Kerbala Journal of Pharmaceutical Sciences

ISSN: 2221-7207(Print) / **ISSN**: 3006-7189 (Online)

Enhancing the Solubility of Class II Drug Via Nanosuspension: A Review

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Received: 02/02/2025
Accepted: 24/03/2025
Published: 30/06/2025

Keywords: Nanosuspensions, Poorly Water-Soluble Drugs, Bioavailability, Particle Size Reduction, High-Pressure Homogenization, Media Milling, Stabilizers, Drug Delivery Systems.

DOI: 10.62472/kjps.v16.i26.101-112

Abstract

Poor aqueous solubility remains a significant challenge in drug development, particularly for biopharmaceutics classification system, a promising approach to enhance solubility and dissolution by reducing particle size and increasing surface area. This review explores the formulation and evaluation of nanosuspensions as an effective strategy to improve the bioavailability of poorly water-soluble drugs. Various techniques, including top-down and bottom-up methods, contribute to nanosuspension preparation, with high- pressure homogenization and media milling being the most widely used. Selection of stabilizers plays a crucial role in preventing aggregation and ensuring long-term stability. Characterization parameters such as particle size, zeta potential, drug content, and in vitro dissolution provide critical insights in to nanosuspension performance. Recent advancements in nanosuspension technology enable enhanced therapeutic efficacy, reduced dosing frequency, and improved patient compliance. Applications extend to oral, parenteral, and ophthalmic drug delivery, offering versatility in pharmaceutical formulations. Challenges related to physical stability, scalability, and regulatory considerations require further investigation to facilitate commercialization. Future research focuses on optimizing formulation techniques, exploring novel stabilizers, and integrating advanced analytical tools for better characterization. Nanosuspensions continue to demonstrate potential in overcoming solubility limitations and enhancing drug absorption, making them a valuable approach in pharmaceutical development.

تعزيز ذوبانية الأدوية من الصنف الثاني من خلال التعليق النانوية: مراجعة علمية

أنسام فلاح عباس، جمال علي عاشور، مريم حسين العيادي

ملخص

لا تزال الذوبانية الضعيفة في الماء تُشكل تحديًا كبيرًا في تطوير الأدوية، وخاصةً في نظام تصنيف المستحضرات الصيدلانية الحيوية، وهو نهج واعد لتعزيز الذوبانية والذوبان عن طريق تقليل حجم الجسيمات وزيادة مساحة السطح. تستكشف هذه المراجعة تركيب وتقييم المعلقات النانوية كاستراتيجية فعالة لتحسين التوافر الحيوي للأدوية ضعيفة الذوبان في الماء. تُسهم تقنيات مُختلفة، بما في ذلك الطرق التنازلية والتصاعدية، في تحضير المعلقات النانوية، ويُعدّ التجانس عالي الضغط وطحن الوسائط الأكثر استخدامًا. يلعب اختيار المُثبتات دورًا حاسمًا في منع التكتل وضمان الاستقرار طويل الأمد. تُوفر معايير التوصيف، مثل حجم الجسيمات، وجهد زيتا، ومحتوى الدواء، والذوبان في المختبر، رؤىً ثاقبة حول أداء المعلقات النانوية. تُمكّن التطورات الحديثة في تقنية المعلقات النانوية من تعزيز الفعالية العلاجية، وتقليل وتيرة الجرعات، وتحسين التزام المريض بالعلاج. تمتد التطبيقات إلى توصيل الأدوية عن طريق الفم والحقن والعين، مما يُتيح تنوعًا في التركيبات الصيدلانية. تتطلب التحديات المتعلقة بالاستقرار الفيزيائي وقابلية التوسع والاعتبارات التنظيمية مزيدًا من البحث لتسهيل التسويق التجاري. تركز الأبحاث المستقبلية على تحسين تقنيات الصياغة، واستكشاف مثبتات جديدة، ودمج أدوات تحليلية متقدمة لتحسين التوصيف. لا تزال المعلقات النانوية تُظهر إمكاناتها في التغلب على قيود الذوبان وتعزيز امتصاص الدواء، مما يجعلها نهجًا قيّمًا في تطوير الأدوية

