RESEARCH PAPER

Innovative Drug Delivery Systems for Neurological Disorders: Pharmaceutical Design, Neuropharmacology, and Clinical Implications

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Abstract
Neurological diseases are an emergent health issue in the world, but effective treatment is hampered by the limited exposure of the brain, systemic toxicity, and the physiological limitation of the blood to the brain barrier (BBB). This review discusses the potential of neuropharmacological principles and pharmaceutical design methods (i.e. physicochemical optimization, prodrug and molecular modification, and formulation engineering) to increase CNS targeting and therapeutic efficacy. Current advances in drug delivery technologies are discussed, including nanotechnology-based platforms (polymeric, lipid-based, and inorganic/hybrid nanocarriers), biological and biomimetic systems (extracellular vesicles, cell-mediated delivery, and peptide/protein targeting), and non-invasive administration routes such as intranasal and microneedle-assisted delivery. Smart and advanced platforms, including stimuli-responsive systems, nucleic acid delivery vectors, multifunctional theranostic designs, and artificial intelligence–assisted formulation development, are highlighted as emerging strategies to improve spatial and temporal control of drug release. Clinical relevance is evaluated across neurodegenerative, neuropsychiatric, cerebrovascular, and neuro-oncological disorders, with emphasis on the increasing role of biomarkers and imaging endpoints in linking delivery performance to therapeutic outcomes. The main challenges of translation, such as lack of predictability of preclinical models over time, long-term safety, the complexity of regulations, and scalability of manufacturing are addressed in the framework of the clinical impact acceleration.

Keywords: blood–brain barrier, CNS drug delivery, nanocarriers, biomimetic delivery, theranostics

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1. Introduction

Neurological disorders constitute one of the largest and fastest-growing causes of morbidity, mortality and long-term disability all over the world. Recent epidemiological evaluations have shown that neurodegenerative diseases, stroke, epilepsy and neuropsychiatric disorders, along with other age and socioeconomic groups, have consistently accrued more burden than many other disease groups in years lived with disability. This increasing burden is not only a result of demographic changes like the ageing of the population but also an outcome of the higher survival rates increasing the duration and complexity of the diseases[1.] Widespread investigations of the Global Burden of Disease framework have also proven that neurological disorders have been experiencing a consistent rise in prevalence and absolute disease burden in recent decades, especially in low- and middle-income areas where access to effective treatments is still low[2]. In addition to clinical prevalence, the social and economic implications of neurological disorders prove the immediate necessity to develop more efficient therapeutic approaches that can enable one to deal with the heterogeneity and progression of the diseases. The translation of epidemiological evidence into productive policy and treatment innovation is one of the most significant issues facing health systems in the world[3].

In spite of progress in neuropharmacology, the traditional approaches to drug delivery have shown little success in the context of treating most of the central nervous system (CNS) disorders. Conventionally administered systemically tends to lead to sub-

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therapeutic drug levels in the brain and, at the same time, increase the probability of pathophysiological effects at the periphery. These constraints are especially acute with chronic neurological and neuropsychiatric disorders, which are treated by pharmacotherapy over a long period and demand a tight regulation of central effects[4]. Also, most molecules that have the potential to be administered therapeutically are unable to be developed because of insufficient brain penetration, suboptimal bioavailability, and unfavourable pharmacokinetics. Standardized formulations may fail to address biological obstacles or allow sustained and targeted delivery of drugs to particular brain areas, resulting in unpredictable clinical consequences and diminished treatment efficacy[5].

The blood-brain barrier (BBB) has been considered the most challenging barrier to effective drug delivery to the CNS. The BBB is composed structurally of closely interwoven endothelial cells, pericytes and astrocytic end-feet and is a strictly controlled process that allows the movement of molecules between the systemic circulation and the brain parenchyma. This is a highly selective barrier, though it is imperative in sustaining neural homeostasis; this block effectively limits the passage of most small-molecule drugs and almost all biologics. Newer experimental systems, such as microengineered BBB-on-a-chip systems, have put the dynamic and disease-modulated nature of BBB activity into the spotlight, making drug delivery solutions even more difficult. The results herein highlight the necessity of delivery systems capable of either non-covalently avoiding or selectively taking advantage of endogenous transport systems without destroying barrier integrity [6].

