A REVIEW ON NANOSUSPENSION FOR SOLUBILITY ENHANCEMENT OF BCS CLASS-II DRUG

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Abstract : Poor aqueous solubility is a major limitation in oral drug delivery, particularly for Biopharmaceutics Classification System (BCS) Class II drugs where dissolution is the rate-limiting step for absorption. Nanosuspension technology has emerged as an effective approach to enhance solubility, dissolution rate, and bioavailability of such poorly water-soluble drugs. Nanosuspensions are submicron colloidal dispersions of pure drug particles stabilized by surfactants or polymers, where reduction in particle size increases surface area and saturation solubility, leading to improved dissolution and absorption. Various preparation methods, including top-down and bottom-up approaches, are employed, and their performance is evaluated through parameters such as particle size, zeta potential, and dissolution behavior. Nanosuspensions offer advantages such as improved bioavailability, dose reduction, and versatility in drug delivery, although challenges like stability and scale-up remain. Marketed formulations of drugs such as fenofibrate, sirolimus, and aprepitant demonstrate the clinical applicability of this technology. Overall, nanosuspensions represent a promising strategy for improving the therapeutic performance of BCS Class II drugs

- **Keywords:** Nanosuspension, BCS Class II drugs, solubility enhancement, bioavailability, nanocrystals, dissolution rate, drug delivery

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INTRODUCTION

In the field rapid changing pharmaceutical science various preparations are used with the aim of more effective and safer therapeutic agents. In the past few decades drug discovery is become more recolonise by the advance technologies like high-throughput screening and combinatorial chemistry [1]

1.1 Oral Drug Delivery Challenges

Oral drug delivery remains the most widely accepted route of drug administration due to its convenience, non-invasiveness, patient compliance, and cost-effectiveness. More than 50% of marketed drug products are administered orally, highlighting its dominance in pharmaceutical therapy [1]. Despite these advantages, the successful development of orally administered drugs is frequently hindered by biopharmaceutical limitations.

A critical requirement for oral absorption is that the drug must first dissolve in gastrointestinal (GI) fluids before permeating across the intestinal epithelium. For poorly water-soluble drugs, dissolution becomes the rate-limiting step in absorption, often resulting in low and variable oral bioavailability. This issue has become increasingly significant in recent years, as a large proportion of newly discovered chemical entities exhibit poor aqueous solubility and high lipophilicity [2].
The gastrointestinal environment itself introduces additional challenges. Variations in gastric emptying time, intestinal motility, luminal pH, enzymatic degradation, and food effects can significantly influence drug dissolution and absorption kinetics [3][4]. These physiological factors may lead to unpredictable plasma concentration profiles, particularly for compounds with dissolution-limited absorption.

Conventional formulation strategies such as salt formation, particle size reduction (micronization), co-solvency, and use of surfactants have been employed to enhance solubility. However, these methods often provide insufficient improvement for highly hydrophobic drugs. Consequently, innovative formulation approaches have gained considerable attention to address solubility-related barriers in oral drug delivery.

Among emerging technologies, nanotechnology-based systems—particularly nanosuspensions—have shown significant promise in enhancing dissolution rate, saturation solubility, and ultimately oral bioavailability of poorly water-soluble drugs[5]. Therefore, overcoming solubility-associated limitations remains a central objective in modern pharmaceutics.

1.2 Importance of Solubility in Drug Absorption

Convenience to patients, non-invasiveness, patient compliance, and cost-effectiveness those reasons which make oral drug delivery as the most widely accepted route of drug administration. More than 50% of marketed drug products are administered orally, highlighting its dominance in pharmaceutical therapy [2].

To Absorption of drug, it must first dissolve in Gastrointestinal fluid Which lead Permitting across the intestinal epithelium. For poorly water-soluble drugs, dissolution becomes the rate-limiting step in absorption, which resulting in low and variable oral bioavailability [3]

A GIT tract's (gastrointestinal tract) environment makes more challenges to absorption of the drug like variation in gastric emptying time, intestinal motility, luminal pH, enzymatic degradation, those physiological factors can lead to unpredictable plasma concentration profiles, particularly for compounds with dissolution-limited absorption [4][5].

salt formation, micronization, and use of co-solvents often provide limited improvement for highly hydrophobic compounds. Therefore, innovative formulation strategies are required to enhance dissolution rate and oral bioavailability [6].

