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NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS FOR POORLY SOLUBLE DRUGS: RECENT ADVANCES AND CHALLENGES

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ABSTRACT: Poor aqueous solubility remains a major challenge in pharmaceutical drug development, resulting in low and variable bioavailability, inconsistent therapeutic responses, and formulation difficulties for many drug candidates. Conventional solubility enhancement techniques such as salt formation, micronization, solid dispersions, cyclodextrin complexation, and surfactant-based systems often provide limited or unstable improvements, particularly for highly lipophilic drugs. In this context, nanoparticle-based drug delivery systems have emerged as an effective and versatile approach to improve the solubility, dissolution rate, and bioavailability of poorly soluble drugs. By reducing drug particle size to the nanometer range and employing carrier-based strategies, nanoparticles enhance surface area, wettability, saturation solubility, and drug absorption while also enabling controlled drug release and protection from degradation. This review critically discusses the physicochemical causes of poor drug solubility, limitations of conventional delivery systems, and the rationale for nanoparticle-based formulations. Various nanoparticle platforms, including nanocrystals, nanosuspensions, lipid-based and polymeric nanoparticles, liposomes, nano-emulsions, and hybrid systems, are evaluated along with recent advances in formulation technologies, characterization, regulatory considerations, and future perspectives.

KEYWORDS: Bioavailability; Drug delivery systems; Nanoparticles; Poorly soluble drugs

INTRODUCTION:

Poor aqueous solubility is widely recognized as one of the most persistent and critical challenges in pharmaceutical drug development. Drug solubility is a fundamental physicochemical property that governs dissolution rate, absorption, systemic bioavailability, and ultimately therapeutic efficacy. With the advancement of modern medicinal chemistry and high-throughput screening techniques, an increasing number of newly discovered drug candidates exhibit high lipophilicity and complex molecular structures, which often result in poor water solubility.[1] It has been consistently reported that approximately 40% of marketed drugs and nearly 70–90% of new chemical entities in the drug

development pipeline suffer from poor aqueous solubility, thereby creating significant formulation and development challenges .[2]

Poorly soluble drugs frequently demonstrate dissolution-rate-limited absorption, particularly following oral administration, which remains the most preferred route due to patient convenience and compliance.[3] Insufficient dissolution of drug molecules in gastrointestinal fluids leads to low and erratic plasma drug concentrations, high inter- and intra-patient variability, and unpredictable pharmacokinetic behaviour. To compensate for poor absorption, higher drug doses are often administered, which may increase the risk of dose-related toxicity, adverse effects, and reduced patient adherence to therapy. These limitations significantly impact the clinical success of many promising drug candidates.

The Biopharmaceutics Classification System (BCS) provides a scientific framework to correlate drug solubility and permeability with absorption characteristics. A large proportion of poorly soluble drugs fall under BCS Class II (low solubility, high permeability) and BCS Class IV (low solubility, low permeability) categories. For BCS Class II drugs, absorption is mainly limited by dissolution rate, whereas BCS Class IV drugs face compounded challenges of both poor solubility and low permeability. In both cases, enhancement of drug solubility is a critical requirement to achieve optimal bioavailability and therapeutic efficacy.[4]

Conventional formulation strategies such as salt formation, micronization, solid dispersions, cyclodextrin complexation, and the use of surfactants or co-solvents have been extensively explored to improve solubility of poorly soluble drugs. However, these approaches are often associated with significant drawbacks including physical and chemical instability, recrystallization during storage, limited bioavailability enhancement, poor scalability, and lack of reproducibility during large-scale manufacturing. These limitations highlight the need for more robust and efficient drug delivery approaches.[5]

In recent years, nanoparticle-based drug delivery systems have emerged as a powerful and versatile platform for overcoming solubility-related challenges. Nanotechnology involves the design of materials with dimensions typically ranging from 1 to 1000 nm, which exhibit unique physicochemical and biological properties compared to conventional dosage forms. Reduction of drug particle size to the nanometer range significantly increases surface area, leading to enhanced dissolution rate as described by the Noyes–Whitney equation, improved saturation solubility, and superior interaction with biological membranes.[6]

A wide variety of nanoparticle platforms have been investigated for the delivery of poorly soluble drugs, including drug nanocrystals, nanosuspensions, lipid-based nanoparticles (solid lipid nanoparticles and nanostructured lipid carriers), polymeric nanoparticles, liposomes, and nanoemulsions. The successful commercialization of several nanoparticle-based drug products further supports the translational and industrial relevance of nanotechnology-driven drug delivery systems.[7] Despite these advancements, nanoparticle-based drug delivery systems still face challenges related to large-scale manufacturing, long-term stability, toxicity, regulatory approval, and stringent quality control requirements. Therefore, a comprehensive evaluation of recent advances and existing challenges is essential to guide future research and facilitate successful clinical translation of nanoparticle-based drug delivery systems for poorly soluble drugs.[8]

