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NANODRUG DELIVERY SYSTEMS AND THEIR CLINICAL RESEARCH STAGES

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Nanodrug delivery systems have become an important and rapidly developing area of research because they can improve the delivery, stability, and safety of therapeutic agents. Conventional drug delivery methods often have several limitations, such as poor drug solubility, low bioavailability, rapid degradation, non-specific distribution, and undesirable side effects. To address these problems, different nanocarriers, including lipid-based, polymeric, protein-based, and inorganic systems, have been developed. These systems can enhance drug accumulation at disease sites, reduce systemic toxicity, and support controlled or targeted drug release, making them attractive tools for more effective therapy.

However, the clinical translation of nanodrug delivery systems remains uneven. While some nanoformulations have successfully entered clinical practice, many promising nanosystems still face important challenges that prevent their widespread medical application. These challenges include the complexity of biological environments, limited targeting efficiency in vivo, difficulties in large-scale and reproducible production, safety concerns, and regulatory uncertainties. As a result, the gap between laboratory success and clinical performance remains a major issue in this field.

This review focuses on that central contrast: nanocarriers offer clear pharmacological advantages, but these benefits do not always translate into reliable clinical outcomes. The paper compares the main advantages of nanodrug carriers with the key barriers limiting their clinical use. It also discusses passive and active targeting, stimuli-responsive release, protein corona formation, and the current translational landscape. In this way, the review aims to provide a balanced understanding of why nanodrug delivery systems are so promising, while also highlighting why their path to the clinic remains challenging.

Keywords: nanodrug delivery, nanomedicine, passive targeting, active targeting, stimuli-responsive release, polymeric nanoparticles

INTRODUCTION

Nanotechnology has changed the way researchers think about drug delivery. In conventional formulations, the active drug is usually the main focus. In nanodrug delivery, the carrier itself also becomes part of the therapeutic design [1, 2]. By adjusting particle size, surface chemistry, charge, and composition, researchers can influence how a drug circulates, where it accumulates, and how it is released [1, 4]. This is especially important in cancer therapy, where free drugs often show poor selectivity and significant toxicity to healthy tissues [2, 3, 12]. In addition, nanocarriers can be engineered to protect fragile therapeutic molecules, improve pharmacokinetic behavior, and create delivery systems with functions that are difficult to achieve through conventional formulations alone [1, 5]. Because of these features,

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nanotechnology is now regarded not only as a formulation strategy, but also as a broader platform for improving therapeutic performance in modern medicine [12].

For this reason, nanocarriers are often presented as tools for improving the therapeutic index of existing drugs. They may enhance solubility, prolong circulation time, protect unstable compounds, and support controlled or site-preferential release [3, 17, 18]. They can also be adapted for a wide range of therapeutic agents, including small molecules, nucleic acids, proteins, and imaging components, which further increases their biomedical relevance [7, 19]. At the same time, the field has moved beyond simple optimism. Recent reviews emphasize that strong preclinical results do not always lead to strong clinical outcomes [12, 15, 16]. Biological complexity, tumor heterogeneity, manufacturing constraints, and regulatory challenges continue to limit successful translation from laboratory design to approved medical products [3, 10, 17].

Why nanoscale delivery matters

The main advantage of nanoscale delivery is not simply “small size.” Rather, it is the ability to control how a therapeutic agent behaves in a biological system. Nanocarriers can reduce premature drug degradation, improve the solubility of poorly water-soluble molecules, and modify biodistribution after administration [1, 2, 17]. In many cases, they also allow higher local drug concentration at the target site than free-drug administration can achieve [3, 12].

Another major advantage is formulation flexibility. Nanocarriers can be designed to carry hydrophobic drugs, hydrophilic drugs, nucleic acids, imaging agents, or combinations of these [2, 7, 19]. This makes them useful not only in therapy, but also in diagnostics and theranostics [8, 9, 20]. In oncology, this flexibility has supported the development of systems that combine delivery, imaging, and controlled release in one platform [2, 9, 20].

However, these advantages must be stated carefully. A nanocarrier does not automatically become clinically effective just because it performs well in vitro. Biological barriers, immune recognition, tumor heterogeneity, and manufacturing limits can all reduce real-world performance. This is why current literature increasingly evaluates nanomedicine not only in terms of design sophistication, but also in terms of reproducibility and clinical relevance [4, 12, 15, 16].

Major classes of nanodrug delivery systems

Among the available systems, lipid-based nanoparticles are the most established in clinical practice (Figure 1). This group includes liposomes, solid lipid nanoparticles, nanoemulsions, and lipid nanoparticles for nucleic acid delivery. Their main advantages are biocompatibility, biodegradability, relative ease of formulation, and the ability to encapsulate a wide range of therapeutic agents. These properties explain why lipid-based platforms occupy an important place in translational nanomedicine[7, 11, 19].

