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REVIEW

Advances in Nanotechnology for Enhancing the Solubility and Bioavailability of Poorly Soluble Drugs

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Abstract: This manuscript offers a comprehensive overview of nanotechnology's impact on the solubility and bioavailability of poorly soluble drugs, with a focus on BCS Class II and IV drugs. We explore various nanoscale drug delivery systems (NDDSs), including lipid-based, polymer-based, nanoemulsions, nanogels, and inorganic carriers. These systems offer improved drug efficacy, targeting, and reduced side effects. Emphasizing the crucial role of nanoparticle size and surface modifications, the review discusses the advancements in NDDSs for enhanced therapeutic outcomes. Challenges such as production cost and safety are acknowledged, yet the potential of NDDSs in transforming drug delivery methods is highlighted. This contribution underscores the importance of nanotechnology in pharmaceutical engineering, suggesting it as a significant advancement for medical applications and patient care.

Keywords: nanotechnology, solubility and bioavailability, poorly soluble drugs, drug delivery systems, pharmaceutical engineering

Introduction

Currently, one of the primary challenges faced by the pharmaceutical industry is the poor water solubility and insufficient bioavailability of drugs.[1,2] Current data suggest that approximately 40% of commercially available pharmaceuticals, as well as a significant majority of investigational drugs, struggle with low solubility.[3,4] This issue can lead to compromised bioavailability and diminished therapeutic effectiveness, often necessitating increased dosages to achieve the desired medicinal impact.[5] The difficulties in dissolving and releasing poorly soluble drugs have restricted the bioavailability of oral solid dosage forms — the most widely used and patient-compliant method of drug delivery — hindering the development and application of many new compound drugs.[6,7] Due to low bioavailability, patients need to consume higher drug dosages to achieve the desired therapeutic effects.[8] However, increasing the dosage can result in more side effects, potentially harming the physical and mental health of patients and decreasing their medication compliance.[9] The issue of low water solubility not only poses significant challenges to medical development but can also lead to various clinical problems, such as variability in patient responses, difficulty in maintaining a safe therapeutic index, increased costs, and the potential risk of toxicity or inefficacy.[10] Therefore, effectively addressing the poor solubility and low bioavailability of drugs has always been a focal point and a significant challenge in pharmaceutical and medical research. To overcome these issues, the development of nanomedicine delivery systems, as an innovative drug delivery strategy, has emerged, breaking through the traditional bottlenecks associated with the solubility and bioavailability of drugs.

Nanomedicine delivery systems primarily encompass two fundamental aspects: Firstly, based on pathological changes, these systems can precisely transport drugs to the specified lesion sites, thereby maximizing therapeutic effectiveness and

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significantly reducing damage to healthy tissues. Secondly, they can control the rate of drug release, ensuring that drug concentration in the blood remains within a safe and effective range, thus mitigating or avoiding toxic and adverse reactions.[11] Composed of nanoparticles smaller than 100 nanometers, these delivery systems feature high permeability and potent retention effects, enhanced drug solubility, multifunctionality, controlled drug release mechanisms, and specific targeting capabilities towards diseased cells.[12] Through nanotechnology-based structural modifications of drugs, these systems not only achieve precise control over drug release and increase drug stability but also prevent premature degradation of the drug molecules before reaching the lesion, thereby enhancing bioavailability and prolonging circulation time of the drug.[11]

Definition and Classification of Poorly Soluble Drugs

Research indicates that the absorption and bioavailability of a drug are influenced not only by the properties of the drug itself but also by factors such as dissolution rate, pH value, route of administration, and first-pass effect.[13] Particularly, poorly soluble drugs with significant pharmacological activities often fail to achieve their full therapeutic potential due to their slow dissolution rates and low solubility,[14,15] leading to issues such as the need for increased drug dosages in clinical settings.[5] It is estimated that about 40% of the compounds on the market and the majority of candidate drugs are poorly soluble,[3,16] mainly categorized under Class II and IV of the Biopharmaceutical Classification System (BCS).[17,18] The BCS guides the setting of dissolution standards for formulations, aiming to reduce the requirements for in vivo bioequivalence (BE).[19,20] Moreover, the theoretical framework of BCS enables formulation scientists to develop drug formulations based on the physicochemical and biopharmaceutical properties of the drug, rather than solely relying on experience. Precise formulation design is required for Class II and IV drugs in the BCS, especially in the case of oral administration. Figure 1 by figdraw elaborately illustrates the classification of the BCS and the feasible formulation choices based on this system.

The Biopharmaceutics Classification System (BCS) categorizes active pharmaceutical ingredients (APIs) by three principal parameters: the dose number (Do), quantifying the API's administered dose relative to its solubility; the dissolution number (Dn), indicating the rate of API dissolution in the gastrointestinal tract; and the absorption number (An), assessing the extent and rate of API absorption. Firstly, the absorption number is determined by the ratio of the effective permeability (Peff) to the radius of the intestine (R) multiplied by the residence time (Tsi) (Equation 1). Secondly, the dissolution number (Dn) is the ratio of residence time to dissolution time, which involves the solubility (Cs), diffusion rate (D), density, initial particle radius (r), and intestinal transit time (Tsi) (Equation 2). Finally, the dose number (Do) is the ratio of the dose concentration to the drug solubility (Equation 3). The fraction of the drug absorbed in the solution, F, follows an exponential function and can be calculated using Equation 4.

$$\mathrm{Dn} = \left(\frac{3D}{r^2}\right)\left(\frac{C_s}{\rho}\right)\langle \mathrm{T_{si}} \rangle = \frac{\langle T_{si} \rangle}{T_{diss}} \tag{1}$$

$$\mathrm{Do} = \frac{M/V_0}{C_s} \tag{2}$$

$$\mathrm{An} = \frac{P_{eff}}{R} X \langle \mathrm{T_{si}} \rangle = \frac{\langle T_{si} \rangle}{T_{diss}} \tag{3}$$

$$\mathrm{F} = 1 - e^{-2An} \tag{4}$$

Note: Cs represents solubility, M is the dose, and V_0 denotes the volume of water consumed with the dose, typically set at 250 mL.

Using digoxin and griseofulvin as examples, it is evident that for digoxin, a smaller particle size (indicating a higher D_n)) can substantially improve the likelihood of its complete absorption. In contrast, digoxin with a larger particle size (representing a lower D_n) is likely to face challenges in dissolution, affecting its absorption profile.[21,22] Micronization's effect on griseofulvin's absorption fraction is relatively modest; thus, adjusting the dose number (D_o) to reach the saturation point for complete absorption is crucial for this medication. The dose number (D_o) fluctuates based on the dose to solubility concentration ratio.With the drug dose being fixed, the required dissolution volume for a single dose of griseofulvin is exceptionally high,[23] thus constraining the

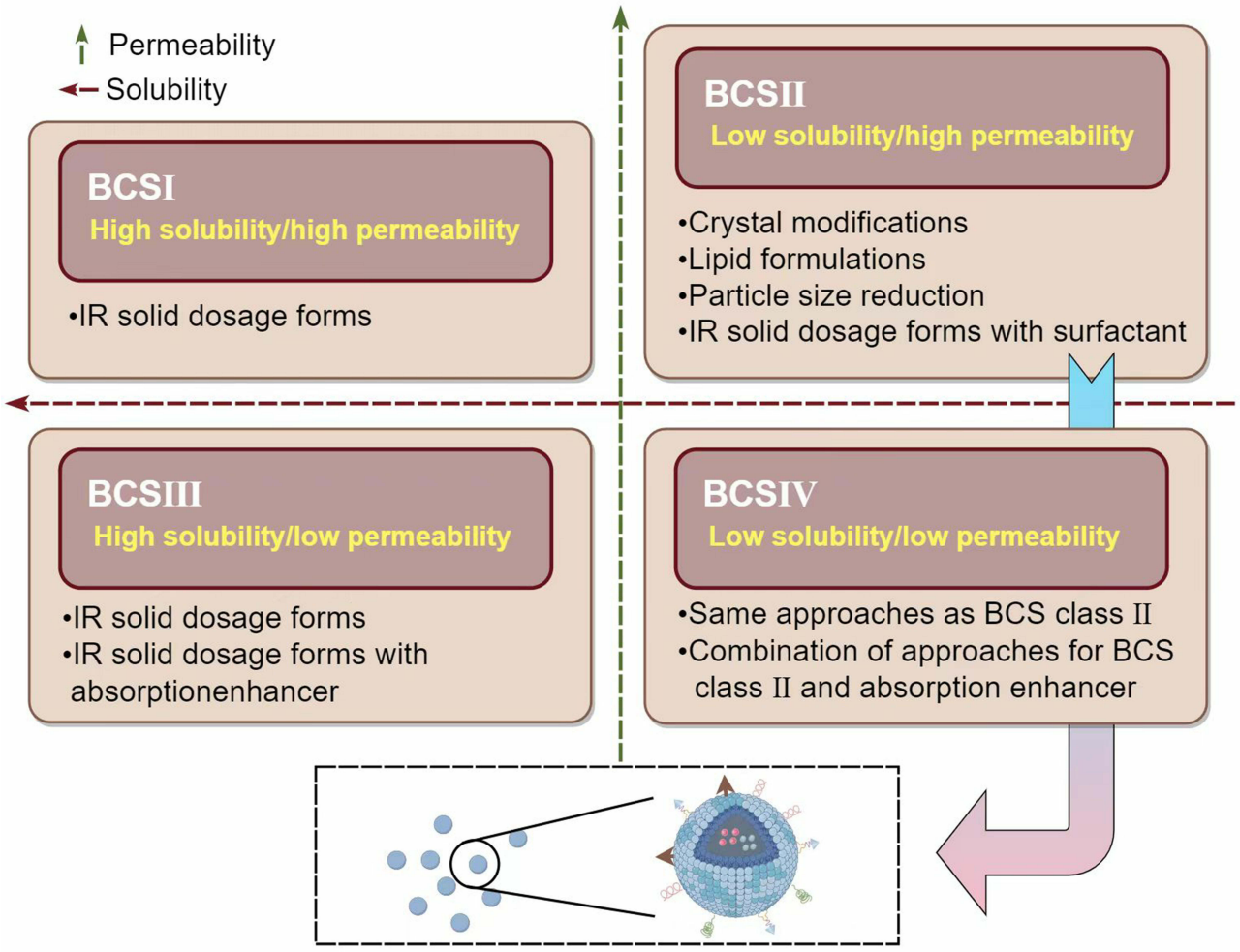

Figure 1 Biopharmaceutics Classification System (BCS) and Feasible Formulation Choices Based on BCS.

dose to a very low level. In this scenario, it becomes imperative to manipulate the only variable – solubility. Should the enhancement in solubility not be significant, griseofulvin might be classified as a drug with solubility limitations.

Class 1BCSII Drugs

Drugs classified under BCS Class II possess molecular characteristics of low solubility and high permeability. Examples of such drugs include morphine, chlorpromazine, and procaine.[11] For BCS Class II drugs, the dissolution rate is a primary limiting factor for bioavailability, where minor changes in the dissolution rate can lead to significant increases/decreases in bioavailability.[24] Over time, the dissolution rate progressively alters the actual concentration of a drug in solution. Moreover, several factors influence the dissolution rate of a drug, as defined by the Noyes-Whitney equation, including effective surface area, diffusion coefficient, diffusion layer thickness, saturation solubility, the amount of drug dissolved, and the volume of dissolution medium.[25]

Current strategies for improving the dissolution rates of BCS Class II drugs include reducing particle size,[26] self-emulsification,[27] pH modification,[28] and crystal modification.[29] Taking pH modification and self-emulsification as examples, firstly, water solubility represents the lipophilic and hydrophilic properties of a molecule. Enhancing the medium's lipophilicity or the molecule's hydrophilicity to improve water solubility is considered a viable strategy. Data collected by varying pH within a range of 1 to 8 is used to establish In Vitro-In Vivo Correlation (IVIVC).[30] The use of organic solvents is seen as a less favorable approach due to the inability to achieve correlation and the fact that controlled release components in controlled release formulations are often determined by the solvent. Also, there is a risk of drug precipitation when pH variations are not suitable

Moreover, the complexity of clinical application of pH modification is significantly increased by the changes in pH over time, location, and surfactant concentration.