But in the recent years the nanotechnology-based system for particularly in this case nanosuspension have shown greater solution by increasing surface area and saturation solubility at the nanoscale level.

1.3 Biopharmaceutics Classification System (BCS)

A scientific framework that categorizes drug substances based on their aqueous solubility and intestinal permeability also known as "The Biopharmaceutics Classification System (BCS)" was first proposed by **Amidon GL** and his colleagues in 1995 to establish predictive relationship between in vitro dissolution and in vivo bioavailability. Since BCS class become fundamental tool in drug research and development, regulatory assessment, and formulation design.
According to the BCS, drug substances are classified into four categories:

- **Class I** – High solubility, High permeability
- **Class II** – Low solubility, High permeability
- **Class III** – High solubility, Low permeability
- **Class IV** – Low solubility, Low permeability [7]

A drug considered highly soluble when the highest therapeutic dose dissolved in 250ml or less aqueous media in pH range 1.0 to 6.8 at 37^0C, which resemble the human/animal physiology. High permeability is generally defined as the extend of absorption in human beings $\geq$85–90% of the administered dose.[8]

The scientific importance of BCS lies in its ability to identify the rate-limiting step in oral drug absorption. For Class I drugs, absorption is typically rapid and complete, with dissolution not being a limiting factor. In contrast, Class II drugs exhibit high membrane permeability but poor aqueous solubility; thus, dissolution becomes the primary barrier to systemic absorption. Class III drugs face permeability-related challenges, whereas Class IV drugs suffer from both solubility and permeability limitations [9].

The BCS framework has also been incorporated into regulatory guidelines by agencies such as the United States Food and Drug Administration and the European Medicines Agency for granting biowaivers for certain immediate-release solid oral dosage forms (4). This regulatory acceptance further emphasizes its significance in pharmaceutical research and development.[10]

Since the solubility and permeability are major factor that directly affect on drug absorption and drug plasma level in body so selecting proper appropriate solubility and Permeability enhancement approaches Becomes very crucial Among many various advanced approaches Nano suspicion technology Has promising solution for overcoming dissolution related limitations associated with BCS class II drugs.

1.4 BCS Class II Drugs: Characteristics and Challenges

BCS Class II drugs Known for their low aqueous solubility and high intestinal permeability. Although it can readily permeate through the gastrointestinal membrane but their poor solubility limits dissolution in gastrointestinal fluids, making dissolution the rate-limiting step in systemic absorption [11]

hydrophobic nature, high lipophilicity (log P), crystalline structure, and strong intermolecular forces within the solid state are major factors which lower the solubility of the Class II drugs. Also, many drugs high molecular weight and poor wettability which reducing the dissolution in the aqueous media [12]. Due to this molecule behaviour insufficient dissolution lead to incomplete absorption and suboptimal therapeutic efficacy.

As we know that presence of food can change the solubilization through bile salt and lipid which can significantly increasing drug absorption. This result in unpredictable pharmacokinetic profiles and inter-patient variability.[13]

Examples of well-known BCS Class II drugs include:

- Carbamazepine
- Ibuprofen
- Ketoconazole
- Fenofibrate
- Cildipine

Those drugs often show high permeability but poor aqueous solubility, which lead to dissolution-controlled absorption [14].

Traditional formulation approaches such as micronization, salt formation, use of co-solvents, and surfactant addition have been employed to improve solubility. However, micronization often fails to produce sufficient enhancement because particle size

reduction to the micrometer range may not significantly increase saturation solubility. Furthermore, polymorphic transformations and agglomeration may limit effectiveness [15].

2. Nanosuspension: Concept and Definition

Nanosuspensions are submicron colloidal dispersions of pure drug particles, typically stabilized by surfactants or polymers, with particle sizes generally ranging between 10 and 1000 nm. These systems are designed to improve the solubility and dissolution rate of poorly water-soluble drugs, particularly those belonging to BCS Class II and Class IV categories [16].

Unlike conventional drug delivery systems, nanosuspensions consist entirely of the active pharmaceutical ingredient (API) dispersed in an aqueous medium, without the need for a carrier matrix. This distinguishes them from other nanocarrier-based systems such as liposomes, nanoemulsions, or polymeric nanoparticles, where the drug is encapsulated within or dissolved in a carrier material [17]. In nanosuspensions, the drug remains in a solid crystalline or partially amorphous state, which contributes to improved physical stability compared to molecular dispersions.