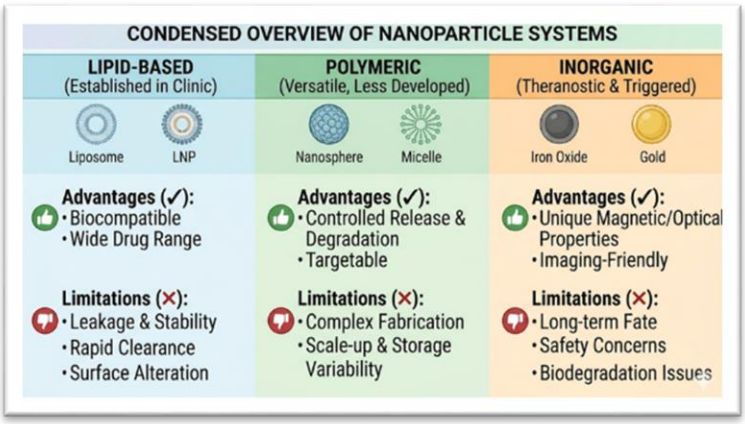

Figure 1. Condensed Overview of Nanoparticle Systems

Still, lipid-based systems should not be discussed only in positive terms. They can also show limited physical stability, drug leakage during storage, rapid clearance in some cases, and formulation sensitivity to composition changes. In biological fluids, their surface may also be altered by adsorbed proteins, which can change targeting behavior and circulation properties [7, 11, 13]. Therefore, their clinical success does not mean they are free of design and translation problems.

Polymeric nanoparticles represent another major class. They are attractive because they offer strong control over size, degradation rate, surface properties, and release behavior. Both natural polymers, such as chitosan, and synthetic polymers, such as PLGA and PLA, have been widely studied. Polymeric nanoparticles can be prepared as nanospheres, nanocapsules, or micellar systems. This versatility makes them useful for sustained release and targeted delivery [6].

At the same time, polymeric systems also have limitations. Their preparation may involve complex fabrication steps, scale-up challenges, and batch-to-batch variability. In addition, a formulation that performs well at laboratory scale may not behave the same way after sterilization, storage, or industrial production [6, 15, 16]. This is one reason why the translational path of polymeric nanocarriers remains slower than the pace of academic publication suggests.

Inorganic nanoparticles, such as iron oxide, gold, and silica-based systems, add another dimension to nanomedicine. Their value often lies in magnetic, optical, or imaging-related properties that are not available in many soft-matter carriers. Because of this, they are especially attractive for theranostic use and externally triggered treatment [8, 20]. However, concerns about long-term fate, biodegradation, and safety evaluation remain stronger for many inorganic systems than for lipid-based platforms [8, 15, 16].

Passive and active targeting: promise and limitation

Targeting is one of the most discussed concepts in nanodrug delivery. Passive targeting is usually linked to the enhanced permeability and retention effect, or EPR effect (Figure 2). In simple terms, nanoparticles may accumulate more easily in tumor tissue because tumor vasculature is often more permeable and lymphatic drainage is less efficient [4, 12]. This idea has shaped nanomedicine research for many years.

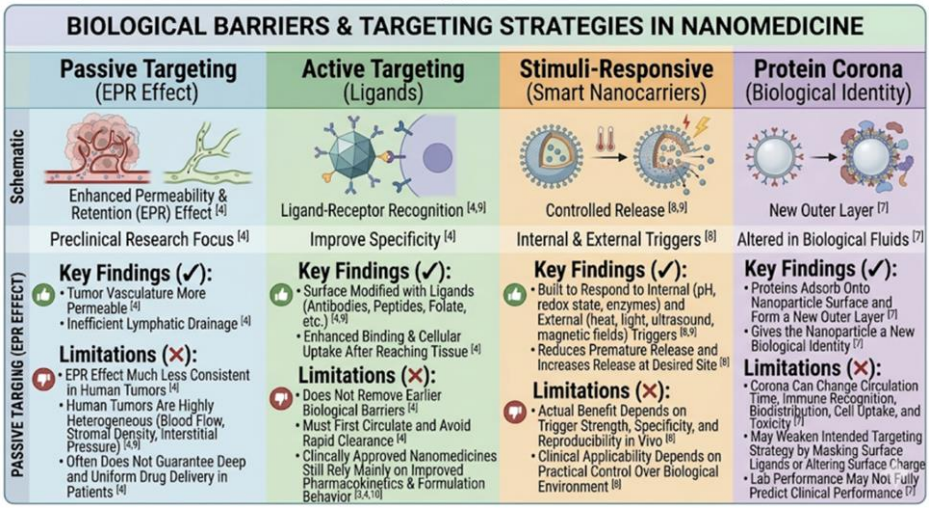

Figure 2. Biological Barriers & Targeting Strategies in Nanomedicine

However, more recent reviews make an important point: the EPR effect is much more consistent in animal models than in human tumors [4, 12, 16]. Human tumors are highly heterogeneous. Differences in blood flow, stromal density, extracellular matrix, and interstitial pressure can strongly affect nanoparticle accumulation [4, 9, 16]. As a result, passive targeting

alone often does not guarantee deep and uniform drug delivery in patients.

To improve specificity, researchers have developed active targeting strategies. In these systems, the nanoparticle surface is modified with ligands such as antibodies, peptides, folate, or other molecules that can recognize target cells [4, 9]. This can enhance binding and cellular uptake after the nanoparticle reaches the relevant tissue. Still, active targeting should not be described as a complete solution. The carrier must first circulate, avoid rapid clearance, and reach the target region. Only then can ligand-receptor recognition play its role.