As for self-emulsification, its advantage over non-physiological pH alterations or organic solvents lies in its ability to mimic the in-vivo environment of the intestine. Bile salts and phospholipids in the gastrointestinal tract can improve the wetting[31] and solubility[32,33] of many lipophilic substances. Additionally, interactions between intestinal fluids, lipids, and food can enhance the formation of emulsions.[34] In vitro, various synthetic surfactants can serve as dissolution media,[35] like Tween 20 (TW20), Sodium Lauryl Sulfate (SLS), and Dodecyl Trimethyl Ammonium Bromide (DTAB). However, there are some differences between emulsions and nanoemulsions, as outlined in Table 1. Singh et al significantly enhanced the oral bioavailability of primaquine by preparing it as a nanoemulsion, demonstrating its potential for treating early-stage malaria with minimal toxicity.[36] Yet, these methods still have limitations. For instance, the formation of salts for neutral compounds is not feasible and can lead to aggregation and other negative effects;[37] strategies like reducing particle size are not applicable for extremely fine powders with poor wettability.

BCS Class IV Drugs

Drugs classified under BCS Class IV are characterized by their low solubility and low permeability, with examples including aluminum hydroxide and acetazolamide. The pharmacokinetic patterns of these drugs can be influenced by various gastrointestinal factors such as gastric emptying, the motility phase, bacteria, enzyme activity, and intraluminal viscosity. Intraluminal viscosity becomes particularly crucial when the drug dose fails to dissolve and/or be absorbed during transit.[38,39] Drug permeability can also change due to physiological factors. Under the dual constraints of solubility and permeability, considering physiological factors like gastric emptying and gastrointestinal transit times to enhance absorption presents significant challenges in the development and formulation of BCS Class IV drugs. Methods to enhance the permeability of BCS Class IV drugs are still in the early stages of research, and their safety is yet to be established.

Applying formulation methods similar to those used for BCS Class II drugs to BCS Class IV drugs can lead to their dissolution and absorption in the gastrointestinal tract. However, this approach might still be limited due to issues with permeability. Despite their solubilization in the gastrointestinal environment, the inherently poor permeability of BCS Class IV drugs can restrict their effective absorption, presenting a unique set of challenges for their formulation and therapeutic efficacy.

Fundamental Principles of Nanomedicine Drug Delivery Systems

Working Principles of Nanomedicine Drug Delivery Systems

Nanoparticle drug delivery systems utilize nanomaterials as carriers, leveraging their ultra-small size, high-energy catalytic activity of surface atoms, and protective capabilities for the encapsulated drugs.[40–42] These systems enable drugs to bypass physiological barriers,[43] reduce or avoid immune clearance and the effects of bodily fluids on the drug,[44,45] and target drugs for cellular or subcellular-level slow release.[46,47] The overarching goals of these

Table 1 Key Differences Between Emulsion and Nanoemulsion

Sr.No.	Emulsion	Nanoemulsion
1	Kinetically less stable	Kinetically more stable
2	Appearance-cloudy/opaque	Appearance-clear
3	Particle size varies from 1–1000μm	Particle size varies from 1–100nm
4	Anisotropic in nature	Isotropic in nature
5	Higher surfactant concentration(20–25%)	Lower surfactant concentration(5–10%)
6	Wet gum method and dry gum method are generally used for preparation	High energy emulsification and low energy Emulsification method are used
7	Creaming, Phase inversion, and sedimentation, etc., stability problems may occur.	These types of problems not occur.

strategies are to enhance drug utilization[48] and minimize drug toxicity and side effects[49] (see Figure 2A). These systems offer a promising avenue in drug delivery by addressing some of the key limitations of conventional drug delivery methods, particularly for drugs that face challenges in solubility, stability, and targeted delivery.

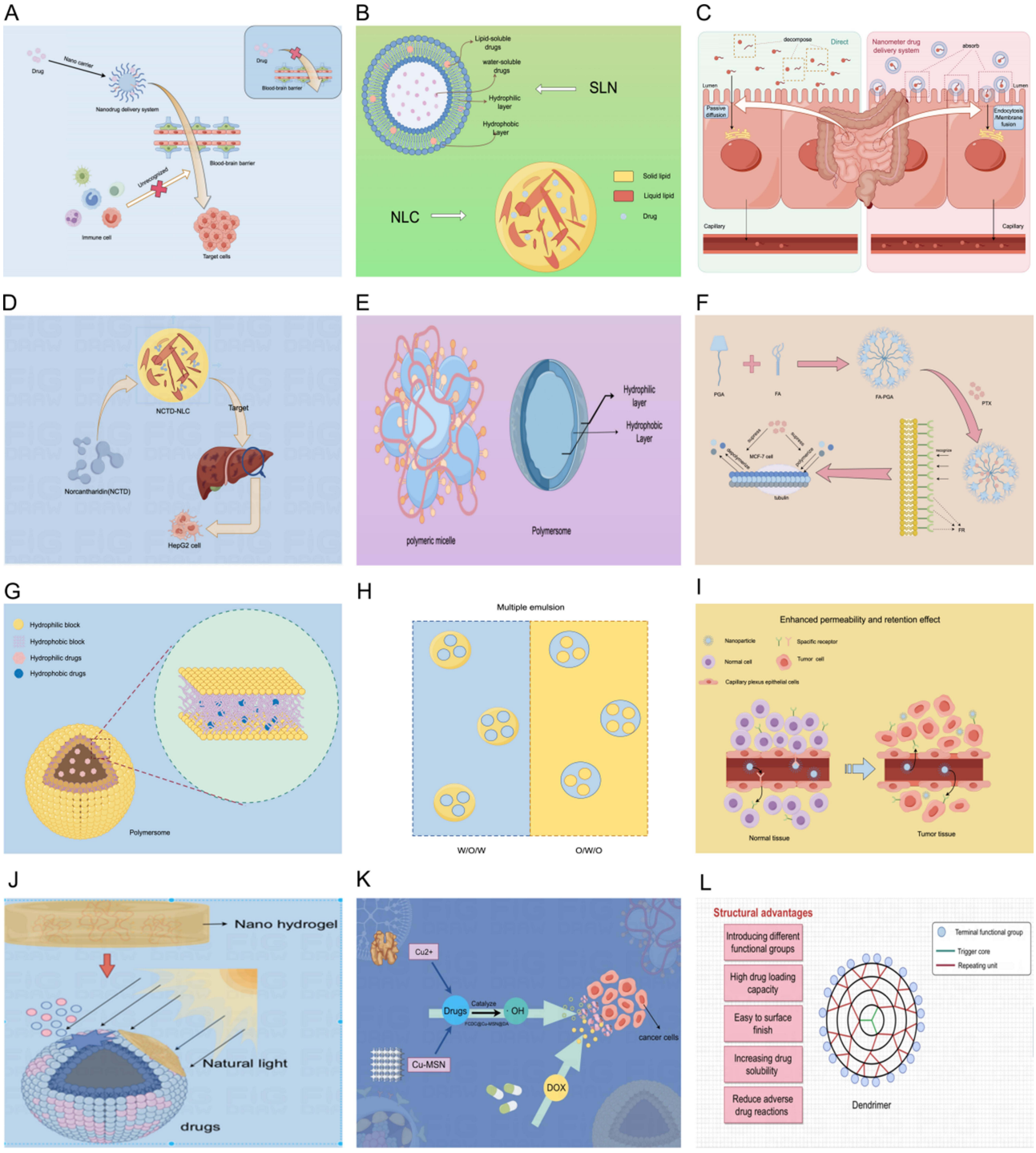

Figure 2 The Basic Principles of Nanodrug Delivery Systems. (**A**) Working Principles of Nanodrug Delivery Systems. (**B**) Two structures of liposomes:SLN and NLC. (**C**) The absorption process of nanodrug delivery systems using SLN as carriers to encapsulate TKIs in the gastrointestinal tract. (**D**) The advantages of NLC as a carrier for Northaritin. (**E**) Polymer micelles and vesicles. (**F**) FA-PGA-PTX micelles can selectively enter FR positive cancer cells through receptor mediated endocytosis. (**G**) Structural basis of hydrophobic and hydrophilic drugs encapsulated in polymer vesicles. (**H**) Multiphase nanoemulsion. (**I**) Enhanced permeability and retention effect. (**J**) Degradation of nano hydrogel under photochemical conditions. (**K**) Working Principle of Inorganic Nanocarriers. (**L**) The Structure and Advantages of Dendritic Polymers.

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Types and Characteristics of Nanomedicine Drug Delivery Systems

Liposomal Nanocarriers

Liposomes are closed vesicles with a lipid bilayer structure, containing an aqueous core, capable of carrying both lipophilic and hydrophilic substances. Their structure allows for various drug transport mechanisms, such as passive diffusion and membrane fusion. Recent advancements have led to the development of new systems like ethosomal nanogels, which have shown efficacy in the topical drug delivery for skin cancer treatment. These systems are widely utilized to carry hydrophilic drugs due to their non-toxicity, biodegradability, and excellent biocompatibility. These innovative formulations highlight the progressive role of liposomes in nanotechnology-based therapeutics.[50,51]

Liposomal nanocarriers are primarily categorized into Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs), as illustrated in Figure 2B. SLNs, with particle sizes ranging from 50 to 1000 nm, are solid colloidal drug delivery systems. They offer benefits such as minimal carrier toxicity, controlled drug release, and targeted delivery. Tyrosine Kinase Inhibitors (TKIs), commonly used oral anticancer agents, are weakly basic and exhibit poor stability and low bioavailability in the gastrointestinal environment. Encapsulating TKIs in SLNs protects the drugs from acidic degradation, aids in traversing physiological barriers in the gastrointestinal tract, and facilitates sustained release. The substantial surface area and adhesive properties of SLNs enhance their absorption in the gastrointestinal tract significantly[52,53] (refer to Figure 2C). Further, modifying SLNs, for instance, with a Polyethylene Glycol (PEG) coating, endows them with a hydrophilic layer, minimizes the clearance by intestinal mucosal secretions, and augments the drug's ability to penetrate mucosal barriers.[54,55]

NLCs, evolved from SLNs, are an innovative class of lipid nanocarriers composed of a mixture of solid (long-chain) and liquid (short-chain) lipids. The presence of liquid lipids lowers the melting point, allowing the carrier to remain solid at body temperature. This feature prevents the recrystallization of solid lipids during the drug loading process, thereby enhancing drug loading capacity and encapsulation efficiency. Thermodynamically, NLCs exhibit a more robust structure compared to SLNs.[56,57] Norcantharidin (NCTD), an anti-cancer drug first discovered in China, faces clinical limitations due to its strong side effects, poor absorption, and weak targeting.[58,59] Studies by Yan Z et al[60] indicate that employing NLCs as carriers for NCTD improves the drug's targeting to tumor tissues, extends its release duration, and increases its concentration in tumor sites, thereby exerting a notable inhibitory effect on HepG2 cells, promoting apoptosis in liver cancer cells. Compared to the oral administration of NCTD alone, NLCs significantly enhance the drug's tumor inhibition rate, improve its utilization, and reduce side effects on normal cells (as shown in Figure 2D). These findings underscore the extensive potential applications of liposomal carriers in cancer therapy.

