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Nanoformulation Strategies: Emerging Innovations in Drug Delivery Systems

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Abstract

Nanotechnology is significantly advancing the pharmaceutical industry by introducing nanosystems that improve drug delivery, therapeutic efficacy, and patient outcomes. Various nanosystems – such as liposomes, dendrimers, polymeric nanoparticles, solid lipid nanoparticles, carbon nanotubes, and metallic nanoparticles – offer benefits like enhanced bioavailability, targeted delivery, improved stability, and reduced side effects. Innovative formulation strategies, including surface functionalization, particle size optimization, and the use of biodegradable carriers, support controlled and sustained drug release. Additionally, production in non-aqueous media further enhances solubility and formulation efficiency. Despite these advancements, nanoformulations face challenges, such as aggregation, manufacturing limitations, and regulatory compliance. Regulatory bodies like the FDA and EMA have established guidelines to ensure the safe development and application of nanomedicine. Looking ahead, nanotechnology plays a vital role in precision medicine, especially for treating cancer, neurological disorders, and infectious diseases. Moreover, expanding applications in diagnostics and vaccine delivery underscore its importance in the future of healthcare.

Keywords: Nanoformulations, nanocarriers, nanotechnology, polymeric nanoparticles, solubility enhancement, therapeutic efficacy

INTRODUCTION

Through creating nanoscale drug-delivery systems that improve treatment results through targeted and controlled drug release, nanotechnology has brought about innovative developments within the pharmaceutical sector. A wide range of pharmaceutical nanosystems – such as liposomes, solid lipid nanoparticles (SLNs), dendrimers, carbon nanotubes (CNTs), polymeric nanoparticles, and metallic nanoparticles – are now used to improve drug stability, solubility, bioavailability, and therapeutic efficacy. These nanosystems offer potential solutions for treating complex and chronic conditions, including cancer, tuberculosis, and neurodegenerative diseases [1].

Formulation of nanoparticles involves strategic approaches like particle size optimization, surface functionalization, and the use of biocompatible carriers. Additionally, preparation methods in nonaqueous media are used to stabilize hydrophobic drugs and enhance formulation performance. Key formulation parameters, such as surface charge, zeta potential, drug loading efficiency, dissolution rate, and thermal behavior (studied using DSC) have a significant impact on the efficacy of nanoparticles. Nanoformulations have benefits, but they also have drawbacks, like drug aggregation, manufacturing limitations, and compliance with strict regulatory standards set by authorities like the USFDA and EMA. Nanoparticle-based technologies continue to expand their applications in targeted therapy,

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diagnostic imaging, and gene delivery [2]. This review highlights the types, formulation strategies, production methods, regulatory considerations, challenges, and prospects of pharmaceutical nanotechnology.

VARIOUS TYPES OF PHARMACEUTICAL NANOSYSTEMS

Nanoparticle delivery systems come in various forms, such as liposomes, and differ in terms of their size, shape, structural composition, and functional capabilities.

Liposomes

Liposomes are spherical vesicles formed by self-assembly of lipid bilayers in aqueous environments. Typically measuring between 50 to 100 nm, liposomes are valued for their biodegradability, biocompatibility, and ability to encapsulate a wide range of biomolecules. Their structural flexibility allows for the delivery of genes, proteins, and peptides, either through passive targeting or with active targeting mechanisms. Liposomes can also be functionalized with specific ligands to enhance cell-specific uptake, improving the therapeutic or diagnostic effect by increasing the concentration of active agents within target cells [3].

Solid Lipid Nanoparticles

solid lipid nanoparticles (SLNs) serve as a promising alternative to conventional colloidal carriers. These nanoparticles range from 50 to 1000 nm and are composed of solid lipid matrices stabilized by phospholipid monolayers. The encapsulated drug is typically either dispersed or dissolved within the hydrophobic core. SLNs offer several advantages including enhanced drug stability, biocompatibility, and extended shelf life. Their ability to prevent drug degradation and control release profiles makes them perfect for delivering drugs specifically in situations like cancer, tuberculosis, and neurological disorders [4]. Furthermore, SLNs find applications in topical formulations, cosmetics, and even as vaccine adjuvants.

Nanotubes of Carbon

Carbon nanotubes (CNTs) are nanoscale cylindrical structures, typically measuring 0.5 to 3 nanometers in diameter and extending up to 20–1000 nanometers in length. Known for their exceptional mechanical strength, thermal stability, and electrical conductivity, carbon nanotubes hold significant promise in biomedical applications. Their nanoscale dimensions enable them to penetrate cellular membranes, allowing direct access to the cytoplasm and nucleus, which makes them effective carriers for gene therapy and peptide delivery. Additionally, CNTs can be modified to improve their solubility and biocompatibility, enhancing in drug-delivery systems. They are also being explored as diagnostic agents, particularly for the early detection of cancer, due to their ability to interact with biological molecules at the molecular level [5].

