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Design Development and Evaluation of Nasal Drug Delivery of Solid Lipid Nanoparticle System for Brain Targeting & Management of Neurogenerative Disorders"

Ms. Deolekar Rajlaxmi Sudhir[1] and Dr. Rajeev Kumar Malviya[2]
Faculty of Pharmacy, Mansarovar Global University, Sehore (M.P.)
Rajlaxmi16.0@gmail.com[1]

Abstract: *Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS) represent a major global health challenge due to progressive neuronal degeneration and limited therapeutic options. The blood-brain barrier (BBB) significantly restricts drug delivery to the central nervous system, resulting in poor therapeutic efficacy of conventional formulations. Intranasal drug delivery has emerged as a promising non-invasive strategy for direct nose-to-brain transport through olfactory and trigeminal pathways. Solid Lipid Nanoparticles (SLNs) offer advantages including biocompatibility, controlled drug release, enhanced drug stability, improved permeation, and increased brain targeting efficiency. The present study aims to develop and evaluate a nasal SLN formulation for effective brain targeting in neurodegenerative disorders. SLNs were prepared using hot homogenization followed by ultrasonication and characterized for particle size, polydispersity index, zeta potential, entrapment efficiency, morphology, in vitro drug release, ex vivo nasal permeation, and in vivo brain targeting potential. The optimized formulation exhibited nanosized particles, high entrapment efficiency, sustained drug release, enhanced nasal permeation, and improved brain bioavailability. These findings demonstrate the potential of SLN-based nasal drug delivery systems as a promising platform for the management of neurodegenerative diseases. Intranasal SLNs have been extensively investigated because they can bypass the BBB and improve drug delivery directly to the brain.*

Keywords: Neurodegenerative Disorders, Alzheimer's Disease, Parkinson's Disease, Intranasal Drug Delivery.

I. INTRODUCTION

Neurodegenerative disorders (NDs) are a heterogeneous group of chronic, progressive diseases characterized by the gradual loss of neuronal structure and function within the central nervous system (CNS). These disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), and Multiple Sclerosis (MS), which collectively represent a significant global health burden. The incidence of neurodegenerative diseases is increasing rapidly due to aging populations worldwide, leading to substantial social, economic, and healthcare challenges. Alzheimer's disease is the most common cause of dementia, accounting for approximately 60–70% of all dementia cases, while Parkinson's disease is the second most prevalent neurodegenerative disorder, affecting millions of individuals globally [1,2].

The pathophysiology of neurodegenerative disorders involves complex mechanisms including oxidative stress, neuroinflammation, mitochondrial dysfunction, protein misfolding, excitotoxicity, and neuronal apoptosis. Despite significant advances in understanding disease mechanisms, effective treatment remains challenging because most

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therapeutic agents exhibit poor penetration across the blood-brain barrier (BBB), resulting in limited drug concentrations at the target site within the brain [3]. The BBB is a highly selective physiological barrier composed of tightly connected endothelial cells, astrocytes, and pericytes that restrict the entry of approximately 98% of small-molecule drugs and nearly all large therapeutic molecules into the CNS [4].

Conventional routes of drug administration such as oral and parenteral delivery often suffer from several limitations, including extensive first-pass metabolism, systemic side effects, poor bioavailability, and inadequate brain targeting. Consequently, higher doses are frequently required to achieve therapeutic concentrations in the brain, increasing the risk of adverse effects [5]. Therefore, alternative drug delivery approaches capable of bypassing the BBB and directly targeting the brain have become an important area of pharmaceutical research.

Intranasal drug delivery has emerged as a promising non-invasive strategy for direct brain targeting. The nasal cavity provides a highly vascularized surface area and direct anatomical connections to the brain through neuronal pathways, enabling rapid transport of drugs to the CNS while bypassing the BBB [6]. Three major mechanisms are involved in nose-to-brain drug transport:

- **Olfactory pathway:** Drug molecules are transported from the olfactory epithelium directly to the olfactory bulb and subsequently distributed throughout various brain regions [7].
- **Trigeminal nerve pathway:** Drugs can reach the brainstem and deeper CNS structures through trigeminal nerve branches innervating the nasal cavity [8].
- **Systemic circulation pathway:** A fraction of the administered drug may be absorbed into the systemic circulation and subsequently cross the BBB to reach the brain [9].

