Available online on http://www.ijhacr.com

International Journal of Health Advancement and Clinical Research (tz) 2024; 2(4); 13-19

Review Article

Nanosuspension: A Promising Drug Delivery System for Poorly Soluble Drugs

Punit Kumar Maharshi [1], Sunil Kumawat [2], Vijay Sharma [3], N Ravindra [4]

[1] Research Scholar, Goenka College of Pharmacy, Lachhmangarh, Sikar.
[2] Associate Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.
[3] Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.
[4] Principal and Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.

Received: 04-10-2024 / Revised: 02-11-2024 / Accepted: 03-12-2024
Corresponding author: Punit Kumar Maharshi
Conflict of interest: Nil

Abstract:

Nanosuspensions are a cutting-edge approach in drug delivery systems aimed at addressing the challenges posed by poorly water-soluble drugs, which constitute a significant proportion of new chemical entities. These sub-micron colloidal dispersions, stabilized by surfactants or polymers, offer remarkable improvements in solubility, dissolution rates, and bioavailability. Nanosuspensions exhibit versatility across multiple administration routes, including oral, parenteral, pulmonary, ocular, and dermal delivery. Preparation techniques such as media milling, high-pressure homogenization, and precipitation enable the production of nanosized drug particles with enhanced therapeutic efficacy and reduced systemic toxicity. This review discusses the advantages of nanosuspensions, including their potential for controlled and targeted drug release, cost-effectiveness, and feasibility for a broad range of drugs. Challenges such as stability issues, energy-intensive preparation methods, and scale-up complexities are also highlighted. Despite these hurdles, nanosuspensions hold immense promise in improving the therapeutic outcomes of poorly soluble drugs, making them a vital tool in modern pharmaceutical sciences.

Keywords: Nanosuspensions, sub-micron colloidal dispersions, bioavailability, dermal delivery, high-pressure homogenization, media milling.

Introduction

Many formulation approaches are available to address the issues of low solubility and low bioavailability of drugs; the conventional approaches embrace micronization, utilising fatty solutions, use of penetration enhancer or cosolvents, salt formation, surfactant dispersion method, precipitation, etc. However, as of right now, over 40% of newly discovered chemical entities being generated through drug discovery programs are lipophilic or poorly water-soluble compounds. A variety of factors, including solubility, stability at room temperature, compatibility with solvent, excipient, and photostability, are crucial to the successful formulation of drugs. Other strategies include vesicular systems like liposomes, solids dispersion, emulsion and microemulsion techniques, as well as inclusion complexes with cyclodextrins. These methods have been shown to be effective as drug delivery systems, but their main drawback is that they are not universally applicable to all medications. Pharmaceutical uses of nanoparticle engineering have been discovered and documented in recent decades. Nanotechnology may be utilised

to address the issues using the several methods previously discussed. The science and engineering done at the nanoscale (10–9 m) is called nanotechnology. [1,2]

Nanosuspensions are sub-micron colloidal dispersions of poorly water-soluble drugs stabilized by surfactants or polymers. They are designed to enhance the solubility, dissolution rate, and bioavailability of drugs, addressing challenges posed by their poor solubility. Prepared through techniques like high-pressure homogenization, media milling, and precipitation, nanosuspensions reduce particle size to the nanometer scale, increasing surface area and improving drug absorption. Key stabilizers, such as Poloxamers and Tween, prevent particle aggregation and maintain stability. Nanosuspensions are versatile, with applications in oral, parenteral, topical, ocular, and pulmonary drug delivery. They offer advantages like improved therapeutic efficacy, reduced systemic toxicity, and feasibility for various drug types. However, challenges include particle aggregation, stability issues, and scale-up complexities. Despite these hurdles, nanosuspensions are a promising platform for delivering poorly soluble drugs effectively. [3,4]

Advantages of Nanosuspensions

Improved Solubility and Bioavailability:

Nanosuspensions significantly enhance the solubility of poorly water-soluble drugs, leading to improved dissolution rates and higher bioavailability.

Versatility in Administration Routes:

They can be administered via oral, parenteral, ocular, pulmonary, and dermal routes, making them suitable for various therapeutic applications.

Enhanced Absorption:

The reduced particle size increases surface area, facilitating faster absorption and improved drug efficacy.

Stability of Hydrophobic Drugs:

Nanosuspensions stabilize hydrophobic drugs without requiring toxic organic solvents, preserving the drug's activity and safety. [5]

Controlled Drug Release:

By modifying stabilizers or formulations, nanosuspensions can be engineered for sustained or targeted drug delivery.

Feasibility for a Wide Range of Drugs:

Both hydrophilic and hydrophobic drugs can be formulated into nanosuspensions, increasing the scope of this technology.