Dendrimers

Dendrimers, on the other hand, are highly branched, tree-like macromolecules composed of synthetic or natural components. A central core, several internal layers (generations), and functional surface groups make up its structure. Produced through precise polymerization techniques, dendrimers are monodispersed, meaning they have uniform size and shape. Their well-defined structure allows for controlled drug loading and release, and they are particularly useful for targeted delivery of therapeutic agents to specific sites, such as the liver and macrophages, making them valuable in treating infectious and inflammatory conditions [1].

Polymeric Nanoparticles

Polymeric nanoparticles are nanoscale carriers formed from biodegradable and biocompatible block copolymers that naturally self-assemble into core-shell micellar structures in aqueous environments. These nanoparticles are widely employed for encapsulating small drug molecules, proteins, and nucleic acids, ensuring comprehensive protection of the therapeutic agents from degradation. With sizes ranging from 10 to 1000 nanometers, polymeric nanoparticles offer significant advantages in controlled

and sustained drug release, improving therapeutic efficiency while minimizing side effects. Their customizable surface properties and structural flexibility make them highly suitable for targeted drug delivery and site-specific therapy [6].

Metallic Nanoparticles

Metallic nanoparticles represent another important class of nanocarriers and include particles like iron oxide, silver, gold nanoparticles, nanoshells, and nanocages. These materials are typically below 100 nm in size and exhibit unique optical, magnetic, and electronic properties, making them valuable in both diagnostic imaging and therapeutic applications, such as drug delivery, photothermal therapy, and biosensing [7].

Gold Nanoparticles

Gold nanoparticles, commonly referred to as colloidal gold, are particularly for their biocompatibility, and surface functionalization. Their interaction with light enhances various optical phenomena, such as light absorption, scattering, fluorescence, and surface-enhanced Raman scattering (SERS). Due to these properties, gold nanoparticles are extensively used in detecting disease biomarkers, including those related to cancer and cardiovascular conditions. Their multifunctional nature has made them integral to both diagnostic tools and therapeutic strategies in modern nanomedicine [8].

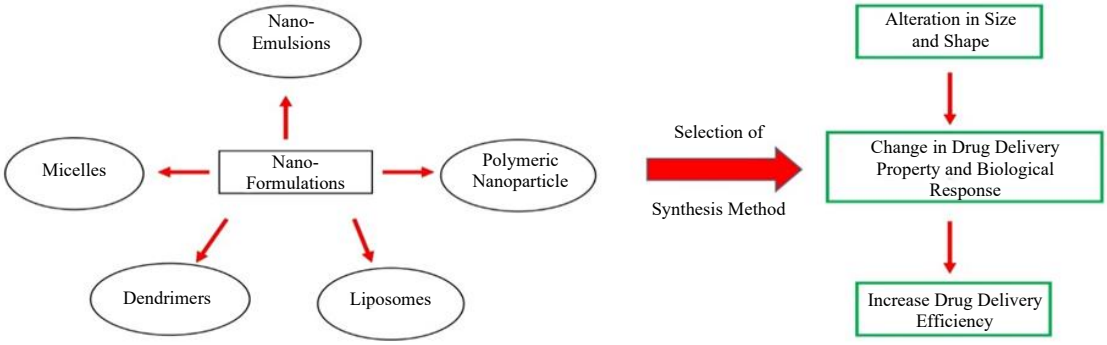

Figure 1. Schematic Representation of Nano-Formulations and Their Role in Enhancing Drug Deliver.

CHARACTERISTICS OF DRUG FORMULATIONS USING NANOPARTICLES

Nanoparticles can enter the human body through various routes, such as injection, inhalation, or oral administration. Once inside, if identified as foreign substances, they may be engulfed and eliminated by macrophages, which poses a significant in the effectiveness of nanoparticle-based drug-delivery systems. However, the rate and extent of this clearance are influenced by factors like the size of the nanoparticles and their surface properties [9].

Surface Charge

The surface charge of nanoparticles plays a crucial role in determining their interaction with biological systems. It significantly affects the electrostatic interactions between the nanoparticles and various bioactive molecules. An essential parameter used to assess the surface charge is the zeta potential, which indirectly reflects the stability of colloidal dispersions. A higher zeta potential value – either positive or negative – typically indicates better stability and reduced chances of particle aggregation in suspension [10].