The primary objective of nanosuspension technology is to enhance the dissolution rate and saturation solubility of poorly soluble drugs by reducing particle size to the nanometer scale. According to the **Noyes–Whitney equation**, a reduction in particle size leads to an increase in surface area, thereby accelerating the dissolution rate. Additionally, nanosized particles exhibit increased saturation solubility due to the **Ostwald–Freundlich equation**, which explains the effect of curvature on solubility at the nanoscale [18].

Nanosuspensions can be administered via multiple routes, including oral, parenteral, ocular, pulmonary, and topical delivery systems. However, their application in oral drug delivery has gained particular attention due to their ability to overcome dissolution-limited absorption in BCS Class II drugs [19].

Another key feature of nanosuspensions is the role of stabilizers, which prevent aggregation and ensure physical stability of the nanosized particles. Stabilization is achieved through steric hindrance, electrostatic repulsion, or a combination of both, depending on the type of stabilizer used [20]. Due to these advantages, nanosuspension technology has emerged as a versatile and effective formulation strategy for enhancing solubility, dissolution rate, and bioavailability of poorly water-soluble drugs. It serves as a simple yet powerful approach without altering the chemical structure of the drug molecule.

2.1 Mechanism of Solubility Enhancement in Nanosuspensions

Nanosuspension technology enhances the solubility and dissolution behaviour of poorly water-soluble drugs primarily through particle size reduction to the nanometer range. This size reduction leads to several physicochemical changes that collectively improve drug dissolution and oral bioavailability.

Increased Surface Area

Reduction of drug particle size to the nanoscale significantly increases the surface area available for dissolution. According to the **Noyes–Whitney equation**, the dissolution rate is directly proportional to the surface area of the drug particles [21]. As particle size decreases, the total surface area increases exponentially, resulting in a faster dissolution rate. This is particularly beneficial for BCS Class II drugs, where dissolution is the rate-limiting step in absorption.

Increased Saturation Solubility

In addition to enhancing dissolution rate, nanosuspensions can increase the apparent saturation solubility of drug particles. This phenomenon is explained by the **Ostwald–Freundlich equation**, which states that smaller particles exhibit higher solubility due to increased surface curvature and higher surface energy [22]. The elevated saturation solubility increases the concentration gradient between the gastrointestinal fluid and the absorption membrane, thereby enhancing drug diffusion and absorption.

Enhanced Dissolution Velocity

The combined effect of increased surface area and increased saturation solubility leads to a significant enhancement in dissolution velocity. Faster dissolution ensures that a greater fraction of the drug is available in dissolved form within a shorter time, improving the likelihood of absorption before drug elimination or degradation occurs.

Improved Wettability and Dispersibility

Nanosuspensions are typically stabilized using surfactants or hydrophilic polymers, which improve the wettability of hydrophobic drug particles. Enhanced wettability facilitates better interaction between the drug surface and dissolution medium, further accelerating dissolution. Additionally, uniform dispersion of nanoparticles prevents aggregation, ensuring consistent dissolution behaviour [23].

Reduced Diffusion Layer Thickness

According to diffusion layer theory, the thickness of the stagnant diffusion layer surrounding a dissolving particle influences the dissolution rate. Nanosized particles reduce the effective diffusion layer thickness, thereby enhancing mass transfer and accelerating dissolution [24].

2.2 Methods of Preparation of Nanosuspensions

Nanosuspensions can be prepared using various techniques broadly classified into **top-down approaches, bottom-up approaches, and combination methods**. These techniques aim to reduce particle size to the nanometer range while maintaining stability and preventing aggregation.

2.2.1 Top-Down Approaches

Top-down methods involve the **mechanical size reduction of coarse drug particles** into nanosized particles using high-energy processes. These methods are widely used due to their scalability and industrial applicability.

a) Media Milling (Nanomilling)

Media milling is one of the most commonly used techniques for the preparation of nanosuspensions. In this method, drug particles are dispersed in a liquid medium containing stabilizers and subjected to milling using high-energy grinding media such as zirconium oxide beads. The collision and shear forces generated during milling reduce the particle size to the nanometer range.

This method offers advantages such as reproducibility, suitability for large-scale production, and applicability to a wide range of poorly soluble drugs. However, disadvantages include potential contamination from milling media, long processing time, and high energy consumption [25].

b) High-Pressure Homogenization

High-pressure homogenization involves forcing a drug suspension through a narrow gap under extremely high pressure (100–2000 bar). The intense shear forces, cavitation, and particle–particle collisions result in size reduction to the nanoscale.