This point is important for a balanced review. Active targeting is valuable, but it does not remove the earlier biological barriers. That is why clinically approved nanomedicines still rely mainly on improved pharmacokinetics and formulation behavior rather than highly complex targeting mechanisms [3, 10, 15, 16].

Stimuli-responsive and smart nanocarriers

After targeting, the next important design feature is controlled release. Many modern systems are built to respond to internal or external stimuli. Internal triggers include pH, redox state, enzymes, and other biochemical differences between healthy and diseased tissues. External triggers may include heat, light, ultrasound, or magnetic fields [5, 9]. The goal is to reduce premature release during circulation and increase release at the desired site.

These smart systems are especially interesting in cancer therapy, where the tumor microenvironment can differ from normal tissue in acidity, oxidative state, and enzyme profile. Stimuli-responsive nanoparticles can therefore improve local release behavior. However, the actual benefit depends on whether the trigger is strong enough, specific enough, and reproducible enough in vivo [5, 9]. In other words, smart design remains promising, but clinical applicability still depends on practical control over the biological environment (Figure 2).

Protein corona

An important issue in nanomedicine is the formation of the protein corona. When nanoparticles enter blood or other biological fluids, proteins adsorb onto their surface and form a new outer layer. This means that the particle seen by the body is not exactly the same particle that was designed in the laboratory. In practice, the protein corona gives the nanoparticle a new biological identity (Figure 2) [13, 14].

This is important because the corona can change circulation time, immune recognition, biodistribution, cell uptake, and toxicity. It may also weaken an intended targeting strategy by masking surface ligands or altering surface charge [13, 14]. For this reason, the difference between planned nanoparticle design and real in vivo behavior is often partly a protein-corona problem. This concept helps explain why laboratory performance may not fully predict clinical performance.

Theranostics and multifunctionality

Another important advantage of nanotechnology is its use in theranostics. This term refers to the combination of therapy and diagnosis in one nanosystem. A nanocarrier can be designed not only to deliver a drug, but also to help visualize where the system accumulates or how it behaves in the body. This is especially relevant in cancer research, where imaging and treatment often need to work together. Inorganic nanoparticles are frequently discussed in this context because some of them have magnetic, optical, or contrast-related properties that support imaging applications. However, theranostic systems are usually more complex than conventional drug carriers. Their translation to the clinic can therefore be more difficult because complexity increases the demands for safety testing, reproducibility, and regulatory evaluation [8, 9, 20].

Clinical research stages and the translational gap

The clinical development of nanomedicine has clearly progressed, but the number of clinically successful systems is still limited compared with the amount of preclinical research (Figure 3). A 2023 analysis of *ClinicalTrials.gov* identified 486 nanoparticle-related clinical trials from 2002 to 2021, with liposomes and protein-based formulations as the dominant groups [10]. This already shows that translation is real, but also selective.

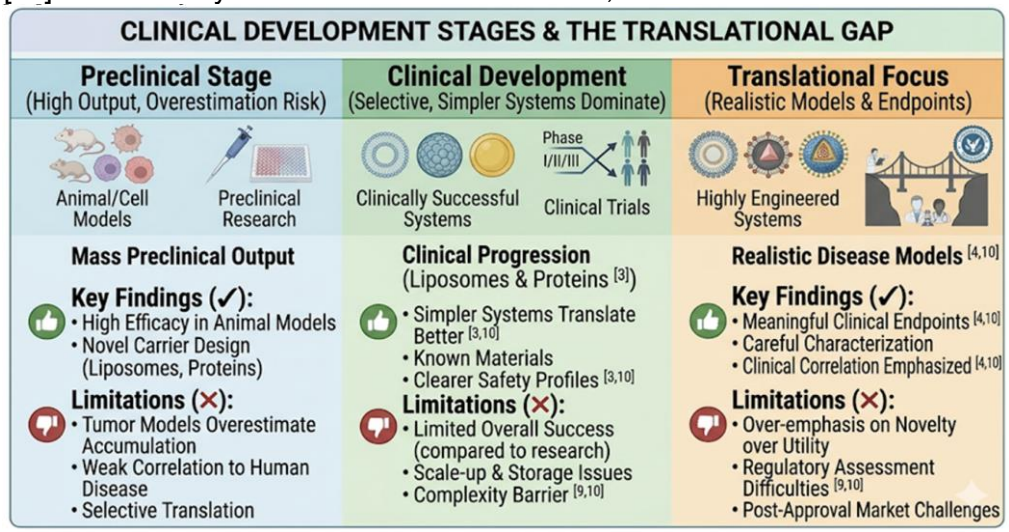

Figure 3. Clinical Development Stages and The Translational Gap

One major lesson from the literature is that simpler systems often translate better than more complex ones. Formulations with known materials, scalable manufacturing, and clearer safety profiles have a better chance of reaching approval. By contrast, highly multifunctional or heavily engineered systems may face difficulties in large-scale production, storage stability, toxicity evaluation, and regulatory assessment [15, 16, 17, 18].