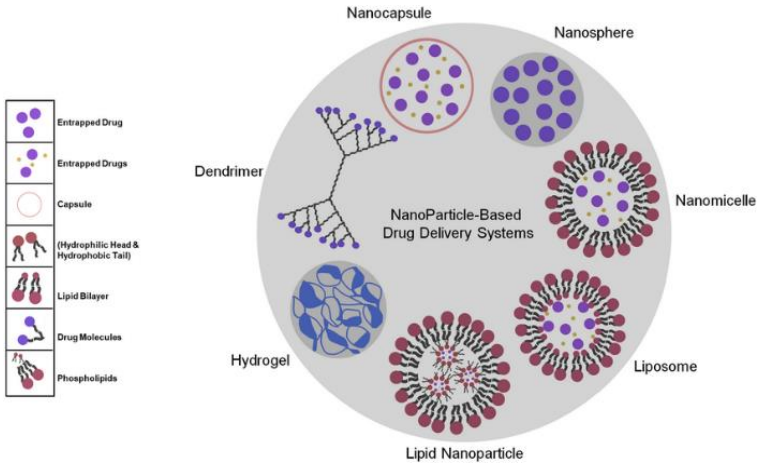

Figure 1: Schematic representation of nanoparticle-based drug delivery for poorly soluble drugs

Poorly Soluble Drugs: Challenges in Conventional Drug Delivery

Poor solubility remains a critical barrier in achieving optimal therapeutic performance of many pharmaceutical drugs. Despite advances in medicinal chemistry and formulation science, a large number of active pharmaceutical ingredients (APIs) continue to exhibit low aqueous solubility, which significantly compromises their dissolution, absorption, and bioavailability. Conventional drug delivery systems often fail to address these challenges adequately, resulting in formulation inefficiencies and suboptimal clinical outcomes. Understanding the physicochemical causes of poor solubility and the inherent limitations of traditional solubility enhancement techniques is essential before considering advanced delivery platforms such as nanoparticle-based systems.

Causes of Poor Solubility

- **High Lipophilicity**

High lipophilicity is a major contributing factor to poor aqueous solubility in drug molecules. Many modern drug candidates are intentionally designed to be lipophilic to enhance interaction with biological targets; however, excessive lipophilicity reduces drug affinity for aqueous dissolution media. Drugs with high log P values demonstrate poor dissolution behavior in gastrointestinal fluids, which leads to incomplete absorption following oral administration.[9]

- **Strong Crystal Lattice Energy**

The crystalline structure of a drug plays a crucial role in determining its solubility. Drugs with strong crystal lattice energy possess tightly packed molecules stabilized by intermolecular forces such as hydrogen bonding, dipole–dipole interactions, and van der Waals forces. High lattice energy requires greater energy input for molecular detachment during dissolution, thereby reducing solubility and dissolution rate. Crystalline drugs with high lattice energy frequently exhibit poor dissolution behaviour, even when administered in finely divided form.[10]

- **Low Wettability**

Wettability refers to the ability of a liquid to spread over the surface of a solid drug particle. Poorly soluble drugs are often hydrophobic in nature, leading to low wettability and reduced contact between drug particles and dissolution media. This limits the penetration of aqueous fluids into the powder bed and decreases the effective surface area available for dissolution. Poor wettability is particularly problematic in oral dosage forms, where rapid wetting is essential for efficient drug dissolution and absorption.[11]

- **Polymorphism**

Polymorphism is the phenomenon in which a drug substance exists in more than one crystalline form, each possessing distinct physicochemical properties. Different polymorphs of the same drug may exhibit significant variations in solubility, dissolution rate, stability, and bioavailability. While metastable or amorphous forms generally show higher solubility, they are thermodynamically unstable and may convert to more stable but less soluble forms during processing or storage. Such transformations can lead to variability in drug performance and pose serious challenges in formulation development and quality control.[12]

Limitations of Conventional Solubility Enhancement Approaches

Several conventional formulation strategies have been developed to improve the solubility of poorly soluble drugs. Although these approaches have been used successfully in some cases, they often suffer from critical limitations that restrict their effectiveness and industrial applicability.

- **Salt Formation**

Salt formation is widely employed to enhance the solubility of ionizable drugs by converting them into more soluble salt forms. While this approach can significantly improve dissolution rate and solubility, it is limited to drugs possessing suitable acidic or basic functional groups. Additionally, salt forms may exhibit pH-dependent solubility, hygroscopicity, chemical instability, and polymorphic conversion, which can adversely affect product stability and bioavailability. Furthermore, salt formation does not guarantee improved in vivo performance in all cases.[13]

- **Micronization**

Micronization involves reducing the particle size of drugs to the micrometer range to increase surface area and dissolution rate. Although this technique can enhance dissolution to some extent, it does not improve the intrinsic solubility of the drug. Moreover, micronized particles often exhibit high surface energy, leading to aggregation and poor powder flow properties. These issues can negate the benefits of particle size reduction and limit the effectiveness of micronization for extremely poorly soluble drugs.[14]

- **Solid Dispersions**

Solid dispersion systems consist of a poorly soluble drug dispersed in a hydrophilic polymer matrix to enhance dissolution and bioavailability. While solid dispersions can significantly improve drug release, they are often associated with problems such as physical instability, recrystallization during storage, moisture sensitivity, and difficulties in large-scale manufacturing. The long-term stability of amorphous drug forms within solid dispersions remains a major concern for commercial development.[15]

- **Cyclodextrin Complexation**

Cyclodextrins improve solubility by forming inclusion complexes with hydrophobic drug molecules, thereby increasing their apparent aqueous solubility. Despite their effectiveness, cyclodextrin-based formulations require precise molecular fit and high complexation efficiency. Excessive use of cyclodextrins may increase formulation cost and raise concerns regarding toxicity, especially with parenteral administration. In addition, rapid dissociation of complexes in vivo may result in unpredictable drug release profiles.[16]