1. Introduction

The formulation and evaluation of nanosuspension have been extensively explored as an advanced approach to enhance the solubility and bioavailability of biopharmaceutics classification system (BCS) class II drugs (Ahmed & Pirbal, 2023). These drugs have been characterized by low aqueous solubility and high permeability, resulting in dissolution-limited absorption, which has posed significant challenges in pharmaceutical development (Sadeghi et al., 2020). To overcome these limitations, various nanosuspension preparation techniques have been developed, including high-pressure homogenization, media milling, precipitation, and ultrasonication. Through these methods, drug particles have been reduced to nanometer scale, leading to substantial increase in surface area and an improvement in dissolution rate based on the principles of the noyes-whitney equation (Al-Mayahy et al., 2019). The stabilization of nanosized drug particles has been achieved by incorporating surfactants and stabilizers, which have played a crucial role in preventing aggregation and maintaining long -term stability (Al-Badry et al., 2023). Extensive research has been conducted to evaluate the impact of nanosuspensions on drug solubility, dissolution kinetics, and overall therapeutic performance. A significant enhancement in bioavailability has been observed, particularly in drugs with poor water solubility, allowing for better absorption and improved pharmacokinetic profiles (Sabri et al., 2020). Various characterization techniques have been employed, including particle size analysis, zeta potential measurement, differential scanning calorimetry, and x-ray diffraction, to assess the physicochemical properties of nanosuspensions (Pınar et al., 2023). The influence of formulation variables on particle size, stability, and drug release profile has been systematically studied to optimize nanosuspension formulations. Moreover, in vitro and in vivo studies have been conducted to establish the correlation between nanosuspension characteristics and their biopharmaceutical performance (Al-Badry et al., 2023; Pınar et al., 2023; Sabri et al., 2020). The sacksful application of nanosuspensions has been demonstrated in different routes of drug administration, including oral, parenteral, ophthalmic, and pulmonary delivery systems (Leone & Cavalli, 2015). The challenges associated with the physical and chemical stability of nanosuspensions have been addressed through advanced formulation strategies, ensuring their suitability for large scale production and clinical applications (Annu & Singhal, 2022). The regulatory aspects of nanosuspension have been carefully considered to ensure compliance with pharmaceutical guidelines and standards for safety and efficacy. Advances in nanosuspension technology have contributed to development of novel drug delivery systems capable of improving the therapeutic outcomes of poorly soluble drugs (Sahu et al., 2021). The combination of nanotechnology and pharmaceutical science has provided a promising platform for the formulation of effective nanosuspension based drug delivery systems (Rinoldi et al., 2021). Continuous advancements in formulation techniques and characterization methods have facilitated the optimization of nanosuspension formulations for various therapeutic applications (Tian et al., 2021). The integration of computational modeling and experimental approaches has further enhanced the understanding of nanosuspension behavior and performance (Elsebay et al., 2023). The potential of nanosuspensions in personalized medicine and targeted drug delivery has been recognized, paving the way for future innovations in pharmaceutical nanotechnology. The research on nanosuspensions has provided valuable insights into their formulation, evaluation and application in enhancing the solubility of BCS class II drugs (Elsebay et al., 2023; Rinoldi et al., 2021; Tian et al., 2021).

1.1.Preparation of Nanosuspension

The preparation of nanosuspensions involves the reduction of particle to the nanoscale to enhance their solubility, dissolution rate, and bioavailability (Guan et al., 2022). Various methods have been utilized for preparation of nanosuspensions, each aimed at achieving fine control over particle size, stability, and drug release characteristics (Aldeeb et al., 2024). The process generally begins with the selection of an appropriate drug that has low solubility but high permeability, making it suitable for formulation into a nanosuspension (Attia et al., 2021).

In the preparation process, the drug first dispersed into a suitable solvent or a mixture of solvents. This step is crucial for ensuring that the drug is well-dissolved or at least well-dispersed in the medium before particle size reduction is achieved using several techniques, with the most commonly used methods being high-pressure homogenization and media milling (Al Haj et al., 2008; Vinchhi et al., 2021).

1.2.High-Pressure Homogenization

high-pressure homogenization involves the forced passage of the drug suspension through a narrow gap at high pressure. As the suspension is forced through this gap, the drug particles are subjected to mechanical stress, shear forces and turbulence, leading to reduction in particle size to nanoscale. The process is repeated for several cycles to ensure that desired particle size is achieved as shown in Fig.1 (Bravo & Oliva, 2017; Kruszelnicka, 2022).