Cost-Effective:

Nanosuspensions are simpler and more economical to produce compared to other advanced drug delivery systems like liposomes or nanoparticles. [6]

Disadvantages of Nanosuspensions

Stability Issues:

Nanosuspensions may face challenges like particle aggregation, Ostwald ripening, and sedimentation over time, requiring advanced stabilizers.

Energy-Intensive Preparation:

Top-down methods like media milling and high-pressure homogenization are energy-intensive and may require sophisticated equipment.

Scale-Up Challenges:

Ensuring reproducibility and maintaining uniform particle size during large-scale production can be complex and costly.

Drug-Specific Formulation Requirements:

The choice of stabilizers and preparation techniques must be optimized for each drug, making the formulation process labor-intensive.

Potential for Contamination:

Methods like media milling risk contamination from milling beads, which

must be addressed to ensure product safety.

Residual Solvent Issues:

Bottom-up methods like precipitation may leave residual solvents in the formulation, necessitating additional purification steps. [7]

Properties of Nanosuspensions

Particle Size and Surface Area

Nanosuspensions typically have a particle size range between 10 nm to 1 µm.

The significantly increased surface area enhances the dissolution rate and bioavailability of poorly water-soluble drugs.

Saturation Solubility

The reduction in particle size leads to an increased surface-to-volume ratio, which enhances saturation solubility as described by the Ostwald-Freundlich equation.

Higher solubility facilitates faster drug absorption and therapeutic action.

Dissolution Rate

Nanosuspensions exhibit improved dissolution rates due to their smaller particle size and increased surface area, as explained by the Noyes-Whitney equation.

This property is especially beneficial for drugs with poor water solubility. [8]

Stability

Stabilizers (e.g., surfactants, polymers) prevent particle aggregation and sedimentation, ensuring the stability of nanosuspensions during storage.

Stability against Ostwald ripening is achieved by maintaining uniform particle size and using appropriate stabilizers.

Crystalline or Amorphous Nature

Nanosuspensions can maintain the crystalline state of the drug or convert it to an amorphous state, depending on the preparation method.

The crystalline state ensures stability, while the amorphous state can improve solubility and dissolution.

Zeta Potential

Nanosuspensions have a high zeta potential (±30 mV or more), which indicates strong electrostatic repulsion between particles, preventing aggregation.

This property is crucial for maintaining colloidal stability. [9]

Rheological Properties

The viscosity of nanosuspensions depends on particle concentration, stabilizer type, and particle size.

Low-viscosity nanosuspensions are preferred for parenteral and pulmonary applications, while moderate viscosity is suitable for topical use.

High Drug Loading

Nanosuspensions enable high drug loading without the need for solubilizing agents, making them suitable for poorly soluble drugs.

Versatility

Nanosuspensions are compatible with various routes of administration, including oral, parenteral, ocular, pulmonary, and dermal delivery.

Reduced Food Effect

The improved dissolution and solubility of nanosuspensions reduce the dependence of drug absorption on food, making them more consistent in therapeutic performance.

Enhanced Adhesion and Bioadhesion

Nanosuspensions exhibit excellent adhesion properties to biological membranes, enhancing drug absorption and efficacy, especially for topical and mucosal delivery.

Modification of Pharmacokinetics

Nanosuspensions can alter drug release profiles, offering the potential for sustained, controlled, or targeted drug delivery.

They also enhance bioavailability by

avoiding first-pass metabolism for certain administration routes like parenteral or pulmonary. [10, 11]

Method of preparation

Media Milling

Media milling uses high-energy mechanical grinding to reduce particle size. The drug, dispersed in a liquid medium containing stabilizers, is ground using milling beads made of zirconium oxide or stainless steel. The impact and shear forces generated by the rotating beads break the drug particles into nanosized dimensions. This method is widely used due to its scalability and ability to produce highly stable nanosuspensions. However, drawbacks include the potential for contamination from the milling beads and high energy requirements.

High-Pressure Homogenization (HPH)

In this method, the drug suspension is forced through a narrow homogenization gap under high pressure, typically 100–1500 bar. The extreme shear forces and cavitation effects break the drug particles into nanoparticles. Multiple homogenization cycles are often required to achieve the desired particle size and uniformity. HPH is effective for large-scale production and provides nanosuspensions with narrow size distributions. However, it is energy-intensive and may generate heat, necessitating careful temperature control to avoid drug degradation. [12]

Precipitation

Precipitation is a simple and cost-effective method. The drug is first dissolved in a solvent, and the resulting solution is rapidly mixed with an antisolvent where the drug has low solubility. This causes the drug to precipitate as nanosized particles. Stabilizers are added to prevent particle growth and aggregation. While the method is easy to implement, it requires careful selection of solvents and stabilizers to avoid residual solvent issues and incomplete precipitation.