Another difficulty is that preclinical models do not always reflect human disease accurately. Tumor models in animals may overestimate accumulation or treatment response. As a result, a nanoparticle can appear highly effective in preclinical studies but show weaker benefit in patients. This is why current translational research increasingly emphasizes realistic disease models, careful characterization, and clinically meaningful endpoints rather than only novel carrier design [4,12, 16].

EXPERIMENTAL

Nanodrug delivery systems can be prepared through different synthesis and processing methods depending on the type of carrier, the physicochemical properties of the drug, and the intended therapeutic application. The main preparation approaches include lipid film hydration, solvent injection, emulsification, nanoprecipitation, ionic gelation, coacervation, self-assembly, co-precipitation, sol-gel processing, and microfluidic techniques. In most cases, the experimental design aims to control particle size, surface charge, morphology, drug-loading efficiency, release behavior, and colloidal stability.

Lipid-based nanoparticles are commonly prepared by thin-film hydration, ethanol injection, reverse-phase evaporation, high-pressure homogenization, microemulsion methods, and microfluidic mixing. In the thin-film hydration method, lipids are first dissolved in an organic solvent. The solvent is then evaporated to form a thin lipid film on the wall of the flask. This dry film is hydrated with an aqueous phase, allowing vesicles to form. The resulting liposomes are usually reduced in size by sonication, extrusion, or homogenization. This method is widely used for liposomal drug delivery systems because it allows incorporation of

both hydrophilic and hydrophobic drugs, depending on the structure of the liposome [7, 11].

Ethanol injection is another simple method for lipid-based carrier preparation. In this approach, lipids are dissolved in ethanol and then injected into an aqueous phase under stirring. When the lipid solution contacts water, lipid molecules self-assemble into nanosized vesicles or lipid particles. This method is relatively simple, but the final particle size and distribution can be affected by the injection rate, lipid concentration, temperature, and mixing intensity. For more advanced lipid nanoparticles, especially nucleic acid delivery systems, microfluidic mixing is commonly used. In microfluidic preparation, the lipid phase and aqueous phase are rapidly mixed in small channels, which supports better control of particle size, polydispersity, and reproducibility [19].

Solid lipid nanoparticles and nanostructured lipid carriers are often prepared by high-pressure homogenization, hot homogenization, cold homogenization, or ultrasonication. In hot homogenization, the lipid phase is melted above its melting point and mixed with the drug. This lipid-drug mixture is then dispersed in an aqueous surfactant solution and homogenized to form nanoparticles. In cold homogenization, the drug-loaded lipid melt is first cooled and solidified, then ground and dispersed under high pressure. These methods are useful for producing lipid particles with controlled size and improved drug stability, although temperature-sensitive drugs may require careful processing conditions [7].

Polymeric nanoparticles are commonly prepared by nanoprecipitation, emulsion solvent evaporation, solvent diffusion, dialysis, ionic gelation and self-assembly methods. Nanoprecipitation is widely used for hydrophobic drugs and biodegradable polymers such as PLGA and PLA. In this method, the polymer and drug are dissolved in a water-miscible organic solvent such as acetone or acetonitrile. This organic phase is then added dropwise into an aqueous phase containing a stabilizer. As the solvent diffuses into water, the polymer precipitates and forms nanoparticles. The organic solvent is then removed by evaporation or reduced pressure. Particle size can be controlled by polymer concentration, solvent type, stirring rate, surfactant concentration, and the ratio between organic and aqueous phases [6].

The emulsion solvent evaporation method is also frequently used for polymeric nanoparticles. In the single emulsion method, a polymer and hydrophobic drug are dissolved in an organic solvent and emulsified into an aqueous phase containing a stabilizer. After emulsification, the organic solvent is evaporated, leaving solid polymeric nanoparticles. For hydrophilic drugs, proteins or nucleic acids, double emulsion methods are often preferred. In a water-in-oil-in-water system, the aqueous drug solution is first emulsified into the polymer-containing organic phase. This primary emulsion is then dispersed in a second aqueous phase. After solvent removal, nanoparticles containing hydrophilic agents are formed. However, double emulsion methods may cause drug leakage or denaturation of sensitive biomolecules if the processing conditions are not optimized [6].

Natural polymer-based nanoparticles can also be produced by ionic gelation or coacervation. Chitosan nanoparticles are commonly prepared by ionic gelation using negatively charged crosslinking agents such as tripolyphosphate. In this method, positively charged chitosan chains interact with anionic crosslinkers and form nanosized particles under mild aqueous conditions. This approach is useful for sensitive drugs because it does not require high temperature or harsh organic solvents. However, particle size and stability depend strongly on polymer concentration, pH, molecular weight, degree of deacetylation, and the polymer-to-crosslinker ratio [6].

Polymeric micelles are usually formed through self-assembly of amphiphilic block copolymers in aqueous media. These copolymers contain both hydrophilic and hydrophobic segments. In water, the hydrophobic segments form the inner core, while the hydrophilic segments form the outer shell. Hydrophobic drugs can be loaded into the core by dialysis, solvent evaporation or direct dissolution methods. Polymeric micelles are especially useful for poorly water-soluble drugs, but their stability after dilution in the bloodstream remains an important consideration [6, 17].