- **Use of Surfactants**

Surfactants enhance drug solubility by reducing interfacial tension and facilitating micellar solubilization of poorly soluble drugs. However, high concentrations of surfactants are often required to achieve significant solubility enhancement, which may cause gastrointestinal irritation, toxicity, and formulation instability. Surfactant-based systems may also exhibit sensitivity to physiological conditions such as bile salt concentration and gastrointestinal motility, leading to variability in drug absorption.[17]

Rationale for Nanoparticle-Based Drug Delivery Systems

The limitations associated with conventional drug delivery approaches for poorly soluble drugs have necessitated the exploration of alternative formulation strategies that can provide consistent solubility enhancement, improved bioavailability, and better therapeutic performance. Among the various advanced delivery platforms investigated, nanoparticle-based drug delivery systems have emerged as a rational and scientifically validated approach for overcoming solubility-related challenges. The rationale for employing nanoparticles lies in their unique physicochemical properties, which enable superior drug dissolution, absorption, and in vivo performance compared to traditional dosage forms.

- **Particle Size Reduction and Surface Area Enhancement**

One of the primary rationales for nanoparticle-based drug delivery is the dramatic reduction in particle size, typically to the nanometer range, which results in a substantial increase in surface area. According to classical dissolution theory, an increase in surface area directly enhances the dissolution rate of poorly soluble drugs. Nanoparticles reduce the diffusion layer thickness surrounding drug particles, thereby accelerating mass transfer into the dissolution medium. This effect is particularly beneficial for drugs exhibiting dissolution-rate-limited absorption, such as BCS Class II compounds.[18]

- **Improvement in Saturation Solubility**

In addition to improving dissolution rate, nanoparticles can increase the apparent saturation solubility of poorly soluble drugs. The Kelvin–Ostwald–Freundlich equation explains that a decrease in particle size leads to an increase in dissolution pressure, which enhances solubility at the nanoscale. This phenomenon is not achievable through conventional micronization techniques and represents a significant advantage of nanoparticle-based systems for solubility enhancement.[19]

- **Enhanced Wettability and Dispersion**

Nanoparticles often exhibit improved wettability due to the presence of stabilizers, surfactants, or polymeric coatings on their surface. These excipients reduce interfacial tension between the drug particles and aqueous dissolution media, promoting rapid wetting and uniform dispersion. Improved wettability ensures greater surface contact with gastrointestinal fluids, leading to enhanced dissolution and absorption of hydrophobic drugs.[20]

- **Improved Permeation and Absorption**

Nanoparticle-based drug delivery systems can enhance drug absorption by improving interaction with biological membranes. Due to their small size, nanoparticles exhibit closer contact with the intestinal epithelium and may be taken up via endocytosis or paracellular pathways. In some cases, nanoparticles facilitate lymphatic transport, thereby bypassing hepatic first-pass metabolism and further improving systemic bioavailability.[21]

- **Protection of Drug from Degradation**

Poorly soluble drugs are often susceptible to chemical and enzymatic degradation in physiological environments. Encapsulation of drugs within nanoparticle matrices provides a protective barrier against degradation, improving stability during storage and transit through the gastrointestinal tract. This protective effect enhances the effective concentration of the drug available for absorption and contributes to improved therapeutic outcomes.

- **Controlled and Sustained Drug Release**

Nanoparticle-based systems offer the ability to modulate drug release profiles through careful selection of carrier materials and formulation parameters. Polymeric and lipid-based nanoparticles can be engineered to provide sustained or controlled drug release, reducing dosing frequency and minimizing peak-to-trough fluctuations in plasma drug concentration. This controlled release behavior enhances patient compliance and reduces the risk of dose-related toxicity.[22]

- **Improved Reproducibility and Dose Uniformity**

Conventional formulations of poorly soluble drugs often suffer from batch-to-batch variability due to inconsistent dissolution and absorption. Nanoparticle formulations, when properly optimized, offer improved reproducibility and dose uniformity by maintaining consistent particle size distribution and drug loading. This characteristic is particularly important from a quality assurance and regulatory perspective.

- **Clinical and Translational Justification**

The clinical success of several nanoparticle-based drug products has provided strong translational justification for this approach. Marketed nanomedicines have demonstrated enhanced bioavailability, reduced dosing requirements, and improved therapeutic efficacy compared to conventional formulations. These successes have encouraged continued research and regulatory acceptance of nanoparticle-based drug delivery systems.[23]

Classification of Nanoparticle-Based Drug Delivery Systems

Nanoparticle-based drug delivery systems represent a diverse group of carrier platforms designed to improve the solubility, dissolution rate, stability, and bioavailability of poorly soluble drugs. These systems are classified based on their composition, structural organization, and mechanism of drug incorporation. Each class of nanoparticles offers unique advantages and faces specific limitations, making them suitable for different categories of poorly soluble drugs and routes of administration.[24]

- **Drug Nanocrystals**

Drug nanocrystals are nanosized particles composed almost entirely of the pure active pharmaceutical ingredient (API), stabilized by surfactants or polymers. Unlike carrier-based systems, nanocrystals provide extremely high drug loading and are particularly effective for BCS Class II drugs, where absorption is dissolution-rate limited.

Reduction of drug particles to the nanometer range leads to a significant increase in surface area, enhanced dissolution velocity, and improved saturation solubility. Several studies have demonstrated that nanocrystal formulations result in faster onset of action and improved oral bioavailability compared to conventional micronized formulations.[25]

- **Nanosuspensions**

Nanosuspensions are submicron colloidal dispersions of poorly soluble drugs stabilized using surfactants or polymeric stabilizers. They are suitable for drugs that are insoluble in both aqueous and organic solvents and can be administered via oral, parenteral, pulmonary, and ocular routes.

