RESEARCH PAPER

Development and Characterization of Propylene Imine-Loaded Convolvuline Dendrosomes for the Management of Neurodegenerative Diseases: A Comprehensive Review

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Abstract
Neurodegenerative diseases are gradually developing diseases of progressive loss of structure and function of neurons; due to the complex and multifaceted pathophysiology of neurodegenerative diseases, there is a great challenge in their therapeutic management. Pathological mechanisms associated with these diseases include abnormalities in protein aggregation, impaired autophagy, apoptosis of neurons, oxidative stress, mitochondrial dysfunction, and neuroinflammation in Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis [2,3,5,8]. The progression of these disorders is also complicated by the presence of the blood–brain barrier (BBB) in this case, which has the capacity to rigorously control the movement of molecules across the barrier and can restrict the delivery of a large number of therapeutic agents [1,4,7,14]. In this context, the development of efficient drug delivery devices towards the brain has become a key research direction in the fields of pharmaceutical and nanomedicine.
The highly-branched nanoscale macromolecules called dendrimers have gained significant research interest as drug delivery systems due to their well-defined structure, surface functionality, internal cavities useful for accommodating drug molecules, the ability to conjugate and decorate their surface, and the ability to self-assemble into distinct particles [21-24]. The terminal functional groups enable the chemical modification of PPI dendrimers, and the nanoscale structure can be tailored to develop approaches in drug delivery and targeting, which makes them very interesting for neurological applications [23,29]. Recent research has shown that surface-functionalized PPI dendrimers can enhance their delivery into the brain and their cellular uptake, while retaining some of the advantages concerning the highly cationic dendritic systems [31,32]. The use of a natural product payload is a further objective that can be investigated in this platform, and convolvuline, a compound found in Convolvulus species, could be a potential natural product payload since experimental evidence for the use of a convolvuline-loaded PPI dendrosome remains to be established [33].
In the present review, the pathological basis of neurodegenerative diseases, the role of the BBB in restricting the entry of drugs into the CNS, structural and pharmaceutical properties of dendrimers and PPI dendrimers are discussed, and the rationale behind the development of propylene imine-loaded convolvuline dendrosomes is discussed at last. In particular, formulation development and characterization, particle size, PDI, zeta potential, Cellular uptake, BBB transport, biological safety, morphology, drug-loading, entrapment efficiency, and in vitro release of the drug are given special mention. The review also analyzes existing evidence for the feasibility of dendrimer-mediated CNS delivery, significant research gaps, and future directions that need to be explored to improve the usage of PPI-based dendrosomal systems. Taking all this into consideration, propylene imine-loaded convolvuline dendrosomes are a new, interesting research idea to improve brain targeting, but more systematic disease-appropriate, pharmaceutical, pharmacokinetic, and toxicological studies are required to confirm their therapeutic applications.

Keywords: Neurodegenerative diseases; propylene imine; poly(propylene imine); dendrimers; dendrosomes; convolvuline; nanocarriers; blood–brain barrier; CNS drug delivery; Alzheimer's disease; Parkinson's disease.
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1. Introduction

Neurodegenerative diseases are a heterogeneous group of chronic, increasingly progressive disorders in which selective neuronal dysfunction, degeneration, and ultimately neuronal loss occur. The most significant neurodegenerative diseases with significant impacts on cognition, movement, behaviour, independence and quality of life include Alzheimer's Disease (AD),

Parkinson's Disease (PD), Huntington's disease (HD) and Amyotrophic lateral sclerosis (ALS) [2,3]. While the clinical symptoms and pathological target organs are variable, a number of common biological mechanisms have been implicated in the injury to the neurons, such as oxidative stress, mitochondrial dysfunction, neuroinflammation, abnormal protein folding and aggregation, excitotoxicity, impaired intracellular trafficking and apoptosis [2,3,5]. Multiple pathological mechanisms involved in the disease make disease-modifying treatment particularly challenging.

