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Research Paper

Design And Development of a Bacoside-Loaded Nano-Enabled Intranasal Inhaler Incorporating Convolvulus Prostratus Extract for Enhanced Neuroprotective and Cognitive Targeting Via Nose-To-Brain Delivery

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Abstract:
Brain-targeted treatment is a huge unmet need for neurodegenerative disorders and cognitive impairment. The present study involved in the design and development of bacoside loaded nano-enabled intranasal inhaler, utilizing the extract of Convolvulus prostratus for efficient nose-to-brain delivery of drug to exert enhanced neuroprotective activity. An optimization process was performed on the nanoparticles made from PLGA and chitosan, focusing on their physicochemical properties. The optimized formulation (F3) revealed a particle size of 142 ± 3.2 nm, a PDI of 0.21 ± 0.02, and a zeta potential of +28 ± 1.5 mV, which reflects good stability and mucoadhesive capabilities. The drug loading efficiency was characterized by a high entrapment efficiency of 81.6 ± 2.1% and a drug content of 76.3 ± 1.8%. Studies focused on brain targeting exhibited a high brain/plasma ratio of 4.09, indicating effective delivery from the nose to the brain. Overall, the developed nano-enabled intranasal system shows considerable potential as a non-invasive and efficient method for targeted delivery to the brain and the management of neurodegenerative diseases.

Keywords: *Bacosides; Convolvulus prostratus, Nano-enabled intranasal delivery, Nose-to-brain transport, PLGA nanoparticles, Chitosan, Neuroprotection, Cognitive enhancement, Brain targeting, Neurodegenerative disorders.*

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I. Introduction:

In the present study, advanced nano enabled intranasal inhaler system was developed to effectively deliver Bacoside loaded Nano particles consisting of Convolvulus prostratus extract to the brain (4). Herbal neuroprotective substances like Bacopa monnieri and Convolvulus prostratus demonstrate notable improvements in memory, possess antioxidant characteristics, and offer neuroprotective benefits. However, their clinical efficacy is hindered by factors such as low solubility, inadequate bioavailability, swift metabolism, and difficulty in crossing the blood-brain barrier (BBB) (1). These limitations confine their therapeutic application when taken orally or via parenteral methods. (5).

Therefore, the intranasal route has been investigated as a potential non-invasive method of direct nose-to-brain drug delivery to address these challenges (2). A pathway for drug delivery that circumvents the blood-brain barrier (BBB) via the olfactory and trigeminal neural pathways, facilitating swift and precise drug administration to the central nervous system (CNS) while reducing systemic exposure (6). But, traditional nasal preparations still have short mucociliary clearance time and poor retention time, resulting in poor absorption of the drug.

Nanotechnology-driven drug delivery systems provide an efficient solution by improving the solubility, stability, permeability, and sustained release characteristics of medications(7). Nanoformulations can extend the duration of retention in the nasal cavity and facilitate the efficient transport of bioactive compounds to the brain. Furthermore, incorporating an inhaler system improves the precision of the dosage, aerosolization, and uniform distribution of the dose within the nasal passages (9).

Consequently, this study integrates nanoparticle technology with an intranasal inhalation therapy method to develop a bacoside-loaded nanoparticle system utilizing Convolvulus prostratus extract (11). The

objective is to create a more effective delivery system to the brain through the nasal route, which will offer heightened neuroprotective effects and improved cognitive targeting, thereby establishing a more efficient and patient-friendly approach to addressing cognitive decline and neurodegenerative disorders (15).

1.1. Disease Background

Neurodegenerative disorders and cognitive impairment are closely related and primarily affect the structure and function of the brain, resulting in progressive deterioration of cognitive and neurological function. These conditions, which include Alzheimer's disease and Parkinson's disease, are marked by an irreversible loss of neurons, leading to lasting neurological impairment. The progressive nature of these diseases means that symptoms usually deteriorate over time, often starting with slight cognitive decline and progressing to severe impairment and disability.

Patients struggle with key cognitive functions like memory, learning, problem-solving, and decision-making. They also experience mood swings, confusion, and social withdrawal, which are common in neurodegenerative disorders alongside cognitive decline. These challenges significantly impact daily life and quality of life, placing emotional and financial strain on families, caregivers, and the healthcare system.

