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Review Article

Recent Advances in Pharmacological Evaluation of Novel Drug Delivery Systems

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ABSTRACT

The evolution of drug delivery science has ushered in a new era of precision therapeutics, driven by the development of Novel Drug Delivery Systems (NDDS) that aim to overcome the limitations of conventional dosage forms. This review provides a comprehensive analysis of recent advances in pharmacological evaluation strategies for NDDS, encompassing in vitro, ex vivo, and in vivo models across diverse therapeutic domains. Emphasis is placed on disease-specific evaluation approaches, regulatory considerations, and emerging research trends, including personalized drug delivery, theranostics, nanomedicine, and artificial intelligence–assisted design. Challenges such as the translational gap between preclinical and clinical outcomes, manufacturing scalability, and long-term safety concerns are critically examined. The discussion also highlights future perspectives in smart, targeted, and patient-tailored delivery systems that promise to transform clinical outcomes. By integrating current innovations with strategic evaluation methods, NDDS research can bridge the path from laboratory innovation to successful clinical translation, ultimately enhancing therapeutic efficacy and patient care.

INTRODUCTION

Drug delivery plays a pivotal role in modern pharmacotherapy, bridging the gap between the physicochemical properties of an active pharmaceutical ingredient (API) and its intended therapeutic effect in the human body. While the discovery of potent drugs has expanded significantly over the last few decades, the clinical success of these molecules depends heavily[1] on their ability to reach the target site in an effective concentration for a desired duration, without causing unacceptable side effects. Conventional dosage forms such as tablets, capsules, injections,

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and topical preparations, though widely used, often suffer from significant[2,3] limitations. These include poor aqueous solubility, low permeability, erratic absorption, rapid metabolism, systemic toxicity, and the inability to achieve site-specific delivery. Such drawbacks often lead to suboptimal therapeutic outcomes, necessitating frequent dosing, which in turn affects patient compliance.[4-6]

In response to these challenges, the concept of Novel Drug Delivery Systems (NDDS) has emerged as a revolutionary approach to optimize the delivery of therapeutic agents. NDDS are designed to improve the pharmacokinetic and pharmacodynamic profiles of drugs, enhance solubility and stability, enable controlled and targeted release, reduce dosing frequency, and minimize adverse effects. These systems encompass a wide range of platforms such as liposomes, nanoparticles, micelles, dendrimers, transdermal patches, and stimuli-responsive carriers, each offering unique advantages for specific clinical applications.[7-9]

However, the mere design of an innovative delivery system is insufficient without rigorous pharmacological evaluation. Comprehensive pharmacological assessment is essential to determine the safety, efficacy, and therapeutic superiority of NDDS over conventional formulations. This evaluation involves a combination of in-vitro assays, ex-vivo models, and in-vivo studies to assess parameters such as drug release kinetics, permeability, biodistribution, therapeutic efficacy, and toxicity. The integration of advanced analytical techniques and imaging modalities further enhances the reliability of such assessments. Ultimately, pharmacological evaluation not only validates the scientific premise of NDDS but also supports regulatory approval and clinical adoption, ensuring that novel formulations deliver tangible benefits to patients.[10-13]

Table 1: Comparison between Conventional Dosage Forms and Novel Drug Delivery Systems[14-18]

Parameter	Conventional Dosage Forms	Novel Drug Delivery Systems (NDDS)
Drug solubility	Limited improvement; often requires co-solvents or salts	Significant enhancement via nanocarriers, lipid-based systems
Bioavailability	Often low due to poor absorption or first-pass metabolism	Improved through targeted delivery and absorption enhancement
Drug release	Immediate or short duration	Controlled, sustained, or stimuli-triggered release
Targeting ability	Minimal, mostly systemic distribution	Site-specific delivery using ligands, antibodies, or stimuli
Toxicity	Higher systemic toxicity due to off-target exposure	Reduced by localized delivery and controlled release
Dosing frequency	Often high due to rapid clearance	Reduced via sustained or depot formulations
Patient compliance	Moderate; affected by frequent dosing and side effects	Improved through reduced dosing and enhanced therapeutic outcomes

Classification of Novel Drug Delivery Systems (NDDS):