New systems of delivering drugs have been identified as an encouraging effort to deal with multifactorial issues that come with CNS therapeutics. The development of pharmaceutical sciences and nanotechnology has allowed the design of carriers that could enhance the drug solubility, stability, targeting precision, and controlled release in the brain. These systems have the potential to improve the therapeutic efficacy and reduce systemic toxicity and dose frequency[7]. However, nanoparticle-based delivery systems have demonstrated significant potential in enabling delivery to the brain via surface modification, receptor-mediated targeting and stimuli-responsive delivery methods. Their versatility in a large variety of neurological indications has been emphasized in recent studies, but there are still challenges in translation[8]. The use of specific delivery methods employing disease-specific pathophysiology alongside modern carrier design is a very important first move towards making neurological disorders a precision therapy[9,10].

This current review will focus on offering an overall and unified summary of the advances in the development of ingenious drug delivery systems in neurological conditions, with a special focus on the interaction between the design of a pharmaceutical, neuropharmacology, and clinical translation. This review aims at establishing the main advances made, the main challenges, and the future research directions by critically exploring the emerging delivery technologies and biological and regulatory factors. Especially, the focus is put on the approaches to increase the potential of translational and long-term clinical applicability, which will correspond to the increasing need for sustainable and patient-centred CNS therapeutic approaches.

2. Neuropharmacological and Pathophysiological Basis of CNS Drug Delivery

2.1 Neuroanatomical and Physiological Barriers to Drug Transport

The most sensitive nervous system is under protective measures of extremely specialized anatomical and physiological structures that control the nature of the exchange of molecules and maintain neural homeostasis. These barriers have a decisive role in the accessibility of drugs to central targets on a neuropharmacological basis. An arachnoid barrier, blood -brain barrier (BBB), blood -cerebral fluid barrier, and arachnoid barrier all help to limit the access of exogenous molecules, permitting only a few molecules to enter the brain parenchyma under highly regulated circumstances[11]. The BBB is the most restrictive interface of these. It consists of endothelial cells, which are linked together by sophisticated tight junctions, and are supported by pericytes and astrocytic end-feet, which restrict paracrine diffusion and regulate transcellular transport. This structural arrangement places very strict requirements on drug size, polarity, and lipophilicity, and this can seriously decrease the permeability of the majority of therapeutic agent[12].

2.2 Neuropharmacokinetics and Neuropharmacodynamics

Neuropharmacokinetics involves the mechanisms that regulate the absorption, distribution, metabolism and elimination of drugs in the CNS, and neuropharmacodynamics deals with drug target interactions and biological reactions. Unlike the peripheral tissues, the brain is highly regionally heterogeneous in blood flow, transporter distribution, and cellular composition, which results in spatially heterogeneous drug exposure and therapeutic properties[11]. Most recent methodological developments have greatly contributed to the knowledge of neuropharmacodynamic processes on a high-spatial resolution. Spatial mass spectrometry techniques have now enabled specific mapping of drug localization, metabolite formation and target engagement in different regions of the brain. Such understandings have enhanced the explanation of dose-response, and have demonstrated in hitherto unknown complexities of CNS drug action[13].

2.3 Disease-Induced Alterations in BBB and Brain Microenvironment

Pathological alterations that interfere with the integrity of the BBB and alter the microenvironment of the brain are often linked to neurological disorders. Tight junction

organization, alteration of transporter expression, and elevation of the barrier permeability can be damaged by neuroinflammatory processes, oxidative stress, and glial cell dysfunction. Inflammatory astrocytes, as evident in experimental models, have been shown to be key intermediates of BBB maladaptation, especially in neurodegenerative diseases like Parkinson[14]. Parallel to it, the remodeling of the extracellular matrix, which is disease-associated, the interstitial fluid dynamics, and the prolonged inflammatory signaling all affect the distribution and efficacy of the drugs in the CNS. These alterations might temporarily enhance drug penetration, but can also have the effect of augmenting off-target effects and neurotoxicity, making therapeutic optimization difficult[15].

2.4 Implications for Targeted CNS Therapy

A great challenge to the effective CNS drug delivery is posed by the combined effects of anatomical barriers, neuropharmacokinetic variability, and disease-induced pathophysiological changes. The therapeutic strategies should be in a position to attain sufficient brain exposure in both intact and compromised BBB conditions and with selective specificity to pathological targets[12]. Sensitivity to the factors of neuropharmacology and disease-specific modification, therefore, requires a mechanistic interpretation of the principles of rational design of present delivery systems. By matching the characteristics of drugs and formulating technologies to the changing conditions of the brain microenvironment, perhaps therapeutic efficacy, systemic toxicity, and the constraints of conventional CNS treatments can be improved[13].