Furthermore, due to their strong skin permeability, high drug loading capacity, controllable drug release, and biocompatibility, SLNs and NLCs are extensively applied in dermatological drug delivery. The presence of solid lipids considerably reduces the exchange of active substances with the aqueous phase, aiding in the prevention of degradation of unstable chemical compounds. These properties provide novel therapeutic approaches for treating skin disorders such as psoriasis and acne, demonstrating a broad spectrum of applications.[61,62]

Polymer Nanocarriers

Polymer nanocarriers are versatile platforms in the field of drug delivery. These carriers, constructed from either naturally occurring macromolecules or carefully designed synthetic polymers, are renowned for their straightforward synthetic routes. Beyond simple polymeric nanoparticles, the field has seen the evolution of sophisticated structures such as polymer micelles and polymer vesicles, which are depicted in Figure 2E. These advanced forms are derived from the self-assembly of amphiphilic block copolymers in aqueous solutions, leading to nanostructures with distinct hydrophobic and hydrophilic regions.

Polymer micelles are characterized by their unique architecture with a hydrophobic core that can sequester poorly soluble drugs, surrounded by a hydrophilic shell that imparts stability and stealth features in the biological milieu. This design translates to enhanced drug loading capacities, improved encapsulation efficiencies, and favorable biocompatibility profiles, making them ideal candidates for therapeutic delivery. Their core-shell structure is not only crucial for protecting the active pharmaceutical ingredients from premature degradation but also for facilitating controlled release profiles, which is paramount in achieving sustained therapeutic effects.

Furthermore, the hydrophilic shell of the micelles can effectively mask the drug from the body's immune surveillance system, particularly the reticuloendothelial system (RES), thereby minimizing opsonization and subsequent phagocytic uptake. This

stealth property allows for the micelles to circulate for extended periods, which, in conjunction with the enhanced permeability and retention (EPR) effect, enables them to accumulate preferentially in tumor tissues through passive targeting mechanisms. The EPR effect is especially pronounced in pathological conditions with compromised lymphatic drainage, such as cancer, where it can be exploited to deliver high drug concentrations directly to the site of the tumor, enhancing the efficacy of the treatment while reducing systemic toxicity.[63,64] In summary, polymer nanocarriers, particularly polymer micelles, offer a multifunctional and tunable platform for drug delivery applications, combining efficient drug encapsulation with the potential for targeted and controlled release, which are critical attributes in the advancement of nanomedicine. Drug encapsulation within these micelles can be achieved through covalent bonding, direct dissolution, self-assembly with solvent evaporation, dialysis, or emulsion solvent evaporation techniques. Lee et al[65] investigated the self-assembled conjugated micelles of folate (FA)-PGA-PTX, demonstrating that, compared to free PTX, FA-PGA-PTX microparticles significantly reduced toxicity to normal cells while notably decreasing cell viability in folate receptor (FR)-positive MCF-7 cancer cells, indicating their excellent targeting ability and controlled drug release property, as seen in Figure 2F.

Polymer vesicles, formed from amphiphilic block polymers, possess a bilayer closed hollow structure, spherical or near-spherical in shape. Their internal layer, formed from hydrophilic block polymers, can encapsulate hydrophilic drugs, while the vesicle wall, composed of hydrophobic block segments, offers permeability and the capability to carry hydrophobic drugs. The outermost layer, also formed by hydrophilic segments, provides high encapsulation efficiency for water-soluble drugs as seen in Figure 2G. Wang et al[66] developed amphiphilic polymer vesicles to co-deliver hydrophilic Doxorubicin (DOX) and hydrophobic Taxol (TAX). Compared with systems carrying DOX or TAX alone, these co-delivery systems exhibited a more pronounced inhibitory effect on tumor growth, demonstrating synergistic effects and significant clinical treatment implications. The molecular weight of these polymer vesicles, generally above 1000, ensures their high stability and sustained release characteristics. Chen et al[67] polymer vesicles loaded with Ciprofloxacin (CIP) for treating bacterial keratitis (BK) revealed that polymer vesicle carriers could enhance ocular surface adhesion, corneal permeability, and bacterial targeting, thereby improving bioavailability and showing significant potential in treating BK and other bacterial infections.

Nanoemulsions

Nanoemulsions, primarily composed of water, oil, surfactants, and co-surfactants, typically range in size from 10 to 100 nm. They represent a low-viscosity, thermodynamically unstable, isotropic, and either transparent or semi-transparent colloidal dispersion system.[68,69] The formation of nanoemulsions, involving the combination of two immiscible liquids via an emulsifier, results in either biphasic (O/W or W/O) or multiphasic systems[70] (refer to Figure 2H). Nanoemulsions as drug carriers possess several advantages:①Enhanced Drug Stability: Encapsulation of drugs within the oil phase of nanoemulsions can shield them from hydrolysis and oxidation, thereby augmenting the stability of the pharmaceuticals.[71]②Increased Solubility and Bioavailability: As drug carriers, nanoemulsions can enhance the solubility and absorption rate of drugs, thereby improving their overall bioavailability. Ding L et al[72] discovered that perfluorocarbon nanoemulsions, compared to poly-cationic/small interfering RNA (siRNA) complexes, demonstrated a more robust inhibition of pancreatic tumor growth due to the enhanced permeability and retention (EPR) effect, suggesting a promising future in the controlled therapy of pancreatic cancer.③Improved Patient Compliance: The liquid form of nanoemulsions facilitates multiple administration routes, including oral, intravenous, and topical applications. Niu Z et al[73] found that nanoemulsion-based delivery of Coenzyme Q10 showed 1.8 to 2.8 times higher bioavailability when administered orally, compared to other mediums, highlighting the potential of nanoemulsions as oral drug carriers (refer to Figure 2).④Taste Masking: Nanoemulsions can conceal the bitter taste of oils and drugs, making them more palatable when used as oral drug carriers.[71]⑤Stability: Nanoemulsions are less prone to issues like flocculation, creaming, and sedimentation.[74]⑥However, nanoemulsions also exhibit certain limitations. For instance, their stability can be significantly affected by external factors such as temperature and pH.[75] They are prone to processes like Ostwald ripening, droplet coalescence, and coagulation, which can lead to system destabilization and reduced shelf life.

Nanohydrogels

Nanohydrogels are hydrophilic yet water-insoluble polymers with a three-dimensional cross-linked network structure at the nanoscale. They are characterized by high biocompatibility, high water content, small surface-to-volume ratio, and low cytotoxicity. These properties endow nanohydrogels with numerous advantages such as efficient localized sustained-release,

avoidance of macrophage phagocytosis, and enhanced cell recognition, making them suitable for various drug delivery strategies.[76,77] Granata G et al[78] found that self-assembling injectable nanohydrogels could protect curcumin from chemical or photochemical degradation (as shown in Figure 2J), and maintain a sustained release of the drug. By combining the mechanical properties of hydrogels with the advantages of nanomicelles in drug delivery, these self-assembling injectable nanohydrogels emerge as a novel material with broad application prospects in drug delivery.

Moreover, nanohydrogels can be synergistically combined with nanoparticles through physical encapsulation, electrostatic interactions, and covalent cross-linking. This formation of nano-composite hydrogels not only integrates the inherent characteristics of both components but also overcomes traditional drawbacks of nanohydrogels such as fragility and poor mechanical properties.[79] For instance, El-RefaiE et al[80] developed a new type of self-assembling hyaluronic acid gel composite with a core of elastic nanovesicles using 1% hyaluronic acid. When used for non-invasive transdermal delivery of hyaluronic acid, in vivo studies demonstrated that this composite gel of elastic nanovesicles enhanced the transdermal penetration into the knee joint sixfold compared to conventional hyaluronic acid gels.

Nanohydrogels, due to their intricate cross-linked nanostructures, present exciting opportunities in the biomedical field. These versatile carriers have been particularly notable for their role in targeted drug delivery and tissue engineering, given their excellent water retention capacity and tunable degradation rates. For instance, their hydrophilic nature allows for responsive drug release that can be triggered by environmental changes, such as pH, temperature, or ionic strength. This responsiveness can be tailored to ensure that the therapeutic agents are released in a controlled manner at the site of action, thus maximizing efficacy while minimizing side effects.Furthering their functionality, recent studies have highlighted the potential of nanohydrogels for dual delivery systems. These systems can simultaneously carry hydrophobic and hydrophilic drugs, releasing them in a synchronized manner, which is particularly advantageous for combination therapies. The application of such dual delivery systems has been studied in cancer therapy, where the coordinated release of chemotherapeutic agents and bioactive molecules has shown to significantly impede tumor growth while promoting healthy cell proliferation.

Another promising aspect of nanohydrogels is their application in regenerative medicine. Their biocompatibility and similarity to the natural extracellular matrix make them ideal scaffolds for cell growth and tissue regeneration. Modified nanohydrogels have been engineered to support the repair and regeneration of various tissues, including cartilage, nerve, and vascular systems. By incorporating growth factors or specific cell-signaling molecules, nanohydrogels can be transformed into bioactive platforms that not only deliver drugs but also actively participate in the healing and regenerative processes.While the body of research on nanohydrogels is vast, continued exploration into their interaction with biological systems, long-term biocompatibility, and the development of scalable manufacturing processes will further cement their place in the future of drug delivery and tissue engineering. By addressing these areas, the next generation of nanohydrogels could offer even more robust and precise delivery of therapeutics, opening new avenues for treatment strategies.

Inorganic Nanocarriers

Inorganic nanocarriers, composed of materials such as metals, metal oxides, and magnetic substances, constitute an inorganic nanoscale drug delivery system. They are advantageous due to their straightforward synthesis, ease of surface modification, high drug loading capacity, small size, large specific surface area, and good biocompatibility. Mesoporous silica, characterized by its interconnected pore structure, can reduce the resistance to drug diffusion, thus facilitating the movement of drugs into the dissolution medium, making it a commonly used inorganic nanocarrier.[81] Zhang et al[82] demonstrated that mesoporous silica enhances the dissolution rate and bioavailability of the hydrophobic drug Telmisartan (TEL) when orally administered. Compared to the commercial product Micardis, the relative bioavailability of TEL loaded onto MSNs was 154.4%±28.4%. In contrast to crude TEL powder, MSN-loaded TEL significantly improved in dissolution rate. Furthermore, permeability studies on the human colon cancer (Caco-2) cell line indicated that MSNs enhanced the drug's permeability, reduced drug loss, and improved the absorption of orally administered drugs, as depicted in Figure 2K. This offers a promising new approach for the effective treatment of cancer.

Dendritic Polymer Nanocarriers

Dendritic polymer materials are a new type of artificial nanomaterials characterized by their three-dimensional, highly-ordered structure. They can be molecularly tailored in terms of size, shape, structure, and functional groups. Generally

composed of an initiating core, internal repeat units, and terminal functional groups, these materials have evolved through several synthetic approaches, including divergent, convergent, a hybrid of divergent-convergent, and solid-phase synthesis methods. By attaching different functional groups to the peripheries of dendritic polymers, these materials can fulfill specific applications. They are noted for their high drug loading capacity, ease of surface modification, controlled drug release, increased drug solubility, and reduced adverse drug reactions, as illustrated in Figure 2L.[83,84] Zhuo et al[85] synthesized poly(amidoamine) (PAMAM) dendrimers with a cyclic core. When conjugated with the anticancer drug 5-fluorouracil, the free drug was slowly released in phosphate-buffered saline simulating the human body environment, thereby mitigating adverse drug reactions. Another study[86] used dendritic polymers as gene carriers, protecting DNA from degradation and mediating about six times higher gene expression in tumors compared to the PEI transfectant, indicating high transfection efficiency and stability. Thus, dendritic polymers offer a promising, safe, and effective vector for gene therapy, introducing new avenues for drug delivery in gene treatment strategies.