Novel Drug Delivery Systems encompass a diverse range of innovative platforms developed to address the limitations of conventional dosage forms. The classification of NDDS can be approached from various perspectives based on the carrier material (lipid-based, polymer-based), the route of administration (oral, transdermal, parenteral, pulmonary, ocular), or the delivery mechanism (controlled release, targeted delivery, stimuli-responsive release). Each system is designed with a specific goal, such as improving

solubility, enhancing bioavailability, achieving site-specific delivery, or providing controlled and sustained release of therapeutic agents. The following major categories highlight the technological diversity within NDDS.[19-22]

1. Lipid-Based Drug Delivery Systems

Lipid-based carriers such as liposomes, niosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are highly effective in improving the solubility of hydrophobic drugs and facilitating targeted delivery. Liposomes, composed of phospholipid bilayers, can encapsulate both hydrophilic and lipophilic drugs, offering biocompatibility and reduced systemic toxicity. Niosomes, formed from non-ionic surfactants, are chemically stable and cost-effective alternatives. SLNs and NLCs provide controlled drug release and physical stability, making them suitable for both systemic and topical delivery.

2. Polymeric Drug Delivery Systems

Polymeric carriers include polymeric nanoparticles, micelles, dendrimers, and nanogels, which utilize natural or synthetic polymers to encapsulate or conjugate drugs. Polymeric micelles enhance the solubility and stability of poorly soluble drugs, while dendrimers provide highly branched, nanoscale structures with modifiable surfaces for drug attachment or targeting ligands. Nanogels offer high water content, biodegradability, and responsiveness to environmental stimuli, making them ideal for localized delivery in cancer, inflammation, and ocular disorders.

3. Hybrid and Composite Systems

Hybrid drug delivery systems combine the advantages of lipid and polymeric carriers, resulting in lipid–polymer hybrid nanoparticles, nanocomposites, and bio-conjugated systems. These platforms provide superior stability, controlled release, and targeting capabilities. For instance, lipid–polymer hybrids use a polymeric core for sustained release and a lipid shell for biocompatibility and enhanced cellular uptake.

4. Targeted Drug Delivery Systems

Targeted systems utilize ligand-conjugated carriers, antibody–drug conjugates (ADCs), aptamer-based delivery, and magnetic nanoparticles to deliver drugs specifically to diseased cells or tissues. This strategy minimizes off-target toxicity and enhances therapeutic efficacy. Targeting can be achieved via active mechanisms (ligand–receptor interaction) or passive mechanisms (enhanced permeability and retention effect in tumors).[23-24]

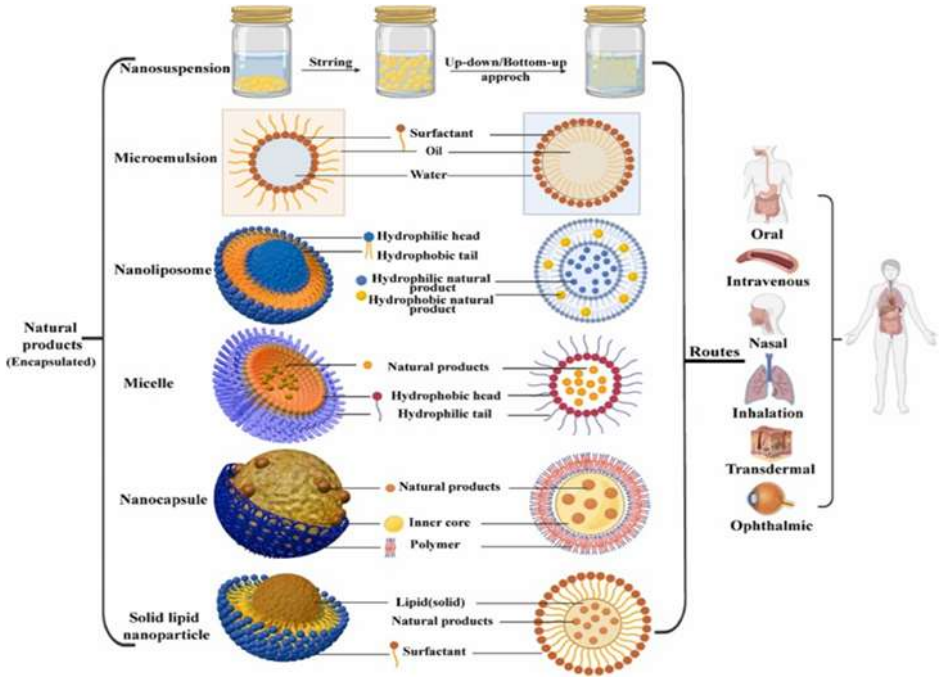

Figure 1: Various types of NDDS (e.g., liposomes, polymeric nanoparticles)