Surface Properties

To achieve efficient drug delivery, nanoparticles must possess ideal surface characteristics, such as the right curvature, reactivity, and surface ligands. These properties are vital in ensuring target specificity, preventing aggregation, and maintaining stability under physiological conditions. Properly

designed surfaces also improve binding to specific receptors, enhancing the therapeutic efficacy of the drug formulation [11].

Drug Release and Loading Capacity

Nanoparticles are engineered to enhance the bioavailability of drugs, reduce systemic clearance, and improve stability, allowing the therapeutic agents to reach targeted tissues effectively. However, the release profile of drugs from nanoparticle matrices is influenced by factors, such as pH, temperature, drug solubility, desorption, diffusion, and the swelling or erosion of the matrix. Various analytical techniques, such as UV spectroscopy, HPLC, ultracentrifugation, ultrafiltration, gel filtration, and centrifugal ultrafiltration are employed to evaluate drug release behavior and loading efficiency [12].

Particle Size

The biological behavior of nanoparticles is strongly influenced by their size and shape. Particles with smaller dimensions possess a larger surface area relative to their volume, enabling faster drug release because a greater proportion of drug is exposed at or near the surface. In addition, particle size plays a critical role in determining cellular internalization, distribution within the body, potential toxicity, and the efficiency of site-specific targeting [13].

Zeta Potential

Zeta potential serves as an important parameter for assessing the stability of nanoparticle suspensions. Values typically between ±20 mV and ±30 mV are regarded as ideal for ensuring good colloidal stability, helping to prevent particle aggregation and maintaining formulation integrity during storage and use [14].

Differential Scanning Calorimetric Studies (DSC)

DSC is a thermal analysis technique used to study drug-excipient compatibility. It works by comparing the thermograms of pure active pharmaceutical ingredients (APIs) and their mixtures, providing insights into possible interactions and any changes in the melting point, which can affect formulation stability [15].

Dissolution Velocity and Saturation Solubility

The solubility of nanosuspensions is evaluated by comparing it with that of microparticles, focusing particularly on their in vivo performance. To facilitate this assessment, the nanosuspension is initially converted into a solid form, and solubility studies are conducted using various temperatures and time intervals, following standard pharmacopeial procedures. These studies aim to determine the saturation solubility, which is significantly influenced by several key factors: the nature of the active pharmaceutical ingredient (API), the type of dissolution medium, and the temperature at which the study is performed.

One of the critical principles behind enhanced solubility in nanosuspensions is the reduction in particle size. According to the Kelvin–Oswald equation, a decrease in particle size leads to an increase in surface area, which in turn raises the saturation solubility of the substance. This is especially evident in compounds with a low melting point, where smaller particles dissolve more readily due to their higher surface energy and improved interaction with the solvent [16].

The Ostwald equation is as under:

$$\text{Log } Css / \log C = (2\sigma v) / (2.303RT\rho r) \quad (1)$$

In the given equation, Css represents the saturation solubility, while C denotes the solubility of larger particles. V stands for the volume of the particle, T indicates the temperature, γ is the interfacial tension, ρ is the solid density, and r refers to the radius of the particle. According to this relationship, saturation solubility increases as particle size decreases, highlighting the inverse relationship between particle size and saturation solubility [16].

This phenomenon can be further supported by the Noyes–Whitney equation, which explains the rate of drug dissolution:

$$dc/dt = DA/h\ (Cs\text{-}C) \quad (2)$$

where, dc/dt is dissolution rate of drug.

D is rate constant for diffusion.

A is surface area.

h is distance of diffusion is saturated solubility.

C is concentration around particle.

For nanoparticles, reducing particle size greatly enlarges the available surface area. According to the dissolution equation, this increase in surface area results in a higher dissolution rate, as the two are directly proportional. Moreover, smaller particle size also improves saturation solubility, producing a combined effect that further accelerates and enhances drug dissolution. This phenomenon is especially beneficial for poorly water-soluble drugs, as it leads to better bioavailability and improved therapeutic outcomes [16].

STRATEGIES FOR FORMULATING NANOPARTICLES

Precipitation Method

The nanoparticle production technique developed in the 1980s involves dissolving the active pharmaceutical ingredient (API) in an organic solvent, while excipients, such as polymers, surfactants, and stabilizers are dissolved in an inorganic solvent that is miscible with the organic phase. The process begins by gently agitating the mixture and gradually introducing the organic solvent containing the API into the inorganic solvent solution. This results in the precipitation of nanoparticles due to the rapid mixing of the two phases [17].

