation creation can be attributed to their advantages, including applicability to various pharmaceuticals, simplicity of scaling up, and minimal use of excipients, as well as improved solubility, dissolution rate, and bioavailability [95–97]. Nanosuspensions can be used to administer drugs through cutaneous, pulmonary, parenteral, ophthalmic, and especially oral routes, effectively treating various illnesses. The rise of nanostructured-based commercial products highlights these benefits [98]. Further commercialization of nanosuspension is expected with the completion of clinical research into alternative administration methods, in addition to existing commercial products [99, 100]. Despite significant advancements in nanosuspension formulations, challenges remain in stabilizer

Table 3 Marketed formulations of nanosuspensions

Trade name	Drug	Company	Status	Indication
Rapamune	Sirolimus	Wyeth	Marketed in 2003	Immunosuppressive
Megace ES	Megestrol	Par Pharmaceuticals	Marketed in 2005	Cachexia
Invega Sustenna	Palperidone palmitate	Janssen Pharma	Marketed in 2009	Schizophrenia

Table 4 Patented nanosuspension formulations

Patent publication number	Year	Status	Title	Ref.
US9616019B2	2017	Active	Nanosuspension of a poorly soluble drug through microfluidization	[86]
WO2019028457A2	2019	Active	Injectable nanosuspension formulation of diethylstilbestrol	[87]
US10251866B2	2019	Active	Pharmaceutical nanosuspension	[88]
WO2021216022A1	2021	Active	Etodolac nanosuspension gel formation	[89]
AU2021102565A4	2021	Active	Carboxy-methylated polymer-based nanosuspension formulation	[90]
AU2021106637A4	2021	Active	Fisetin nanosuspension composition and process	[91]
US11504324B2	2022	Active	Nanosuspension formulation	[92]
US11285104B1	2022	Active	Oral nanosuspension gel of 5-fluorouracil for targeted colorectal cancer treatment	[93]

selection, stability maintenance, and the lack of *in vivo* investigations and clinical trials. Therefore, more clinical studies are necessary to improve pharmacokinetic data from different nanosuspension administrations. Establishing theoretical models will aid in the formulation and optimization of nanosuspensions. Future technologies and supporting devices that offer great stability and easy scaling up will become increasingly crucial [101]. The technology and concept of nanosuspension formulations can be evaluated by the number of products in clinical trials and on the market as well as by their release dates. The field of nanosuspension drug delivery will continue to expand, providing interesting opportunities for both oral and non-oral modes of administration due to its simple formulation processes and extensive applications.

Conclusions

Pharmaceutical experts have always faced the challenge of formulating medications with poor solubility. Nanosuspension formulations present a promising solution in this context. Nanosuspensions can effectively address the bioavailability issues of hydrophobic or poorly soluble drugs using the various strategies discussed in this review, either alone or in combination. Nanosuspension-based drug delivery systems, such as nanosuspension-eye drop formulation, itraconazole nanosuspension formulation, and other dual/hybrid formulation systems, can improve the bioavailability and stability of pharmaceuticals. These formulations can be produced using cost-effective and straightforward techniques, such as media milling and nanoprecipitation. Nanosuspensions can be administered in various ways, ensuring sustained safety and effectiveness. Today, various nanosuspensions are commercially available. The continuous progress in nanosuspension-based drug delivery systems is anticipated to sustain enthusiasm for nanosuspension technology, which is noted for its simplified formulation processes and a wide range of possible applications.

CRediT Author Statement

Conceptualization, **N.P. Mane** and **B.R. Rane**; writing-original draft preparation, **N.P. Mane** and **B.R. Rane**; writing-review and editing, **N.P. Mane**, **B.R. Rane**, and **A.S. Jain**. **N.P. Mane** created all the figures presented. The graphical abstract created by **B.R. Rane** with BioRender.com. All authors have read and agreed to the published version of the manuscript.

Conflict of Interests

The authors declare that no competing interest exists.

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