5. Stimuli-Responsive Drug Delivery Systems

These "smart" delivery systems release drugs in response to internal stimuli (pH, redox potential, enzymes) or external triggers (temperature, magnetic field, ultrasound, light). Examples include pH-sensitive nanocarriers for tumor-specific release and thermosensitive liposomes for hyperthermia-triggered delivery.[25-28]

6. Other NDDS Platforms

Several other innovative delivery systems include transdermal patches, gastroretentive floating systems, osmotic pumps, microneedles, and inhalable nanoparticles. These platforms enhance patient compliance, provide non-invasive administration routes, and enable localized drug action.

Table 2: Major Categories of Novel Drug Delivery Systems and Their Key Features

Category	Examples	Key Advantages	Applications
Lipid-based systems	Liposomes, niosomes, SLNs, NLCs	Improve solubility, biocompatible, controlled release	Cancer therapy, vaccines, antifungal delivery
Polymeric systems	Polymeric micelles, dendrimers, nanogels	Stability, tunable release, targeting potential	Anticancer, ocular, CNS drug delivery
Hybrid systems	Lipid–polymer hybrids, nanocomposites	Combined benefits of lipid and polymer systems	Gene therapy, sustained release injections
Targeted systems	Ligand-conjugated carriers, ADCs, aptamer systems	Site-specific delivery, reduced toxicity	Oncology, autoimmune diseases
Stimuli-responsive	pH-sensitive, thermo-responsive, enzyme-triggered	On-demand drug release, precision dosing	Tumor therapy, infection control
Other platforms	Transdermal patches, gastroretentive systems	Non-invasive, prolonged gastric retention, improved compliance	Pain management, antidiabetic therapy

Pharmacological Evaluation Parameters for Novel Drug Delivery Systems[29-48]

The successful design of a Novel Drug Delivery System (NDDS) must be supported by comprehensive pharmacological evaluation to confirm its therapeutic superiority over conventional formulations. Pharmacological evaluation is an integrated process combining in-vitro, ex-vivo, and in-vivo studies, aimed at assessing the safety, efficacy, and mechanism of action of the delivery system. These evaluations not only help in understanding the drug release kinetics and biodistribution but also form the basis for regulatory approvals and clinical translation.

NDDS often exhibit altered pharmacokinetic and pharmacodynamic behavior due to changes in drug solubility, stability, or targeting ability. Therefore, evaluation protocols must be tailored to account for the unique characteristics of the delivery system. Broadly, pharmacological evaluation can be divided into three major stages: *in-vitro*, *ex-vivo*, and *in-vivo* studies, often complemented by analytical and imaging techniques for better mechanistic insights.

In-vitro Pharmacological Evaluation

In-vitro testing serves as the first line of screening for NDDS, providing essential data on the formulation's fundamental characteristics before animal or human trials. Such studies simulate physiological conditions to evaluate drug release, permeability, stability, and cytotoxicity. By conducting these tests early in development, researchers can optimize formulation parameters and predict potential in-vivo performance with minimal resource expenditure.

1. Drug Release Studies

Drug release profiling is one of the most critical in-vitro evaluations, as it helps determine the rate and mechanism by which the drug exits the delivery system. This is typically conducted using USP dissolution apparatus, including Type I (basket method), Type II (paddle method), and modified Franz diffusion cells for semisolid formulations. The choice of apparatus depends on the dosage form and intended route of administration.

Mathematical modeling is employed to interpret release kinetics, with common models including Zero-order (constant release rate), First-order (release rate dependent on drug concentration), Higuchi model (release governed by diffusion), and Korsmeyer–Peppas equation (mechanistic modeling for polymeric systems). For targeted delivery systems, pH-dependent drug release studies are essential, simulating environments such as gastric (pH 1.2), intestinal (pH 6.8), and colonic (pH 7.4) conditions to ensure site-specific release.