Protein-based nanoparticles may be prepared by desolvation, emulsification, coacervation, or thermal gelation. Albumin is one of the most studied proteins for nanoparticle

preparation because of its biocompatibility and ability to bind various drugs. In the desolvation method, a desolvating agent such as ethanol is slowly added to an aqueous protein solution under stirring. This reduces protein solubility and leads to nanoparticle formation. Crosslinking may then be used to stabilize the particles. Protein-based nanoparticles can also be prepared through emulsification methods, where the protein phase is dispersed in an oil phase or organic phase and then solidified. These systems are attractive for drug delivery because proteins can provide natural biodegradability and functional groups for surface modification [10, 21].

Inorganic nanoparticles are prepared through methods such as co-precipitation, sol-gel synthesis, hydrothermal treatment, seed-mediated growth, thermal decomposition, and the Stöber method. Iron oxide nanoparticles are often synthesized by co-precipitation of ferrous and ferric salts in an alkaline medium. In this process, Fe^{2+} and Fe^{3+} ions react with a base such as ammonia or sodium hydroxide to form magnetite nanoparticles. The reaction temperature, pH, stirring rate, salt ratio, and atmosphere can affect particle size, crystallinity, and magnetic behavior. Surface coating with polymers, silica, citrate, dextran or other stabilizers is usually required to improve colloidal stability and reduce aggregation in biological media [8, 20].

Gold nanoparticles are commonly produced by chemical reduction methods. In a typical synthesis, a gold salt such as chloroauric acid is reduced by agents such as citrate, sodium borohydride, or ascorbic acid. Citrate can act as both reducing and stabilizing agent. The size and shape of gold nanoparticles depend on the concentration of the gold precursor, reducing agent, stabilizer, temperature, and reaction time. Seed-mediated growth can be used to prepare anisotropic structures such as gold nanorods. These particles are valuable in theranostic systems because of their optical properties, but their surface modification is essential for drug loading and biological compatibility [8, 20].

Silica nanoparticles are often prepared by sol-gel processing, especially through the Stöber method. In this method, tetraethyl orthosilicate is hydrolyzed and condensed in an alcohol-water-ammonia mixture to form silica particles. Mesoporous silica nanoparticles can be prepared by using surfactants as structure-directing agents. After particle formation, the surfactant template is removed to create pores suitable for drug loading. These porous structures are useful because they can carry high amounts of drug and allow surface functionalization. However, their biodegradation, long-term safety, and clearance behavior must be carefully considered [8, 20].

After synthesis, nanodrug delivery systems usually require post-processing steps such as purification, size reduction, sterilization, drying, and surface modification. Purification can be carried out by centrifugation, dialysis, ultrafiltration or size-exclusion chromatography to remove free drug, unreacted materials, organic solvents, and excess surfactants. Size reduction can be achieved by sonication, membrane extrusion, or high-pressure homogenization. Surface modification may include PEGylation, ligand conjugation, charge adjustment, or coating with polymers and biomolecules. These modifications are used to improve stability, prolong circulation time, reduce immune recognition, or support active targeting [4, 13, 14].

Drug loading can be performed during nanoparticle formation or after carrier preparation. In passive loading, the drug is incorporated during synthesis by dissolving or dispersing it with the carrier materials. In active loading, the drug is introduced after particle formation by using concentration gradients, pH gradients, or specific interactions between the drug and carrier. The choice of loading method depends on drug solubility, molecular size, charge, and stability. Drug-loading efficiency and encapsulation efficiency are important parameters because they directly influence dose, release behavior, and therapeutic usefulness [1, 6, 7].

The prepared nanocarriers are usually characterized by several physicochemical methods. Dynamic light scattering is used to determine average particle size and polydispersity index. Zeta potential analysis is used to evaluate surface charge and colloidal stability. Transmission electron microscopy or scanning electron microscopy can show particle morphology and size distribution. Fourier-transform infrared spectroscopy, X-ray diffraction,

differential scanning calorimetry, and thermogravimetric analysis may be used to study chemical interactions, crystallinity, and thermal behavior. Drug-loading efficiency, encapsulation efficiency, and in vitro release profiles are usually determined by UV-Visible spectroscopy, fluorescence spectroscopy or high-performance liquid chromatography, depending on the drug [1, 6, 7].

In vitro release studies are commonly performed using dialysis bags, membrane diffusion systems, or direct dispersion methods. The drug-loaded nanoparticles are placed in a release medium that simulates physiological or pathological conditions. For cancer-related studies, release media with different pH values are often used to compare normal physiological pH with acidic tumor or endosomal conditions. Samples are collected at specific time intervals and analyzed to determine the cumulative amount of drug released. These studies help evaluate whether the nanocarrier provides sustained, controlled, or stimuli-responsive release [5, 9].

For clinical translation, the experimental preparation of nanodrug delivery systems must also consider reproducibility and scalability. A method that works at laboratory scale may not always be suitable for industrial production. Parameters such as batch-to-batch consistency, sterility, residual solvent content, storage stability, lyophilization behavior, and regulatory acceptability are critical. Therefore, methods such as microfluidics, high-pressure homogenization and controlled nanoprecipitation are increasingly important because they can offer better process control and scale-up potential compared with less reproducible laboratory methods [15, 16, 17, 18].