Smart Responsive Nanomedicine Drug Delivery Systems

With the advancement of modern medical technology, smart responsive nano drug delivery systems (NDDS) are being extensively used in the treatment of various diseases such as cancer. These systems can be classified into different types based on their response to external stimuli, including pH, light, temperature, and enzymes. They can control the physicochemical properties of the drug delivery system by manipulating external factors like pH, enabling precise drug targeting.[87,88]

Cerium dioxide is known for its property of scavenging reactive oxygen species (ROS) and is frequently used to inhibit mitochondrial oxidative stress in the treatment of sepsis-induced acute kidney failure. However, due to the tendency of cerium dioxide nanoparticles to agglomerate and their lack of mitochondria-targeting, Hui Yu et al[89] developed an ROS-responsive NDDS, which successfully targeted the mitochondria, effectively reducing oxidative stress and inflammation.

Owing to the variability in pH levels among different human body cells and tissues, Wang et al[90] developed a pH-responsive LDP nanopolymer system. This system consistently releases in an environment with pH=7.4, while rapidly releasing in a pH=5.0 environment. Compared to free DOX, it showed enhanced toxicity against CAL-72 cells, indicating its ability to control drug release and prolong the drug's circulation time. Hence, smart responsive NDDS not only improve drug targeting but also precisely control drug release. They hold promising prospects in treating complex microenvironment diseases like tumors.

Mechanisms of Nanomedicine Drug Delivery Systems for Improving Solubility of Poorly Soluble Drugs

Nanotechnology

Nanotechnology in drug delivery is categorized into two approaches: direct nanonization of the active pharmaceutical ingredient or the drug itself, and encapsulation of the drug within nanocarriers. Utilizing the ultra-small scale of nanoparticles allows drugs to overcome physiological barriers like the blood-brain barrier (BBB) and nasal transport barriers, offering novel administration routes. Nanocarriers, with their large surface area and ease of surface modification, can be attached with numerous functional groups, facilitating enhanced cellular entry and therapeutic efficacy, thus improving drug delivery efficiency.[91,92]

For instance, nasal drug delivery systems utilizing materials such as liposomes and nanoemulsions, enhanced for mucosal penetration, can improve drug adherence and permeation through the nasal epithelial barrier, significantly enhancing mucosal diffusion and absorption,[93] thereby making nasal delivery more efficient as demonstrated in Figure 3A. This innovation provides new pathways and therapeutic methods in clinical medicine.Direct nanonization of drugs typically involves passive diffusion and unsaturated transport primarily through the pores of capillary endothelial cells. In contrast, the application of nanocarriers primarily utilizes receptor-mediated transport and adsorption-mediated transport under electric charge, constituting saturated transport methods to breach the BBB.[94] For example, Sun et al[95] developed butyl cyanoacrylate nanoparticles coated with Polysorbate-80, leveraging the surfactant's adsorption of apolipoproteins for tight binding with apolipoprotein receptors on the BBB. Similarly, Lu et al[96] found that cationized bovine serum albumin nanoparticles exhibited an eightfold increase in BBB permeability compared to their non-cationized counterparts, as depicted in Figure 3B.

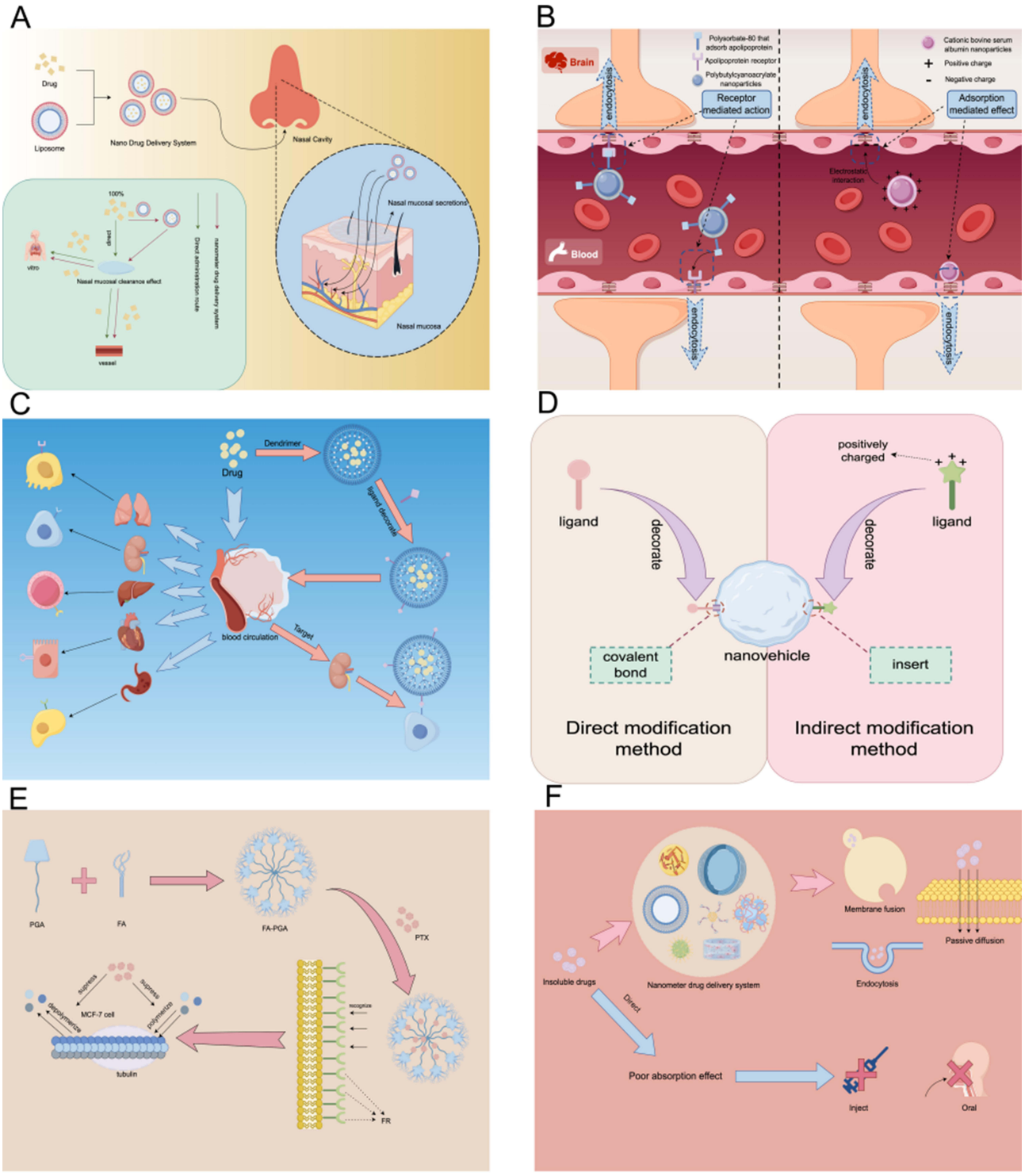

Figure 3 Mechanism of improving the solubility of insoluble drugs through nano drug delivery systems. (**A**) Transnasal administration using liposome nanodelivery system. (**B**) The mechanism of receptor mediated transport and adsorption mediated transport breaking through the blood-brain barrier. (**C**) Surface modification technology to improve drug targeting. (**D**) Direct and indirect modification methods. (**E**) Transferrin and Tamoxifen Modified Polymer Dendritic Polymer PAMAM for the Treatment of Brain Glioma. (**F**) Carrier mediated technology.

Surface Modification Techniques

Nanocarrier surfaces can be modified through adsorption or covalent attachment of ligands, altering their surface charge, aggregation potential, hydrophilicity, and fluidity. These modifications enhance the targeting of particles to specific cells,

increasing cellular uptake and, consequently, drug efficacy, as illustrated in Figure 3C. There are primarily two methods for active targeting modifications: one involves the direct modification by covalently bonding ligands to drug carriers with active functional groups;[97] the other uses an indirect modification method where positively charged ligands are inserted into the membrane,[98] as shown in Figure 3D.

Li et al[99] modified poly(amidoamine) (PAMAM) dendrimers with transferrin and tamoxifen for the treatment of gliomas. The transferrin ligand enables the drug delivery system to cross the blood-brain barrier, while the tamoxifen ligand, targeting modifications, allows the delivery system to further accumulate in the tumor region once inside the brain. This dual-targeting approach not only improves drug efficacy but also reduces toxicity to normal cells, as depicted in Figure 3E. Zhao et al[100] designed dendritic poly-L-lysine (DGL) nanoparticles modified with placental-like chondroitin sulfate A-binding peptides (plCSA-BP) to deliver HDZK-BYSB107 and Lingzhi red pigment (DGL/CSA-PNPs). The plCSA-BP specifically binds to chondroitin sulfate A, highly expressed in the trophoblast of the placenta, enabling DGL/CSA-PNPs to accumulate in choriocarcinoma tissues, thereby achieving effective tumor suppression.

Carrier-Mediated Techniques

Carrier-mediated drug delivery refers to the encapsulation of poorly soluble drugs in carriers like liposomes and polymeric micelles, exploiting their high solubility. This methodology facilitates the uptake of these drugs by target cells through passive diffusion, membrane fusion, and endocytosis, thus addressing the issue of drug solubility as illustrated in Figure 3F. Erlotinib (Er), a frontline agent in non-small cell lung cancer (NSCLC) therapy, is a small hydrophobic molecule inhibiting the epidermal growth factor receptor (EGFR). Its clinical efficacy and usability are hindered by low water solubility and permeability. Wang et al[101] covalently bonded Er with azido-modified DNA strands, creating a novel anti-cancer drug delivery system. Leveraging the high solubility of the nano-DNA structure, the enhanced permeation and retention (EPR) effect, and robust intracellular uptake, this system significantly improves the bioavailability of Er.

Traditional nano drug delivery systems face challenges such as susceptibility to immune cell uptake and potential toxicity. In contrast, biomimetic nano drug delivery systems, encapsulating drugs within cell membranes, inherit functional properties from the source cells, including immune evasion, extended circulation, and targeted recognition capabilities. These systems are increasingly applied in clinical settings, extensively used for delivering chemotherapeutics, phototherapeutic agents, and cancer vaccines.[102] For instance, Wang et al[103] noted that nano-formulations wrapped in macrophage-cancer cell hybrid membranes exhibit superior immune evasion and homotypic adhesion, enabling prolonged in vivo retention and targeted accumulation, significantly inhibiting the growth of colorectal cancer cells. Hence, biomimetic nano delivery systems demonstrate extensive application potential in cancer treatment and management, heralding a promising future.

Mechanisms of Enhanced Bioavailability in Nanomedicine Drug Delivery Systems

The formidable efficacy of many drugs contrasts starkly with their low bioavailability upon entering the body, a disparity influenced by cellular physiological absorption barriers and drug stability, thus constraining their application.[104] Nano drug delivery systems can enhance drug bioavailability by capitalizing on the material's favorable properties such as pH-responsiveness, bioadhesion, biocompatibility, biodegradability, modifiability, and processability.