This approach is considered both simple and economically viable, making it suitable for large-scale applications. A key requirement for this method is that the API must be soluble in the selected organic solvent, and the organic solvent itself must be fully miscible with the inorganic phase to ensure effective particle formation. The technique enables the formation of fine nanoparticles without the need for complex equipment or expensive materials. It also allows better control over particle size and distribution by adjusting parameters, such as solvent ratios, temperature, and stirring speed. Due to its practicality and efficiency, this nanoprecipitation method has been successfully utilized in the formulation of drugs like Carbamazepine and Griseofulvin, both of which benefit from improved solubility and bioavailability in nanoparticulate form. Overall, this method represents a foundational step in the development of drug-delivery systems using nanotechnology, offering enhanced therapeutic performance and formulation stability [18].

Milling Method

The nanoparticle production method introduced in the 1990s is based on a high-energy milling technique. In this process, active pharmaceutical ingredients (APIs) are combined with surfactants and milling beads, which are then placed into a specialized milling chamber. The chamber is subjected to rapid rotation through a high-speed motor, generating the necessary mechanical energy to reduce the particle size and form nanoparticles dispersed in a suspension.

This top-down approach is effective in reducing large particles into nanoscale dimensions. However, due to the intense energy input, there is a potential risk of product degradation and contamination,

especially if heat-sensitive drugs are involved. The materials commonly used to construct the milling chamber include zirconium oxide, glass, and polystyrene resin, chosen for their durability and resistance to wear. This technique can be applied in both aqueous and organic media, allowing to produce both diluted and concentrated nanosuspension formulations. It is particularly useful for poorly water-soluble drugs, improving their solubility and bioavailability. Despite its advantages, the method is time-consuming and may compromise suspension stability over extended milling periods [19].

Homogenization Method

The nanoparticle production method introduced in the 1990s utilizes high-pressure homogenization to generate nanosuspensions. In this process, a mixture of the active pharmaceutical ingredient (API) and excipients is forced through a narrow gap in a homogenizer at extremely high pressure. This results in intense shear forces and cavitation, breaking down particles into the nanoscale range. The technique relies on high kinetic energy and can be precisely controlled to achieve the desired particle size and temperature. There are two approaches to this technique: hot and cold homogenization. Hot homogenization involves heating the lipid phase to melt it and then mixing it with an aqueous phase. However, this method is unsuitable for thermolabile drugs, as they may degrade at elevated temperatures. Despite this limitation, high-pressure homogenization is widely used in the formulation of parenteral drugs, as well as in the food and cosmetic industries [20].

Critical parameters, such as pressure, number of homogenization cycles, and temperature must be closely monitored to ensure consistency and product quality. In laboratory settings, pressures ranging from 100 to 1500 bars are typically used. The result is the formation of nanoparticles with reduced particle size, enhanced surface area, and improved bioavailability. This approach has been successfully applied in the production of nanoparticle-based formulations for drugs, such as Albendazole, Ibuprofen, Spironolactone, Nifedipine, Omeprazole, and Fenofibrate. An example includes Triglide tablets, which contain Fenofibrate nanoparticles and are used in the treatment of hypercholesterolemia [21].

Spray Drying Method

This method is widely used in the manufacture of tablets and powders by initially forming a macrosuspension of the active pharmaceutical ingredient (API) and excipients in an appropriate solvent. The suspension is subsequently processed through high-pressure homogenization to produce a nanosuspension. The final solid dosage form is obtained by removing the solvent through freeze-drying or spray drying. Of these techniques, spray drying is preferred due to its cost efficiency and suitability for large-scale production [22].

Spray drying transforms the nanosuspension into a fine powder or crystalline form by atomizing the liquid into droplets and rapidly drying them with heated air, typically in a laminar airflow. The process parameters, particularly the ratio of excipients and surfactants to the drug, play a key role in controlling the nanoparticle loading capacity and stability of the final product. Initially, spray drying was limited by its ability to produce particles no smaller than 2 μm. However, advancements in technology have significantly improved its efficiency, now allowing the production of particles as small as 300 nm, with yields reaching up to 90%. This makes it suitable for large-scale pharmaceutical manufacturing. The resulting dry powders are versatile in their applications. They can be used for pulmonary drug delivery via inhalation, encapsulated in capsules or tablets, or formulated as carriers for controlled drug release. This method is especially beneficial for enhancing drug stability, improving bioavailability, and enabling targeted delivery, particularly in cases where the drug has poor solubility [23].