Nanosuspensions enhance bioavailability by maintaining the drug in a dispersed state and increasing dissolution rate. However, instability phenomena such as Ostwald ripening and particle aggregation remain significant challenges during long-term storage.[26]

- **Lipid-Based Nanoparticles**
  - **Solid Lipid Nanoparticles (SLNs)**

Solid lipid nanoparticles consist of solid lipids that remain solid at room and body temperature, stabilized by surfactants. Poorly soluble drugs are incorporated into the lipid matrix, improving solubility and protecting the drug from degradation.

SLNs promote lymphatic uptake of lipophilic drugs, thereby reducing first-pass metabolism and improving systemic bioavailability. Despite these advantages, SLNs often suffer from limited drug loading and drug expulsion during storage due to lipid crystallization.[27]

  - **Nanostructured Lipid Carriers (NLCs)**

Nanostructured lipid carriers were developed to overcome the drawbacks of SLNs. They are composed of a mixture of solid and liquid lipids, creating an imperfect lipid matrix that accommodates higher drug loading and reduces drug expulsion.

NLCs have demonstrated improved encapsulation efficiency, better physical stability, and superior bioavailability for poorly soluble drugs compared to SLNs.[28]

- **Polymeric Nanoparticles**

Polymeric nanoparticles are prepared using biodegradable and biocompatible polymers such as polyesters and polysaccharides. Drugs can be encapsulated within the polymer matrix or adsorbed onto the particle surface, allowing controlled and sustained drug release.

These systems protect poorly soluble drugs from environmental degradation and provide prolonged therapeutic action. However, challenges related to complex manufacturing processes and potential polymer-associated toxicity must be carefully addressed.

- **Liposomes**

Liposomes are spherical vesicular systems composed of phospholipid bilayers surrounding an aqueous core. Poorly soluble drugs are typically incorporated into the lipid bilayer, enhancing solubility and bioavailability.

Liposomes have demonstrated strong clinical relevance, with several formulations approved for clinical use. However, issues such as drug leakage, limited physical stability, and high production costs can restrict their widespread application.[29]

- **Nanoemulsions and Self-Nanoemulsifying Drug Delivery Systems**

Nanoemulsions are kinetically stable dispersions of oil and water stabilized by surfactants, with droplet sizes typically below 200 nm. Self-Nanoemulsifying Drug Delivery Systems are isotropic mixtures that spontaneously form nanoemulsions upon contact with gastrointestinal fluids.

These systems improve solubility by dissolving poorly soluble drugs in the oil phase and enhancing absorption through rapid dispersion and increased interfacial surface area. However, thermodynamic instability and surfactant-related toxicity remain concerns.

- **Inorganic and Hybrid Nanoparticles**

Inorganic nanoparticles such as mesoporous silica and gold nanoparticles have been explored for drug delivery due to their high surface area and tunable pore structures. Hybrid nanoparticles combining organic and inorganic components offer multifunctional properties but face significant toxicity and regulatory challenges.

Table No 1: Nanoparticle-Based Drug Delivery Systems advantage and limitations

Nanoparticle System	Key Advantage	Major Limitation
Nanocrystals	High drug loading	Aggregation
Nanosuspensions	Multiple routes	Ostwald ripening
SLNs	Biocompatibility	Low drug loading
NLCs	High encapsulation	Formulation complexity
Polymeric NPs	Controlled release	Polymer toxicity
Liposomes	Clinical acceptance	Leakage
Nano-emulsions	Rapid absorption	Surfactant toxicity
Dendrimers	Targeted delivery	Cytotoxicity

- **Dendrimers**

Dendrimers are highly branched, monodisperse macromolecules with a well-defined architecture. Poorly soluble drugs can be either encapsulated within internal cavities or conjugated to surface functional groups.

Dendrimers improve solubility, enable controlled release, and allow surface modification for targeted delivery. Despite their potential, concerns regarding cytotoxicity and cost limit their clinical translation. [30]

Evaluation and Characterization of Nanoparticle-Based Drug Delivery Systems

Comprehensive evaluation and characterization of nanoparticle-based drug delivery systems are critical to ensure product quality, safety, efficacy, and regulatory compliance. Due to their complex structure and nanoscale dimensions, nanoparticles require advanced physicochemical, in vitro, and in vivo characterization techniques. Proper characterization not only supports formulation optimization but also plays a key role in establishing critical quality attributes (CQAs) and ensuring batch-to-batch consistency.[31]

Table No 2: Characterization Parameters and Their Significance

Parameter	Technique	Significance
Particle size	DLS	Solubility & bioavailability
PDI	DLS	Formulation uniformity
Zeta potential	Electrophoretic mobility	Stability
Morphology	SEM / TEM	Structural integrity
Drug loading	HPLC / UV	Dose accuracy
Drug release	Dissolution studies	Therapeutic performance
Stability	ICH studies	Shelf life
PK studies	In vivo analysis	Bioavailability

Recent Advances in Nanoparticle-Based Drug Delivery Systems

In recent years, significant advancements have been made in nanoparticle-based drug delivery systems to overcome the limitations associated with poor aqueous solubility of drugs. Innovations in formulation techniques, surface engineering, targeting strategies, and manufacturing technologies have substantially improved the performance, stability, and translational potential of nanoparticle systems. These advances have enabled enhanced bioavailability, improved therapeutic efficacy, and better patient compliance for poorly soluble drugs. [32]

- **Surface Modification and Functionalization**

Surface modification has emerged as a key strategy to improve the performance of nanoparticle systems. Functionalization of nanoparticles with polymers, ligands, or biomolecules enhances stability, prolongs circulation time, and improves interaction with biological membranes.