Solvent Evaporation

In this approach, the drug is dissolved in a volatile organic solvent, which is emulsified into an aqueous phase containing stabilizers. The solvent is then evaporated, leaving behind nanosized drug particles. This method is particularly useful for drugs that are soluble in organic solvents but insoluble in water. However, it requires additional steps to remove residual solvents, which may increase complexity and cost. [13]

Nanoedge Technology

Nanoedge combines precipitation and high-pressure homogenization. In the first step, precipitation is used to produce nanocrystals of the drug. These are then subjected to high-pressure homogenization to achieve uniform particle size and enhance stability. This dual approach ensures better control over particle size distribution and prevents aggregation, making it suitable for industrial-scale production.

Nanoprecipitation-Homogenization

This hybrid method uses precipitation to initially form nanoparticles, followed by homogenization to refine size and stabilize the suspension. The method is ideal for drugs with complex solubility profiles and ensures better reproducibility and scalability. [14]

Applications of Nanosuspensions

Nanosuspensions have emerged as a versatile drug delivery system with applications across various therapeutic areas and routes of administration. Their ability to enhance the solubility and bioavailability of poorly soluble drugs makes them suitable for multiple uses. Below are the key applications of nanosuspensions, explained in detail:

- **Oral Drug Delivery**

Nanosuspensions improve the dissolution rate and bioavailability of poorly water-soluble drugs when administered orally. By

reducing particle size, they increase the surface area available for dissolution, overcoming the solubility limitations in the gastrointestinal tract. Additionally, nanosuspensions bypass the need for complex formulations, such as solid dispersions or inclusion complexes. Drugs like fenofibrate and carbamazepine have been successfully formulated into oral nanosuspensions, reducing variability caused by food intake and enhancing therapeutic outcomes. [15]

- **Parenteral Drug Delivery**

Injectable nanosuspensions are particularly useful for delivering drugs with poor solubility that cannot be formulated as conventional aqueous or oily solutions. Nanosuspensions provide a higher drug concentration in a small injection volume, improving drug availability at the target site. They also eliminate the need for toxic organic solvents used in traditional parenteral formulations. Drugs like paclitaxel and amphotericin B have been successfully delivered as parenteral nanosuspensions, improving their safety and efficacy profiles.

- **Pulmonary Drug Delivery**

Nanosuspensions are suitable for delivering drugs via the pulmonary route using nebulizers or inhalers. The small particle size ensures deep penetration into the alveoli, leading to effective localized drug delivery with minimal systemic side effects. Pulmonary nanosuspensions are particularly beneficial for treating respiratory conditions like asthma, chronic obstructive pulmonary disease (COPD), and lung infections. Formulating drugs as nanosuspensions ensures stability in the nebulized state and better dispersibility. [16]

- **Ocular Drug Delivery**

Nanosuspensions offer improved drug retention and bioavailability for ocular treatments. Poorly water-soluble drugs often face challenges in penetrating the corneal barrier, leading to low therapeutic efficacy. Nanosuspensions increase drug solubility, improve adhesion to the ocular surface, and enable sustained drug release, reducing the need for frequent dosing. Drugs like indomethacin and ciprofloxacin have been formulated as ocular nanosuspensions for treating conditions such as uveitis and bacterial infections.

- **Topical and Dermal Drug Delivery**

Topical nanosuspensions enhance the penetration of drugs into the skin layers, improving their therapeutic action for dermal conditions like psoriasis, acne, and fungal infections. They provide a uniform distribution of drug particles, increasing drug availability at the site of action. Nanosuspensions are also non-greasy and cosmetically appealing, making them suitable for use in creams, gels, and lotions.

- **Targeted Drug Delivery**

Nanosuspensions can be engineered for targeted drug delivery, such as to cancer cells or infected tissues. By modifying the surface of nanoparticles with ligands or antibodies, nanosuspensions can selectively deliver drugs to specific sites, enhancing therapeutic efficacy while reducing systemic toxicity. For instance, anticancer drugs like doxorubicin have been formulated as nanosuspensions to target tumor tissues effectively. [17]

- **Veterinary Applications**

Nanosuspensions are widely used in veterinary medicine for delivering poorly soluble drugs to animals. They improve drug absorption and bioavailability in species with diverse gastrointestinal physiology. Veterinary nanosuspensions offer advantages such as ease of administration and reduced dosing frequency, improving compliance. [18]

- **Sustained and Controlled Release**

Nanosuspensions are effective for designing sustained or controlled-release drug formulations. By modifying the

stabilizers or using specific preparation techniques, nanosuspensions can provide prolonged drug release, reducing dosing frequency and improving patient adherence. This is particularly beneficial for chronic conditions requiring long-term therapy.