Production of Nanoparticle in Nonaqueous Media

This technique eliminates the need for solvent removal following homogenization by utilizing nonaqueous media, such as polyethylene glycol (PEG) or self-emulsifying drug-delivery systems (SEDDS). It is particularly suitable for directly filling soft or hard gelatin capsules. By conducting the homogenization process in these nonaqueous environments, the formulation remains stable and ready

for encapsulation without requiring additional drying or solvent evaporation steps. This approach simplifies the manufacturing process and is especially advantageous for drugs requiring enhanced solubility and bioavailability [24].

Pelletization Method

Although nanosuspensions offer good stability, they need to be converted into solid dosage forms for effective oral administration. To achieve this, several solidification techniques can be employed, including lyophilization (freeze-drying), spray drying, extrusion followed by spheronization, or coating onto inert carriers, such as sugar pellets. These methods help transform the liquid nanosuspension into a solid, stable, and easily handled form [25].

In this process, the nanosuspension containing the active pharmaceutical ingredient (API) is first combined with suitable matrix-forming excipients. These excipients stabilize the nanoparticles and provide the required structure for the final dosage form. Depending on the chosen technique, the formulation may be dried, extruded into strands, and then rounded into small, uniform spheres through spheronization. Alternatively, it can be layered onto sugar spheres to create drug-loaded pellets. The end product is typically a dry, free-flowing powder or small spherical pellets that are easy to encapsulate or compress into tablets. These solid forms maintain the enhanced solubility and bioavailability of the original nanosuspension while improving storage stability, ease of handling, and patient compliance. This conversion plays a critical role in translating nanosuspension-based formulations into commercially viable oral drug-delivery systems [19].

Emulsified Solvent

The evaporation method for nanoparticle formulation involves dissolving the drug along with a suitable polymer in an organic solvent that does not mix with water. This organic solution is gradually added to an aqueous phase containing a stabilizing surfactant. Homogenization is applied to promote proper emulsification and uniform particle dispersion. Once a stable emulsion is formed, the organic solvent is eliminated – usually by evaporation – leading to the formation of nanoparticles. To obtain a dry and stable product, lyophilization (freeze-drying) is commonly performed as the final step. This technique typically requires a large volume of the aqueous phase, in the diffusion of the organic solvent from the internal phase into the surrounding medium. For water-soluble drugs, a double emulsion system (water-in-oil-in-water) is often preferred, as it provides better drug entrapment efficiency and enhanced stability.

The efficiency and quality of this method are influenced by several critical factors, such as the type and properties of the drug and polymer, the duration and intensity of homogenization, and the choice of solvents. For successful nanoparticle formation, the selection of the polymer and surfactant must be compatible with the drug and the process conditions. Although this technique is especially useful for encapsulating water-soluble drugs, variations in formulation components and process parameters can significantly affect the final product characteristics, including particle size, drug loading efficiency, and stability [26].

Hot Melted Production

This method involves melting the formulation matrix material and homogenizing it at elevated temperatures, typically determined by the melting point of the matrix components. The drug is incorporated into the molten phase, and the mixture is subjected to high-shear homogenization to achieve nanoscale particle dispersion. A commonly used equipment for this purpose is the Micro Lab 40 homogenizer, which is equipped with a temperature-controlled jacket to maintain the required thermal conditions during processing. The process begins by heating the matrix material until it is fully liquefied. The active pharmaceutical ingredient (API) is then added and uniformly dispersed within the molten matrix using vigorous mixing. Homogenization at high temperature ensures that the drug particles are evenly distributed and reduced to nanoscale size. The temperature control provided by the homogenizer jacket helps maintain consistency throughout the procedure, preventing premature solidification and ensuring uniform particle size [27].

After the desired particle size is achieved, the system is gradually cooled to room temperature, leading to the solidification of the nanoparticles. The cooling step is critical as it allows the nanoparticles to retain their uniform size and stable structure without aggregation. This hot homogenization technique is particularly suitable for thermally stable drugs and lipid-based matrices. It enables the production of solid nanoparticles with improved solubility and bioavailability, making it an effective strategy for enhancing drug-delivery performance. The solidified nanoparticles can later be processed into various dosage forms, including capsules, tablets, or suspensions [28].

Method of Direct Compression

Nanoparticle powder can be produced from a nanosuspension using techniques, such as spray drying or similar drying methods. This powder form is particularly useful for oral administration, especially when dealing with acid-sensitive drugs. The dry nanoparticles can be filled into capsules for easy delivery and enhanced protection in the gastrointestinal tract. To create tablet formulations, the nanoparticle powder is combined with suitable matrix-forming agents, such as micro-sized polymer powders, lipids, or lactose. These excipients provide structure and support to the formulation. The spray-drying process transforms the nanosuspension's liquid phase into a solid dispersion by embedding the active pharmaceutical ingredient (API) within the matrix materials, resulting in a free-flowing, dry powder [29].