Polyethylene glycol (PEG) coating (PEGylation) has been widely adopted to reduce opsonization and reticuloendothelial system uptake, thereby increasing systemic bioavailability of poorly soluble drugs.

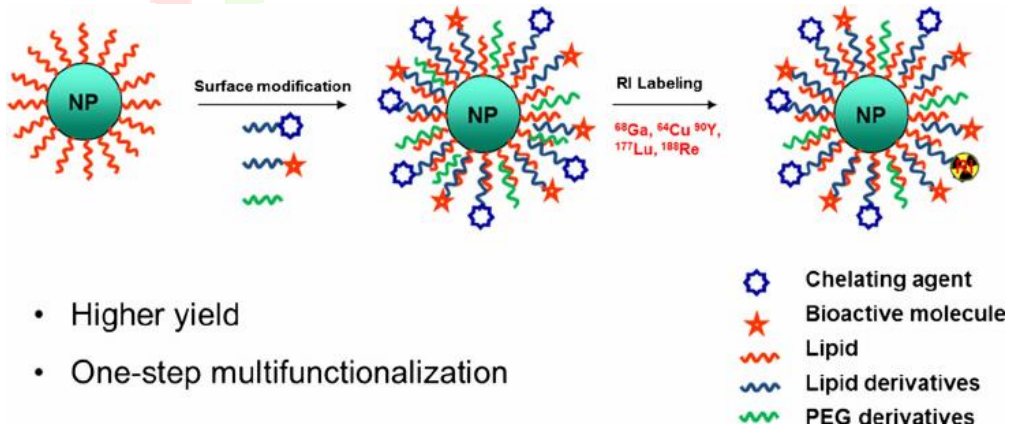

Figure 2: Role of nanoparticle surface modification in overcoming biological and formulation limitations

- **Advanced Nanofabrication Techniques**

Modern nanofabrication techniques have enabled precise control over particle size, morphology, and drug loading. Methods such as high-pressure homogenization, microfluidization, nanoprecipitation, and supercritical fluid technology have been optimized to produce uniform nanoparticles with narrow size distribution. Recent studies have shown that continuous manufacturing approaches improve batch-to-batch consistency and scalability of nanoparticle formulations, addressing one of the major barriers to industrial translation.[33]