Traditional pharmacological interventions have yielded significant symptomatic results, but have often been hampered by poor pharmacokinetics, undesirable side effects, poor solubility, and inadequate tissue distribution or level of drug activity at the site of neuronal disease [2,5,8]. The brain is largely protected from the blood, which is a very important consideration for CNS pharmacotherapy. The BBB is a highly selective neurovascular interface consisting of specialized endothelial cells aggregating together at the tight junctions and surrounded by pericytes, astrocytes, basement membranes, and associated cellular structures [4,7,11]. It has a primary physiological role of maintaining a stable environment for neuronal activity, but these same limiting properties make it one of the most significant challenges for pharmaceutical delivery to the brain [1,4,7].

The BBB inhibits paracellular diffusion and controls transcellular transport by specific transporters and receptor-mediated mechanisms. As a result, many drugs with in vitro activity turn out to be unable to obtain therapeutically relevant levels in the brain when administered systemically [1,7,14]. Research over the last few years has thus focused on methods that can alter the pharmacokinetic and physicochemical properties of therapeutic compounds, rather than just the administered dosage [5,11].

One of the most widely explored approaches to solve this challenge is nanotechnology. Nanocarriers may thus be able to enhance the dispersion of poorly water-soluble compounds in aqueous media, to prevent/delay degradation of the active molecules, to modulate circulation time, and to enhance cellular uptake and deliver a controlled drug release [14,17]. Importantly, the surface of nanocarriers can be chemically modified to target special receptors on the BBB or biological transport pathways [1,7]. It has been recently reviewed that dendrimer-based nanocarriers are especially interesting due to their highly branched structure, which allows for relatively precise control of the particle size, surface chemistry, and loading with molecules [1].

Dendrimers are three-dimensional, highly branched macromolecules consisting of a central core, repeated branching units, and a multifunctional external surface [21–24]. Their structure offers multiple possibilities to incorporate therapeutic molecules into internal domains or to graft drugs and targeting molecules onto the surface [22, 23]. The properties of dendrimers have stimulated a great deal of research in the fields of drug delivery, imaging, gene therapy, and multifunctional nanomedicine [21-24].

Poly(propylene imine) dendrimers are an interesting family of dendrimers for CNS applications. The highly branched propylene-imine backbone of PPI dendrimers, together with their numerous end amino groups, makes them an extremely functional surface for chemical modification [23,29]. Although the surface charge is positive, it can participate in interactions with the negatively charged biological membranes; however, the excess of the positive charge can also be a cytotoxic factor [23,27]. Thus, surface modification to achieve a balance between cell interaction, BBB transport, and biological safety is an increasing trend in contemporary PPI studies [1,31].

The proposed formulation is supported by recent evidence. Sahu et al. produced an oleic-acid-conjugated PPI G5 dendrimer for the targeted delivery of tacrine hydrochloride and successfully conjugated the drug, loaded it onto the dendrimer, had it taken up by cells, and performed a preliminary safety evaluation [31]. In another study, maltose and histidine were attached to PPI to provide improved biocompatibility and BBB-related delivery characteristics, highlighting the value of surface engineering in the design of PPI-based CNS systems [32]. The results indicate a possible alternative use of PPI dendrimers beyond passive drug delivery to the brain to facilitate the delivery of therapeutic compounds.

Natural products are another important research area in the pharmaceutical industry since plants are the source of structurally diverse molecules with potentially useful biological activities. Various phytochemicals such as flavonoids, alkaloids, phenolic compounds, carbohydrates, terpenes, sterols, tannins, and other constituents with reported pharmacological activities have been identified in the Convolvulus species [33]. However, therapeutic efficacy is not an inherent property of natural origin. The potential for a single compound to be a pharmaceutical agent is determined by the identity, purity, stability, solubility, bioavailability, pharmacokinetics, and toxicity of the compound, as well as the ability to reach the biological target [33].

The formulation of a propylene imine-loaded convolvuline dendrosomal system could thus be considered an attempt to merge a bioactive component of natural origin with a highly polyfunctional nanocarrier. The basic concept is that the incorporation

of convolvuline into a dendrosomal system may enhance the physicochemical stability and delivery properties of the compound and may provide possibilities for controlled release and surface modification for CNS targeting. It is important to note, however, that the evidence presented for using dendrimers and PPI systems for delivery to the CNS should not be interpreted as evidence that PPI dendrosomes containing convolvuline have already been proven to be therapeutic. The latter should be considered as a new formulation concept as of today that needs systematic experimental study.