This technique can be performed using different methods such as hot homogenization and cold homogenization, depending on drug properties. It is widely used in industrial applications due to its scalability and ability to produce stable nanosuspensions.

However, repeated homogenization cycles are often required, and there is a risk of temperature-induced degradation for heat-sensitive drugs [26].

2.2.2 Bottom-Up Approaches

Bottom-up methods involve the **formation of nanoparticles from molecular-level drug solutions**, typically through precipitation techniques.

a) Precipitation Method (Solvent–Antisolvent Method)

In this method, the drug is first dissolved in a suitable organic solvent and then rapidly mixed with a non-solvent (antisolvent), usually water, containing stabilizers. The sudden decrease in solubility leads to rapid nucleation and formation of nanosized particles.

This method is simple, cost-effective, and does not require high energy input. However, challenges include controlling particle growth, avoiding aggregation, and selecting appropriate solvents and stabilizers [27].

b) Solvent Evaporation Method

In this technique, the drug is dissolved in a volatile organic solvent, which is then emulsified in an aqueous phase containing stabilizers. Upon evaporation of the solvent, nanosized drug particles are formed.

Although effective, the use of organic solvents and the need for their complete removal are major limitations of this method [28].

2.2.3 Combination Methods

Combination approaches integrate both top-down and bottom-up techniques to overcome the limitations of individual methods.

a) Nanoedge Technology

Nanoedge technology involves initial precipitation of drug nanoparticles (bottom-up) followed by high-pressure homogenization (top-down) to further reduce particle size and improve stability.

This hybrid approach offers better control over particle size distribution and minimizes aggregation, resulting in highly stable nanosuspensions [29].

2.3 Stabilizers Used in Nanosuspensions

Stabilizers play a crucial role in the formulation of nanosuspensions by preventing aggregation and maintaining the physical stability of nanosized drug particles. Due to the high surface energy associated with nanoparticles, there is a strong tendency for particles to agglomerate, which can lead to an increase in particle size and loss of nanoscale advantages. Therefore, the selection of appropriate stabilizers is essential for the successful formulation of nanosuspensions.

Stabilizers function by providing **steric stabilization, electrostatic stabilization, or a combination of both**, thereby preventing particle–particle interaction and ensuring uniform dispersion in the medium.

2.3.1 Types of Stabilizers

a) Polymeric Stabilizers

Polymeric stabilizers provide **steric hindrance** by forming a protective layer around drug particles. This layer prevents close contact between particles and inhibits aggregation.

Commonly used polymeric stabilizers include:

- Hydroxypropyl methylcellulose (HPMC)

- Polyvinylpyrrolidone (PVP)
- Poloxamers

These polymers are widely used due to their biocompatibility, non-toxicity, and effectiveness in stabilizing nanosuspensions [30].

b) Surfactants

Surfactants reduce interfacial tension and improve wettability of hydrophobic drug particles. They provide **electrostatic stabilization** by generating surface charge, which results in repulsion between particles.

Common surfactants include:

- Sodium lauryl sulfate (SLS)
- Tween 80
- Span 80

Surfactants are particularly useful in enhancing dispersion and preventing aggregation during and after nanosuspension preparation [31].

c) Combination Stabilizers

In many formulations, a combination of polymeric stabilizers and surfactants is used to achieve **both steric and electrostatic stabilization**. This dual mechanism provides enhanced stability compared to using a single stabilizer alone.

2.3.2 Mechanism of Stabilization

Steric Stabilization

In steric stabilization, polymer chains adsorb onto the surface of drug particles, creating a physical barrier that prevents particles from coming into close contact. This reduces the likelihood of aggregation and ensures long-term stability.

Electrostatic Stabilization

Electrostatic stabilization involves the development of surface charge on particles, resulting in repulsive forces between similarly charged particles. This repulsion prevents aggregation and maintains dispersion stability.

2.3.3 Factors Affecting Stabilizer Selection

The selection of stabilizer depends on several factors, including:

- Nature and physicochemical properties of the drug
- Type of preparation method used
- Desired particle size and stability
- Route of administration
- Compatibility and toxicity profile

An ideal stabilizer should provide effective stabilization at low concentration, be non-toxic, and not interfere with drug activity or bioavailability.