RESULTS AND DISCUSSION

The reviewed literature shows that nanodrug delivery systems have clear therapeutic potential because they can modify several important aspects of drug behavior, including solubility, stability, circulation time, biodistribution and release kinetics. These advantages are especially relevant for drugs with poor aqueous solubility, rapid degradation or high systemic toxicity [1, 2, 3]. However, the same literature also shows that improved nanoscale design does not automatically lead to improved clinical outcomes. The central finding of this review is therefore the contrast between strong pharmaceutical potential and difficult clinical translation.

Among the different nanocarrier types, lipid-based nanoparticles appear to have the strongest clinical position. Liposomes, lipid nanoparticles, solid lipid nanoparticles, and nanoemulsions are widely studied because of their biocompatibility, biodegradability, and ability to carry both hydrophilic and hydrophobic therapeutic agents [7, 11]. Lipid nanoparticles have also become especially important for nucleic acid delivery because they can protect fragile molecules such as mRNA and support intracellular transport [19]. Their clinical progress suggests that materials with established biocompatibility, simpler formulation principles, and scalable preparation methods have a greater chance of translation.

At the same time, lipid-based systems are not free from limitations. Their stability may be affected by lipid composition, oxidation, aggregation, storage conditions,and drug leakage. After administration, interaction with blood proteins may also change their surface properties, circulation behavior, and targeting ability [7, 13, 14]. This means that even clinically successful nanocarrier classes require careful formulation control and biological evaluation.

Polymeric nanoparticles show another important direction in nanodrug delivery. Their main advantage is the possibility of controlling particle size, degradation rate, surface properties, and release behavior through polymer selection and formulation design. Biodegradable polymers such as PLGA and PLA are useful for sustained release, while natural polymers such as chitosan are valuable because of their biocompatibility and ability to form nanoparticles under mild conditions [6]. These properties make polymeric carriers highly flexible for different administration routes and therapeutic purposes.

However, polymeric nanoparticles also show why flexibility does not always mean easy translation. Their preparation may involve organic solvents, surfactants, multistep fabrication,

and sensitive processing conditions. Small changes in polymer concentration, solvent type, emulsification conditions, or drying method can affect particle size, drug loading, and release profile [6]. As a result, polymeric systems require strict control of reproducibility, sterilization, storage stability, and scale-up before they can move reliably toward clinical use [15, 16].

Inorganic nanoparticles provide unique opportunities that are not easily achieved with lipid or polymeric systems. Iron oxide nanoparticles offer magnetic properties that can be used for magnetic targeting, magnetic resonance imaging, and hyperthermia. Gold nanoparticles provide optical and photothermal properties, while mesoporous silica nanoparticles can offer high drug-loading capacity because of their porous structure [8, 20]. These features make inorganic nanoparticles attractive for theranostic and externally triggered treatment strategies.

Nevertheless, inorganic nanoparticles also raise stronger concerns about long-term safety, biodegradation, clearance, and organ accumulation. Surface coating and functionalization can improve their colloidal stability and biocompatibility, but they also increase formulation complexity. Therefore, their clinical translation depends not only on their functional advantages, but also on whether their long-term biological fate can be clearly understood and controlled [8, 15, 16].

The comparison of carrier classes suggests that clinical translation often favors systems that are not necessarily the most complex, but the most reproducible and biologically predictable. Highly engineered multifunctional systems may appear attractive in preclinical studies, but they can become difficult to manufacture, characterize, sterilize, and regulate. In contrast, simpler systems with known materials, scalable production, and clearer safety profiles are more likely to progress toward clinical application [15, 16, 17, 18].

Targeting remains one of the most important but most challenging aspects of nanodrug delivery. Passive targeting through the enhanced permeability and retention effect has strongly influenced cancer nanomedicine research. In theory, nanoparticles can accumulate in tumor tissue because of leaky tumor vasculature and poor lymphatic drainage [4, 12]. However, this effect is much more variable in human tumors than in many animal models. Differences in vascular structure, blood flow, stromal density, extracellular matrix and interstitial pressure can limit nanoparticle penetration and cause uneven drug distribution [4, 12, 16]. For this reason, passive targeting cannot be treated as a guaranteed mechanism of clinical success.

Active targeting was developed to improve specificity by modifying nanoparticle surfaces with ligands such as antibodies, peptides, folate, or other receptor-recognizing molecules [4, 9]. This approach can increase cellular uptake after the carrier reaches the target site. However, active targeting does not remove earlier biological barriers. Nanoparticles must first remain stable in circulation, avoid rapid immune clearance, and reach the target tissue in sufficient amounts. In addition, the protein corona may mask surface ligands and reduce receptor recognition [13, 14]. Therefore, active targeting should be understood as an additional strategy rather than a complete solution to the delivery problem.

Stimuli-responsive nanocarriers offer a more controlled approach by aiming to release drugs under specific internal or external conditions. Internal triggers such as pH, redox state, and enzymes are especially relevant in cancer therapy because tumor tissue and intracellular compartments can differ from healthy tissue in acidity, oxidative conditions, and enzyme expression [5, 9]. External triggers such as heat, light, ultrasound, or magnetic fields may also provide more spatial control over drug release. However, the usefulness of these systems depends on whether the stimulus is strong, specific, and reproducible enough in vivo. A system that responds well under controlled laboratory conditions may show weaker performance in patients if the biological trigger is variable or insufficient.