This powder is well-suited for further processing through direct compression techniques. By compressing the nanoparticle-loaded matrix powder, tablets with extended or controlled drug release profiles can be developed. The incorporation of polymers and lipids helps regulate the drug release rate, allowing for prolonged therapeutic effects and reduced dosing frequency. Overall, this approach offers a versatile and efficient method for converting nanosuspensions into solid dosage forms, improving the drug's stability, bioavailability, and patient compliance. It is particularly advantageous for formulating drugs that require protection from gastric environments or need controlled release for optimal therapeutic performance [30].

NANOMEDICINE AND DRUG DELIVERY SYSTEM FUTURE

Nanomedicine is an emerging and dynamic field that has significantly advanced in recent years, with over 1500 patents filed and numerous clinical trials conducted. It has especially shown promise in the diagnosis and treatment of cancer, where nanotechnology has enabled more precise drug-delivery strategies. Nanoparticles can be engineered to transport therapeutic agents directly to cancerous or tumor cells, minimizing damage to healthy tissues and preserving normal cellular functions. This precision in targeting enhances treatment efficacy while reducing side effects, making nanomedicine a transformative approach in modern oncology.

Despite these advancements, challenges remain. One significant issue is the variation in nanoparticle sizes, ranging from nanometers to sub-micrometers, which affects their behavior in biological systems. Uniformity in size, improved drug loading efficiency, and controlled drug release mechanisms are areas that require further investigation. Metallic nanoparticles, especially gold and silver, have shown great potential in diagnostic imaging and therapy. Gold nanoparticles, in particular, are known for their selective absorption in soft tumor tissues, making them suitable for hyperthermia-based treatments where heat is used to destroy malignant cells [31].

Future studies should focus on identifying disease-specific biomarkers that allow precise drug targeting without affecting healthy cells. Moreover, developing reliable drug release mechanisms at target sites, evaluating therapeutic effects at cellular levels, and constructing predictive mathematical models are essential for clinical translation. While current research is mostly focused on materials and formulation, comprehensive animal studies and multidisciplinary approaches are crucial for therapeutic validation. As the demand for precision medicine continues to rise globally, the future of nanomedicine is promising. Nevertheless, long-term safety assessments are necessary to understand and mitigate the potential toxicological risks to humans and the environment [32].

NANO-FORMULATION REGULATIONS

Nanoformulations revolutionize the healthcare industry, bringing substantial changes to existing medical practices, especially in terms of ethics, environmental safety, and medical regulation. As these advanced technologies become more integrated into pharmaceutical development and clinical applications, there is a growing need for stringent oversight to ensure their safe and ethical use [33].

To address this, various regulatory frameworks have been established, particularly in regions, such as the European Union and the United States. In the EU, the European Medicines Agency (EMA) plays a central role in evaluating and supervising the use of nano-based medicinal products. In the US, the Food and Drug Administration (FDA) is responsible for ensuring that nanoformulations used in pharmaceuticals meet strict safety and efficacy standards. These agencies are especially focused on monitoring the potential risks associated with hazardous nanomaterials, particularly those used in drug-delivery systems.

In addition to these primary regulatory authorities, several other international organizations and legislative bodies contribute to the ethical governance of nanotechnology. For instance, different committees and working groups within the United Nations and European Commission also help shape policies and ensure compliance with ethical, legal, and environmental norms. Their efforts aim to create a balanced approach that encourages innovation while safeguarding public health and the environment. Overall, as nanoformulations continue to evolve and find wider application in medicine, the establishment of global regulatory standards and ethical frameworks will be crucial for their safe integration into modern healthcare systems [34].

Table 1. Comparison of FDA and EMA Regulatory Frameworks for Pharmaceutical and Nanotechnology Products.

Category	United States (USA)	European Union (EU)
Main Regulatory Authority	U.S. Food and Drug Administration (FDA)	European Medicines Agency (EMA)
Key Divisions / Committees	1. Center for Drug Evaluation and Research (CDER)	1. Committee for Medicinal Products for Human Use (CHMP).
	2. Center for Devices and Radiological Health (CDRH)	2. Innovation Task Force (ITF).
	3. Center for Biologics Evaluation and Research (CBER)	3. New and Emerging Technologies (N&ET) Working Group.
	4. Nanotechnology Interest Group (NTIG)	
	5. Nanotechnology Task Force	
Major Legislations	1. Federal Food, Drug, and Cosmetic Act (1938)	1. Directive 2001/83/EC concerning Medicinal Products for Human Use.
	2. Public Health Service Act (1944)	2. Regulation (EC) No. 726/2004 on centralized approval and supervision of medicines.
	3. Toxic Substances Control Act (TSCA, 1976)	3. Regulation (EC) No. 1394/2007 covering Advanced Therapy Medicinal Products (ATMPs).