- **Use in Bioavailability Enhancement Studies**

Nanosuspensions are extensively employed in preclinical and clinical studies to evaluate the potential of poorly soluble drugs. By improving solubility, they provide an accurate assessment of a drug's bioavailability, ensuring its suitability for further development. [19]

Conclusion

Nanosuspensions represent a transformative advancement in drug delivery systems, offering effective solutions for the formulation challenges of poorly water-soluble drugs. Their ability to enhance solubility, bioavailability, and therapeutic efficacy while maintaining versatility across various administration routes underscores their potential in diverse clinical applications. Although challenges like particle aggregation, stability maintenance, and scalability must be addressed, continuous advancements in preparation techniques and stabilizer optimization are paving the way for their widespread adoption. With their cost-effectiveness and adaptability for both hydrophilic and hydrophobic drugs, nanosuspensions are poised to play a pivotal role in overcoming solubility-related barriers in drug development, enabling the delivery of next-generation pharmaceuticals with enhanced safety and efficacy profiles.

References

1. Patel, V.R. and Agrawal, Y.K., Nanosuspension: An approach to enhance solubility of drugs. Journal of advanced pharmaceutical technology & research, 2011; 2(2): 81-87.
2. Krishna KB, Prabhakar C. A review on nanosuspensions in drug delivery. Int J Pharma and Bio Sci. 2011; 2(1):549-8.
3. Aher SS, Malsane ST, Saudagar RB. Nanosuspension: an overview. Asian Journal of Research in Pharmaceutical Science. 2017;7(2):81-6.
4. Geetha, G., Poojitha, K. and Khan, A," Various Techniques for Preparation of Nanosuspension- A Review",International Journal of Pharma Research & Review, 2014; 3 (9): 30-37.
5. Patravale, V., Date, A. and Kulkarni, R, "Nanosuspensions A Promising Drug Delivery Strategy", Jpp, 2004; 56: 827-840.
6. Jassim ZE, Rajab NA. Review on preparation, characterization, and pharmaceutical application of nanosuspension as an approach of solubility and dissolution enhancement. J Pharm Res. 2018; 12:771-4.
7. Prajapati, S., Bansal, M., & Gupta , R. K, An Overview on Nanosuspension Technology. International Journal of Health Advancement and Clinical Research (tz),2023; 1(4): 48–53.
8. Patravale B, Abhijit AD, Kulkarni RM, Nanosuspensions: a promising drug delivery strategy, Journal of Pharmacy and Pharmacoloy, 2004; 827–840.
9. Jayaprakash R, Krishnakumar K, Dineshkumar B, Jose R, Nair SK. Nanosuspension in drug delivery-A review. Sch. Acad. J. Pharm. 2016; 5:138-41.
10. Pattnaik S, Swain K, Rao JV; Nanosuspensions: a strategy for improved bioavailability. International Journal of Pharmacy and Biological Sciences, 2013; 3: 324-327.
11. Soumya M, Gupta S, Jain R, Mazumder R; Solubility enhancement of poorly water-soluble drug by using nanosuspension technology. International Journal of Research and Development in Pharmacy and Life Sciences. 2013; 2: 642-649.
12. Rabinow BE. Nanosuspensions in drug

delivery. Nature reviews Drug discovery. 2004 ;3(9):785-96.
13. Liu Y, Xie P, Zhang D, Zhang Q. A mini review of nanosuspensions development. Journal of drug targeting. 2012; 20(3):209-23.
14. Patel, D., Zode, S.S. and Bansal, A.K., Formulation aspects of intravenous nanosuspensions. International journal of pharmaceutics, 2020; 586: p.119555.
15. Geetha G, Poojitha U, Khan KA. Various techniques for preparation of nanosuspension-a review. International Journal of Pharma Research & Review. 2014; 3(9):30-7.
16. Yadav G, Singh. S. Nanosuspension: A promising drug delivery system. Scholars Academic Journal of Pharmacy, 2012; (5): 217-243.
17. Arunkumar N, Deecaraman M, Rani C. Nanosuspension technology and its applications in drug delivery. Asian Journal of Pharmaceutics (AJP). 2009; 3(3):168-173.
18. Bhowmik D, Harish G, Duraivel S, Kumar BP, Raghuvanshi V, Kumar KS. Nanosuspension-A novel approaches in drug delivery system. The Pharma Innovation. 2013; 1(1):50.
19. Ahire E, Thakkar S, Darshanwad M, Misra M. Parenteral nanosuspensions: a brief review from solubility enhancement to more novel and specific applications. Acta pharmaceutica sinica B. 2018; 8(5):733-55.