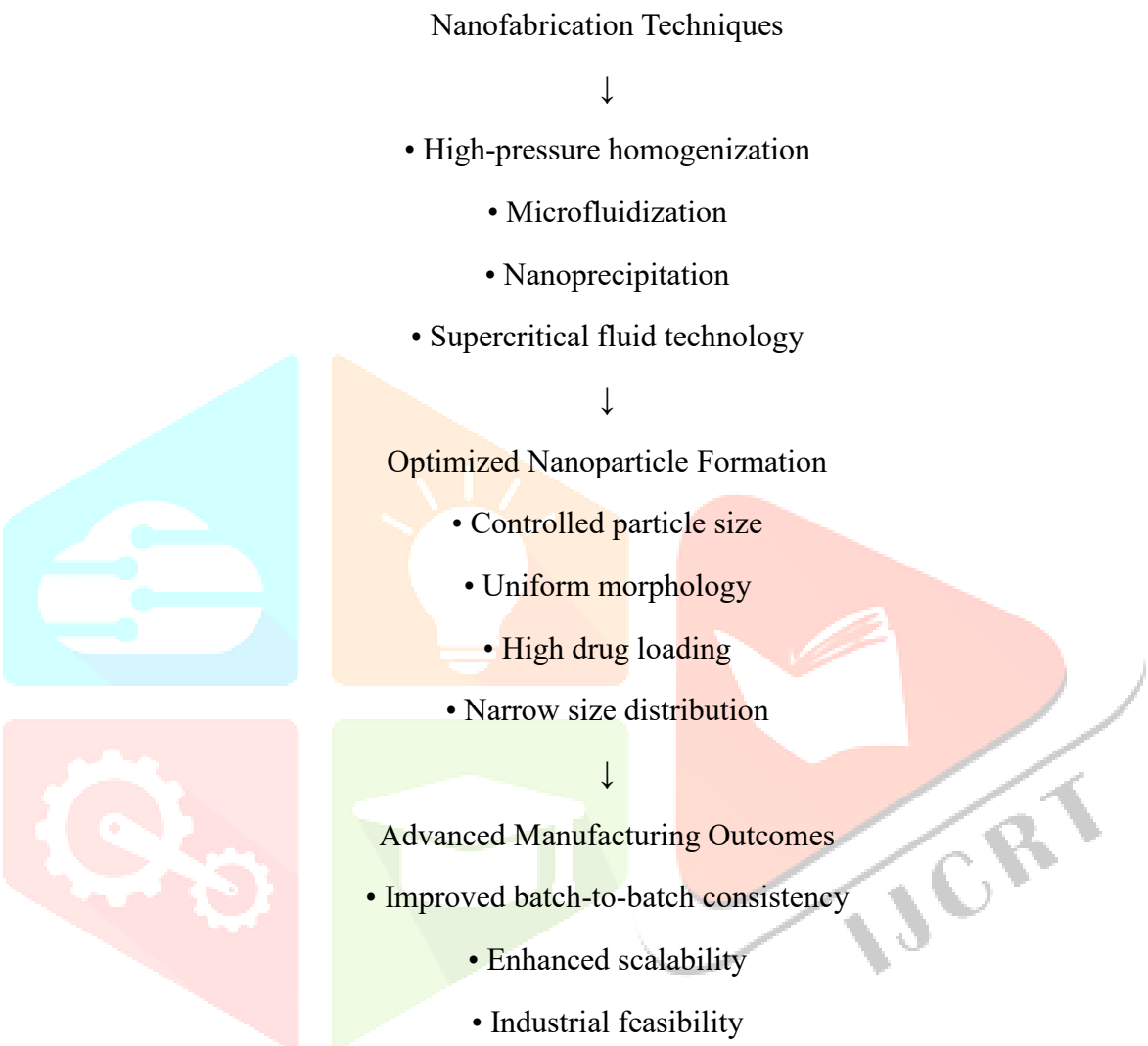

Figure 3: Schematic representation of advanced nanofabrication approaches for nanoparticle formulation

- **Targeted Nanoparticle Drug Delivery**

Targeted nanoparticle delivery systems have gained considerable attention for improving site-specific drug delivery while minimizing systemic toxicity. Ligand-mediated targeting using antibodies, peptides, sugars, or small molecules allows nanoparticles to selectively bind to specific receptors overexpressed on diseased tissues. Targeted delivery has been particularly successful in oncology and central nervous system applications, where poorly soluble drugs require precise localization to achieve therapeutic efficacy.[34]

- **Stimuli-Responsive Nanoparticles**

Stimuli-responsive or “smart” nanoparticles represent a major recent advancement in drug delivery technology. These systems are designed to release drugs in response to specific internal stimuli (pH, enzymes, redox potential) or external stimuli (temperature, light, magnetic field) pH-responsive

nanoparticles have been extensively studied for oral delivery of poorly soluble drugs, as they allow controlled drug release in specific regions of the gastrointestinal tract.[35]

- **Lipid Nanoparticles and mRNA-Inspired Technologies**

The success of lipid nanoparticles in mRNA vaccine delivery has accelerated research into their application for poorly soluble drugs. Lipid nanoparticles provide efficient encapsulation, enhanced stability, and improved cellular uptake, making them suitable for delivering lipophilic small molecules and biologics.

Recent advances include ionizable lipid systems that improve drug loading efficiency and reduce toxicity compared to earlier lipid formulations.[36]

- **Hybrid and Multifunctional Nanoparticles**

Hybrid nanoparticles combining polymeric, lipid, or inorganic components have been developed to exploit the advantages of multiple carrier systems. These multifunctional nanoparticles exhibit improved stability, controlled release, and enhanced solubility enhancement compared to single-component systems.

Such hybrid systems allow simultaneous drug delivery, imaging, and targeting, expanding their potential in precision medicine.[37]

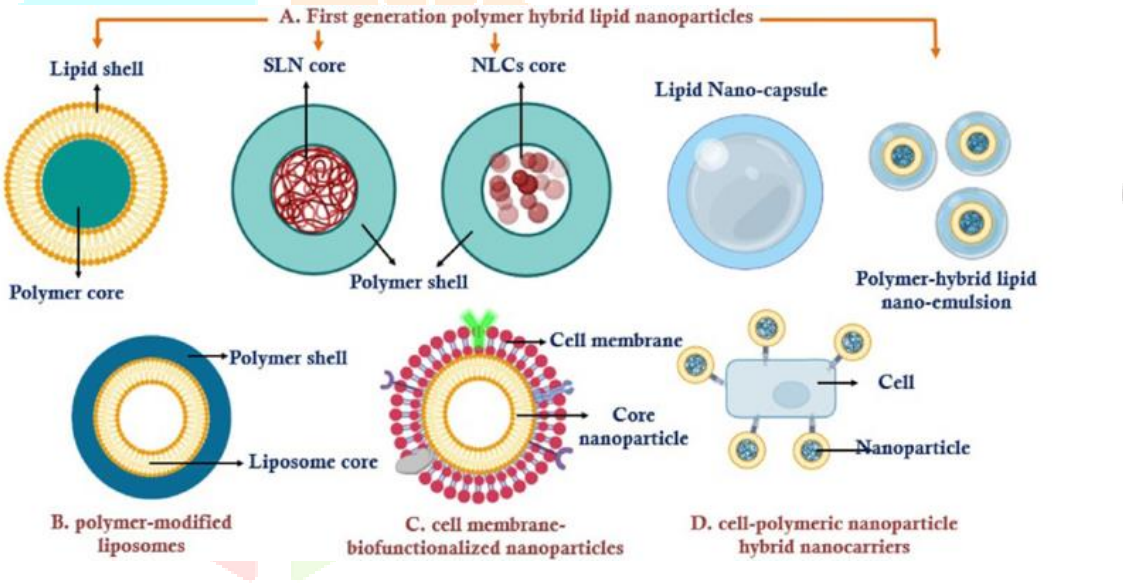

Figure 4: Schematic representation of evolution of polymer-lipid hybrid nanoparticles.

A. First-generation polymer hybrid lipid nanoparticles B. polymer-modified liposomes

C. cell membrane-biofunctionalized nanoparticles D. cell-polymeric nanoparticle hybrid nanocarriers

- **Artificial Intelligence and Data-Driven Formulation Design**

Artificial intelligence (AI) and machine learning tools are increasingly being applied to nanoparticle formulation development. These tools assist in optimizing formulation variables, predicting stability, and reducing experimental trial-and-error approaches.