2.4 Characterization of Nanosuspensions

Characterization of nanosuspensions is essential to evaluate their physicochemical properties, stability, and performance. Proper characterization ensures that the formulation meets the desired criteria for particle size, stability, and bioavailability. Various analytical techniques are employed to assess different parameters of nanosuspensions.

2.4.1 Particle Size and Size Distribution

Particle size is one of the most critical parameters influencing the dissolution rate and bioavailability of nanosuspensions. Reduction in particle size increases surface area, thereby enhancing dissolution.

Particle size and polydispersity index (PDI) are commonly measured using **Dynamic Light Scattering (DLS)**. A low PDI value (<0.3) indicates uniform particle size distribution and good stability of the formulation [32].

2.4.2 Zeta Potential

Zeta potential is a measure of the surface charge of nanoparticles and provides information about the stability of nanosuspensions. It indicates the degree of electrostatic repulsion between particles.

Generally:

- ±30 mV → good stability (electrostatic stabilization)
- ±20 mV → moderate stability
- Low values → risk of aggregation

Higher absolute zeta potential values prevent particle aggregation and ensure long-term stability of the nanosuspension [33].

2.4.3 Morphology (Shape and Surface Characteristics)

The shape and surface morphology of nanoparticles are studied using techniques such as:

- Scanning Electron Microscopy (SEM)
- Transmission Electron Microscopy (TEM)

These techniques provide detailed information about particle shape, surface texture, and aggregation state, which influence dissolution and stability [34].

2.4.4 Crystalline State and Polymorphism
The physical state of the drug (crystalline or amorphous) significantly affects solubility and stability.
Techniques used include:

- X-ray Diffraction (XRD)
- Differential Scanning Calorimetry (DSC)

These methods help identify any changes in crystallinity or polymorphic transitions during nanosuspension preparation [35].

2.4.5 Saturation Solubility and Dissolution Studies
Saturation solubility studies are performed to evaluate the enhancement in solubility achieved through nanosizing.
In vitro dissolution studies are conducted to compare the dissolution rate of nanosuspensions with that of pure drug or conventional formulations. A significant increase in dissolution rate confirms the effectiveness of nanosuspension formulation [36].

2.4.6 Stability Studies
Stability studies are carried out to assess physical and chemical stability over time. Parameters evaluated include:

- Particle size growth
- Sedimentation
- Aggregation
- Drug degradation

Stability studies are typically conducted under different temperature and humidity conditions to predict shelf life [37].

2.5 Advantages and Limitations of Nanosuspensions
Nanosuspension technology has gained significant attention as an effective approach for improving the solubility and bioavailability of poorly water-soluble drugs, particularly BCS Class II compounds. By reducing drug particles to the nanometer range, nanosuspensions introduce unique physicochemical advantages. However, alongside these benefits, certain limitations must also be carefully addressed during formulation and development.

2.5.1 Advantages of Nanosuspensions
One of the most important advantages of nanosuspensions is their ability to **enhance solubility and dissolution rate**. When drug particles are reduced to the nanoscale, their surface area increases dramatically. According to the **Noyes–Whitney equation**, this increased surface area leads to a faster dissolution rate. In addition, nanosized particles exhibit higher saturation solubility due to increased surface energy, which further contributes to improved drug dissolution in gastrointestinal fluids [38].

Another major advantage is the **improvement in oral bioavailability**. For BCS Class II drugs, where dissolution is the rate-limiting step, nanosuspensions ensure that a greater amount of drug is available in dissolved form. This leads to more efficient absorption across the gastrointestinal membrane and results in enhanced and more consistent bioavailability [39].

Nanosuspensions also offer significant **flexibility in the route of administration**. They can be formulated not only for oral delivery but also for parenteral, ocular, pulmonary, and topical applications. This versatility makes them a valuable platform technology in drug delivery, especially for drugs that face formulation challenges with conventional systems. Another important benefit is the **possibility of dose reduction**. Since nanosuspensions improve drug absorption, lower doses may be sufficient to achieve the desired therapeutic effect. This can help in reducing dose-related side effects and improving patient compliance, which is particularly important for long-term therapies.