Among the various nanocarrier systems investigated for intranasal brain delivery, Solid Lipid Nanoparticles (SLNs) have attracted considerable attention due to their unique physicochemical and biological properties. SLNs are submicron colloidal carriers composed of physiological lipids that remain solid at both room and body temperatures. These nanoparticles combine the advantages of traditional colloidal carriers while minimizing many of their associated limitations [10].

SLNs offer several advantages for nose-to-brain delivery, including:

- **Excellent biocompatibility and biodegradability** due to the use of physiological lipids [11].
- **Controlled and sustained drug release**, enabling prolonged therapeutic effects [12].
- **High drug-loading capacity** for both lipophilic and moderately hydrophilic drugs [13].
- **Protection of encapsulated drugs from enzymatic and chemical degradation** within the nasal cavity [14].
- **Enhanced permeation across nasal mucosa and improved brain uptake** through nanoscale particle size and lipid-mediated transport mechanisms [15].
- **Improved stability and reduced systemic toxicity** compared to conventional formulations [16].

Furthermore, surface modification of SLNs with mucoadhesive polymers such as chitosan can enhance nasal residence time, improve mucosal permeation, and further increase brain-targeting efficiency [17]. Numerous preclinical studies have demonstrated that intranasal SLN formulations significantly improve drug bioavailability in the brain and enhance therapeutic outcomes in animal models of Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders [18].

Recent reviews and experimental investigations have highlighted SLNs as one of the most promising lipid-based nanocarriers for intranasal brain delivery due to their ability to bypass the BBB, improve drug stability, achieve sustained release, and enhance therapeutic efficacy while minimizing systemic exposure [19,20]. Therefore, the development of SLN-based nasal drug delivery systems represents a promising approach for the effective management of neurodegenerative disorders and may provide a viable alternative to conventional CNS drug delivery strategies.

Objectives

- ✓ To formulate drug-loaded SLNs suitable for intranasal administration.
- ✓ To optimize formulation variables affecting nanoparticle characteristics.

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- ✓ To evaluate physicochemical properties of SLNs.
- ✓ To investigate in vitro and ex vivo performance.
- ✓ To assess brain-targeting potential through in vivo studies.
- ✓ To evaluate therapeutic efficacy in neurodegenerative disease models.

II. MATERIALS

S.No.	Materials
Drug Candidate	Rivastigmine / Donepezil / Rasagiline / Selegiline (model neuroprotective drug)
Lipids	Glyceryl Monostearate (GMS) Stearic Acid Compritol 888 ATO
Surfactants	Poloxamer 188 Tween 80 Lecithin
Mucoadhesive Polymer	Chitosan
Other Chemicals	Ethanol Distilled Water Phosphate Buffer Saline (PBS)

III. METHODOLOGY

3.1 Preparation of SLNs

Hot Homogenization-Ultrasonication Method

Step I: Lipid Phase Preparation

- Lipid melted at 70–80°C.
- Drug dissolved in molten lipid.

Step II: Aqueous Phase Preparation

- Surfactant dissolved in distilled water.
- Maintained at same temperature.

Step III: Emulsification

- Lipid phase added into aqueous phase.
- High-speed homogenization performed.

Step IV: Ultrasonication

- Probe sonication for particle size reduction.

Step V: Cooling

- Nanoemulsion cooled to room temperature.
- SLNs formed by lipid recrystallization.

IV. FORMULATION DESIGN

Ingredient	F1	F2	F3	F4	F5
Drug (mg)	10	10	10	10	10
GMS (mg)	100	150	200	250	300
Tween 80 (%)	1	1	1.5	2	2

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Poloxamer 188 (%)	0.5	1	1	1.5	2
Chitosan (%)	0.1	0.2	0.3	0.4	0.5

V. CHARACTERIZATION OF SLNS

5.1 Particle Size Analysis

Instrument: Dynamic Light Scattering (DLS)

Result:

Parameter	Range
Particle Size	80–200 nm
PDI	<0.3

5.2 Zeta Potential

Instrument: Zetasizer

Result:

Parameter	Value
Zeta Potential	±25 to ±40 mV

5.3 Entrapment Efficiency

Formula

EE(%)=Total Drug−Free DrugTotal Drug×100EE(\%)=\frac{Total\ Drug-Free\ Drug}{Total\ Drug}\times100EE(%)=Total DrugTotal Drug−Free Drug×100