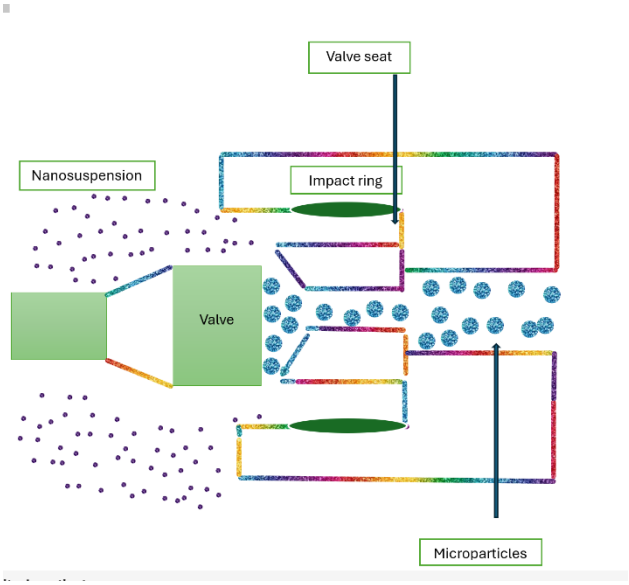

Figure1. Schematic Diagram of High-Pressure Homogenization for Nanosuspension Preparation

The drug suspension is forced through a narrow gap at high pressure via a valve system. Upon exiting the valve, particles collide with an impact ring and valve seat, generating intense shear forces and cavitation that reduce drug particles to the nanoscale. The result is a stable nanosuspension of smaller particles, improving solubility and bioavailability.

1.3.Media Milling

Media milling also known as wet milling, is another widely used method for producing nanosuspensions. In this process, a milling chamber is filled with the drug suspension along with milling media, such as beads made of ceramic or glass [23]. The suspension is agitated to create friction between the milling media and the drug particles, causing the particles to break down into smaller sizes. The milling process is monitored to ensure that the particles are reduced to required size, usually between 200 to 600 nanometers (Elsebay et al., 2023).

1.4.Precipitation Method

The precipitation method has widely used for nanosuspension preparation. In this technique, the drug was dissolved in a suitable solvent and then precipitated by adding a non-solvent under controlled conditions. Rapid mixing and stabilizer incorporation were essential to prevent particle growth and aggregation as shown in Fig.2 (Islam et al., 2022).

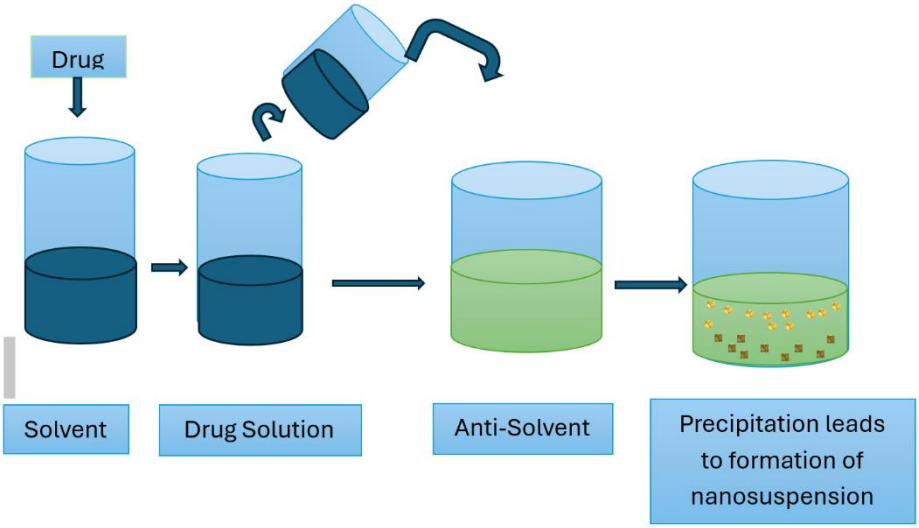

Figure2. Schematic Representation of Anti-Solvent Precipitation Method for Nanosuspension Preparation

The drug is first dissolved in a suitable solvent to form a drug solution. This solution is then rapidly added to an anti-solvent under controlled conditions, leading to precipitation of the drug particles due to reduced solubility. The resulting fine particles form a nanosuspension. This method is advantageous for thermolabile compounds and requires appropriate stabilizers to prevent particle aggregation.

1.5.Ultrasonication Method

Ultrasonication was used as a simple and effective method to break down drug particles into nanoscale sizes. High-frequency ultrasonic waves were applied to disrupt large aggregated, resulting in stable nanosuspensions with enhanced solubility as shown in Fig.3 (Guan et al., 2022).