Enhancing Cellular Uptake

Microemulsion drug delivery systems enhance the permeability of mucosal and intestinal epithelial cells through the abundant use of surfactants in Self-Microemulsifying Drug Delivery Systems (SMEDDS), thereby promoting drug absorption.[105] In nano drug delivery systems, lipid components can be degraded under the action of pancreatic enzymes and bile, increasing transmembrane transport and absorption of the drug.[106] Solid Lipid Nanoparticles (SLNs) leverage their biocompatibility and biodegradability to protect drugs from chemical degradation, thereby enhancing cellular uptake.[107,108] Nano drug delivery systems can augment active transport through pathways such as folate, bile acids,

and betaine transporters.[109] Nano carriers demonstrate Enhanced Permeability and Retention (EPR) effect, passively targeting tumor tissues, enriching in tumor sites, and increasing the likelihood of uptake by tumor cells.[110] Furthermore, nano carriers, upon surface ligand modification, can actively target specific cells or tissues through receptor-mediated endocytosis, thus increasing the chances of uptake by target cells,[111] as illustrated in Figure 4.

Promoting Intracellular Release

Certain emulsifiers in Self-Microemulsifying Drug Delivery Systems (SMEDDS) can inhibit the efflux action of P-glycoprotein (P-gp) on drugs, thereby enhancing intracellular drug absorption.[112] Many delivery systems employ pH-responsive mechanisms to stably encapsulate drugs under suitable pH conditions, avoiding interaction with unfavorable environments. At neutral pH, they can degrade or swell to release the drug,[113,114] as depicted in Figure 5. Nano drug delivery systems can be engineered with enzyme-sensitive formulations, such as PEGylated liposomes modified with the cell-penetrating peptide PF, which under the action of MMP-2, shed PEG-2, thereby exposing PF. This transformation results in the reversal of the liposome's surface charge from negative to positive, facilitating uptake by tumor tissues,[115] as shown in Figure 6. Controlled drug release can be achieved by manipulating external energy sources to influence functional nanoparticles. For example, magnetothermal effects generated by alternating magnetic fields control the release of loaded doxorubicin and magnetic Fe3O4 liposomes, enabling magnetothermal-chemotherapy combined treatment for ovarian cancer.[116,117]

Avoiding Early Metabolism of Drugs

Nano drug delivery systems can exploit the size difference between drugs and digestive enzymes to fabricate porous inorganic nanoparticle carriers, safeguarding the drug from enzymatic degradation.[118,119] Additionally, these systems can utilize the hydrophobic interactions between the nanocarriers and digestive enzymes to shield the drug from

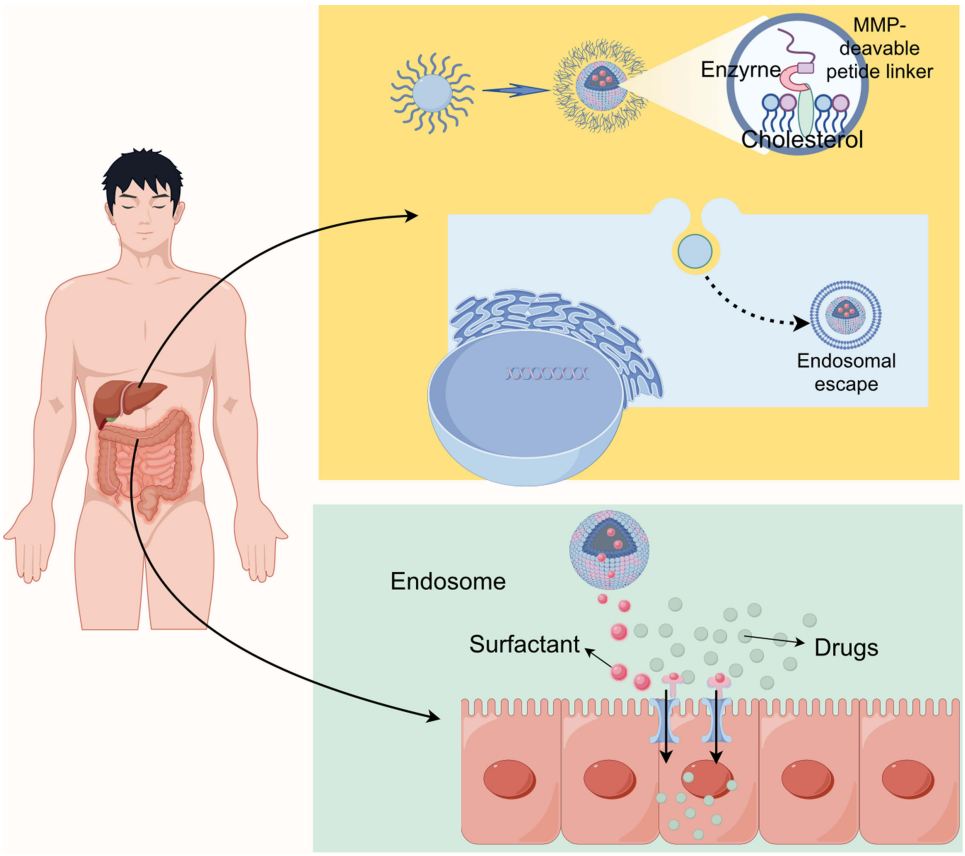

Figure 4 Mechanism of Enhanced Cellular Uptake by Nanomedicine Drug Carriers.

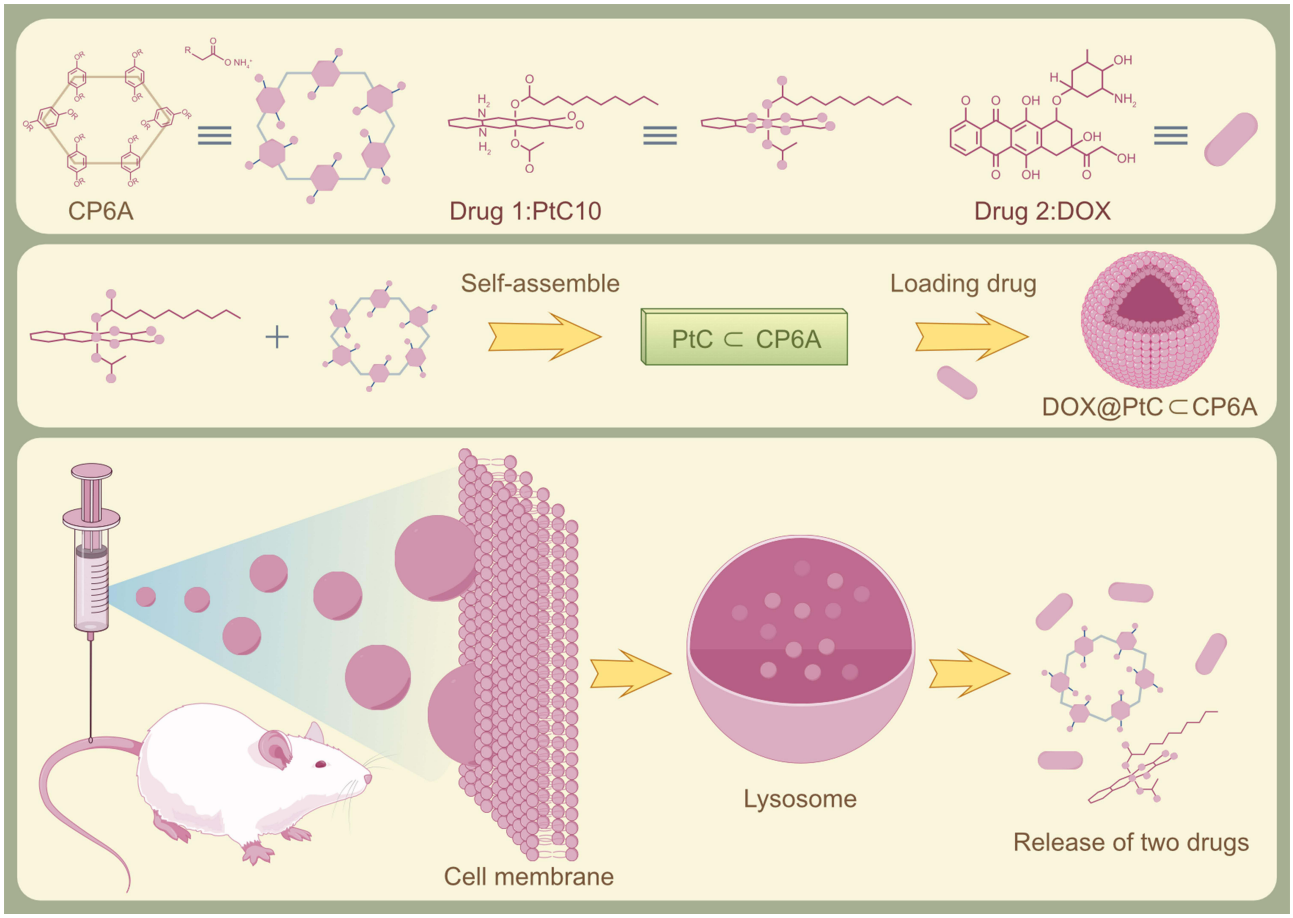

Figure 5 pH-Responsive Mechanism.

degradation.[120,121] Thermosensitive and biodegradable targeted nanoparticle hydrogels remain in a liquid state at room temperature but transform into a gel at body temperature. This conversion creates a depot system capable of sustained drug release over extended periods, enhancing in vivo retention and significantly improving clinical therapeutic efficacy.[122] As depicted in Figure 7, unmodified traditional nano-drugs, upon entering the circulatory system, are predominantly phagocytized by hepatic macrophages, leading to a short half-life and low bioavailability. In contrast, nanoparticles modified with polyethylene glycol (PEG) exhibit increased solubility and markedly enhanced ability to evade macrophage recognition. This significant reduction in phagocytosis by hepatic macrophages prolongs blood circulation time, thereby effectively increasing the drug's bioavailability.[123]

Advantages and Challenges of Nanomedicine Drug Delivery Systems

Advantages

The development of nanometer drug delivery systems (NDDS) plays a crucial role in addressing the inherent issues of poorly soluble drugs, such as enhancing solubility and stability while achieving controlled release, prolonging circulation time, and facilitating targeted delivery.[124] By intelligently designing drug delivery systems, it is possible to enhance drug efficacy without altering the drug's chemical structure.[125,126] This supports the emergence of various novel administration routes, including local intrabody administration, mucosal absorption delivery,[127] and oral administration of peptide drugs.[128] Taking mucosal absorption delivery as an example, the combination of PVCL-PVA-PEG with all four types of cellulose polymers (MC, HPMC, sodium CMC, and cationic HEC) can reversibly enhance viscosity at physiological nasal temperatures. Specifically, the thickening effect of PVCL-PVA-PEG combined with sodium CMC is synergistically