REGULATORY ASPECTS

In recent years, the utilization of nanomaterials and nanotechnology has significantly expanded in both the medical and cosmeceutical sectors, offering promising solutions to a wide range of healthcare needs. Despite this growth, there remains a noticeable gap in comprehensive regulatory frameworks that ensure the safe and ethical use of nanomedicine. In particular, the regulation of nanocosmetic products – especially those targeting anti-aging effects – is still developing, highlighting the urgent need for clear and robust guidelines.

While the U.S. Food and Drug Administration (FDA) oversees the safety and quality of nanotechnology-based cosmetics, these products are not subject to pre-market approval. However, if

any cosmetic ingredient is found to alter bodily functions, it may be classified as a "drug" under the Food, Drug, and Cosmetic Act (FD&C Act), thereby requiring stricter regulatory scrutiny. Importantly, the responsibility for ensuring product safety before market release lies with the manufacturer [35].

To address safety concerns, the FDA released a document titled "Guidance for Industry: Safety of Nanomaterials in Cosmetic Products" in 2014. Though non-binding, this guidance outlines recommended practices for evaluating the safety of cosmetics that include nanomaterials. Key considerations include the physicochemical properties of nanoparticles, their size distribution, agglomeration tendencies, presence of impurities, exposure routes, and dosage measurements for both in vitro and in vivo toxicological testing. These regulatory recommendations aim to promote responsible innovation in nanotechnology while protecting public health. Establishing such standards is vital for ensuring the long-term safety, efficacy, and ethical use of nanomaterials in the rapidly growing cosmetic and healthcare industries [36].

CHALLENGES IN THE DEVELOPMENT OF DRUG NANOFORMULATIONS

Nanoformulations offer promising potential in drug delivery, but they face several obstacles in enhancing uptake and therapeutic efficiency. Key challenges include drug stability, mechanisms of degradation, and adherence to FDA quality standards. One major limitation is the self-aggregation of nanoformulations at low drug concentrations, which significantly affects the stability of the formulation and causes inconsistency in drug entrapment. A notable example is the nanoform of doxorubicin, which tends to aggregate in biological fluids due to high ionic strength, ultimately reducing its solubility and therapeutic effectiveness. To address this issue, the use of smaller nanoparticles – preferably under 20 nanometers – is recommended, as they offer better dispersion and stability [37].

Another factor influencing the effectiveness of nano-drug delivery is the swelling behavior of nanoparticles. While swelling can enhance drug release at the target site, it may also negatively impact bioavailability and solubility by increasing the particle size. To manage this, techniques, such as employing pH-sensitive coatings or incorporating capping agents can help control the swelling process and improve drug performance. Additionally, manufacturing challenges and non-compliance with FDA's Current Good Manufacturing Practices (cGMPs) the scalability and market readiness of many nanoformulated drugs. These formulations often struggle to meet quality and safety standards required for approval. Therefore, future research should aim at developing cost-effective methods to scale up production while ensuring regulatory compliance. Overcoming these technical and regulatory barriers is essential to unlocking the full potential of nanoformulations in modern medicine [38].

APPLICATIONS OF NANOPARTICLES

Nanoparticle-Mediated Gene Delivery

Gene therapy is an innovative technique that treats diseases by altering or regulating gene expression through the delivery of genetic material into cells. Nanoparticles have emerged as promising carriers for gene therapy because of their unique size, shape, surface properties, and biological compatibility. This method has shown potential in managing various genetic disorders, including cancer, hemophilia, hypercholesterolemia, neurodegenerative diseases, and autoimmune conditions [39].

Despite its potential, gene therapy faces several delivery-related challenges. These include low encapsulation efficiency, instability in the bloodstream, degradation before reaching target cells, limited endocytosis by target cells, poor endosomal escape, and overall reduced delivery effectiveness. Additionally, concerns regarding pharmacological toxicity must be addressed to ensure safety and efficacy. To overcome these limitations, researchers are exploring different nanoparticle systems as gene carriers. These include lipid-based nanoparticles, polymer-based nanoparticles, and inorganic nanoparticles, each offering unique advantages in enhancing gene delivery performance. A recent advancement in this field is the development of polynucleotide vaccines. These vaccines stimulate the production of antigenic proteins near antigen-presenting cells, triggering a strong immunological response. Compared to conventional protein-based vaccines, polynucleotide vaccines are more cost-

effective, easier to manufacture, and offer better stability and storage properties, making them highly suitable for widespread clinical use [40].