3. Pharmaceutical Design Considerations for CNS Targeting

3.1 Physicochemical Properties Influencing Brain Penetration

The physicochemical properties of the drug molecules are the decisive factor in defining whether the drugs are able to reach their targets in the central nervous system. The parameters like molecular weight, lipophilicity, ionization state, and the ability to form hydrogen-bonds are directly related to passive diffusion across biological membranes and transporter systems. A CNS-optimized drug should have adequate lipophilicity to cross lipid-rich permeability barriers, and aqueous solubility to ensure systemic bioavailability and drug targeting of receptors[16]. These can be applied to carrier-based systems at the nanoscale, where particle size, surface charge and surface chemistry have a strong impact on cellular uptake and intracellular trafficking. These differences in properties may alter endocytosis pathways of uptake, thus altering the efficiency of drug release and treatment of neural tissues[17].

3.2 Prodrug and Molecular Modification Strategies

Strategies of prodrug and molecular modification have become common methodologies in trying to increase the CNS therapeutics penetration into the brain and to achieve a better pharmacokinetic profile. Modification of active compounds can be carried out structurally to temporarily hide undesired physicochemical characteristics, e.g. too high polarity, metabolism in vivo breakdown, etc., without affecting the therapeutic effect. After gaining access to the CNS, the active drug is enzymatically restored, and the active drug can then act site-specifically[18]. Such strategies enable reasonable optimization of drug candidates that would be unsuccessful otherwise because of a low BBB permeability or a short half-life. Combined with neuropharmacological knowledge, prodrug design is a potent approach to the matching of the molecular properties to CNS delivery needs.

3.3 Formulation Design and Controlled Release Approaches

Formulation design is also important in effecting successful CNS targeting as well as the molecular optimization. Sustained release systems are especially useful in the case of neurological conditions, in which a long-term treatment interval and constant drug concentration in the brain are essential. Complex formulations can eliminate the dosing schedule, decrease toxicity during peak, and enhance adherence to the medication. Alternative methods of drug administration, like intranasal administration, have been of growing interest in CNS drug delivery as they may avoid the BBB and deliver drugs straight to the brain. Nanoformulations for nasal delivery have shown increased drug stability, better brain delivery and lower systemic exposure, thus indicating their applicability in transducing the CNS in systemic delivery of drugs, which is formulation-driven[19].

3.4 Stability, Scalability, and Translational Design Principles

Although the potential of novel pharmaceutical designs holds a significant therapeutic potential, their translation capabilities are limited to stability, reproducibility and scalability. The formulations to be used in the CNS delivery should be physicochemically and biologically stable during the manufacturing, storage, and delivery period. Simultaneously, the concept of scalability is necessary to make sure that the innovations developed on a laboratory level can be consistently implemented on an industrial and regulatory level. Integration of scalability design consideration in the initial development is emerging as a requirement of successful clinical translation. Systems-level research teaches the need to balance experimental sophistication and realistic feasibility in order to facilitate the bridging of advanced CNS drug delivery systems between the bench and bedside[20]. The significant anatomical and physiological obstacles to brain drug delivery and the consequent limitations of pharmaceutical design that dictate effective CNS targeting are summed up in Figure 1. These are the essential pharmaceutical design factors that determine the brain penetration and CNS targeting efficacy (Table 1).

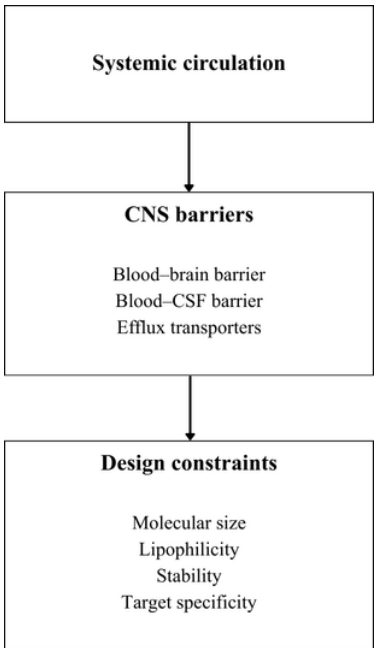

Figure 1. Central nervous system barriers and pharmaceutical design constraints influencing brain drug delivery

Table 1. Key pharmaceutical design parameters influencing CNS drug delivery

Design parameter	Role in CNS delivery	Impact on BBB penetration
Molecular weight	Influences diffusion	Lower MW favors penetration
Lipophilicity	Membrane interaction	Moderate lipophilicity optimal
Ionization state	Transport efficiency	Neutral molecules favored
Stability	In vivo persistence	Higher stability improves exposure
Target specificity	Receptor engagement	Enhances therapeutic index

4. Nanotechnology-Based Drug Delivery Systems

Drug delivery systems based on nanotechnology have become established as a foundation of new approaches to the targeting of the central nervous system (CNS), providing a solution to the long-term pharmacokinetic and biological challenges. These systems can be used to improve the solubility of drugs, prevent premature degradation, regulate drug release, and increase interactions with biological barriers by manipulating materials at the nanoscale. These properties render nanocarriers especially useful in neurological routes of application in which a refined spatial and temporal regulation of drug exposure is required[21].