Protein corona formation is one of the clearest examples of the difference between designed nanoparticle properties and real biological behavior. When nanoparticles enter blood or other biological fluids, proteins adsorb onto their surface and create a new biological identity [13, 14]. This can alter particle size, surface charge, circulation time, biodistribution, immune recognition, toxicity, and cellular uptake. It may also interfere with targeting by covering ligands or changing surface interactions. Therefore, nanoparticle characterization should not be

limited to measurements in water or simple buffer systems. More biologically relevant testing conditions are necessary to understand how a carrier may behave after administration.

The clinical research landscape confirms that nanomedicine has made real progress, but this progress remains selective. A clinical trial analysis reported 486 nanoparticle-related clinical trials between 2002 and 2021, with liposomes and protein-based formulations among the dominant groups [10]. This shows that nanodrug delivery systems are not only theoretical platforms, but active clinical candidates. However, the number of approved nanoformulations remains limited compared with the large number of preclinical studies. This gap reflects the difficulty of converting laboratory performance into consistent therapeutic benefits in patients.

One important reason for this gap is the limited predictive value of some preclinical models. Animal tumor models may overestimate nanoparticle accumulation or therapeutic response because they do not fully reproduce the complexity of human tumors. Human disease involves greater heterogeneity in vascularization, immune response, extracellular matrix structure, and patient-to-patient variability [4, 12, 16]. Future studies therefore need more realistic models, clinically meaningful endpoints, and standardized characterization methods.

Manufacturing is another major factor influencing translation. A nanocarrier must not only be effective in small-scale experiments, but also reproducible at largerscales. Parameters such as particle size, polydispersity, drug-loading efficiency, surface charge, sterility, residual solvent content, storage stability and release behavior must remain consistent between batches. These requirements are sometimes less visible in early academic studies, but they are essential for clinical development and regulatory approval [15, 17, 18].

Overall, the results indicate that the future of nanodrug delivery depends on balance. Nanocarriers must be advanced enough to improve drug performance, but simple and stable enough to be manufactured, characterized, and regulated. Lipid-based systems currently show the strongest clinical presence, polymeric systems provide strong control over release and degradation, and inorganic systems offer valuable theranostic functions. However, all of these systems face challenges related to biological complexity, immune interaction, targeting efficiency, reproducibility, and safety.

Thus, the main issue in nanodrug delivery is not a lack of scientific potential. The main challenge is translating that potential into reliable clinical benefit. Future progress will depend on designing nanocarriers that remain effective not only under ideal laboratory conditions, but also in realistic biological and clinical environments.

CONCLUSION

Nanodrug delivery systems remain one of the most promising areas in pharmaceutical and biomedical research. They offer important advantages, including improved solubility, modified biodistribution, controlled release, and the possibility of combining therapy with diagnosis. Lipid-based and polymeric systems have shown particular value because of their versatility and broad therapeutic potential.

At the same time, the field should be discussed with balance. Efficient targeting is still difficult in real biological systems. Protein corona formation, tumor heterogeneity, immune clearance, manufacturing challenges, and regulatory demands all limit clinical translation. For this reason, the future of nanomedicine depends not only on designing smarter particles, but also on designing systems that remain effective under realistic biological and clinical conditions.

Overall, the value of nanodrug delivery systems lies in their ability to improve how drugs behave in the body. Their main challenge lies in converting that theoretical advantage into consistent clinical benefit. A strong review paper should therefore present both sides together. That contrast is what defines the present stage of the field.

REFERENCES

[1] Patra, J. K.; Das, G.; Fraceto, L. F.; Campos, E. V. R.; Rodriguez-Torres, M. del P.; Acosta-Torres, L. S.; Diaz-Torres, L. A.; Grillo, R.; Swamy, M. K.; Sharma, S.; Habtemariam, S. and Shin, H.-S. Nano based drug delivery systems: Recent developments and future prospects, *Journal of Nanobiotechnology*, **2018**, v. 16(1), pp. 1–33, https://doi.org/10.1186/s12951-018-0392-8

[2] Giri, P. M.; Banerjee, A. and Layek, B. A recent review on cancer nanomedicine, *Cancers*, **2023**, v. 15(8), pp. 1–34, https://doi.org/10.3390/cancers15082256

[3] Rodríguez, F.; Caruana, P.; De la Fuente, N.; Español, P.; Gámez, M.; Balart, J.; Llurba, E.; Rovira, R.; Ruiz, R.; Martín-Lorente, C.; Corchero, J. L. and Céspedes, M. V. Nano-based approved pharmaceuticals for cancer treatment: Present and future challenges, *Biomolecules*, **2022**, v. 12(6), pp. 1–27, https://doi.org/10.3390/biom12060784

[4] Chen, Z.; Kankala, R. K.; Long, L.; Xie, S.; Chen, A. and Zou, L. Current understanding of passive and active targeting nanomedicines to enhance tumor accumulation, *Coordination Chemistry Reviews*, **2023**, v. 481, article 215051, https://doi.org/10.1016/j.ccr.2023.215051