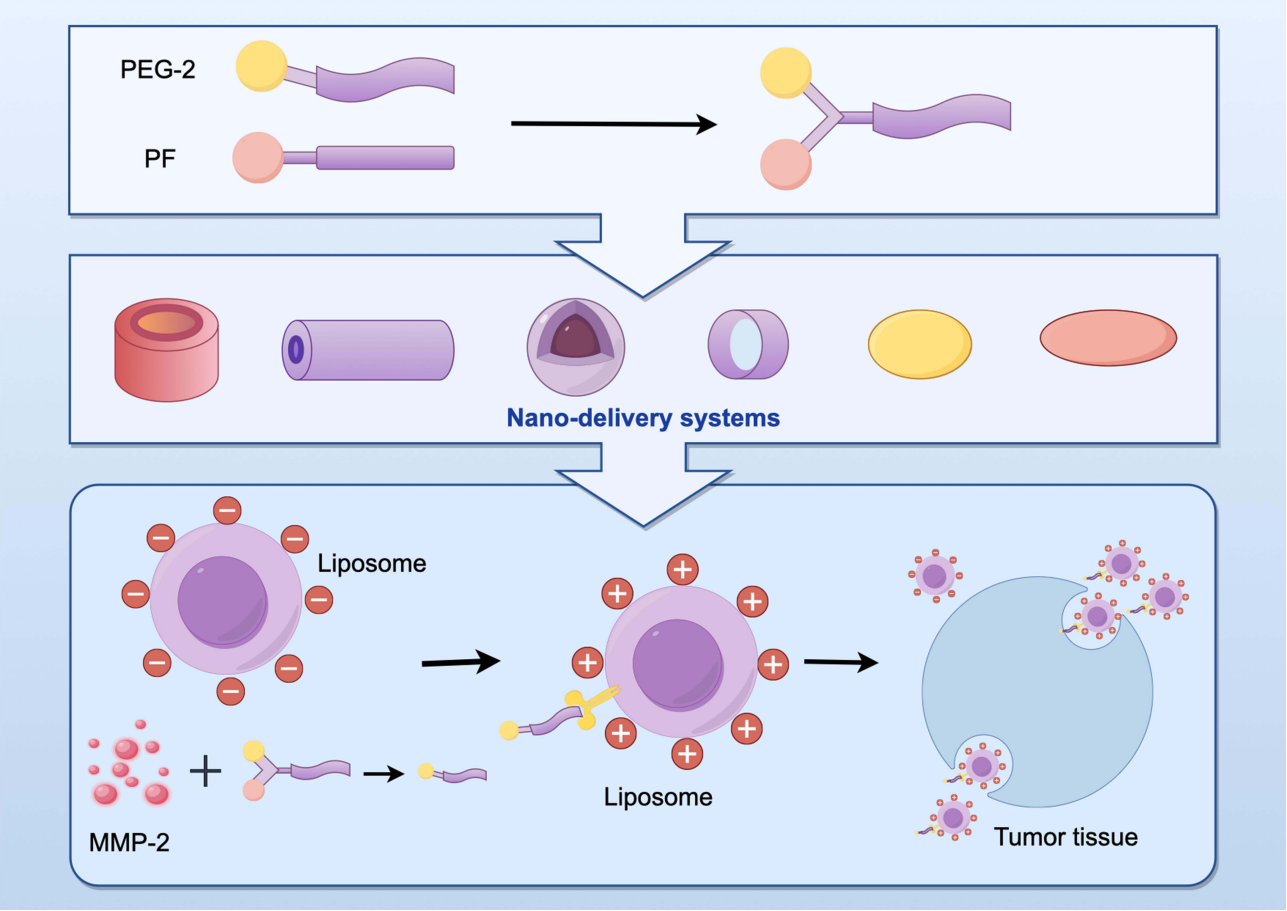

Figure 6 Altering Lipid Surface Charge in Nano Drug Delivery Systems.

enhanced. The cellulose derivatives facilitate the transport of drug molecules across the nasal epithelium without causing irreversible changes, simultaneously enhancing the performance characteristics of nasal drug formulations.

Enhancing Drug Stability

The hydrophobic nature of many pharmaceutical compounds significantly impedes their bioavailability. Encapsulation of these drugs within nanoparticles is a strategy to augment their solubility.[129,130] For instance, nanocrystals of varying sizes exhibit different affinities and functionalities, with 660 nm crystals favoring follicular accumulation and 250 nm crystals optimizing rapid dissolution. Further, exposure to light, oxygen, moisture, and the enzymatic degradation within the body, as well as adverse physiological conditions, can lead to premature drug decomposition or alteration before reaching the intended target site. This premature degradation severely hampers the therapeutic efficacy of drugs. Therefore, enhancing drug stability constitutes a critical approach to ensure the therapeutic performance of pharmaceuticals. Nanocarriers, characterized by their diminutive size, extensive surface area, and ease of modification, provide a more stable and secluded environment for the drugs. This sequestration significantly mitigates pre-target degradation or inactivation issues, thereby improving the stability of the drug during its delivery.[126,131]

Prolonging Circulation Time

The journey of drug molecules to their site of action entails traversing through several physiological barriers, including blood, tissue, cellular, and intracellular transport barriers, as illustrated in Figure 8.[131] In the context of drug delivery, nanocarriers navigate these obstacles, particularly within the gastrointestinal tract. This process involves a complex interplay of mechanisms such as the endocytosis by epithelial cells, phagocytosis in the m-cell rich regions of Peyer's Patches, absorption across intestinal interstitial spaces, and paracellular uptake under pathological conditions.[132,133]

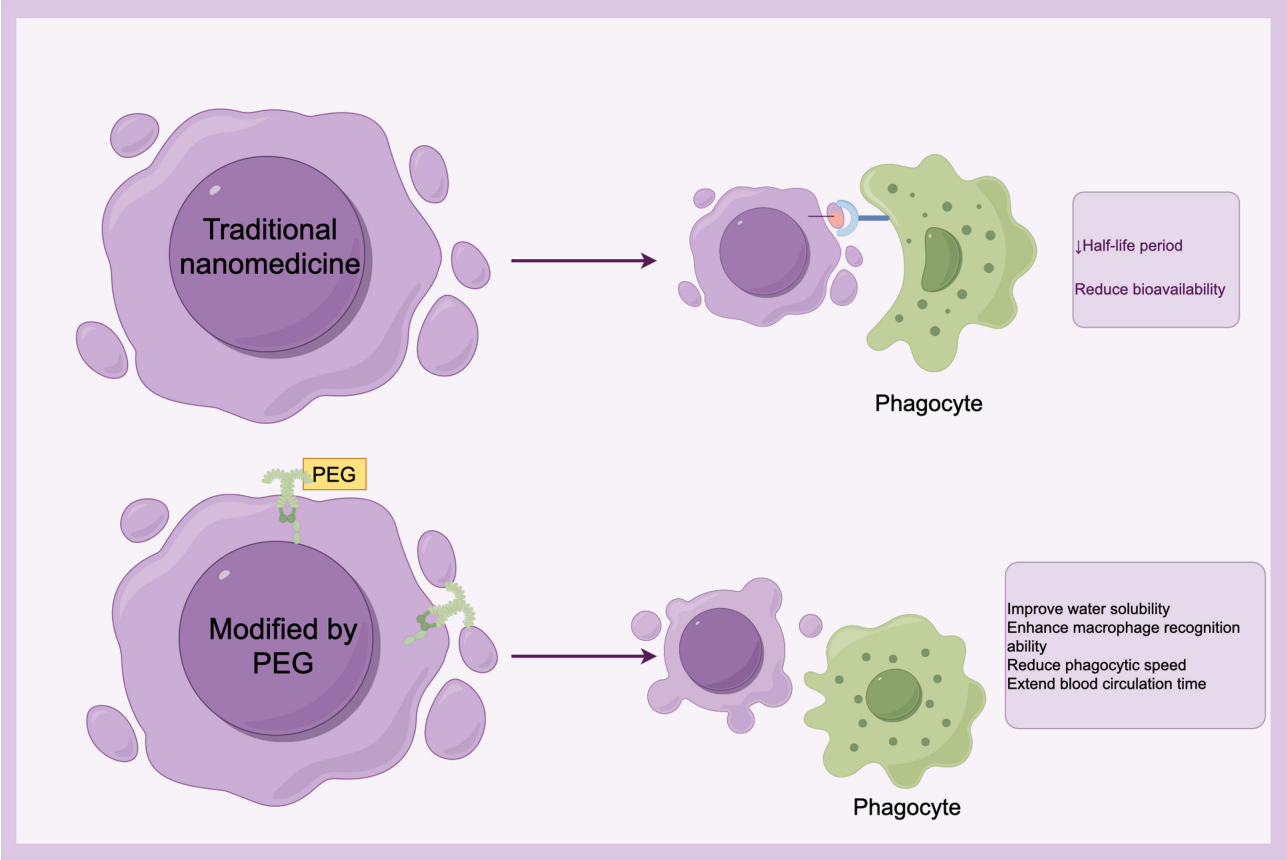

Figure 7 Mechanism of Phagocytosis Avoidance by PEG-Modified Lipid Molecules.

Nanocarriers (NCs) primarily enter cells either passively or actively. Passive penetration occurs through the plasma membrane, while active penetration chiefly involves endocytic pathways, such as pinocytosis or phagocytosis.[134] Furthermore, parameters like the shape, size, flexibility, stiffness, and surface functional groups of Nanodrug Delivery Systems (NDDS) significantly influence cellular uptake efficiency.[135–137] Due to size constraints and other factors, biopharmaceutical drugs typically cannot permeate cell membranes through osmosis. In contrast, the dimensions of nano drug carriers typically range between 10–1000 nm,[138] much smaller than cells and various cellular organelles. Therefore, employing NCs for encapsulation facilitates the traversal across the plasma membrane,[139,140] reaching intracellular target sites.

Modifying the surface characteristics of nanoparticles, such as with Polyethylene Glycol (PEG) modifications, can create "stealth" nanoparticles,[44,141] impeding the Reticuloendothelial System (RES) from phagocytosing drugs entering the bloodstream.[142–144] This modification significantly extends the drug's half-life in the blood. The primary intracellular barrier during delivery is the endosome/lysosome system. Functionally modified nanocarriers utilize mechanisms like the proton sponge effect to disrupt, destabilize, or fuse with the lysosomal membrane, thereby preventing drug degradation or inactivation in the presence of various enzymes and acidic conditions, as shown in Figure 9.

More fragile or functionally critical organs often develop specific barriers, such as the blood-brain barrier (BBB) safeguarding the central nervous system, the blood-testis barrier, and the placental barrier, as depicted in Figure 10. The BBB, in particular, poses a significant challenge due to its highly selective nature. The tight junctions of its endothelial cells, reinforced by the actions of astrocytes and pericytes, greatly hinder the delivery of pharmaceuticals to the central nervous system.[145] However, effective strategies can circumvent the BBB, such as surface modifications designed based on the transference of transferrin (Tf) across the BBB.[146,147] Studies indicate that carbon-based nanomaterials (NMs) can cross the BBB through the facilitative actions of the olfactory mucosa and nerves, but this comes with a concomitant increase in potential risks.[148]

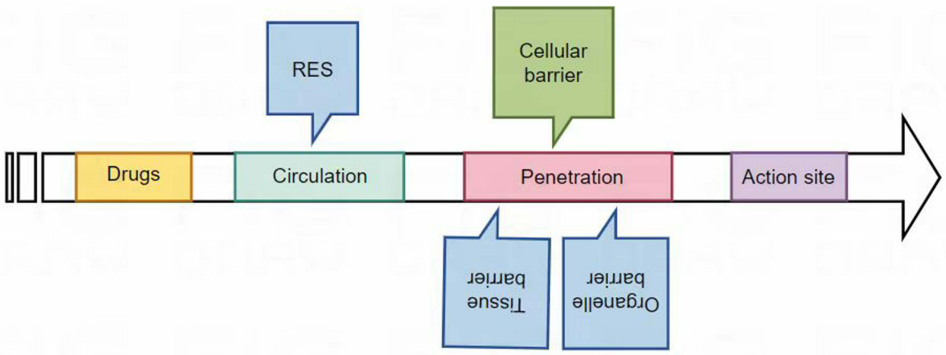

Figure 8 Physiological Barriers During Drug Delivery to the Target.