In addition, nanosuspensions have a relatively **simple composition**. Unlike other nanocarrier systems such as liposomes or polymeric nanoparticles, nanosuspensions consist mainly of pure drug particles stabilized by small amounts of surfactants or polymers. This reduces formulation complexity and minimizes the risk of toxicity associated with carrier materials. Finally, nanosuspensions are particularly useful for **highly hydrophobic drugs** that are poorly soluble in both aqueous and organic solvents. In such cases, traditional solubility enhancement techniques may fail, whereas nanosizing provides a direct and effective solution by modifying physical properties without altering the chemical structure of the drug [40].

2.5.2 Limitations of Nanosuspensions
Despite their advantages, nanosuspensions also present certain challenges that must be carefully managed. One of the primary concerns is **physical instability**. Due to their high surface energy, nanoparticles have a natural tendency to aggregate over time. This can lead to an increase in particle size and a reduction in the benefits associated with nanosizing. Additionally, phenomena such as Ostwald ripening may occur, where smaller particles dissolve and redeposit onto larger particles, further affecting stability.

Another limitation is the **dependence on stabilizers**. Stabilizers are essential to prevent aggregation and maintain dispersion stability. However, selecting the appropriate stabilizer and its concentration can be challenging. Inappropriate selection may result in poor stability or even toxicity issues, especially for parenteral formulations. The **manufacturing process** of nanosuspensions can also be complex. Techniques such as high-pressure homogenization and media milling require specialized equipment, high energy input, and precise control of process parameters. This can increase production costs and complicate formulation development.

In the case of media milling, there is also a risk of **contamination from milling media**, such as zirconium or other grinding materials. This can affect the purity and safety of the final product if not properly controlled. Another practical challenge is related to **scale-up and reproducibility**. Although nanosuspension techniques are scalable, maintaining uniform particle size distribution and consistent quality during large-scale production can be difficult. Finally, **stability during storage** is a concern. Nanosuspensions may undergo sedimentation, aggregation, or crystal growth over time, especially under varying temperature and humidity conditions. To overcome this, additional strategies such as lyophilization (freeze-drying) or incorporation of suitable stabilizers may be required.

2.6 Marketed Products of Nanosuspensions

Nanosuspension technology has successfully evolved into a commercially viable formulation approach for enhancing the solubility and bioavailability of poorly water-soluble drugs, particularly those belonging to BCS Class II [41]. Several pharmaceutical products developed using nanosuspension or nanocrystal technology have been approved and marketed globally, demonstrating the practical applicability of this approach in overcoming dissolution-related limitations [41].

One of the most well-known examples is fenofibrate, marketed as TriCor® and Triglide®, which is a poorly water-soluble lipid-lowering agent. The nanosuspension formulation of fenofibrate significantly improves its dissolution rate and oral bioavailability, leading to enhanced therapeutic efficacy and reduced variability in drug absorption [42]. Similarly, sirolimus (Rapamune®), an immunosuppressant drug with low aqueous solubility, has been successfully formulated as a nanosuspension to improve its dissolution characteristics and ensure more consistent systemic exposure, which is critical in transplant therapy [42].

Aprepitant (Emend®), used for the prevention of chemotherapy-induced nausea and vomiting, is another important example where nanosizing enhances dissolution and facilitates rapid absorption following oral administration [43]. In the field of oncology, paclitaxel (Abraxane®) represents a significant advancement in nanoparticle-based formulations, where improved solubility and elimination of toxic solubilizing agents result in enhanced safety and therapeutic effectiveness [43].

Megestrol acetate (Megace ES®), used as an appetite stimulant, also demonstrates improved oral bioavailability when formulated as a nanosuspension, resulting in better clinical outcomes [42]. Additionally, paliperidone palmitate (Invega Sustenna®) is a long-acting injectable nanosuspension formulation that provides sustained drug release and improves patient compliance by reducing dosing frequency [43].

3. Recent Advances and Future Perspectives

In recent years, nanosuspension technology has undergone significant advancements, driven by the increasing number of poorly water-soluble drug candidates emerging from modern drug discovery processes. The integration of nanotechnology with pharmaceutical formulation has enabled the development of more efficient and targeted drug delivery systems, particularly for BCS Class II drugs [44].

One of the major recent advancements in nanosuspension technology is the improvement in **particle size control and uniformity** through advanced processing techniques such as high-pressure homogenization and combinative approaches like Nanoedge technology. These developments have allowed the production of nanosuspensions with narrow particle size distribution, leading to improved stability, reproducibility, and dissolution performance [45]. Another important area of progress is the **development of surface-modified nanosuspensions**, where stabilizers and functional excipients are used not only for physical stabilization but also for enhancing drug targeting and absorption. Surface modification can improve mucoadhesion, increase residence time in the gastrointestinal tract, and facilitate better interaction with biological membranes, ultimately enhancing drug absorption [46].