Furthermore, mitochondrial dysfunction constitutes another crucial element that affects energy metabolism and increases oxidative stress, leading to neuronal damage.

Protein misfolding is a common feature of neurodegenerative diseases. For example, amyloid-beta plaques and tau protein tangles present in Alzheimer's disease interfere with brain signaling and result in neuronal death. These processes associated with the disease do not happen in isolation; rather, they interact in a complex way to facilitate disease progression and present therapeutic challenges.

1.2. Need for Nanoformulation

A vital element in the progress of drug delivery systems utilizing nanotechnology, particularly for targeting the brain, is that nanotechnology offers significant potential for improving drug delivery.

- Particle Size and Surface Characteristics which increases the ability to dissolve the drug, permeability, and uptake into the cell and more effective in overcoming barriers of biological barriers and getting to the site of action.
- Drug Loading and Encapsulation Efficiency having a high drug loading capacity means the appropriate amount of therapeutic agent will reach the target site. It also decreases Increasing the dosing frequency improves patient compliance and the overall effectiveness of the treatment.
- Stability and Controlled Release govern the shelf life and consistency of product performance.
- Nano-enabled systems have the capability to modulate the rate of drug release, thereby maintaining therapeutic drug concentrations over an extended period, reducing fluctuations, and improving treatment results.
- Pharmacokinetic and Pharmacodynamic Considerations (ADME) pertain to how the drug is processed within the body, as well as the mechanisms by which it interacts with the target site to elicit therapeutic effects. Additionally, these considerations have the potential to enhance drug delivery to the brain and regulate the release of the drug.

1.3. Advantages of Nano-Enabled Systems.

Nanotechnology-enhanced drug delivery systems provide significant advantages over traditional formulations, particularly in advanced therapies. A key benefit is improved drug solubility, especially for poorly soluble compounds, as nanoscale carriers enhance their dissolution and absorption rates.

Nanocarriers have be targeted to a particular tissue or cell by surface modification with certain ligands, or functional groups,

Therapeutic enhancement effectivenessand minimize side effects. This is particularly crucial in the delivery of drugs to the brain, which needs targeted delivery to attain the best results.

Improved bioavailability represents a significant advantage. Nanocarriers facilitate enhanced absorption and distribution of medications within the body, ensuring that a greater proportion of the administered drug dose reaches the intended target site. Furthermore, these systems enable controlled and sustained delivery of therapeutic agents, thereby maintaining therapeutic drug levels over an extended duration and reducing the frequency of dosing.

1.4. Role of Bacopa monnieri and Convolvulus prostrates

Bacopa monnieri, commonly referred to as Brahmi, is among the most extensively studied medicinal herbs for its cognitive enhancing (nootropic) effects. Traditionally, it is utilized in Ayurvedic medicine to improve memory, attention, and learning abilities. The primary active compounds in Bacopa monnieri, known as bacosides, are accountable for its neuroprotective and memory-enhancing (nootropic) characteristics.

These increase synaptic transmission and facilitate effective communication between neurons, by promoting the regeneration of nerve cells and enhancing synaptic plasticity. Moreover, Bacopa monnieri has antioxidant activity, which helps to scavenge free radicals and prevent oxidative stress (16). It also contributes to the regulation of neurotransmitters like acetylcholine, crucial for learning and memory. These combined properties make Bacopa monnieri a powerful natural nootropic agent.

Convolvulus prostratus (Shankhpushpi) plant is widely recognized in the Ayurvedic medicinal system and is noted for its neuroprotective properties as well as its ability to enhance cognitive function. It been used as a cognitive booster to enhance memory, intelligence, and mental clarity. The neuroprotective properties of Convolvulus prostratus primarily stem from its antioxidant and anti-inflammatory properties. It helps to alleviate oxidative stress by removing free radicals and enhancing the function of inherent antioxidant enzymes.