This distinction is reiterated by the recent literature. In 2025, Bharadwaj, Roullin, and Chain's review showed that PPI is one of the important dendrimer classes studied for BBB delivery and highlighted the importance of PEGylation, ligand conjugation, and biomimetic surface engineering to increase BBB permeability and biocompatibility [1]. Likewise, recent reviews have pointed out the neurological drug delivery potential, while toxicity, elimination, manufacturing, and BBB heterogeneity for different diseases are highlighted as major translational challenges [2,8]. Therefore, the preparation of convolvuline-loaded PPI dendrosomes has a multidisciplinary character, which includes nanotechnology, pharmaceutical characterization, neurosciences, and pharmacokinetics and toxicity.

This review is therefore aimed at critically revisiting the scientific basis and the development strategy of the propylene imine-loaded convolvuline dendrosomes in the management of neurodegenerative diseases. The focus is particularly on the link between neurodegenerative pathology, BBB limitations, dendrimer architecture, PPI surface chemistry, drug loading, physicochemical characterization, release behaviour, cellular uptake, BBB transport, and therapeutic evaluation.

2. Neurodegenerative Diseases: Pathophysiology and Therapeutic Challenges

2.1 Alzheimer’s Disease

Alzheimer's disease (AD) is the most common form of dementia, evidenced by progressive loss of memory, cognition, behaviour, and functional ability. It is a multifactorial process with accumulation of abnormal amyloid-β (Aβ), hyperphosphorylation of tau protein, synaptic dysfunction, oxidative stress, neuroinflammation, mitochondrial impairment, and progressive neuronal loss [2,3,5]. Accumulated Aβ has been shown to cause damage to synapses and trigger inflammatory responses, and abnormal aggregation of tau causes disruption of neuronal structure and transport [3,15]. Microglia and astrocytes, when chronically activated, also mediate damage to neurons by releasing inflammatory mediators and by oxidizing them [15,28].

The treatment of AD is a challenge because it is mostly symptom management for the disease process and may not be able to alter the underlying disease process [2,5]. Furthermore, the blood–brain barrier (BBB) has the ability to block the passage of many therapeutic agents into the brain, resulting in consequently low concentrations at the site of pathology [1,4,7]. Dendrimer-based systems might offer a solution to this limitation because of their nanoscale size, which enables the ability to package the drug, achieve a controlled release, and modify the surface for better brain delivery [21-24]. Dendrimers have also been shown to have anti-inflammatory and anti-amyloidogenic properties, relevant to the multifactorial nature of the AD pathology. Based on this, the use of a PPI dendrosomal system for delivery to the brain with a sustained release of a bioactive compound could be a viable alternative, though its anti-Alzheimer's activity needs to be validated experimentally.

2.2 Parkinson’s Disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that is mainly characterised by the degeneration of dopaminergic neurons in the substantia nigra and disruption of dopamine signalling [2,12]. The primary motor features are bradykinesia, rigidity, resting tremor, and postural instability, and cognitive, psychiatric, autonomic, and sleep-related symptoms can also be seen [12]. PD is characterized by a lack of dopamine, as well as oxidative stress, mitochondrial dysfunction, neuroinflammation, impaired protein clearance, and α-synuclein aggregation [3,12,28].

While dopamine replacement is still an important part of PD treatment, traditional PD treatment carries with it pharmacokinetic challenges, shifts in response to therapy, and potential adverse effects over time [12]. Moreover, there is no definite evidence that symptomatic therapy can stop progressive neuronal deterioration. Nanocarrier systems have thus gained interest as a means of stabilizing drugs, and extend the drug exposure, and increase its delivery to the CNS [6,12].

One promising feature of dendrimers is their highly branched structure, which allows for the internal incorporation of drugs and multiple surface functionalization or targeting groups [21-24]. The ligands of the dendrimer can be modified with suitable ligands or hydrophilic groups in order to enhance biocompatibility and the interaction with the BBB [1,29,31]. Based on this, a possible approach to enhancing the delivery of neuroprotective compounds in PD may be to use convolvulin-loaded PPI dendrosomes. The potential benefits of such a formulation for enhancing neuronal uptake, lowering oxidative stress and inflammation, and ultimately

protecting dopaminergic neurons need to be determined in further studies.