The application of nanosuspensions is also expanding beyond conventional oral delivery. Recent research has focused on their use in **parenteral, ocular, pulmonary, and targeted drug delivery systems**, where nanosized particles offer advantages such as improved tissue penetration and controlled drug release. This has opened new opportunities for delivering drugs that were previously difficult to formulate using traditional approaches [45]. Furthermore, there is growing interest in combining nanosuspension technology with other advanced drug delivery systems, such as **solid dispersions, lipid-based systems, and polymeric carriers**, to achieve synergistic effects in solubility and bioavailability enhancement. These hybrid systems represent a promising direction for future research and development [46].

Despite these advancements, certain challenges remain, particularly in terms of long-term stability, large-scale manufacturing, and regulatory acceptance. Future research is expected to focus on addressing these limitations through the development of more robust stabilizers, improved processing techniques, and better understanding of nanoscale drug behaviour. Overall, nanosuspension technology holds significant potential for the future of pharmaceutical development. With continuous innovation and technological advancements, it is expected to play a crucial role in improving the delivery and therapeutic performance of poorly water-soluble drugs, especially those classified under BCS Class II [44].

4. Applications of Nanosuspensions

- **Oral**

Particle size reduction for making nanosuspension or nanoparticle is critical task from decades. Now our technology can enable the production size to 100-200nm size in reproducible manner. The submicron particle can be stabilized by the or polymer in nanosuspension. Which can be process into the more standard form like tablet and capsule which is suitable for the oral administration. Those nanoformulation van help with the BCS class II and IV compounds like liquid-filled capsule or solid

dispersion in the amorphous state. A nanocrystalline in vitro improve bioavaibility reduce variability and alleviate positive food effect on orally administered molecule. [46]

- **Parenteral Drug Delivery**

Nanotechnology has tested for parental delivery of several molecules Some of those molecules have how the city because of Uncontrolled systemic distribution or non-target they required very specific and targeted nanoparticle approach for example doxorubicin An effective anti-cancer had serious side effect like cardiotoxicity therefore its use is limited but encapsulation of this drug can be potentially improve drug targeting which Reduces their side effects Those can be achieve from polymer mediated delivery system. An FDA approve 130 nm albumin-bound paclitaxel nanoparticle, in January 2005 for the treatment of breast cancer.[47]

- **Ocular Drug Delivery**

Ocular drug delivery is highly challenging due to the complex anatomical and physiological barriers of the eye, including the corneal epithelium, tear turnover, nasolacrimal drainage, and blood–ocular barriers, which significantly limit drug absorption. As a result, conventional ophthalmic formulations such as eye drops often exhibit very low bioavailability, with only a small fraction of the administered dose reaching the intraocular tissues [48].

Nanosuspension-based drug delivery systems have emerged as an effective strategy to overcome these limitations. These systems consist of nanosized drug particles that enhance solubility and dissolution rate, thereby improving drug availability at the site of action. The small particle size also facilitates better penetration across ocular barriers and increases interaction with the corneal surface [49].

One of the major advantages of nanosuspensions in ocular delivery is their ability to enhance corneal retention and permeability. Due to their reduced size and increased surface area, nanoparticles exhibit prolonged residence time on the ocular surface, minimizing rapid precorneal elimination caused by tear fluid and blinking. This results in improved drug absorption and enhanced therapeutic efficacy compared to conventional formulations [50].

In addition, nanosuspensions can be designed to provide controlled and sustained drug release, which helps maintain therapeutic drug concentrations for extended periods. This not only improves treatment outcomes but also reduces dosing frequency, thereby enhancing patient compliance, particularly in chronic ocular conditions [51].

Recent advancements have focused on the development of surface-modified nanosuspensions using polymers and charged stabilizers to improve mucoadhesion and site-specific delivery. These modifications enhance drug localization within ocular tissues and reduce systemic exposure. Furthermore, ligand-based targeting approaches are being explored to achieve selective delivery to specific regions of the eye [52].

Nanosuspensions have demonstrated potential in the treatment of various ocular disorders, including glaucoma, cataracts, infections, and retinal diseases. Their ability to improve solubility, enhance drug stability, and provide sustained release makes them a promising platform for ocular drug delivery [53].