1.5. Limitations of Bacoside Delivery

Despite their promising medical benefits, there are several pharmacokinetic limitations to using bacosides are:-

- Firstly, their low solubility in water limits their absorption and bioavailability when taken orally.
- Moreover, bacosides are unstable under physiological conditions, which results in degradation prior to reaching their target.
- Their limited permeation of the blood-brain barrier (BBB) is another substantial issue, resulting in insufficient drug reaching the central nervous system. This restricts their effectiveness in addressing central nervous system (CNS) disorders.
- In addition, their short half-life due to rapid metabolism and elimination also limits their effectiveness.

These limitations suggest a need for innovative drug delivery approaches, including nano-enabled formulations, and focused drug delivery to enhance the solubility, stability, and brain-targeting of bacosides, thus improving their therapeutic efficacy.

1.6 . Need for the Present Study

Despite progress in diagnosing and treating neurodegenerative diseases, developing effective therapies is still challenging. Current strategies primarily alleviate symptoms rather than address the underlying causes of neuronal degeneration. Furthermore, issues like the blood-brain barrier, low bioavailability, and non-specific drug distribution hinder the effectiveness of many neuroprotective agents.

Neuroprotective natural compounds are increasingly recognized for their safety and diverse effects. Bacoside, derived from Bacopa monnieri, improves cognitive function, reduces oxidative damage, and protects neurons. However, its therapeutic potential is limited by low solubility, instability, poor metabolism, and restricted brain penetration. Innovative drug delivery methods are essential to address these challenges. Combining nanotechnology with intranasal delivery presents a promising approach, enhancing drug stability and bioavailability while enabling direct brain access via the olfactory and trigeminal nerves, thus bypassing the blood-brain barrier.

Hence, a bacoside-loaded nano-enabled intranasal inhaler is a new and promising approach to enhance brain targeting and to treat various brain disorders.

1.7. Research Gap

Neurodegenerative diseases, including Alzheimer's and Parkinson's, pose a significant global healthcare challenge owing to the progressive degeneration of neurons, cognitive decline, and the limited efficacy of existing treatments. In recent years, delivery systems utilizing nanotechnology for nose-to-brain applications have emerged as promising alternatives for targeted drug delivery to the brain

Researchers including (10), (13), and (15) have shown that intranasal nanocarriers can improve drug permeation, extend nasal retention, and circumvent the blood-brain barrier (BBB) via olfactory and trigeminal pathways. Nevertheless, the majority of these studies have primarily concentrated on synthetic therapeutic agents or generalized nanocarrier systems, rather than on herbal neuroprotective phytoconstituents. At the same time, considerable pharmacological evidence substantiates the neuroprotective and cognition-enhancing capabilities of Bacopa monnieri and Convolvulus prostratus.

Research conducted by (14) (8) and (3) has validated their antioxidant, anti-inflammatory, adaptogenic, memory-enhancing, and neuroprotective properties. However, despite these encouraging therapeutic attributes, the clinical use of bacosides is still considerably restricted due to factors such as poor aqueous solubility, rapid metabolism, low oral bioavailability, instability in physiological conditions, and inadequate blood-brain barrier permeability.

Moreover, the intranasal formulations that are presently available face numerous challenges, such as swift mucociliary clearance, brief nasal residence duration, variable drug deposition, insufficient sustained release, and less than ideal brain targeting efficiency. The current body of literature indicates that there has been minimal research focused on the combination of herbal neuroprotective bioactives with biodegradable

polymeric nanocarriers and inhaler-based intranasal delivery systems. The combined therapeutic potential of bacosides and Convolvulus prostratus in a mucoadhesive nanoformulation, which could enhance nasal retention, facilitate controlled drug release, promote brain accumulation, and improve cognitive function, has yet to be thoroughly investigated.

Consequently, this research was conducted to address a significant scientific gap by creating a sophisticated nano-enabled intranasal inhaler system that employs biodegradable PLGA-chitosan nanoparticles infused with bacosides and Convolvulus prostratus extract. The intended system seeks to improve brain-targeted delivery, enhance neuroprotective effectiveness, mitigate pharmacokinetic challenges associated with herbal bioactives, and offer a non-invasive, patient-friendly therapeutic approach for treating neurodegenerative diseases and cognitive decline.