2.3 Huntington's Disease

Huntington's disease (HD) is an inherited disorder of the central nervous system that is caused by an increase in the number of CAG repeats in the HTT gene, causing the production of mutant huntingtin protein [3]. The disease presents with progressive motor impairments, mental changes, and psychiatric symptoms. Mutant huntingtin disrupts the normal function of multiple cellular processes such as mitochondrial function, transcription, intracellular transport, protein degradation, and synaptic activity [3]. Neuronal dysfunction is further exacerbated by oxidative stress, neuroinflammation, and abnormal protein aggregation.

However, the genetic nature of HD has opened up a new interest in advanced therapeutic approaches such as nucleic acid-based therapies, aimed at preventing the expression of the mutant huntingtin. In the brain, on the other hand, delivery of such therapeutic molecules is still challenging due to their size, instability, and limited BBB permeability [7,11,14]. The multifunctional surfaces of dendrimers could be useful as a delivery platform, as they can be modified to facilitate cellular uptake and could interact with therapeutic molecules [22,23]. PPI dendrimers, in particular, offer a great number of functional groups to attach drugs or ligands, but due to their cationic nature, this needs to be carefully optimized to ensure low toxicity [23,27]. Direct evidence for the use of convolvuline-PPI therapy for HD is still scant, and the dendrosomal approach could represent a future platform to achieve the delivery of a neuroprotective agent if its efficacy against the pathological mechanisms involved in HD is proven.

2.4 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by degeneration of upper motor neurons and lower motor neurons leading to muscle weakness, abnormal motor function, dysphagia and respiratory dysfunction [2,3]. It has several mechanisms of pathogenesis such as oxidative stress, mitochondrial dysfunction, protein misfolding and aggregation, excitotoxicity, impaired axonal transport, and neuroinflammation [3]. All these mechanisms interact to promote the progressive damage to motor neurons and limit the development of effective disease-modifying therapies.

Novel drug delivery approaches that can enhance drug stability, CNS exposure, and cellular targeting are needed, due to the limited therapeutic options available for ALS [7,11]. Dendrimers could be used due to their ability to encapsulate or conjugate therapeutic molecules, and their surface can be modified to enhance biological distribution [21-24]. PPI-based systems are especially appealing due to their surfaces being functionalized for targeting and for controlled drug delivery; however, with highly cationic surfaces, toxicity needs to be carefully evaluated [23,27,31]. In this context, the possibility of using PPI dendrosomes loaded with convolvuline as a potential delivery platform for neuroprotection could be explored. Their therapeutic impact in ALS, however, would need to be confirmed by disease-specific cell and animal studies that assess oxidative stress, inflammation, motor-neuron survival, pharmacokinetics, and functional outcome.

In general, there are common pathological mechanisms for all three diseases (AD, PD, and HD), such as oxidative stress, neuroinflammation, mitochondrial dysfunction, and progressive neuronal loss, as well as common problems such as the inability to deliver drugs across the BBB [1–5,7]. The common features give a justification to explore multifunctional nanocarriers like PPI dendrosomes for the delivery of drugs to the CNS.

Table 1. Major pathological mechanisms in neurodegenerative diseases and their relevance to nanotherapeutic delivery

Pathological mechanism	**Major consequence**	**Potential relevance of dendrosomal delivery**
Oxidative stress	Lipid, protein, and DNA damage	Delivery of compounds with antioxidant potential
Neuroinflammation	Chronic neuronal injury	Delivery of anti-inflammatory or neuroprotective agents
Mitochondrial dysfunction	Reduced ATP and increased ROS	Intracellular delivery of protective compounds

Protein aggregation	Synaptic and cellular dysfunction	Potential delivery of anti-aggregation agents
Excitotoxicity	Excessive neuronal stimulation	Controlled delivery of neuroprotective agents
Apoptosis	Progressive neuronal loss	Sustained therapeutic exposure
BBB dysfunction	Reduced drug access to the brain	Targeted nanoscale transport

3. Blood–Brain Barrier and Nanocarrier-Mediated CNS Delivery

The BBB is a special type of physiological barrier that tightly regulates the molecular traffic between systemic circulation and the brain parenchyma. The endothelial cells have low paracellular permeability due to the presence of extensive tight junctions, and transport proteins control the movement of nutrients and other endogenous molecules [4,7]. Intracellular levels of xenobiotics and therapeutic drugs can also be lowered by efflux transporters [5,14].