Despite these advantages, challenges such as physical stability, irritation potential, and large-scale manufacturing remain. However, ongoing research and advancements in nanotechnology are expected to address these issues and further expand the application of nanosuspensions in ophthalmic drug delivery [48].

- **Targeted Drug Delivery**

Targeted drug delivery has gained significant attention in recent years as an advanced strategy to enhance therapeutic efficacy while minimizing systemic side effects. Conventional drug delivery systems often distribute the drug non-specifically throughout the body, leading to reduced drug concentration at the desired site and increased risk of toxicity. In this context, nanosuspension-based drug delivery systems have emerged as a promising approach for achieving site-specific and controlled drug delivery [54].

Nanosuspensions consist of pure drug particles in the nanometer range, which can be engineered to improve drug accumulation at specific target sites. Their small particle size allows enhanced permeability and retention (EPR) effect, particularly in tumour tissues, where leaky vasculature facilitates the accumulation of nanosized particles. This property makes nanosuspensions highly suitable for targeted delivery in cancer therapy [55].

One of the key strategies in targeted delivery using nanosuspensions is surface modification. By coating nanoparticles with polymers, surfactants, or ligands, it is possible to enhance their interaction with specific biological receptors. Ligand-functionalized nanosuspensions can selectively bind to target cells, improving drug localization and reducing off-target effects. This approach has shown promising results in targeted delivery to tumour cells, inflamed tissues, and specific organs [56].

In addition to active targeting, nanosuspensions also enable passive targeting through their physicochemical properties. The nanoscale size facilitates prolonged circulation time and reduced clearance by the reticuloendothelial system (RES), allowing more drug to reach the target site. This enhances therapeutic efficiency without the need for complex targeting mechanisms [57].

Furthermore, nanosuspensions can be utilized for targeted delivery across biological barriers, such as the blood–brain barrier (BBB), which is otherwise difficult to penetrate using conventional formulations. Recent studies have demonstrated that nanosized drug particles can improve drug transport across such barriers, opening new possibilities for the treatment of neurological disorders [58].

Another important advantage of nanosuspension-based targeted delivery is the ability to provide controlled and sustained drug release at the target site. This ensures prolonged therapeutic action, reduces dosing frequency, and improves patient compliance. It also helps in maintaining optimal drug concentration within the therapeutic window [59].

Despite these advantages, challenges such as stability, potential toxicity of surface modifiers, and large-scale production remain. However, ongoing advancements in nanotechnology and formulation strategies are expected to overcome these limitations and further enhance the potential of nanosuspensions in targeted drug delivery applications [54].

5. Ultrasonication as an Alternative Method for Nanosuspension Preparation

Ultrasonication has emerged as an effective and relatively simple technique for the preparation of nanosuspensions, particularly as a bottom-up or combinative approach. This method utilizes high-frequency ultrasonic waves to generate acoustic cavitation, leading to the formation and collapse of microbubbles in the liquid medium. The intense energy released during cavitation results in particle size reduction and improved dispersion of drug particles [60].

In nanosuspension preparation, ultrasonication is often employed either alone or in combination with precipitation methods to enhance particle size reduction and achieve uniform distribution. The technique facilitates the breakdown of drug particles into the nanometer range and prevents agglomeration by providing sufficient energy to overcome interparticle attraction forces [61].

One of the major advantages of ultrasonication is its **simplicity, cost-effectiveness, and scalability**, making it suitable for laboratory-scale as well as pilot-scale production. Additionally, it does not require complex equipment compared to high-pressure homogenization or media milling, which makes it an attractive alternative for initial formulation development [62].

Ultrasonication also contributes to improved **stabilization of nanosuspensions** by enhancing the interaction between drug particles and stabilizers such as surfactants and polymers. This results in better dispersion stability and reduced particle aggregation, which are critical factors for maintaining nanosuspension quality [63].

However, certain limitations must be considered, including the possibility of **temperature rise during sonication**, which may lead to drug degradation, and challenges in achieving uniform particle size at large scale. Therefore, optimization of process parameters such as sonication time, amplitude, and temperature control is essential for successful formulation [64].

Overall, ultrasonication represents a promising and versatile technique for nanosuspension preparation, offering advantages in terms of efficiency, simplicity, and adaptability. Its integration with other formulation approaches is expected to further enhance its applicability in the development of nanosuspension-based drug delivery systems.

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