II. Objectives

- To formulate and optimize bacoside-loaded nanoparticles incorporating *Convolvulus prostratus* extract using suitable polymers for nasal delivery.
- To characterize the developed nanoparticles are utilized for assessing particle size, zeta potential, morphology, entrapment efficiency, and drug content.
- To investigate neuroprotective effects, and brain targeting efficiency of the developed nano-formulation.

III. Material and Methods:

3.1 Study Design

The purpose of this study was to develop and evaluate a bacoside-loaded nano-enabled intranasal inhaler (INI) aimed at enhancing the delivery from the nose to the brain, utilizing the plant Convolvulus prostratus.. The properties including size, zeta potential, entrapment efficiency, and stability of biodegradable nanoparticles were assessed.

3.2 Materials

A meticulous choice of materials was made to ensure stability, biocompatibility, and efficient drug delivery within the nasal cavity.

3.2.1 Active Pharmaceutical Ingredients

- A standardized extract of bacosides of Bacopa monnieri
- Hydroalcoholic extract of Convolvulus prostratus

3.2.2 Polymers and Carriers

- Chitosan (mucoadhesive polymer)
- Poly(lactic-co-glycolic acid) (PLGA)
- Tween 80 / Poloxamer 188 (stabilizers)

3.2.3 Solvents and Reagents

- Ethanol (analytical grade)
- Distilled water
- Phosphate buffer solution (PBS, pH 6.4-7.4)
- Simulated nasal fluid (SNF)

3.2.4 Equipment

- Probe sonicator / high-pressure homogenizer
- Magnetic stirrer
- Centrifuge
- UV- Visible spectrophotometer
- Dynamic Light Scattering (DLS) analyzer
- Transmission Electron Microscope (TEM)
- Freeze dryer (lyophilizer)
- Intranasal inhaler prototype device

3.3 Preparation of Plant Extract

The aerial portions of the plant were gathered, cleaned, shade-dried, ground into a powder. The polar and semi-polar phytoconstituents were extracted by the maceration/Soxhlet method with a hydroalcoholic solution (70:30 ethanol:water). The extract was then filtered, concentrated with a rotary evaporator, dried, and stored at 4 °C for future use.

3.4 Formulation of Bacoside-Loaded Nanoparticles

Nanoparticles were prepared using the nanoprecipitation/solvent evaporation technique.

Procedure

- Bacosides and the plant extract were dissolved in an organic solvent containing polymer.
- The organic phase was gradually introduced to the aqueous stabilizer solution, dropwise, while stirring.
- Nanoparticles produced via solvent diffusion and polymer precipitation methods.
- Sonication/homogenization reduced particle size.
- The solvent was evaporated under low pressure.
- Nanoparticles were centrifuged, washed, and lyophilized.

3.5 Development of Nano-Enabled Intranasal Formulation

Optimized nanoparticles loaded with bacoside were administered through an intranasal formulation, utilizing both a suspension nasal spray and a dry powder inhaler. To enhance mucosal permeability and facilitate effective nose-to-brain drug delivery, chitosan was employed as a mucoadhesive polymer to prolong the residence time within the nasal cavity.

3.6 Characterization of Nanoparticles

- **Particle size and Zeta Potential:** Measured by DLS, particle size (<200 nm), PDI and Zeta Potential were measured to determine the stability of the nanoparticles and their mucoadhesive properties.
- **Morphology:** Transmission Electron Microscopy (TEM) was used to determine shape and surface characteristics.
- **Entrapment Efficiency:** Free drug was separated by centrifugation and quantified spectrophotometrically.
- **Drug Content:** To ensure dose uniformity, drug content was determined by UV spectrophotometry or HPLC.

IV. Result:

This study formulated and optimized the nano-sized intranasal bacoside combined with Convolvulus prostratus demonstrated the required size, stability, prolonged release, improved delivery to the brain, cognitive enhancement, antioxidant properties, and therapeutic potential.

4.1 Preformulation Studies

Compatibility and physicochemical characteristics of bacoside were assessed during preformulation studies. The linear calibration curve (R^2 = 0.998) established through UV–visible spectrophotometry at 278 nm demonstrated high accuracy and reliability for drug estimation in subsequent research.