AI-driven design has shown promise in accelerating development timelines and improving reproducibility of nanoparticle-based drug delivery systems.[38]

Challenges and Limitations of Nanoparticle-Based Drug Delivery Systems

Despite the significant advantages of nanoparticle-based drug delivery systems in enhancing solubility and bioavailability of poorly soluble drugs, their widespread clinical and commercial application remains limited by several scientific, technical, regulatory, and safety challenges. Understanding these limitations is essential for realistic assessment of nanotechnology-driven drug delivery and for guiding future research toward successful translation.

- **Scale-Up and Manufacturing Challenges**

One of the major challenges associated with nanoparticle-based drug delivery systems is scaling up laboratory-scale formulations to industrial-scale production. Many nanoparticle preparation techniques, such as nanoprecipitation, solvent evaporation, and emulsification, are difficult to reproduce consistently at large scale. Small variations in process parameters can significantly affect particle size, drug loading, and stability.

Additionally, maintaining batch-to-batch uniformity during large-scale manufacturing is challenging due to sensitivity of nanoparticles to shear stress, temperature, and mixing conditions. These issues complicate industrial adoption and increase production costs.[39]

- **Physical and Chemical Stability Issues**

Nanoparticles are inherently thermodynamically unstable systems due to their high surface energy. During storage, they may undergo aggregation, agglomeration, Ostwald ripening, or drug expulsion, which can compromise solubility enhancement and therapeutic performance.

Chemical instability, including oxidation and hydrolysis of drug molecules or carrier materials, further limits shelf-life. Maintaining long-term stability under different storage conditions remains a major hurdle for commercialization.[40]

- **Toxicity and Safety Concerns**

Although many nanoparticle carriers are composed of biocompatible materials, concerns regarding nanotoxicity persist. The small size and large surface area of nanoparticles may lead to unintended interactions with biological systems, including cellular membranes, proteins, and genetic material.

Accumulation of nanoparticles in organs such as the liver, spleen, and lungs has raised concerns about long-term toxicity, immunogenicity, and inflammatory responses. Comprehensive safety evaluation is therefore required before clinical application.[41]

- **Regulatory and Approval Challenges**

The regulatory landscape for nanoparticle-based drug delivery systems is still evolving. Regulatory agencies often lack standardized guidelines specific to nanomedicines, leading to uncertainty in approval pathways. Variability in characterization methods, lack of harmonized definitions, and insufficient understanding of in vivo behaviour complicate regulatory assessment. Extensive documentation and additional safety data are often required, increasing development timelines and costs.[42]

- **Complexity of Characterization and Quality Control**

Nanoparticle formulations require advanced analytical techniques for characterization, including particle size analysis, surface charge measurement, morphology evaluation, and in vitro–in vivo correlation studies. These sophisticated techniques increase development complexity and cost.

Establishing robust quality control parameters and validated analytical methods for routine manufacturing remains challenging, particularly for multifunctional nanoparticle systems.

- **Limited Clinical Translation**

Despite extensive preclinical research, relatively few nanoparticle-based drug delivery systems have successfully reached the market. Translational gaps arise due to differences between preclinical models and human physiology, as well as challenges in predicting long-term safety and efficacy.

Clinical trial design for nanomedicines is complex, requiring specialized endpoints, biodistribution studies, and long-term monitoring.[43]

- **Economic and Cost Constraints**

Nanoparticle-based drug delivery systems often involve complex manufacturing processes, specialized equipment, and stringent quality control measures, leading to high production costs. These economic factors may limit accessibility and affordability, particularly in resource-limited settings.

Cost–benefit considerations play a crucial role in determining whether nanoparticle formulations can replace conventional drug delivery systems in routine clinical practice.

Regulatory and Quality Considerations for Nanoparticle-Based Drug Delivery Systems

The development and commercialization of nanoparticle-based drug delivery systems require rigorous regulatory evaluation to ensure their quality, safety, and efficacy. Due to their complex structure, unique physicochemical properties, and nanoscale dimensions, nanomedicines pose challenges that are not adequately addressed by traditional regulatory frameworks designed for conventional dosage forms. As a result, regulatory agencies have emphasized the need for enhanced characterization, robust quality control strategies, and risk-based development approaches for nanoparticle-based formulations.

- **Regulatory Landscape for Nanomedicines**

Currently, there are no universally harmonized regulations exclusively dedicated to nanoparticle-based drug delivery systems. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) evaluate nanomedicines under existing pharmaceutical guidelines, supplemented with additional requirements specific to nanomaterials.[44]

- **Quality by Design (QbD) Approach**

The Quality by Design (QbD) paradigm has been strongly recommended for the development of nanoparticle-based drug delivery systems. QbD emphasizes a systematic understanding of formulation and process variables and their impact on critical quality attributes.

For nanoparticle systems, CQAs typically include particle size, size distribution, surface charge, morphology, drug loading, release profile, and stability. Identifying critical material attributes (CMAs) and critical process parameters (CPPs) is essential to ensure consistent product quality and performance.

- **Analytical and Characterization Requirements**

Advanced analytical techniques are required to characterize nanoparticle-based formulations. Regulatory authorities emphasize the use of validated methods to assess particle size, surface charge, morphology, drug content, and in vitro release behavior.

Orthogonal analytical approaches are often recommended to ensure reliability and reproducibility of characterization data. Inadequate characterization remains one of the major reasons for regulatory delays in nanomedicine approval .