4.1 Polymeric Nanoparticles for CNS Delivery

Polymeric nanoparticles (PNPs) are also among the best-investigated nanocarrier models in CNS drug delivery, because of their structural flexibility and modulable physicochemical characteristics. Polymers that are biodegradable can be designed to maximise the particle size, surface charge and functionalization, which in turn affect the circulation time, cellular uptake and brain penetration. These properties enable polymeric systems to be able to carry a broad spectrum of therapeutic agents, such as small molecules and biologics[22]. Notably, surface modification approaches, including ligand conjugation and stealth coating, have been utilized to improve the contact with brain endothelial cells and translocation across CNS barriers. This design flexibility makes polymeric nanoparticles a promising delivery platform for neurologically targeted therapy.

4.2 Lipid-Based Nanocarriers

Nanocarriers that are based on lipids such as liposomes, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have shown potential in the treatment of neurological disorders. The ease of interaction with cellular barriers and maximum drug encapsulation

ability is due to their biocompatible composition and structural similarity to biological membranes. These types of systems prove especially useful in enhancing the stability and bioavailability of lipophilic drugs that are to be delivered to the CNS[23]. Besides protecting the drug, lipid-based nanoformulations also allow controlled release of the drug and lower systemic toxicity. Their flexibility to surface alteration further promotes specific delivery plans, which further lead to better therapeutic outcomes in neurological models of disease.

4.3 Inorganic and Hybrid Nanocarriers

Another type of nanotechnology-based delivery systems with novel physicochemical and functional capabilities is inorganic and hybrid nanocarriers. The materials available include metal, silica, and composite nanoparticles, which have high structural stability, tunable surface chemistry and multifunctionality, including imaging and diagnostic properties. Hybrid systems (those using both organic and inorganic components) will be designed to be a combination of the beneficial qualities of each platform, allowing greater accuracy in their targeting and greater flexibility in their tuberculosis treatment options[24]. Although these systems have bright prospects of CNS applications, their complexity requires special optimization to have the balance between functionality, biocompatibility and safety.

4.4 Safety, Biodistribution, and Clinical Translation Challenges

Although they have a therapeutic potential, nanotechnology-based drug delivery systems are associated with serious safety, biodistribution and clinical translation issues. The accumulation of nanocarriers into the non-target organs, the possible long-term toxicity, and inconsistencies in biological reactions continue to be issues of concern. Such concerns especially pertain to chronic neurological illnesses that involve repeated or sustained medication[21]. Natural compounds like resveratrol have been investigated in nanocarrier systems to enhance neuroprotective effect besides reducing the toxicity. Nonetheless, the development of such nanoformulations into clinical applications needs to be evaluated in terms of pharmacokinetics, long-term safety, and compliance with the regulatory requirements. To overcome these obstacles, nanotechnology-based CNS therapies have to proceed from experimental studies to approved clinical treatments[25]. Figure 2 gives a simplified overview of the innovative drug delivery systems targeting the central nervous system, including nanotechnology-based delivery systems, biological and biomimetic systems and non-invasive delivery routes. Table 2 presents a comparative analysis of the key innovative CNS drug delivery platforms with their strengths and weaknesses.