While this is a widely accepted view of the BBB as a barrier, this is a very simple one. The BBB is a dynamic transport interface that includes receptor-mediated, carrier-mediated, and adsorptive mechanisms that can be taken advantage of for drug delivery [1,7]. These mechanisms can be addressed by modifying the size, surface charge, hydrophilicity, and the density of the ligand on the nanocarriers [1,17].

The dendrimer architecture is ideally suited for such engineering, as many terminal groups can be modified without changing the internal dendrimer architecture [21-24]. Surface ligands can be carbohydrates, peptides, antibodies, lipids, or any other molecule that binds to the endothelial transport mechanisms [1,17]. The terminal amino groups offer many chemical sites that can be used for the functionalization of PPI dendrimers, which makes them particularly attractive. A single application of transferrin-functionalized PPI dendrimers will be illustrated. Demeule and coworkers examined polypropylenimine dendrimers functionalized with transferrin and showed the feasibility of this approach for delivery to the brain [29]. The rationale was based on receptor-mediated transport, which occurs at the BBB mediated by transferrin receptors. Lipid-based targeting strategies have been used more recently. Sahu et al. also developed a system that was used for the targeted delivery of tacrine to the brain after functionalizing the dendrimer PPI G5 with oleic acid [31]. The study proved that the PPI surface modification could be integrated with a full characterization of the formulation, drug loading, safety evaluation, and cell internalization strategy [31].

Thus, the most recent development indicates that rather than utilizing the intrinsic properties of an unmodified dendrimer, multifunctional surface engineering is likely to be the more promising tack to take [1]. Any nonspecific interactions can be minimized, and the colloidal behaviour can be enhanced with PEGylation, and targeting ligands may enhance interaction with specific BBB transport pathways. Immune recognition may be further decreased and biodistribution modified by biomimetic coatings [1].

However, penetration into the BBB does not necessarily mean therapeutic targeting. Proving a nanoparticle can get into brain tissue is just the beginning. It is also important to establish if the active compound is liberated in the brain, if it can access the target neuronal or glial population, if it is pharmacologically active, and if the exposure is adequate to alter the disease pathology.

4. Dendrimers and Poly(propylene Imine) as CNS Nanocarriers

Dendrimers have been designed as highly branched macromolecules with well-defined molecular architecture and have since found wide application in medicine [21–24]. They are composed of a central core, branching generations, and the functional groups at the periphery. Generally, a higher generation leads to larger molecule size and more terminal groups, which will increase the opportunity for drug association and surface modification [21,23].

Certain drug molecules can be contained within the dendrimer's internal cavities via hydrophobic, electrostatic, or other non-covalent interactions, while surface groups can be employed for covalent attachment [22,23]. This dual role can enable dendrimers to serve as delivery vehicles and targeting sites for drugs. They can also allow the simultaneous binding of drugs, imaging agents, and targeting ligands to make multifunctional systems [1,22].

The branched architecture of PPI dendrimers makes them especially interesting as they carry tertiary amines in their interior and primary amines on their

surface [23]. These properties affect the binding to the drug, the behaviour in water, interaction with cells, and the functionalization of surfaces. The presence of high amounts of amino groups can ensure interaction with the negatively charged cell membranes and allow cellular uptake. But too many cationic charges can cause detrimental effects on the integrity of the membranes and increase cytotoxicity [23,27].

Therefore, surface chemistry is a critical aspect to be optimized in the design of a PPI system. Modification of dendrimer surfaces with PEG, carbohydrates, lipids, or targeting ligands can enhance their biocompatibility and BBB transport was recently highlighted [1]. This is supported by experimental studies on PPIs. Maltose/histidine functionalized PPI dendrimers showed better biological activity than the highly cationic systems, and oleic acid-functionalized PPI G5 dendrimers have recently been tested for the delivery of tacrine to the brain [31,32].

The studies are especially relevant for the proposed convolvuline formulation since they demonstrate that PPI is not a mere carrier material. Instead, it offers a chemical platform whose biological properties can be tailored by well-designed surface engineering.