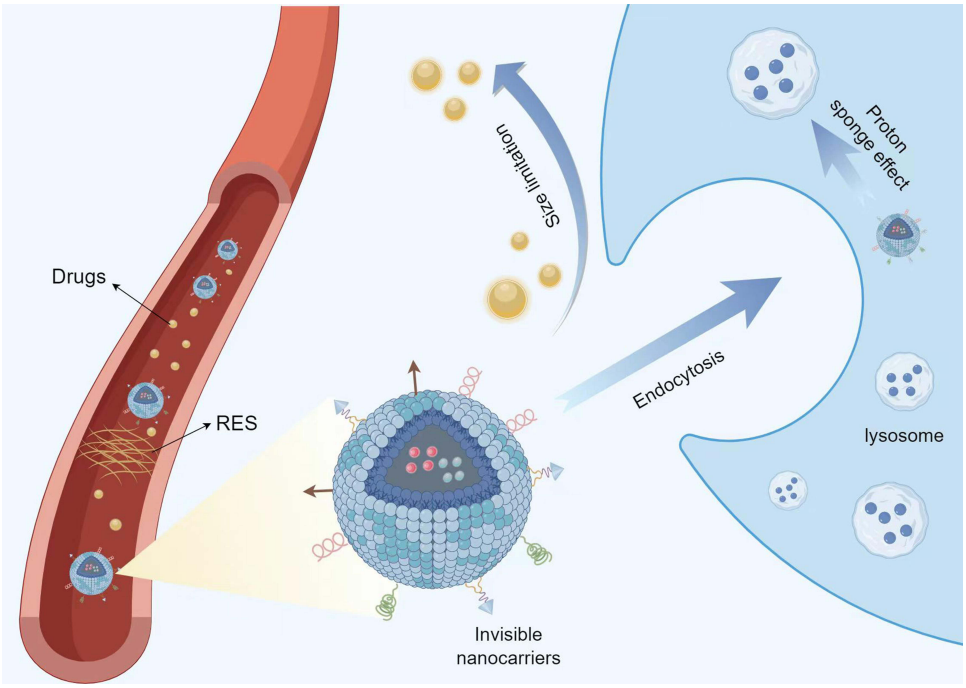

Figure 9 Basic Mechanisms of Nanocarrier Action.

Targeted Delivery and Combination Therapy with Multiple Drugs

Nanodrug delivery systems primarily encapsulate drugs either internally within the carrier or through modifications on the carrier surface. Nanomaterials, endowed with multiple unique characteristics such as surface effects, catalytic properties, and chemical reactivity, can be tailored based on their features and closely linked information about pathological sites. This precision enables the concentrated delivery of drugs at the disease locus, effectively preventing premature drug release, thus enhancing therapeutic efficacy while minimizing toxic side effects on healthy tissues.[149] Generally, targeted delivery encompasses both passive and active targeting strategies. Passive targeting relies on the intrinsic properties of the nanodrug delivery system and the physiological or pathological characteristics of the target site to facilitate effective drug accumulation, such as pH-responsive polymer nanoparticles, protease-degradable nanogels, or nanoparticles incorporating disulfide/selenide linkages susceptible to GSH reduction.[150] Active targeting, on the other

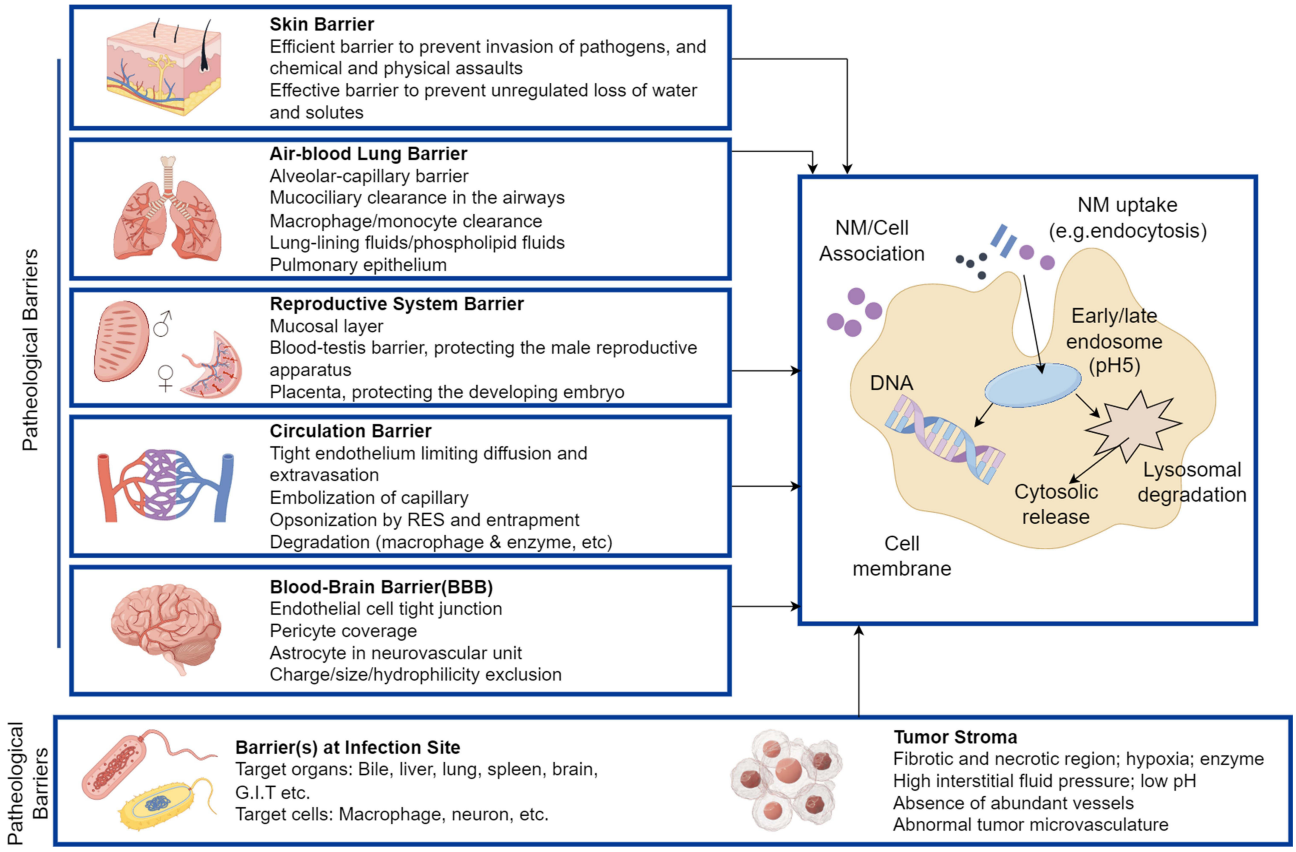

Figure 10 Types and Mechanisms of Specific Barriers.

hand, is achieved through the specific interaction and binding of the nanodrug delivery system's surface with targeted molecules or proteins at the desired site (eg, ligand-receptor interactions, antibody-antigen interactions, lectin-sugar interactions), leading to the selective concentration of the drug at targeted tissues or cells.[151] This active targeting is further categorized into biologically directed, in vivo stimulus-directed, and ex vivo stimulus-directed types.

Additionally, the unique physicochemical properties of nanomaterials, particularly their exceptional optical, electrical, thermal, and magnetic characteristics, enable their use as probes for disease diagnostics.[152] From another perspective, the high surface energy and surface reactivity of nanomaterials also allow them to function as carriers for controlled drug release, integrating multiple functionalities, as illustrated in Figure 11. Furthermore, the same nanocarrier can be engineered to load multiple drugs, facilitating combination therapy to enhance treatment outcomes.

Challenges

Cost Issues

The cost considerations of nanodrug delivery systems encompass various aspects such as investment in equipment and technology, raw material costs, expenses related to quality control and testing, the impact of economies of scale, and the costs associated with safety evaluations. For instance, in terms of equipment and technology, the formulation of nanoparticles often necessitates the use of organic solvents, ultrasonication, high-speed homogenization, grinding, emulsification, crosslinking, filtration, centrifugation, and lyophilization techniques, all requiring significant financial and technical expertise. Regarding raw materials, the use of metallic nanoparticles, nanomicelles, and similar materials, whose preparation and purification can substantially increase the production costs of nanodrug delivery systems.

When it comes to quality control and testing, due to the small pore size of standard filtration membranes, larger particle size distributions and particles around 220 nm can pose significant filtration challenges. If the average particle size is not significantly lower than 220 nm, a substantial amount of active ingredients might be lost during the filtration

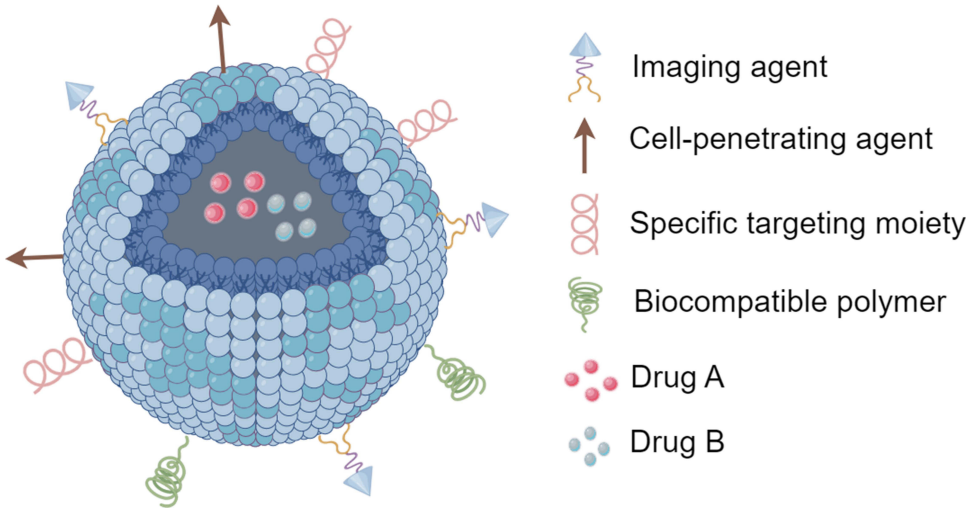

Figure 11 Multifunctional Nanoparticles for Drug Delivery.

process.[153] To reduce the costs of nanodrug carriers and ensure their effective and intended use in vivo, innovative approaches and design principles are required.

Safety Concerns

Nanocarriers, despite their efficiency in encapsulating, adsorbing, or covalently linking drug molecules to enhance local drug concentration and reduce dosing frequency, present unique challenges due to their special properties. These include potential adverse reactions in the body, such as immune responses and toxicity. Drugs delivered via nanoentities may behave differently from those administered in normal or conventional forms. For instance, poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles administered intravenously showed a significantly reduced uptake by liver Kupffer cells in rats, compared to free drugs. Moreover, nanoparticles are prone to accumulation in the body, potentially harming healthy tissues.