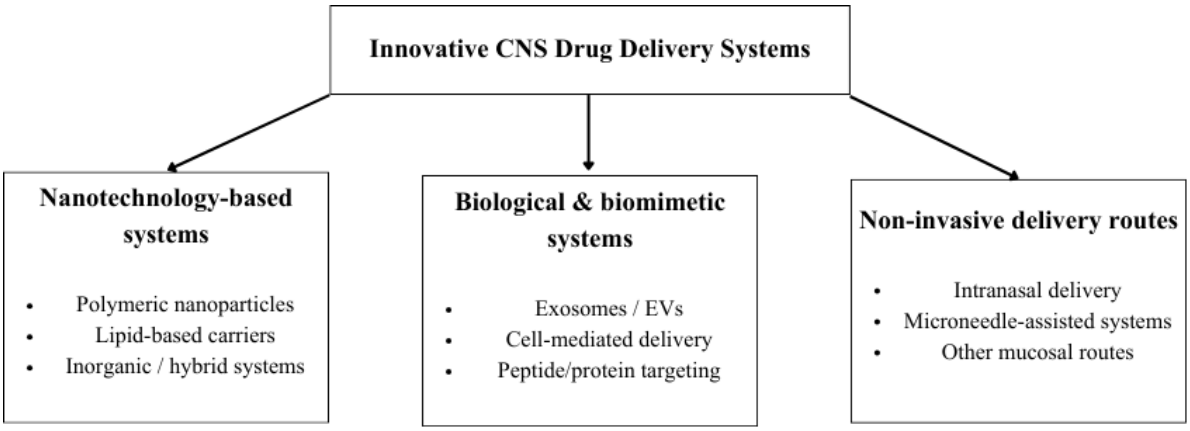

Figure 2. Classification of innovative drug delivery systems for central nervous system targeting

Table 2. Comparison of innovative CNS drug delivery systems

Delivery system	Representative examples	Key advantage	Major limitation
Polymeric nanoparticles	PLGA, chitosan	Tunable release	Scale-up challenges
Lipid-based carriers	Liposomes, SLNs, NLCs	High biocompatibility	Stability issues
Inorganic / hybrid systems	Gold, silica hybrids	Multifunctionality	Long-term safety
Exosomes / EVs	Cell-derived vesicles	Natural targeting	Manufacturing complexity
Intranasal delivery	Nanoformulations	BBB bypass	Limited dose volume

5. Biological and Biomimetic Drug Delivery Systems

Biological and biomimetic drug delivery systems seek to increase the selectivity of CNS targets, through exploitation of endogenous biological structures, or a bio-mimicking physiological interface to increase compatibility, circulation persistence and barrier evasion. Relative to completely synthetic carriers, biomimetic designs can be less focused on immune avoidance, longer systemic clearance and enhanced affinity to CNS transport pathways, all of which are specifically germane to chronic neurological diseases that demand sustained and safe exposure[26]. Examples of biomimetic platforms based on blood include the use of natural cellular properties (membrane composition and

native intrinsic trafficking patterns) to facilitate systemic stability and more efficient delivery to brain-associated pathological niches[27].

5.1 Exosome- and Extracellular Vesicle-Based Delivery

Extracellular vesicles (EVs) such as exosomes have attracted great attention as CNS delivery proteins due to their ability to act as natural intercellular messengers and their capability to deliver complex biological cargo. The shape of their lipid bilayer ensures that therapeutics within it are not degraded by enzymes, and they can enter the cell through pathways that resemble some biological communication routes. EV-based systems have been considered in the context of delivering small molecules, proteins and nucleic acids in the context of neurological diseases, and especially in regard to their capability of facilitating biologically-inspired targeting and minimizing non-specific systemic exposure[28].

5.2 Cell-Mediated Drug Delivery Strategies

Cell-mediated delivery involves the use of living cells in an active form as transporters, which may migrate, home to inflammatory signals or cross biological interfaces that generally inhibit diffusion of free drugs. These approaches are appealing in CNS disorders since pathological locations are frequently chemotactically stimulated and immunologically activated to be used to enhance local drug delivery. The present method focuses on the optimization of cargo loading, cell preservation and performance, as well as on the predictable behaviour of the trafficking to guarantee the predictable delivery result and reduce systemic toxicity[29].

5.3 Peptide- and Protein-Based Targeting Systems

Protein and peptide-based targeting techniques can be used to deliver to the CNS by taking advantage of molecular recognition and receptor-mediated interactions, thus providing a high level of specificity and the possibility of mechanism-based interaction with the BBB. The popularity of peptide engineering, protein stabilization systems and conjugation chemistry has increased the possibility of delivering bio-engineered products to the brain, including systems aimed at increasing transport, preserving the integrity of the nucleic acid, and improving intracellular delivery to neural cells. Such systems are more and more poised as the technologies that make possible therapeutics that localize their activities instead of exposing the entire tissue to treatment[30].