2. Permeation and Absorption Studies

Permeation studies assess the ability of the drug to cross biological membranes, a crucial determinant of bioavailability. In NDDS research, Parallel Artificial Membrane Permeability Assay (PAMPA) and Caco-2 cell monolayer models are widely used for predicting intestinal absorption. For topical and transdermal formulations, the Franz diffusion cell setup is employed, using synthetic membranes or biological tissues to measure drug permeation rates. Such studies are essential in determining whether the enhanced solubility or encapsulation provided by NDDS translates into improved membrane transport.

3. Stability Testing

Stability testing ensures that the NDDS retains its intended physical, chemical, and therapeutic properties over time. This includes accelerated and real-time stability studies conducted according to ICH guidelines, where formulations are exposed to controlled variations in temperature, humidity, and light. Physical stability is evaluated by monitoring particle size, polydispersity index (PDI), and zeta potential, while chemical stability involves tracking drug degradation or loss of potency. Stability data are critical for determining storage conditions and shelf life.

4. Cytotoxicity and Biocompatibility

Safety at the cellular level is assessed through cytotoxicity assays. Commonly used tests include the MTT assay, which measures mitochondrial activity as an indicator of cell viability; the neutral red uptake assay, which evaluates lysosomal integrity; and the LDH release assay, which detects cell membrane damage. For NDDS intended for intravenous administration, hemolysis assays are performed to determine potential red blood cell damage. Collectively, these evaluations provide early indicators of formulation safety.

Ex-vivo Pharmacological Evaluation

Ex-vivo testing bridges the gap between controlled in-vitro conditions and the complexity of living systems. These studies use isolated tissues or organs to assess pharmacological responses in a setting that preserves natural physiological structures.

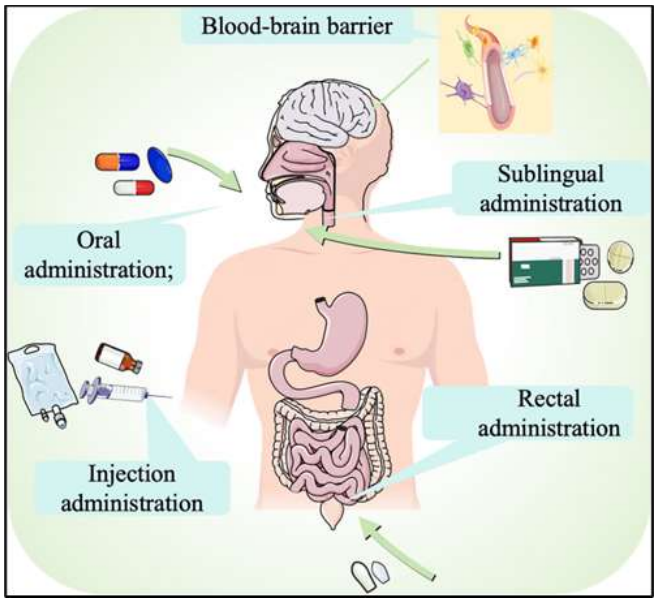

Figure 2: Blood–Brain Barrier with Traditional Drug Limitations

In-vivo Pharmacological Evaluation[49-58]

In-vivo studies remain the gold standard for evaluating the therapeutic performance, safety, and pharmacokinetic behavior of NDDS in a living organism. These experiments provide data on drug absorption, distribution, metabolism, and excretion (ADME), as well as on therapeutic efficacy and safety profiles.

1. Pharmacokinetics (PK)

Pharmacokinetic studies determine how the body handles the drug over time. Parameters such as Cmax (maximum plasma concentration), Tmax (time to reach Cmax), AUC (area under the curve), t½ (elimination half-life), clearance, and volume of distribution are calculated from plasma concentration-time profiles. These studies are

typically performed in small animals such as rats or rabbits before progressing to large animals like dogs or primates.

2. Pharmacodynamics (PD)

Pharmacodynamic evaluation measures the biological and therapeutic effects of NDDS. These studies often employ disease-specific models — for example, tumor regression in cancer models, glucose regulation in diabetic models, or seizure suppression in epilepsy models. Additional parameters, such as onset of action, intensity of response, and duration of effect, are also assessed to determine the clinical relevance of the delivery system.