Utilizing magnetic nanoparticles (NPs) can have harmful consequences. For example, drugs and NPs crossing the blood-brain barrier (BBB) need careful consideration for effective treatment of brain disorders. The medicinal properties of iron oxide NP ions and the abundance of lysophosphatidic acid (LPA) can temporarily disrupt tight junctions, allowing iron oxide NP ions to enter brain cells. This opens up opportunities for treating neurological disorders but also poses a risk of unintended iron accumulation in the brain. Normally, iron oxide NP ions have a half-life of 6 minutes in plasma, primarily depositing in the liver and spleen. In experiments with mice treated with LPA-modified iron oxide NP anions in the brain and spleen, no signs of peripheral immune cell infiltration were found, and microglia and astrocytes showed no significant activation. These findings suggest that temporary disruption of the BBB might be a safe and effective way to enhance the delivery of iron oxide NP anions to the brain. Hence, the application of nanotechnology in drug delivery systems must meet biocompatibility and biosafety requirements to avoid adverse reactions in humans.[154] There is an urgent need to develop nanomaterials with good biocompatibility and degradability to mitigate the limitations their use imposes on the industrialization and clinical application of nanodrug delivery systems.[155,156]

Sterile manufacturing of nanodrugs also presents challenges. For instance, when involving biomaterials, the risk of nanoparticle destruction increases with sterilization techniques like gamma irradiation or autoclaving.[157] Environmental safety in nanoparticle manufacturing is another concern. During dry material processing, nanoparticles can disperse into the air, potentially causing lung toxicity.[158] Extreme caution is thus required in the manufacturing processes of nanomedical drugs. Personal protective equipment is essential during manufacturing because some nanoparticles can penetrate skin barriers, posing a potential risk of skin contact.[159] Nanoparticles manufactured entirely in a liquid environment, much like standard pharmaceutical liquid production, might significantly reduce environmental impacts.

Lack of Standardization and Scalability

The majority of nanomedicines exhibit complex properties, divergent from those produced by conventional pharmaceutical methodologies. Traditional drug manufacturing often fails to replicate the nano-scale three-dimensional, multi-component systems inherent to these medicines. A comprehensive understanding of key components and their interactions is imperative. This knowledge facilitates the early identification of critical characteristics during the development of nanomedicines, enabling the selection of appropriate large-scale production techniques. These techniques must establish crucial process steps and analytical standards to ensure the reproducibility of the final products. Currently, a unified standard for the preparation and evaluation of nanomaterials is lacking. Despite a broad array of nanomedicines being approved, the absence of specific regulatory guidelines for their development and characterization hinders their clinical potential.

Pharmaceuticals are generally regulated by the U.S.[160] Food and Drug Administration (FDA) under two primary legislations: the Federal Food, Drug, and Cosmetic Act (FDCA), which encompasses all chemically synthesized drugs and devices, and the Public Health Service Act (PHSA), which covers biologically-derived therapeutic products.[161,162] Nanomedicines are categorized by the FDA as combination products, assigned traditional regulatory pathways with additional specific requirements to ensure their safety and efficacy. For instance, nanoscale formulations of paclitaxel and Doxil® have received FDA approval as novel anticancer agents, classified as combination products. The current debate over the adequacy of regulatory frameworks and procedures has led to heightened scrutiny of the intrinsic risks associated with nanotechnology and products containing nanoparticles. These concerns include the toxicity of nanoparticles, the potential unintended effects due to their capability to penetrate the Blood-Brain Barrier (BBB), and the long-term implications of nanoparticle use.[163,164]

Furthermore, the production of nanomaterials demands more precise technologies to ensure the stability and consistency of the drug delivery systems. The complexity of the preparation process is a major barrier to the scalable manufacture and commercial application of novel drug delivery systems. Designing more refined industrial equipment and optimizing the production process are crucial to addressing these current challenges.

Latest Research Developments and Case Studies

Advancements in nanotechnology have significantly contributed to the research of drug delivery systems, offering valuable insights.[165] This includes the development of liposomes, nanoparticles, polymeric micelles, and polymer-drug conjugates.[166] To date, nanocarrier systems have been successfully applied in delivering poorly soluble drugs,[167] with 51 nanotechnology-based products implemented in clinical practices.[168–170]

Compared to conventional drug delivery methods, nanomedicine primarily emphasizes targeted drug delivery, supporting effective treatments for various infectious diseases, cancers, diabetes, and neurodegenerative disorders such as Alzheimer's disease.[171,172] Several successful nanocarriers, including dendrimers, nanoparticles, liposomes, and carbon nanotubes, have been commercialized. These carriers achieve precise targeting and rapid accumulation at the site of action without reliance on any biological system intervention.[173–175] However, challenges remain in optimizing delivery module efficiency and drug properties, such as biocompatibility and biodegradability.[176] Numerous ongoing clinical trials are expected to propel the advancement of novel nanotherapeutics and highlight future directions for improvement in this field.[174,175] This article selects typical examples from this area for analysis, as illustrated in Table 2.

Table 2 Selected Exemplary Cases in This Field

Categories	Year of Approval	Pharmaceutical Formulations	Companies	Clinical Applications
Liposomal Nanoparticles	2015	Irinotecan	Merrimack Pharmaceuticals (Cambridge, UK)	Metastatic pancreatic cancer
	2021	Recombinant CSP	ClaxoSmithKline (Middlesex, UK)	Malaria
	2021	BNT162b2	Pfizer (NewYork, NY, USA) and BioNTech (Mainz, Germany)	COVID-19

(*Continued*)

Table 2 (Continued).

Categories	Year of Approval	Pharmaceutical Formulations	Companies	Clinical Applications
Polymeric Nanoparticles	2012	Docetaxel	Samyang Pharmaceuticals (Seoul Republic of Korea)	MBC, NSCLC, and ovarian cancer
	2015	PTX	Oasmia Pharmaceuticals (Uppsala, Sweden)	Ovarian cancer
Drug Nanocrystals	2018	Aripiprazole lauroxil	AlkermesInc (Waltham, MA, USA)	Schizophrenia
	2021	Cabotegravir	ViiyHealthcareCo. (Brentford, London, UK)	HIV-1 infection
Other Nanomedicines	2010	Ironmolecule with unbranched carbohydrateinon particles	Pharmacosmos (Rorvangsvei, Holbaek, Denmark)	Iron deficiency anemia
	2013	Polynucleariron (III) oxyhydroxide iron particles	ForInt. (Waltham, MA.USA)	Iron deficiency anemia
	2015	Recombinant anti-hemophilic factor VIII	Baxalta (Montgomery, Al, USA)	Hemophilia A

Abbreviations: FDA, Food and Drug Administration; EMA, European Medicines Agency.

Conclusion and Outlook

With the advancement of nanomedicine, nanoscale drug delivery systems (NDDS) have emerged as pivotal tools for enhancing the solubility and bioavailability of poorly soluble drugs, thereby advancing solutions to critical issues in pharmaceutical engineering related to drug solubility and bioavailability. This review comprehensively summarizes the research on NDDS for improving the solubility and bioavailability of insoluble drugs. Initially, we revisit the definition, classification, characteristics of poorly soluble drugs, and the fundamental principles, types, and features of NDDS. Poorly soluble drugs are categorized into BCS Class II and IV,[47] both exhibiting low solubility but differing in permeability - BCS Class II drugs have higher permeability than BCS Class IV,[177] leading to distinct improvement strategies for each class.

NDDS utilize the ultrafine size, catalytic activity, and protective nature of nanomaterials[41,178,179] for drug delivery, thereby enhancing drug utilization and reducing adverse drug reactions.[48] The systems can be classified into six types:[49] lipid-based nanoparticles (LNPs), polymer-based nanoparticles, nanoemulsions, nanogels, inorganic nanoparticles, and dendrimer-based nanoparticles. LNPs have been shown to induce apoptosis in liver cancer cells, enhancing drug efficacy with promising research implications in cancer treatment.[60] Polymer-based nanoparticles exhibit excellent bacterial targeting, enhancing ocular adhesion and corneal permeability,[69] suggesting greater potential in treating bacterial keratitis and other bacterial infections. Nanoemulsions, as oral drug carriers, have demonstrated significantly higher bioavailability than other mediums,[81] indicating their potential as superior oral drug carriers. Nanogels offer localized, sustained release of drugs.[86] Inorganic nanoparticles, catalyzing the formation of highly cytotoxic substances like BCS Class IV, synergize with chemotherapy drugs like Doxorubicin (DOX) to kill cancer cells,[180] offering new avenues for efficient cancer treatment. Dendrimer-based nanoparticles, post combination with anticancer drug 5-fluorouracil, gradually release free 5-fluorouracil,[95] reducing adverse drug reactions and presenting broad application prospects as novel nanomaterials.

Addressing the characteristic challenges of poorly soluble drugs, our analysis of nanonization techniques, surface modification technologies, and carrier-mediated tactics concludes that NDDS can precisely enhance the solubility of these drugs. Nanonization techniques break through biological barriers like the blood-brain barrier and nasal transport barriers, thereby improving drug delivery efficiency[101,102] and introducing new administration routes. Surface modification, altering the physicochemical properties of nanoparticle surfaces, enhances cellular targeting and consequently drug utilization.[110] Carrier-mediated technology involves encapsulating poorly soluble substances

within high-solubility carriers, leading to cellular uptake via passive diffusion, membrane fusion, and endocytosis.[117] Additionally, NDDS enhance cellular uptake, promote intracellular release, and prevent premature drug metabolism, thus improving bioavailability.

Despite challenges in production costs and safety,[119–121] nanomaterials possess unique advantageous properties not shared by the majority of other drug delivery materials,[124] promising to overcome the limitations of traditional delivery methods and materials. Notably, NDDS have recently garnered increasing research attention in the medical field.

Traditional drug delivery methods often require frequent or high dosage administration to achieve therapeutic effects, leading to decreased overall efficacy and patient compliance. In contrast, the application of nanotechnology-based drug delivery systems is increasingly favored and researched. Studies suggest that controlling the particle size and modifying components within nanoscale drug delivery systems can increase drug solubility, control drug release, prolong circulation time, reduce drug clearance rates, selectively enhance cellular uptake, and minimize adverse reactions, thereby enhancing therapeutic outcomes.[181]

In terms of drug particle size, the efficiency of drug delivery can be enhanced by controlling the size of the nanoparticles. For instance, Mistry et al[182] demonstrated the significance of reducing particle size in drug delivery systems by comparing the intranasal delivery efficiency of nanoparticles measuring 100 nm and 200 nm. Controlling the diameter of carbon nanoparticles (NPs) to 150 nm, for example, allows them to enter the lymphatic system without entering the bloodstream, directing them to regional lymph nodes.[183] This indicates that controlling nanoparticle size can determine drug transport pathways, enhancing target specificity.

In terms of surface modification of drugs, firstly, encapsulating drugs with materials such as polysaccharides, solid lipid bodies, or magnetic substances can develop modified coating materials that prolong circulation time, increase absorption rate, reduce drug side effects, and enhance bioavailability.[183] Secondly, adsorption or covalent attachment of ligands can be used for surface modification,[110] altering physical and chemical properties like surface charge, aggregation potential, hydrophilicity, and fluidity. This effectively enhances the targeting of the nanoparticles to cells, improving drug absorption and efficient delivery of the loaded drug. Thirdly, modifiable polymers such as polyethylene glycol (PEG) can be used for drug modification, enhancing the mucosal penetration capability of the nanoparticles while ensuring high safety, thereby increasing drug absorption efficiency.

Therefore, leveraging the unique attributes of nanotechnology to devise novel inventions that enhance the utilization of poorly soluble drugs will be a reliable cornerstone in the field of nanomedicine. Overall, despite some challenges, nanoscale drug delivery systems still offer promising strategies and insights for addressing issues of drug insolubility and low bioavailability.

Abbreviations

BCS, The Biopharmaceutics Classification System; IVIVC, In Vivo Correlation; SLS, Sodium Lauryl Sulfate; DTAB, Dodecyl Trimethyl Ammonium Bromide; PEG, Polyethylene Glycol; NCTD, Norcantharidin; DOX, Doxorubicin; TAX, Taxol; CIP, Ciprofloxacin; TEL, Telmisartan; SMEDDS, Microemulsifying Drug Delivery Systems; EPR, Retention; NDDS, Nanodrug Delivery Systems; RES, Reticuloendothelial System; FDA, Drug Administration; FDCA, Cosmetic Act; PHSA, Public Health Service Act; BBB, Brain Barrier.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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