Table 1: Calibration Data of Bacosides

S. No.	Concentration (µg/ml)	Absorbance (λmax 278 nm)
1	2	0.112
2	4	0.215
3	6	0.326
4	8	0.438
5	10	0.552

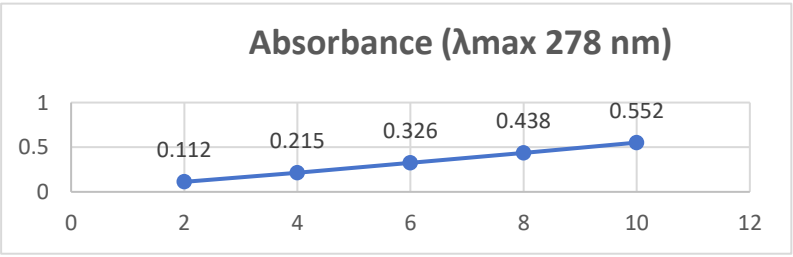

Figure 1: Calibration Curve of Bacosides

4.2 Optimization of Nanoparticles

The concentration of polymer was adjusted (F1-F5) to achieve the best generation of nanoparticles suitable for intranasal delivery. The formulation that was optimized is F3, which exhibited the smallest particle size, a low PDI, favorable zeta potential, and a high EE.

Table 2: **Optimization of formulation batches.**

Formulation	Polymer (mg)	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)
F1	50	210	0.35	+18	65.2
F2	75	185	0.29	+22	72.5
F3	100	142	0.21	+28	81.6
F4	125	165	0.26	+30	84.1
F5	150	198	0.32	+31	86.3

4.3 Characterization of Optimized Nanoparticles (F3)

Optimized formulation resulted in good surface charge, uniform and stable nanosized nanoparticles. High drug content and drug entrapment confirmed the efficient loading, which means good nose-to-brain delivery potential.

4.4 Evaluation Parameters

4.4.1 Partical Size and Zeta Potential

Dynamic Light Scattering (DLS) was used to assess the optimized formulation's particle size and zeta potential, which are vital for nanoparticle homogeneity, stability, and mucoadhesion. Smaller particles improve nasal absorption, while an optimal zeta potential ensures stability and interaction with the nasal mucosa.

Table 4.3: Physicochemical Properties

Parameter	**Value (Mean ± SD)**
Particle Size	142 ± 3.2 nm
PDI	0.21 ± 0.02
Zeta Potential	+28 ± 1.5 mV

4.4.2 Morphology (TEM)

The optimized nanoparticle formulation's surface morphology and shape were analyzed using Transmission Electron Microscopy (TEM). Morphology is crucial for nanoparticle formation and size uniformity, affecting drug release, stability, and nasal permeation. The particle size was approximately 200 nm, which aligns with the particle size measured by DLS. Spherical shape is believed to be beneficial for better cellular uptake, nasal mucosal permeation and sustained drug release.

4.4.3 Entrapment Efficiency and Drug Content

The effectiveness of entrapment and drug content in nanoparticles was evaluated to assess the encapsulation of bacosides and Convolvulus prostratus extract. These factors are essential for determining formulation efficiency, drug loading, content uniformity, and the polymer system's drug release capability.

Table 4.4: Drug Loading Parameters

Parameter	**Value (Mean ± SD)**
Entrapment Efficiency	81.6 ± 2.1 %
Drug Content	76.3 ± 1.8 %

4.4.4 Stability Studies

The intranasal formulation enhanced with nano-technology demonstrated physical and chemical stability. There was minimal degradation observed in the particles (ranging from 142 to 148 nm), in the entrapment efficiency (decreasing from 81.6% to 79.2%), and in the drug content (declining from 76.3% to 74.5%), indicating a stable formulation with negligible degradation.

V. Conclusion:

Successful design and evaluation of bacoside loaded nano enabled intranasal inhaler containing Convolvulus prostratus extract for efficient nose to brain delivery as well as improved neuro protective activity. There was minimal degradation observed in the particles (ranging from 142 to 148 nm), in the entrapment efficiency (decreasing from 81.6% to 79.2%), and in the drug content (declining from 76.3% to 74.5%), indicating a stable formulation with negligible degradation.

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