Nanoparticle Delivery to Subcellular Organelles

Drug delivery focuses on accurately directing therapeutic agents to specific cells or tissues to enhance treatment effectiveness. This is achieved by guiding drug-loaded systems to their intended biological targets. Nanoparticles play a key role in this process, as they can interact with cell surface markers and enter cells via endocytosis. There are two main strategies for nanoparticle-mediated drug delivery: passive targeting and active targeting. In passive targeting, nanoparticles utilize their physical properties – such as size, shape, and composition – to accumulate at specific sites, often relying on the unique characteristics of diseased tissues, like leaky vasculature in tumors. This enables drug accumulation at the target site without requiring specific binding interactions [41].

Active targeting, on the other hand, is achieved by modifying the surface of nanoparticles with specific ligands, such as antibodies, peptides, or other targeting molecules that can selectively bind to receptors expressed on target cells. This specific ligand–receptor interaction enables precise and efficient delivery of drugs to the desired site. Both passive and active targeting approaches provide notable advantages, including enhanced drug bioavailability, minimized off-target side effects, improved uptake of poorly water-soluble drugs, and overall increased therapeutic effectiveness [42]. By utilizing these targeted approaches, nanoparticle-based drug-delivery systems have the potential to revolutionize modern therapeutics.

Nanoparticles for Targeted Imaging

Molecular imaging is an advanced approach that allows the visualization of cellular activities and the evaluation of molecular events in living systems using specially engineered molecular probes. In this context, nanoparticles are particularly important, especially when linked with tumor-specific ligands, as they serve as highly selective agents for tumor identification. Continuous progress in nanotechnology is leading to the creation of innovative nanoparticle-based platforms, which are greatly improving imaging methods for early disease detection and real-time monitoring [43].

The effectiveness of nanoparticles in molecular imaging is largely determined by their characteristics, such as size, surface charge, shape, and hydrophilicity, which influence their distribution and interaction within biological systems. Among the various nanoparticles employed in biomedical imaging, gold nanoparticles, quantum dots, iron oxide nanoparticles, and dendrimers are commonly used due to their unique physicochemical properties. Gold nanoparticles, for example, serve as ultrasensitive fluorescent probes for identifying cancer biomarkers and are capable of detecting viral or bacterial DNA directly. Additionally, metallic nanoparticles, including gold and iron oxide, are being explored as efficient X-ray contrast agents due to their high absorption capabilities and low toxicity. These advances highlight the growing potential of nanoparticles in enhancing diagnostic imaging and improving disease detection accuracy [44].

Nanoparticle-Based Drug Delivery to the Brain

The blood–brain barrier (BBB) is a selective and dynamic protective layer that safeguards the brain from harmful substances. While essential for maintaining brain homeostasis, it significantly delivery of therapeutic agents for central nervous system (CNS) disorders due to its restrictive nature and limited permeability to most drugs. This presents a major obstacle in the treatment of conditions, such as neurodegenerative diseases, genetic disorders, and brain cancers, which often lack effective therapeutic options [45].

Nanotechnology has emerged as a promising strategy to overcome this challenge. Nanoparticles, which are designed to be non-toxic, biodegradable, biocompatible, and non-inflammatory, can penetrate the BBB through passive diffusion or other mechanisms. These engineered nanoparticles can be tailored to carry therapeutic agents directly to the brain, offering targeted drug delivery and controlled release

over time. This precise targeting enhances drug efficiency while minimizing systemic side effects. The application of nanotechnology in brain-targeted drug delivery holds significant potential in transforming the treatment of neurological and CNS-related conditions. By enabling more effective drug transport across the BBB and improving the pharmacokinetic profile of drugs, nanoparticle-based systems [46].

CONCLUSION

Pharmaceutical nanosystems are transforming modern drug delivery with their diverse structures – like liposomes, dendrimers, and metallic nanoparticles – each offering specific benefits, such as enhanced targeting, improved bioavailability, and controlled drug release. Innovative formulation approaches and production methods, especially in nonaqueous media, have further refined nanoparticle stability and functionality. While nanomedicine offers groundbreaking applications in areas like cancer treatment, gene therapy, and diagnostic imaging, several challenges still need to be addressed, including formulation consistency, regulatory approval, and scalability, with growing research and clearer regulatory pathways, nanotechnology plays a vital role in shaping the future of safe, efficient, and precise drug therapies.

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Conflicts of Interest

All authors declare that no conflicts of interest.

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Ethics Statement

Not applicable.

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