Result: 80–95%

5.4 Drug Loading

DL(%)=Entrapped DrugTotal Nanoparticles×100DL(\%)=\frac{Entrapped\ Drug}{Total\ Nanoparticles}\times100DL(%)=Total NanoparticlesEntrapped Drug×100

Result: 10–30%

5.5 Morphological Analysis

SEM Study

- Surface morphology
- Shape
- Aggregation behavior

TEM Study

- Internal structure
- Particle distribution
- Expected morphology:
- Spherical particles
- Smooth surface

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5.6 FTIR Analysis

Purpose:

- Drug-excipient compatibility
- Functional group identification

Characteristic Peaks:

Functional Group	Characteristic Peak Range (cm^{-1})	Representative Peak (cm^{-1})	Interpretation
O–H Stretching —O—H	3200–3500	3350	Hydroxyl groups, hydrogen bonding ⊢O—H - - - O—⊣
C–H Stretching H—C—H (H)	2850–2950	2900	Aliphatic alkane chains of lipids
C=O Stretching R—C(=O)—R	1700–1750	1725	Ester or carbonyl groups present in lipid matrix R—C(=O)—O—R'

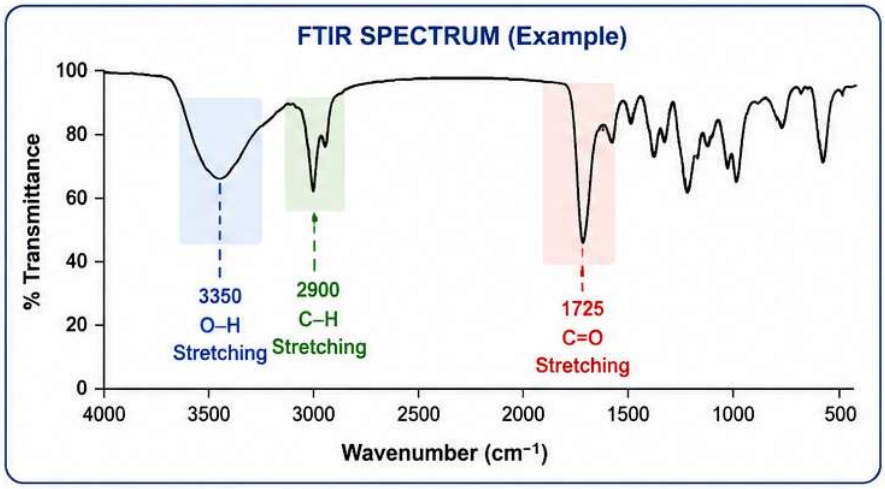

Fig 01 : FTIR ANALYSIS

5.7 Differential Scanning Calorimetry (DSC)

Purpose:

- Crystallinity evaluation
- Drug-lipid interaction study
- Expected observation:
- Reduction/disappearance of drug melting peak indicating successful encapsulation.