5.4 Advantages and Translational Limitations

Biological and biomimetic modes of delivery have had tempting advantages such as increased biocompatibility, reduced potential of disruptive BBB manipulation and increased disease-site selectivity. Nevertheless, translation is still limited by scaling manufacturing problems, variability between batches, consistency in cargo loading and quality-control needs of intricate biological supplies. To overcome these challenges, as well as the strong safety characterization and reproducible performance measures, will be necessary to adopt biomimetic CNS delivery technologies into clinical practice[30]. Table 3 summarizes key biological and biomimetic drug delivery strategies that can be used in CNS targeting

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Table 3. Biological and biomimetic drug delivery systems for CNS targeting

Delivery System	Biological Basis	Primary Advantage	Key Translational Challenge
Exosomes and extracellular vesicles	Native intercellular communication vesicles	High biocompatibility and protected cargo transport	Limited scalability and cargo loading control
Cell-mediated delivery systems	Active cell migration and homing mechanisms	Targeted accumulation at pathological CNS sites	Variability in cell behaviour and trafficking
Peptide-based targeting systems	Receptor-mediated BBB interactions	High specificity and mechanistic targeting	Enzymatic instability and short circulation time
Protein-based delivery systems	Molecular recognition and transport pathways	Enables delivery of biologics with precise engagement	Structural stability and manufacturing complexity

6. Non-Invasive and Alternative Routes for Brain Drug Delivery

These non-invasive and alternative methods of drug delivery have received growing interest as methods to bypass the restrictions that the blood-brain barrier may impose without exerting a lot of patient-related discomfort or posing a significant risk associated with the procedure. The strategies strive to improve brain exposure via physiological means that circumvent or take advantage of endogenous systems of transport and, thus, diminish the use of invasive methods of administration. The latest developments emphasise the increased variety of non-invasive techniques aimed at enhancing the efficiency of CNS drug delivery and treatment outcomes[31].

6.1 Intranasal Nose-to-Brain Drug Delivery

The intranasal drug delivery is one of the most widely studied non-invasive delivery methods of direct brain targeting. This path helps in the transportation of a drug between the nasal cavity and the CNS through olfactory and trigeminal nerve pathways, thus partially bypassing the BBB. Nasal delivery has shown specific potential for immediate drug delivery and lower systemic exposure, and applies to both acute and chronic neurological diseases[32]. The characteristics of the formulations,

mucociliary clearance, and enzyme activity in the nasal cavity are also the major determinants of the efficiency of delivery. To achieve the maximum therapeutic effect using this route, particle size, residence time, and formulation stability should therefore be optimized.

6.2 Transdermal and Microneedle-Assisted Delivery Systems

Another alternative system of delivering CNS drugs is through transdermal systems, especially when the use of microneedles are used in administering them. Microneedles make temporary microchannels in the skin, which allows transdermal absorption of therapeutics with no pain or tissue damage like traditional injections. New technologies (propulsion-assisted and structurally engineered microneedles) have also increased the efficiency and target potential of drug delivery [33]. These systems are especially appealing to patients with neurological diseases that need a long treatment period, as they facilitate better adherence and drug exposure. Their usefulness to target the brain is dependent, however, on systemic pharmacokinetics and CNS penetration.

6.3 Mucosal and Other Emerging Delivery Routes

In addition to nasal and transdermal, other mucosal delivery routes, such as buccal, sublingual, and ocular delivery, have been studied as CNS therapeutic delivery. Some of the benefits of these routes include ease of administration, circumvention of the first-pass metabolism, and possible rapid systemic absorption. The development of formulation design and carrier systems has increased the viability of these alternative pathways to brain targeting, albeit with significant differences in their level of translational maturity[34]. New approaches are still exploring the potential to use physiological and anatomical aspects of these pathways to enhance CNS drug exposure with safety and reproducibility.

6.4 Comparative Evaluation of Alternative Routes

There are numerous factors that affect the effectiveness of non-invasive delivery routes to brain targeting, such as brain morphology, regional blood flow, species-specific anatomy and drug physicochemical properties. Comparative studies have shown that no one route can be considered the best; the choice of route should be determined by therapeutic objectives, pathology of the disease, and pharmacokinetic needs[35]. There is a need, then, to carry out a systematic assessment of the other potential routes of delivery in order to inform rational design of formulation and enhance translational performance. The combination of anatomical, physiological, and pharmacological factors will be used to develop the best non-invasive methods of CNS drug delivery.

7. Smart and Advanced Drug Delivery Platforms

Intelligent and sophisticated drug delivery systems are a paradigm shift in CNS therapeutics that has gone beyond passive drug delivery to have systems that can precisely target, control release and functional integration to make real-time. The platforms are capable of responding to microenvironmental indications as well as therapeutic needs that are disease-specific to allow better spatial and temporal regulation of drug activity. These features can be especially useful in complicated CNS disease conditions, in which heterogeneous tissue microenvironment and dynamic disease pathogenesis constrain the efficiency of standard delivery strategies[36].