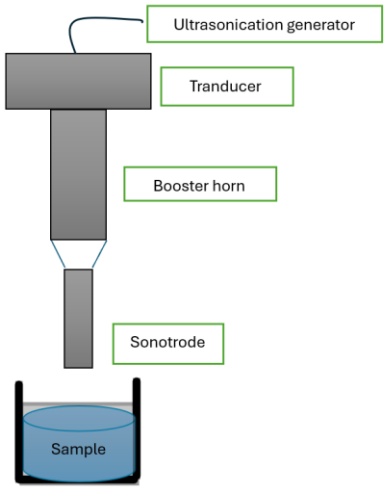

Figure3. Ultrasonication System Setup for Nanosuspension Formulatio

This method employs an ultrasonication generator connected to a transducer, booster horn, and sonotrode, which delivers high-frequency sound waves into the liquid sample. These waves generate cavitation forces that reduce the particle size of the drug to the nanometer range. Ultrasonication is particularly effective in breaking down coarse suspensions and enhancing drug solubility and stabilitv.

1.6.Supercritical Fluid Method

Supercritical fluid technology was explored as a novel approach for nanosuspension formulation. In this method, a supercritical fluid(e.g., carbon dioxide) was utilized to precipitate drug nanoparticles from solution. This process was recognized for its environmental benefits and ability to produce uniform particles (Cortés et al., 2021).

1.7.Stabilizer Used in Nanosuspension Formulation

Stabilizers play a crucial role in nanosuspension formulation as they prevent particle aggregation and ensured the stability of the system. Various types of stabilizers were employed, including surfactants, polymers, and lipids, each contributing to different stabilization mechanism (Guan et al., 2022; Tamang et al., 2022). Surfactants sch as polysorbates and sodium lauryl sulfate were used to reduce interfacial tension and provide steric hindrance, which minimize particle aggregation. Polymers like polyvinylpyrrolidone and hydroxypropyl methylcellulose were incorporated to enhance steric stabilizers such as lecithin were utilized to improve biocompatibility and enhance drug solubilization. The selection of suitable stabilizers depended on factors such as drug properties, intended route of administration, and desired formulation characteristics. A balance between hydrophilic and lipophilic properties was considered to ensure effective stabilization (Elmowafy et al., 2021; Jakubowska et al., 2022; Soroushnia et al., 2021; Tamang et al., 2022). Electrostatic stabilization was achieved through the use of ionic stabilizers that provided a surface charge, thereby preventing particle aggregation due to repulsive forces. the zeta potential of nanosuspension was measured to evaluate electrostatic stabilization, with values above 30 mv indicating good stability. The type and concentration of stabilizers were optimized to achieve minimal particle size and enhance the dispersion of nanosuspensions. Inadequate stabilization led to Ostwald ripening and sedimentation, which affected formulation

stability and drug bioavailability. Compatibility between stabilizer and drug was evaluated to avoid undesired interactions that could compromise drug efficacy (Bhalani et al., 2022; Chen et al., 2022; Jakubowska et al., 2021, 2022; Khan et al., 2022). The role of stabilizers in preventing crystallization and maintaining the amorphous state of the drug was also investigated. Several studies demonstrated that the appropriate selection of stabilizers significantly improved the dissolution rate and bioavailability of poorly water-soluble drugs. Stability studies were conducted to assess the impact of storage conditions on particle size, zeta potential, and drug content. The long-term effectiveness of stabilizers was evaluated to ensure the nanosuspension maintained its intended physicochemical properties. As research in nanosuspension technology advanced, noval stabilizers such as biopolymers and nanostructured materials were explored to enhance stability and drug delivery efficiency (Khan et al., 2022; Mahmood et al., 2023; Maleki et al., 2017; Rocha et al., 2023; Tupe et al., 2023).