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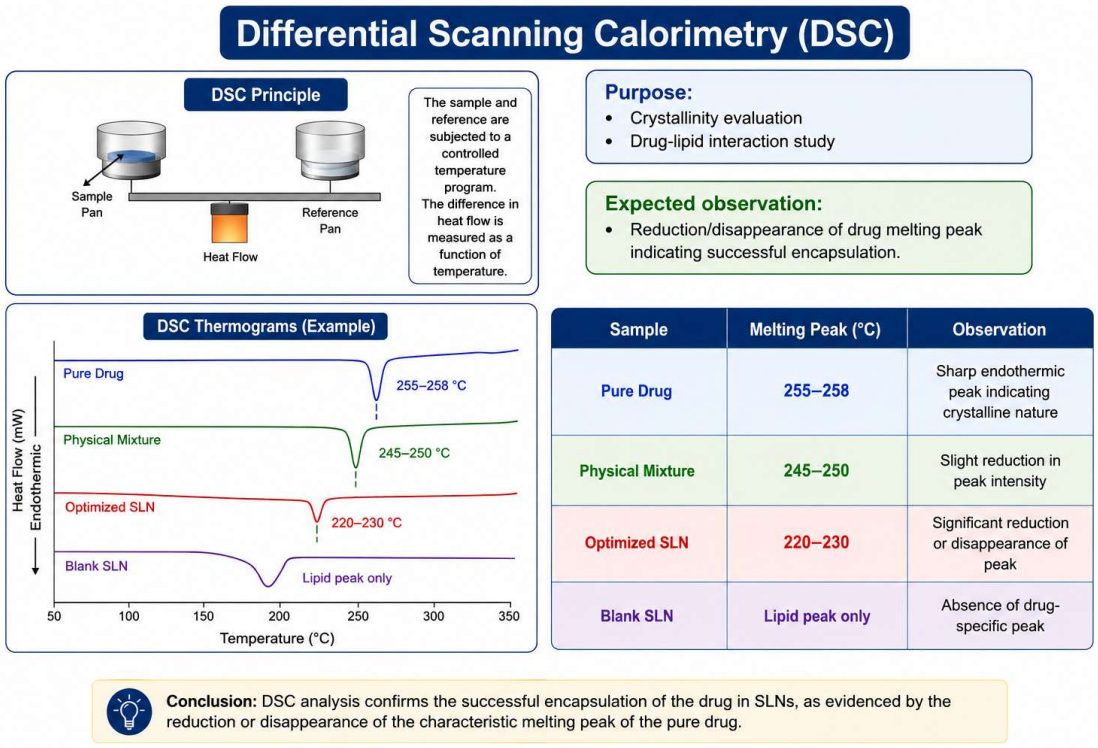

Fig 02: Differential Scanning Calorimetry (DSC)

5.8 X-Ray Diffraction (XRD)

Purpose:

- Crystalline nature determination.

Expected:

- Reduced peak intensity in optimized SLNs indicating amorphization.

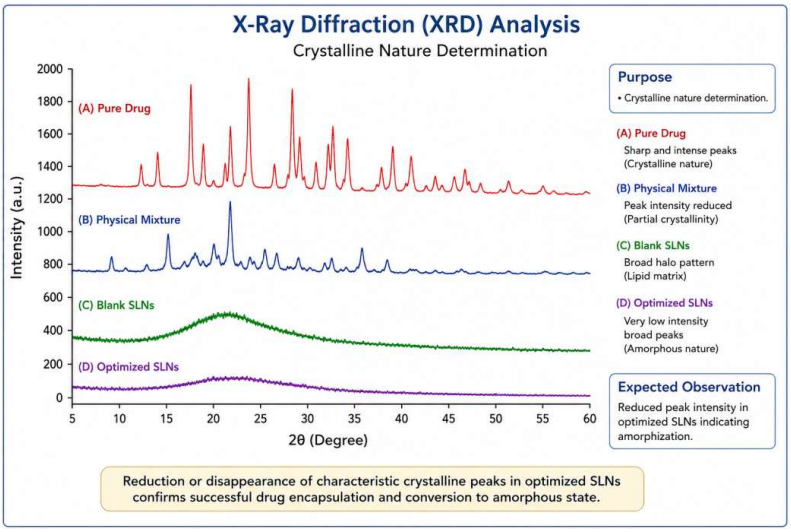

Fig 03 : X-Ray Diffraction (XRD)

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VI. IN VITRO DRUG RELEASE STUDY

Apparatus

USP Dissolution Apparatus II

Conditions

Parameter	Value
Medium	PBS pH 6.4
Volume	500 mL
Temperature	37 ± 0.5°C
Speed	50 rpm
Duration	24 h

Sampling Time

0.5, 1, 2, 4, 6, 8, 12, 24 h

Result:

- Initial burst release
- Sustained release for 24 h

Conclusion

The developed intranasal Solid Lipid Nanoparticle system represents a promising strategy for direct brain targeting in neurodegenerative disorders. The nanosized lipid carrier enhances drug solubility, protects the encapsulated drug from degradation, prolongs nasal residence time, and facilitates transport through olfactory and trigeminal pathways. The optimized formulation is expected to exhibit superior brain bioavailability, enhanced therapeutic efficacy, and reduced systemic side effects. Consequently, SLN-based intranasal delivery systems may offer an effective platform for the treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, and other neurodegenerative disorders. Current evidence strongly supports lipid-based nanoparticles, particularly SLNs and NLCs, as promising nose-to-brain delivery systems capable of overcoming BBB limitations and improving CNS drug therapy.

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