3. Biodistribution Studies

Biodistribution analysis is crucial for confirming whether the NDDS successfully delivers the drug to the intended site while minimizing exposure to non-target tissues. This can be achieved through radiolabeling techniques (e.g., 99mTc, ^14C labeling) or fluorescent tagging, followed by quantification in harvested organs. Imaging technologies such as gamma scintigraphy and fluorescence microscopy enhance real-time tracking of drug localization.

4. Toxicity Assessments

Toxicological evaluation ensures the NDDS does not induce harmful effects. Acute toxicity studies involve administering a single high dose, whereas sub-chronic and chronic toxicity studies assess repeated dosing over extended periods. These assessments include histopathological examination of vital organs (liver, kidney, spleen, lungs) and hematological and biochemical analyses to detect systemic toxicity or organ damage.

Table 3: Overview of Pharmacological Evaluation Techniques for NDDS

Stage	Evaluation Parameter	Method/ Technique	Purpose
In-vitro	Drug release	USP dissolution apparatus, Franz diffusion	Determine release profile and kinetics
	Permeation	Caco-2, PAMPA	Predict intestinal absorption
	Stability	ICH stability protocols	Assess physical and chemical stability
	Cytotoxicity	MTT assay, hemolysis	Evaluate cell viability and biocompatibility
Ex-vivo	Permeation	Excised skin or mucosa	Predict in-vivo penetration
	Mucoadhesion	Detachment force measurement	Assess bioadhesive strength
In-vivo	Pharmacokinetics	Blood sampling, LC-MS/MS	Determine PK parameters
	Pharmacodynamics	Disease-specific animal models	Evaluate therapeutic efficacy
	Biodistribution	Radiolabeling, fluorescence imaging	Confirm targeting efficiency
	Toxicity	Acute/chronic studies, histopathology	Ensure safety and tolerability

Disease-Specific Pharmacological Evaluation Models for Novel Drug Delivery Systems (NDDS)[59-65]

The effectiveness of a Novel Drug Delivery System (NDDS) can only be truly established when it is tested in disease models that accurately reflect the complexity of human pathological conditions. These specialized models allow researchers to investigate not only how the system distributes the drug within the body (pharmacokinetics) and how it influences

biological responses (pharmacodynamics), but also how well it achieves site-specific targeting, sustains therapeutic benefits, and minimizes unwanted side effects.

1. Cancer Models

Cancer continues to be one of the most prominent fields for NDDS development, driven by the critical need to concentrate potent drugs within tumors while sparing healthy tissues. Tumor-bearing animal models are used to study the therapeutic efficacy and targeting capabilities of NDDS-based anticancer formulations. In xenograft models, human cancer cells are implanted into immunodeficient mice, enabling assessment of tumor suppression in a controlled environment. Syngeneic models, where tumors originate from mouse cell lines implanted into immunocompetent hosts, allow for simultaneous evaluation of immune responses. Orthotopic models involve placing tumor cells into the organ of origin, providing a more realistic simulation of metastasis and tumor microenvironment. Patient-derived xenografts (PDX), created by directly implanting patient tumor tissue into mice, offer the highest clinical relevance. Common evaluation endpoints include tumor volume reduction, histopathological changes, survival analysis, and imaging-based confirmation of targeted drug accumulation.

2. Cardiovascular Disease Models

NDDS aimed at cardiovascular therapy are designed to improve targeted drug delivery to the myocardium, vasculature, or ischemic zones while reducing systemic exposure. Myocardial infarction models, created by surgically occluding the left anterior descending (LAD) coronary artery in rodents or larger animals like pigs, replicate ischemic injury for testing cardioprotective formulations. Hypertension models, such as spontaneously hypertensive rats (SHR) or renal artery constriction-induced hypertension, allow evaluation of long-term blood pressure control by antihypertensive NDDS. Therapeutic success is measured by improved cardiac function via echocardiography, reduction in infarct size, stabilization of hemodynamic parameters, and attenuation of pathological remodeling.[66-70]

3. Neurological Disorder Models

Treating neurological diseases presents the formidable challenge of crossing the blood–brain barrier (BBB), making this an important focus in NDDS research. Alzheimer's disease models, such as transgenic mice expressing human amyloid precursor protein, are used to assess NDDS designed for plaque reduction and cognitive improvement. Parkinson's disease can be replicated in animals using neurotoxin-based approaches like 6-hydroxydopamine (6-OHDA) or MPTP, enabling evaluation of neuroprotective and dopaminergic therapies. Epilepsy models, including pentylenetetrazol (PTZ) and kainic acid-induced seizures, are used to test the anti-seizure potential of NDDS. Key measurements include drug penetration across the BBB, behavioral assessments, neurochemical profiling, and imaging-based mapping of drug distribution in brain tissues.[71-74]