[5] Zhao, X.; Bai, J. and Yang, W. Stimuli-responsive nanocarriers for therapeutic applications in cancer, *Cancer Biology & Medicine*, **2021**, v. 18(2), pp. 319–335, https://doi.org/10.20892/j.issn.2095-3941.2020.0496

[6] Beach, M. A.; Nayanathara, U.; Gao, Y.; Zhang, C.; Xiong, Y.; Wang, Y. and Such, G. K. Polymeric nanoparticles for drug delivery, *Chemical Reviews*, **2024**, v. 124(9), pp. 5505–5616, https://doi.org/10.1021/acs.chemrev.3c00705

[7] Waheed, I.; Ali, A.; Tabassum, H.; Khatoon, N.; Lai, W.-F. and Zhou, X. Lipid-based nanoparticles as drug delivery carriers for cancer therapy, *Frontiers in Oncology*, **2024**, v. 14, pp. 1–17, https://doi.org/10.3389/fonc.2024.1296091

[8] Huang, H.; Feng, W.; Chen, Y. and Shi, J. Inorganic nanoparticles in clinical trials and translations, *Nano Today*, **2020**, v. 35, pp. 100972–100996, https://doi.org/10.1016/j.nantod.2020.100972

[9] Sun, L.; Liu, H.; Ye, Y.; Lei, Y.; Islam, R.; Tan, S.; Tong, R.; Miao, Y.-B. and Cai, L. Smart nanoparticles for cancer therapy, *Signal Transduction and Targeted Therapy*, **2023**, v. 8(1), pp. 1–28, https://doi.org/10.1038/s41392-023-01642-x

[10] Namiot, E. D.; Sokolov, A. V.; Chubarev, V. N.; Tarasov, V. V. and Schiöth, H. B. Nanoparticles in clinical trials: Analysis of clinical trials, FDA approvals and use for COVID-19 vaccines, *International Journal of Molecular Sciences*, **2023**, v. 24(1), pp. 1–15, https://doi.org/10.3390/ijms24010787

[11] Chen, J.; Hu, S.; Sun, M.; Shi, J.; Zhang, H.; Yu, H. and Yang, Z. Recent advances and clinical translation of liposomal delivery systems in cancer therapy, *European Journal of Pharmaceutical Sciences*, **2024**, v. 193, article 106688, https://doi.org/10.1016/j.ejps.2023.106688

[12] Shi, J.; Kantoff, P. W.; Wooster, R. and Farokhzad, O. C. Cancer nanomedicine: Progress, challenges and opportunities, *Nature Reviews Cancer*, **2017**, v. 17(1), pp. 20–37, https://doi.org/10.1038/nrc.2016.108

[13] Mahmoudi, M.; Landry, M. P.; Moore, A. and Coreas, R. The protein corona from nanomedicine to environmental science, *Nature Reviews Materials*, **2023**, v. 8, pp. 422–438, https://doi.org/10.1038/s41578-023-00552-2

[14] Caracciolo, G.; Farokhzad, O. C. and Mahmoudi, M. Biological identity of nanoparticles in vivo: Clinical implications of the protein corona, *Trends in Biotechnology*, **2017**, v. 35(3), pp. 257–264, https://doi.org/10.1016/j.tibtech.2016.08.011

[15] Mundekkad, D. and Cho, W. C. Nanoparticles in clinical translation for cancer therapy, *International Journal of Molecular Sciences*, **2022**, v. 23(3), pp. 1–29, https://doi.org/10.3390/ijms23031685

[16] Zhang, P.; Xiao, Y.; Sun, X.; Lin, X.; Koo, S. and Yaremenko, A. V. Cancer nanomedicine toward clinical translation: Obstacles, opportunities, and future prospects, *Med*, **2023**, v. 4(3), pp. 147–167, https://doi.org/10.1016/j.medj.2022.12.001

[17] Thapa, R. K. and Kim, J. O. Nanomedicine-based commercial formulations: Current developments and future prospects, *Journal of Pharmaceutical Investigation*, **2023**, v. 53(1), pp. 19–33, https://doi.org/10.1007/s40005-022-00607-6

[18] Shan, X.; Gong, X.; Li, J.; Wen, J.; Li, Y. and Zhang, Z. Current approaches of nanomedicines in the market and various stage of clinical translation, *Acta Pharmaceutica Sinica B*, **2022**, v. 12(7), pp. 3028–3048, https://doi.org/10.1016/j.apsb.2022.02.025

[19] Hou, X.; Zaks, T.; Langer, R. and Dong, Y. Lipid nanoparticles for mRNA delivery, *Nature Reviews Materials*, **2021**, v. 6(12), pp. 1078–1094, https://doi.org/10.1038/s41578-021-00358-0

[20] Fernandes, D. A. Review on metal-based theranostic nanoparticles for cancer therapy and imaging, *Technology in Cancer Research & Treatment*, **2023**, v. 22, article 15330338231191493, https://doi.org/10.1177/15330338231191493

[21] Qu, N.; Song, K.; Ji, Y.; Liu, M.; Chen, L.; Lee, R. J. and Teng, L. Albumin nanoparticle-based drug delivery systems, *International Journal of Nanomedicine*, **2024**, v. 19, pp. 6945–6980, https://doi.org/10.2147/IJN.S467876