5. Justifications for the Propylene Imine-Loaded Convolvuline Dendrosomes

The formulation is proposed to be a mixture of two different pharmaceutical compounds: a bioactive natural-product payload and a dendritic nanocarrier. The reason for this combination is based on whether, and why, incorporation into the dendrosome enhances the properties that are currently restricting the therapeutic use of the active compound.

The genus Convolvulus has been widely studied with respect to its phytochemical diversity. Flavonoids, alkaloids, phenolic compounds, carbohydrates, terpenes, sterols, tannins, and other secondary metabolites are reported as constituents [33]. Various pharmacological properties, such as antioxidant activity and others, have been reported in experimental literature for different species of Convolvulus, with different strengths of evidence between species, extracts, and individual compounds [33]. Hence, the pharmacologic characterization of the particular convolvuline incorporated in the proposed formulation should be properly determined.

The initial steps toward the pharmaceutical development of convolvuline should include determining its purity, molecular structure, solubility in water, lipophilicity, chemical stability, and activity. The attributes will dictate whether physical encapsulation, electrostatic association, or covalent conjugation will be the most suitable loading method. Dendritic encapsulation of the compound may be capable of enhancing the apparent pharmaceutical performance if the compound is poorly soluble in water or is not stable. Surface engineering of the carrier may be a more important way to break the major limitation of BBB permeability than increasing drug loading.

This distinction is important as it has the potential to lead to low therapeutic efficacy even with high drug loading. Even if a formulation contains a high concentration of the medication, it can be ineffective if the drug is not released from the formulation into the blood, if there is no BBB penetration, or if it is toxic. On the other hand, a formulation containing moderate loading could be therapeutically more effective if it can deliver the drug to the brain efficiently and release it in a controlled manner.

The proposed formulation should then be considered as a multi-variable system: generation of PPI, particle size, surface charge, drug-to-carrier ratio, surface modification, release rate, interaction with BBB, cellular uptake, and biological response. The overall goal should be optimization of the therapeutic index, not maximization of a single formulation parameter.

6. Development and characterization of formulations

Preformulation studies to define the physicochemical properties of the active compound and the PPI dendrimer should be performed to develop the propylene imine-loaded convolvuline dendrosomes. Assessment of drug–carrier compatibility prior to optimization is required since there is a possibility of strong chemical interactions that can affect drug stability or activity. Changes in functional groups can be identified using FTIR, and changes in thermal behaviour can be identified using differential scanning calorimetry. The crystalline or amorphous form of the drug can be determined by X-ray diffraction to see if the incorporation into the dendritic system alters the drug's crystalline or amorphous state [23,24].

Another factor to consider is the PPI generation. More generations result in more surface functionality but also a higher cationic charge and possibly higher toxicity. Hence, when choosing a generation, it should be done based on the desired balance of loading capacity, particle characteristics, BBB interaction, and safety rather than just the highest possible generation [1,23].

Formulation can be by physical encapsulation, electrostatic association, or covalent conjugation. Physical encapsulation has the advantage of not altering the pharmacological activity of the active compound, while covalent attachment can offer more controlled release but can also alter the pharmacological activity. The surface functionalization can be performed before or after drug loading, depending on the functional group chemistry of the chosen ligand and formulation process.

Table 2. Major characterization parameters for propylene imine-loaded convolvuline dendrosomes

Parameter	Recommended technique	Importance
Particle size	Dynamic light scattering	Influences colloidal behaviour and biological distribution
PDI	Dynamic light scattering	Indicates size homogeneity
Zeta potential	Electrophoretic light scattering	Indicates surface charge and stability
Morphology	TEM/SEM/AFM	Determines particle architecture
Drug content	HPLC/UPLC	Confirms formulation potency
Entrapment efficiency	Separation followed by assay	Determines incorporated drug fraction
Drug loading	Quantitative drug assay	Determines carrier capacity
Chemical compatibility	FTIR	Identifies molecular interactions
Thermal behaviour	DSC/TGA	Evaluates thermal stability
Crystallinity	XRD	Determines physical-state changes
Release profile	Dialysis/diffusion method	Determines release behaviour
Stability	Accelerated and long-term studies	Determines shelf stability

Specific parameters such as particle size, polydispersity and zeta potential are of special interest for PPI-based systems. Dynamic light scattering can be used to measure hydrodynamic diameter and PDI, and measurement of zeta potential can be used to measure surface charge and colloidal stability [23,24]. In PPI systems, another relation to biological safety is that the strongly positive surfaces might interact strongly with the negatively charged cell membranes [23,27].