4. Infectious Disease Models

Infectious disease models enable the testing of NDDS loaded with antimicrobial, antiviral, or antifungal agents under biologically relevant infection conditions. Bacterial infection models, such as methicillin-resistant *Staphylococcus aureus* (MRSA)-infected wounds or pneumonia models, help evaluate bacterial clearance and wound healing efficacy. Viral infection models, including influenza-infected ferrets or SARS-CoV-2-infected hamsters, allow for in vivo

antiviral testing. Fungal infection models, such as systemic *Candida albicans* infections in mice, are used to determine antifungal potency. Assessment parameters often include microbial load reduction, immune response markers, histological examination of infected tissues, and improvement in survival outcomes.

5. Metabolic Disorder Models

NDDS for metabolic disorders are designed to provide long-term, controlled delivery of drugs that regulate systemic metabolism. In diabetes research, streptozotocin (STZ)-induced Type 1 diabetes models and high-fat diet-induced Type 2 diabetes models are commonly used to test glucose-lowering NDDS. Obesity models, such as genetically modified *ob/ob* mice or diet-induced obesity in rodents, allow evaluation of anti-obesity agents. Success indicators include improved glycemic control, enhanced insulin sensitivity, reduction in body weight, normalization of lipid profiles, and favorable shifts in metabolic biomarkers.[75-80]

6. Inflammatory and Autoimmune Models

For inflammatory and autoimmune diseases, NDDS evaluation focuses on achieving localized drug delivery to inflamed tissues, reducing systemic drug burden, and minimizing immune-related toxicity. Arthritis models, such as collagen-induced arthritis in mice, provide a platform for testing anti-inflammatory formulations. Inflammatory bowel disease (IBD) models, induced by agents like dextran sulfate sodium (DSS) or trinitrobenzene sulfonic acid (TNBS), simulate chronic inflammation of the gut for evaluating colon-targeted NDDS. Outcomes are measured through macroscopic and microscopic inflammation scoring, cytokine level quantification, and histopathological analysis of tissue healing.

Table 4: Common Disease Models Used for Pharmacological Evaluation of NDDS

Diseases	Model Type	Purpose	Endpoints
Cancer	Xenograft, syngeneic, orthotopic, PDX	Tumor targeting and efficacy	Tumor regression, imaging
Cardiovascular	MI, hypertension models	Cardio-targeted NDDS assessment	Infarct size, cardiac function
Neurological	Alzheimer's, Parkinson's, epilepsy models	BBB penetration, neuroprotection	Behavioral, imaging
Infectious Diseases	MRSA, viral, fungal infection models	Anti-infective NDDS efficacy	Pathogen load, histology
Metabolic Disorders	Diabetes, obesity models	Controlled release and metabolic control	Glucose, insulin, weight
Inflammatory/ Autoimmune	Arthritis, IBD models	Targeted anti-inflammatory delivery	Cytokines, histology

CONCLUSION:

Novel Drug Delivery Systems have emerged as a cornerstone in the pursuit of more effective, safer, and patient-oriented therapeutic solutions. Through advancements in carrier design, targeting strategies, and pharmacological evaluation, NDDS offer the potential to revolutionize the treatment landscape across oncology, neurology, infectious diseases, cardiovascular disorders, and beyond. However, their full clinical potential can only be realized by addressing key barriers such as the inconsistency between preclinical and clinical results, manufacturing complexities, and concerns

over long-term safety and biocompatibility. A multidisciplinary approach that combines advanced material science, biomedical engineering, pharmacology, and regulatory science is essential for overcoming these challenges. The integration of artificial intelligence, real-time diagnostic feedback, and personalized delivery strategies represents the future trajectory of the field. With continued innovation and rigorous evaluation, NDDS stand poised to bridge the gap between bench-side innovation and bedside application, offering more precise, reliable, and impactful therapeutic options for patients worldwide.

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AUTHOR CONTRIBUTIONS: All authors have contributed equally.

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