1.8.Surfactant Used in Nanosuspension Formulation

Surfactants play a crucial role in the formation of nanosuspensions by stabilizing drug particles and preventing aggregation. The function by reducing the interfacial tension between the hydrophobic and drug particles and the aqueous dispersion medium, thereby enhancing the wettability and dispersibility of the drug (Cai et al., 2022). Non-ionic surfactants, such as polysorbates (tween 80, tween 20) and poloxamers (pluronic), contribute to steric stabilization by forming a protective layer around the nanoparticles, which prevents their aggregation through steric hindrance. These surfactants also improve the physical stability of the nanosuspension by minimizing Ostwald ripening and sedimentation (Aguirre-Ramírez et al., 2021; Tenorio-Garcia et al., 2022). Anionic surfactant, including sodium dodecyl sulfate (SDS), enhance electrostatic stabilization by imparting a negative charge to the drug particles. This charge generates repulsive forces between nanoparticles, which prevents their coalescence and maintains a uniform dispersion. Cationic surfactants such as cetyltrimethylammonium bromide (CTAB), provide similar electrostatic stabilization but with a positive surface charge, which can interact with negatively charged biomolecules or cell membranes, leading to potential bio adhesive properties. In some formulation, amphiphilic surfactants, including lecithin, offer dual stabilization mechanisms by combining electrostatic and steric stabilization. Lecithin molecules adsorb onto the particle surface, reducing surface energy and improving dispersion stability (Purohit et al., 2022).

1.9.Organic Solvent

Organic solvents were widely used in nanosuspension formulation to enhance the solubility and bioavailability of poorly water-soluble drugs various techniques were developed to prepare nanosuspensions using organic solvents ensuring controlled particle size and stability(Pulingam et al., 2022) . The solvent evaporation method was commonly employed where the drug was dissolved in a volatile organic solvent such as ethanol or acetone. This solution was then emulsified into aqueous phase containing stabilizers like PVP or Tween 80 after emulsification the organic solvent was evaporated under reduced pressure or continuous stirring leading to precipitation of drug nanoparticles which were stabilized by surfactants (Chatterjee, 2018; Kravanja et al., 2022; Thakkar & Misra, 2017).

Another widely adopted technique was the solvent precipitation method in which the drug was first dissolved in a water- miscible organic solvent upon rapid mixing with an anti-solvent usually water. The sudden supersaturation caused the immediate precipitation of nanosized drug particles the presence of surfactants and polymers prevented particle agglomeration and ensured nanosuspension stability(Bagheri et al., 2022; Farkas & Kramar, 2021) . Supercritical fluid technology was also explored where the drug was dissolved in supercritical fluid such as carbon dioxide upon controlled depressurization. The solubility of the drug in the supercritical fluid was reduced leading to nucleation and formation of nanosized particles. This technique was considered an advanced method due to its ability to produce pure nanoparticles without residual organic solvents (Bagheri et al., 2022; Farkas & Kramar, 2021; Karmakar, 2019).

2. Characterization and Evaluation of Nanosuspension

2.1.Particle Size and Polydispersity Index (PDI)

Dynamic light scattering (DLS) was employed to determine particle size distribution and PDI. A lower PDI value indicates a more uniform particle size distribution, which was critical for nanosuspension stability (Darabian et al., 2022; Karmakar, 2019).

2.2.Zeta Potential Measurement

Zeta potential analysis was conducted to assess the surface charge of nanoparticles. A high zeta potential value above 30 mv was indicative of good electrostatic stabilization, reducing the risk of aggregation (Shaikh et al., 2022).

2.3.Crystallinity and Morphology Analysis

Differential scanning calorimetry (DSC) and X-ray diffraction(XRD) were utilized to examine the crystalline state of the drug. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were used to visualize nanoparticles morphology (Aghrbi et al., 2021).

2.4.Saturated Solubility and Dissolution Studies

Saturated solubility tested were performed to evaluate the solubility enhancement achieved by nanosuspension formulation. In vitro dissolution studies were conducted to compare the drug release profiles of nanosuspensions and conventional formulations (Li et al., 2021).

3. Stability Studies

Long term and accelerated stability studies were conducted to assess the physical and chemical stability of nanosuspensions. changes in particle size, zeta potential, and drug content were monitored over time to ensure formulation robustness (Elshafeey & El-Dahmy, 2021; Sampathi et al., 2022).

4. Pharmacokinetic and Bioavailability Enhancement

Animal and human pharmacokinetic studies were performed to determine the bioavailability improvement achieved through nanosuspension administration [(67)]. Enhanced absorption, higher plasma drug concentrations, and prolonged circulation times were observed in various studies, confirming the effectiveness of nanosuspensions in improving drug performance (Guan et al., 2022).

5. Conclusion

Nanosuspensions have emerged as highly effective strategy for enhancing the solubility and bioavailability of BCS classII drugs. Various formulation techniques, including precipitation, high pressure homogenization, media milling, have been successfully employed to produce stable nanosuspensions. Comprehensive characterization and evaluation parameters were utilized to optimize formulation performance. Future advancements in nanosuspension technology are expected to further enhance drug delivery and therapeutic efficacy.

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