In addition to DLS information, morphological analysis, such as transmission electron microscopy, scanning electron microscopy, or atomic-force microscopy, can be used to get direct particle shape and structural information. Care must be taken when comparing the measurement of DLS with electron microscopy, as the former is given as hydrodynamic diameter in dispersion while the latter is calculated on dried or processed samples.

Other parameters needed for drug formulation are also the drug loading capacity and entrapment efficiency. The efficiencies of entrapment can be obtained in percentage terms of the total drug incorporated into a dendrosomal system, and the amount of drug per unit mass of the whole formulation is a measure of drug loading. They should be measured by a method that has been validated by analytical techniques with appropriate specificity and accuracy, preferably HPLC or UPLC.

7. In-Vitro Release, Cellular Uptake and Biological Evaluation

Therapeutic potential of the proposed formulation cannot be ascertained using only physicochemical characterization. The release of convolvuline from the PPI dendrosome should be determined in release studies to see if it can be released at a suitable rate for intended use. It is important to test free convolvuline at the same time as the others, so that the effects of the carrier on the release behaviour can be assessed.

Data from the release can be fitted by the corresponding mathematical models like zero-order, first-order, Higuchi and Korsmeyer–Peppas models.

To select models, the statistical fit and the ability to interpret the model should be considered, not just the highest correlation coefficient. The aim is to determine which release mechanisms- diffusion, desorption, matrix relaxation, degradation, or all of them- are predominant [23,24].

Another crucial step in the formulation evaluation is the cellular uptake studies. The 2024 PPI study on tacrine showed that the SH-SY5Y cells were treated with PPI dendrimeric conjugates, and fluorescence was observed in the interior of the cells, indicating effective cellular uptake of the formulated system [31]. The same experiments could be repeated using fluorescently labelled convolvuline-PPI dendrosomes, comparing free drug, unmodified PPI formulation, and surface-functionalized formulation.

Increased cellular uptake is not necessarily a marker of therapeutic benefit, however. The positively charged dendrimer can be efficiently taken up by cells and cause cell damage or toxicity within the cells. Thus, it is important to always evaluate uptake in parallel with cellular viability, membrane integrity, and other markers of toxicity [23,27].

In neurological applications, biological evaluation must also contain models of disease-relevant injury. Changes in ROS and antioxidant defence can be studied in oxidative-stress models, and cytokine release and microglial activation in inflammatory models. Depending on the proposed mechanism of convolvuline, other endpoints, including mitochondrial membrane potential, apoptosis, or synaptic markers/protein aggregation, may be relevant.

Comparisons of targeted convolvuline-loaded PPI dendrosomes to non-targeted convolvuline-loaded PPI dendrosomes, blank PPI dendrosomes, and surface-functionalized PPI dendrosomes loaded with the targeted convolvuline would be logical experiments to compare. With such a design, it would be possible to separate the contributions of the active compound, carrier, and targeting modification.

8. Safety, Research Gaps and Future Perspectives

One of the most important factors in the design of dendrimer-based nanomedicines is safety. The biological activity of dendrimers is highly dependent on their generation, concentration, surface charge, chemical structure, and mode of administration [1,23,27]. PPI systems with a very high positive charge can be membrane-disruptive and hence cause cytotoxicity and haemolysis. This can be minimized by modifying the surface, but the system must be fully safety-evaluated before modification [1,31,32].

The study on the oleic-acid-conjugated PPI dendrimers from 2024 is informative, as the researchers did not investigate the brain targeting ability alone. They were also tested for haemolysis, nasal ciliotoxicity, cytotoxicity, and cellular uptake [31]. Such an evaluation of such a multi-dimensional nature could be a helpful model for future development of convolvuline-type PPIs.