7.1 Stimuli-Responsive and Disease-Triggered Systems

One of the applications of stimuli-responsive drug delivery systems is to deliver therapeutic payloads in response to particular internal or external stimuli related to pathological events. These triggers can be the changes in pH, enzyme activity, oxidative stress, or metabolic distortions, in the context of CNS disorders. These systems improve local levels of drug concentration at the target site by linking drug release to disease-related signals and reducing systemic exposure and off-target effects. Different kinds of smart delivery designs that take advantage of pathological brain environments have demonstrated specific potential in the treatment of brain tumours, where successful and controlled drug delivery can greatly enhance the delivery of therapy[36]. PH-sensitive delivery systems, which are among other mechanisms in response to stimuli, have gained much attention because of their capability to detect local biochemical variations. Even though it was first created to be used in other fields, the development of pH-responsive carrier design has yielded useful information that can be applied to CNS drug delivery, indicating its flexibility and possible controlled release in disease-specific microenvironments[37].

7.2 Gene and Nucleic Acid Delivery Approaches

Gene and nucleic acid–based therapeutics promise game-changing potential in the cure of neurological disease as they enable direct manipulation of molecular pathways that drive diseases. Nonetheless, they can be limited in their clinical translation by rapid degradation and poor uptake by cells, as well as the capacity to penetrate CNS barriers. The highest order delivery vectors have thus been produced to secure nucleic acid cargo and to be delivered specifically to neural cells and tissues[38]. These delivery systems aim to balance stability, to achieve efficiency, and to achieve safety so as to effectively express or silence the gene(s) and have minimal immunogenicity and off-target effects. These are key considerations to apply nucleic acid therapeutics to CNS diseases.

7.3 Multifunctional and Theranostic Platforms

The multifunctional drug delivery systems combine therapeutic, diagnostic, and imaging functions into a combined platform that allows monitoring and treatment of CNS disorders simultaneously. These theranostic platforms fill a major gap in the traditional CNS therapeutic approaches as they enable real-time

monitoring of drug delivery, target interaction, and therapeutic feedback. Nanoplatforms made of polymeric materials that include imaging agents and therapeutic payloads have shown a lot of promise in enhancing the diagnostic accuracy and treatment control of brain diseases[39]. Multifunctional delivery systems allow promoting precision medicine in the neurology field by providing adaptive and individually tailored treatment plans.

7.4 Role of Artificial Intelligence in CNS Drug Delivery Design

AI has become an effective facilitator in smart CNS drug delivery platform design and optimization. Complex datasets of drug properties, carrier characteristics, biological barriers, and disease pathology can be combined to inform the formulation design and targeting approaches with the help of AI-driven models. These techniques facilitate prediction of the brain penetration and response to therapy, advance the development schedule, and enhance translational success[40]. AI, in conjunction with sophisticated delivery technologies, is an essential milestone towards personalised and data-informed CNS therapeutics.

8. Clinical Applications in Neurological Disorders

New drug delivery technologies are rapidly showing clinical applicability in a broad spectrum of neurological diseases through enhanced brain targeting, therapeutic selectivity and outcome monitoring. When treating neurodegenerative diseases, more advanced delivery systems can be used to help sustain and localise drug exposure and minimize systemic toxicity. Neurofilaments are examples of biomarkers, which have been found significant in clinical practice as a marker of injury and disease progression of the neuron to assist in the better evaluation of therapeutic response in these disease[41].

The use of CNS-targeted drug delivery systems is also supported clinically by the development of the science of delivery that improves drug penetration and distribution, as well as target accessibility into the brain. The advancements have expanded the therapeutic range of new delivery platforms in a variety of neurological indications, overcoming long-standing issues in pharmacokinetic and biological domains[42].

In neuropsychiatric disorders and neurological disorders, where molecular and functional mechanisms interact with each other, enhanced CNS drug delivery has helped to enhance pharmacological control and minimise anomalies at the periphery, especially with the consideration of long-term treatment[43]. There is added complexity in cerebrovascular diseases and brain tumours related to the aspects of the dynamic pathological conditions and changes in vascular integrity. In such circumstances, the targeted delivery strategies should maximise the concentration of drugs locally and ensure safety, particularly in patients who have malignancy-related cerebrovascular complications[44].