- **Nonclinical and Clinical Evaluation Requirements**

Nanoparticle-based drug delivery systems require comprehensive nonclinical evaluation, including pharmacokinetics, biodistribution, toxicity, and immunogenicity studies. Conventional toxicity testing methods may not fully capture nanoparticle-specific risks, necessitating additional or modified test strategies.

Clinical evaluation must demonstrate not only therapeutic efficacy but also long-term safety, particularly with respect to nanoparticle accumulation and potential immunological effects.

- **Regulatory Expectations for Manufacturing and Control**

Manufacturing processes for nanoparticle-based drug delivery systems must be well-controlled and reproducible. Regulatory agencies expect detailed documentation of manufacturing processes, in-process controls, and batch-to-batch consistency.

Adherence to Good Manufacturing Practices (GMP) is mandatory, and any changes in formulation or manufacturing processes require thorough risk assessment and regulatory justification.[45]

Future Perspectives of Nanoparticle-Based Drug Delivery Systems for Poorly Soluble Drugs

Nanoparticle-based drug delivery systems have significantly advanced the formulation and therapeutic performance of poorly soluble drugs. However, their future success depends on continuous innovation aimed at improving safety, efficacy, manufacturability, and regulatory acceptance. Emerging scientific and technological trends indicate that nanoparticle-based systems will play a central role in next-generation drug delivery and precision therapeutics.

- **Transition Toward Next-Generation Nanocarriers**

Future research is expected to move beyond first-generation nanocarriers toward next-generation nanoparticles with improved structural control, multifunctionality, and enhanced biological performance. These advanced systems are designed to integrate solubility enhancement with targeting, controlled release, and real-time response to physiological conditions, thereby maximizing therapeutic benefit for poorly soluble drugs.

- **Emphasis on Biodegradable and Bioinspired Materials**

One of the key future directions involves the development of biodegradable and bioinspired nanomaterials that minimize long-term toxicity and accumulation in biological tissues. Natural polymers, lipid-mimetic materials, and cell-derived nanocarriers are being explored to improve biocompatibility and immune tolerance while maintaining effective solubility enhancement. Such materials are expected to improve patient safety and regulatory confidence.[46]

- **Advancements in Targeted and Precision Drug Delivery**

Targeted nanoparticle systems represent an important future strategy for improving therapeutic outcomes of poorly soluble drugs. By functionalizing nanoparticles with targeting ligands, drug delivery can be localized to specific tissues or disease sites, reducing off-target effects and systemic toxicity. Precision targeting is particularly valuable for potent hydrophobic drugs used in oncology and chronic disease management.

- **Role of Systems Engineering and Process Optimization**

The future of nanoparticle-based drug delivery also depends on advancements in process engineering and manufacturing science. Integration of real-time monitoring, automation, and process control tools is expected to improve reproducibility, reduce variability, and lower production costs. Such

improvements will be essential for translating nanoparticle formulations from laboratory to commercial scale.[47]

- **Improved Predictive Models and Translational Tools**

Predicting in vivo performance of nanoparticle formulations remains a challenge. Future efforts are expected to focus on improved in vitro–in vivo correlation models, advanced imaging techniques, and predictive biological models that better simulate human physiology. These tools will help bridge the translational gap between preclinical research and clinical outcomes.

- **Long-Term Safety and Risk-Based Evaluation**

As nanoparticle-based drug delivery systems become more complex, future research must emphasize long-term safety evaluation and risk-based assessment. Understanding nanoparticle biodistribution, metabolism, and clearance over extended periods will be critical for ensuring safe clinical use, especially for chronic therapies involving poorly soluble drugs.

- **Evolving Regulatory and Industrial Outlook**

Regulatory agencies are expected to progressively adapt their frameworks to accommodate the unique characteristics of nanomedicines. Future regulatory strategies may involve lifecycle-based evaluation, adaptive approval pathways, and science-driven risk assessment models. Such evolution will facilitate innovation while maintaining high standards of patient safety and product quality.[48]

Table No 3: Key Future Directions in Nanoparticle-Based Drug Delivery

Focus Area	Expected Impact
Next-generation nanocarriers	Enhanced efficacy
Biodegradable materials	Improved safety
Targeted delivery	Reduced toxicity
Advanced manufacturing	Better scalability
Predictive translational models	Faster clinical success
Regulatory evolution	Wider acceptance

CONCLUSION

Poor aqueous solubility continues to pose a significant challenge in pharmaceutical development, limiting the bioavailability, therapeutic efficacy, and clinical success of many drug candidates. Conventional solubility enhancement approaches, including salt formation, micronization, solid dispersions, and surfactant-based systems, often fail to provide consistent and long-term improvement, particularly for poorly soluble drugs. In this regard, nanoparticle-based drug delivery systems have emerged as a scientifically robust and versatile strategy to address solubility-related limitations. By reducing drug particles to the nanometer scale and utilizing carrier-based mechanisms, nanoparticles enhance dissolution rate, saturation solubility, wettability, and drug absorption. A wide range of nanoparticle platforms has demonstrated significant improvements in bioavailability and therapeutic performance compared to traditional dosage forms. Recent advances in formulation design, surface modification, and manufacturing technologies have further expanded their potential. However,

challenges related to stability, scale-up, safety, cost, and regulatory requirements remain. Adoption of Quality by Design and risk-based regulatory approaches will be crucial for successful clinical translation. Overall, nanoparticle-based drug delivery systems represent a promising approach for improving the clinical performance of poorly soluble drugs.

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