One of the biggest hurdles is the differentiation of BBB penetration from therapeutic brain targeting. A nanoparticle might not penetrate into the BBB in a sufficient quantity to deliver the required amount of active particle into the target neuronal population. Future studies should, therefore, incorporate BBB permeability experiments with quantitative brain biodistribution and pharmacodynamic studies [1,7].

Recent studies also show that the design and engineering of dendrimers is progressing towards more advanced surfaces. Recent strategies that have been investigated to improve BBB interaction and decrease toxicity include PEGylation, carbohydrate functionalization, lipid conjugation, biomimetic coatings, and receptor targeting ligands [1]. Predicting permeability through the BBB and designing dendrimers have also been suggested by using AI-based methods, which, however, should be validated experimentally [1].

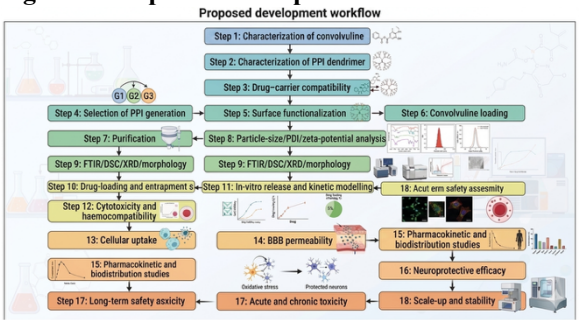
Table 3. Principal research gaps and future priorities

Current gap	**Recommended research direction**
Limited direct evidence for convolvuline-PPI dendrosomes	Systematic formulation-development studies
Uncertain BBB transport of convolvuline	Comparative BBB permeability and brain-distribution studies
Potential PPI-related cationic toxicity	Surface-charge optimization and functionalization
Limited long-term safety evidence	Repeated-dose and chronic toxicology
Uncertain mechanism of neuroprotection	Disease-specific molecular and cellular studies

Lack of standardized formulation parameters	Quality-by-Design approach
Limited translational evidence	Pharmacokinetic and biodistribution studies
Manufacturing complexity	Scale-up and process-validation studies

9. Proposed Experimental Workflow

Figure 1. Proposed development workflow



10. Conclusion

The difficulty of managing neurodegenerative diseases is that the disease process is a complex interplay of mechanisms, and the delivery of therapeutic compounds to the brain is limited by the BBB [2–5]. Nanotechnology-based drug delivery provides a chance to overcome these drawbacks by altering the solubility, stability, pharmacokinetics, cellular uptake, and tissue distribution of the drugs [1,14,17].

One of the most promising dendrimers is the highly branched structure with a multifunctional surface that can be systematically modified for drug loading and targeting [21–24]. The potential for the extensive surface engineering of PPI dendrimers makes them particularly interesting for delivery in the CNS [23,29]. Their cationic properties, however, do need optimization, as increased cellular interaction can lead to increased toxicity [23,27].

Recent studies have shown surface-functionalized PPI dendrimers can offer enhanced brain delivery properties. Oleic-acid-conjugated PPI G5 dendrimers have been evaluated for brain-targeted delivery of tacrine, and other modified PPI systems have been shown to exhibit increased biocompatibility and BBB-related performance [31,32]. The results offer significant advances in technology to study the possibility of using PPI dendrosomes for the delivery of other bioactive molecules.

It is a promising, but still exploratory, research strategy to incorporate convolvuline into the PPI dendrosomal system. Literature on Convolvulus species is very interesting in terms of phytochemical and pharmacological interest, but therapeutic properties, BBB permeability, and formulation behaviour of the specific convolvuline compound should be established experimentally [33]. Therefore, the formulation proposed should not currently be considered a proven treatment for neurodegenerative diseases.

The systematic formulation optimization, detailed physicochemical characterization, controlled-release testing, BBB transport, cellular uptake, pharmacokinetics, biodistribution, and disease-specific efficacy should be performed in future studies. The surface chemistry of PPIs should be addressed carefully, as delivery to the brain and nanotoxicity will be important factors for therapeutic feasibility [1,31]. Optimized and properly validated propylene imine-loaded convolvuline dendrosomes could be used as an effective tool for enhancing CNS delivery of bioactive molecules and may be part of the future nanotherapeutic strategies for neurodegenerative diseases.

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