Imaging-based biomarkers have become a critical part of the assessment of clinical outcomes to track drug distribution, therapeutic effect, and disease development. Such imaging tools are critical in neuro-oncology as they are important to inform treatment decisions, evaluate response to novel methods of advanced drug delivery systems, and further permit translation of novel methods of delivery of CNS drug therapies to the clinic[45]. Figure 3 represents the general translational route of CNS drug delivery systems, which consists of the design of forms and carriers and the clinical use and implementation. Table 4 summarizes the clinical use of the developed CNS delivery systems, the large neurological indications, and the accompanying challenges in translational applications.

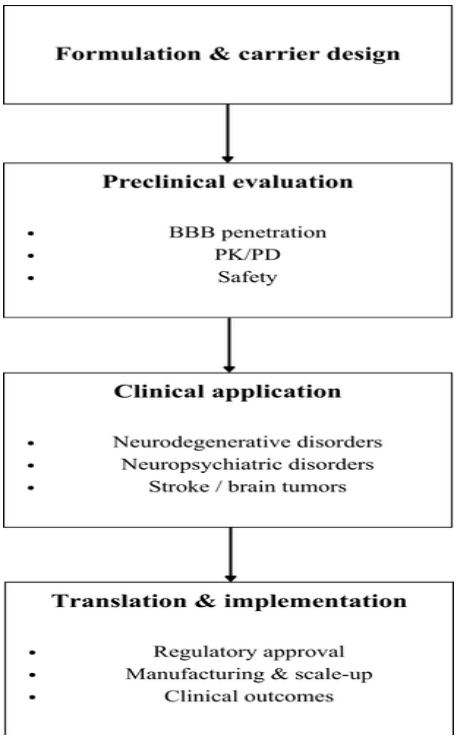

Figure 3. Translational pathway of CNS drug delivery systems from formulation design to clinical implementation

Table 4. Clinical applications and translational considerations of CNS drug delivery systems

Neurological indication	Delivery strategy	Clinical objective	Translational challenge
Neurodegenerative disorders	Nanocarriers, EVs	Sustained delivery	Long-term safety
Neuropsychiatric disorders	Targeted formulations	Reduced side effects	Variable response
Stroke	Rapid delivery systems	Acute intervention	Timing constraints
Brain tumors	Targeted nanocarriers	Localized therapy	Regulatory complexity

9. Clinical Translation, Regulatory, and Safety Challenges

Although technologies of CNS drug delivery have improved, scientific and regulatory challenges limit their implementation in the clinic. The pharmacokinetics in the human brain, the complexity of the disease and the long-term therapeutic effects are not well predicted in preclinical models, and this has added to the high rate of attrition in the development of neurological drugs. The clinical progress is also complicated by safety issues such as chronic toxicity, immunogenicity, and accumulation of advanced delivery systems off-target, which also require extensive, intense testing[46].

The CNS drug delivery systems have been put under a tight spot with the regulatory approval because they are multidisciplinary in nature and need a thorough characterization of their formulation performance, neurological safety, and manufacturing consistency. Simultaneously, the scale-up and quality control of complicated delivery platforms require the presence of strong and repeatable processes to fulfil regulatory requirements and enable clinical adoption[47].

In the future, it is hoped that further development will be made of more predictive human-relevant models, coordinated regulatory frameworks based on advanced delivery technologies, and an early focus on integrating manufacturability into formulation design. This can be further facilitated by the adoption of standardized evaluation criteria and risk-based regulatory strategies, which can speed up clinical translation. These issues must be tackled in advance to bridge the gap between innovation and clinical effect in drug delivery in the CNS.

10. Conclusion

The clinical and societal burden caused by neurological disorders is ever-increasing, but effective CNS therapy is hampered by constraining brain barriers, nonhomogeneous disease pathology, and nonhomogeneous target response. Here, the review sheds light on how neuropharmacological understanding has been incorporated with pharmaceutical design to pursue more rational targeting of the CNS by way of physicochemical optimisation, prodrug design and formulation to enhance stability and exposure. Improvements in nanotechnology (polymeric, lipid-based, and hybrid systems), bio-mimetic systems (extracellular vesicles, cell-mediated carriers and peptide/protein targeting), and non-invasive delivery (particularly intranasal and microneedle-based) broaden the arsenal of improving brain delivery in an effort to minimize systemic toxicity. The use of smart platforms and AI-directed design also enhances accuracy by facilitating responsive release, as well as enhanced

targeting reasons. Notably, novel clinical practices are increasingly based on biomarker-and imaging-guided assessment in order to correlate delivery performance and significant therapeutic outcomes. In general, the discipline is shifting toward proof-of-concept delivery to more clinically anchored approaches that are focused on reproducibility, safety and provable benefit in patients.

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