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DEVELOPMENT AND EVALUATION OF DONEPEZIL-RESVERATROL LIPOSOMAL IN SITU GELS FOR BRAIN TARGETING

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ABSTRACT

Alzheimer's disease is a progressive neurological disorder associated with memory impairment, cognitive decline, and neuronal degeneration. Conventional oral administration of therapeutic agents often faces limitations due to restricted blood-brain barrier permeability and systemic adverse effects. The present study proposes the development of an intranasal liposomal in situ gelling system containing Donepezil and Resveratrol for enhanced brain targeting. Donepezil acts as an acetylcholinesterase inhibitor, whereas Resveratrol possesses antioxidant and neuroprotective properties. Liposomes will be developed using suitable phospholipids and cholesterol through an appropriate preparation technique and incorporated into a thermosensitive or ion-sensitive in situ gel. The formulation will be evaluated for particle size, entrapment efficiency, zeta potential, gelation temperature, viscosity, drug release, nasal permeation, and stability. The proposed delivery system aims to improve nasal retention, facilitate nose-to-brain transport, and provide sustained drug release for potential cognitive enhancement.

Keywords: Donepezil, Resveratrol, Liposomes, In situ gel, Intranasal delivery, Brain targeting, Alzheimer's disease.

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I. INTRODUCTION

Alzheimer's disease is one of the most common neurodegenerative disorders affecting the elderly population. It is characterized by progressive deterioration of memory, learning ability, reasoning, and other cognitive functions. The disease is associated with several pathological changes, including amyloid-beta accumulation, tau protein abnormalities, oxidative stress, neuroinflammation, and neuronal degeneration. These changes gradually affect normal brain functioning and reduce the quality of life of affected individuals. The increasing prevalence of Alzheimer's disease has created a significant need for innovative therapeutic approaches capable of improving drug delivery to the central nervous system. Conventional oral medications provide symptomatic benefits; however, their therapeutic effectiveness may be limited by systemic metabolism and restricted drug distribution into brain tissues.

Donepezil is a commonly prescribed acetylcholinesterase inhibitor used for the symptomatic management of Alzheimer's disease. It increases the availability of acetylcholine in neuronal synapses by inhibiting its enzymatic breakdown, thereby supporting cholinergic neurotransmission. However, conventional oral administration may produce gastrointestinal disturbances and other systemic adverse effects. Resveratrol, a naturally occurring polyphenolic compound, has attracted considerable attention because of its antioxidant, anti-inflammatory, and neuroprotective properties. It may influence oxidative stress pathways, mitochondrial functions, and neuronal survival mechanisms. Combining Donepezil and Resveratrol may provide complementary pharmacological benefits by addressing cholinergic dysfunction and oxidative neuronal damage. Nevertheless, their effective delivery to the brain remains an important formulation challenge.

Intranasal drug administration has emerged as a promising alternative for delivering therapeutic agents directly towards the central nervous system. This route provides opportunities for drug transport through olfactory and trigeminal pathways, potentially reducing dependence on conventional systemic circulation and blood-brain barrier penetration. However, rapid mucociliary clearance, limited nasal residence time, enzymatic degradation, and restricted absorption can affect the performance of intranasal formulations. Liposomes offer a useful carrier platform because they consist of biocompatible phospholipid bilayers capable of incorporating different types of therapeutic molecules. Their structural characteristics may improve drug protection, encapsulation, and controlled release. Previous investigations have demonstrated the potential of liposomal Donepezil formulations for intranasal brain delivery.

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The incorporation of liposomes into an in situ gelling system may further improve the performance of intranasal drug delivery. These formulations are administered as liquids and undergo gel formation after exposure to physiological nasal conditions. Suitable polymers such as Poloxamer 407, Poloxamer 188, and gellan gum may provide temperature-sensitive or ion-sensitive gelation properties. The resulting gel can increase nasal retention and support prolonged drug release. Therefore, the proposed study focuses on developing Donepezil-Resveratrol-loaded liposomal in situ gels and evaluating their physicochemical, pharmaceutical, and nasal delivery characteristics. The formulation may provide a promising platform for improving brain targeting and supporting the management of cognitive dysfunction.

II. FORMULATION DEVELOPMENT AND PREPARATION OF LIPOSOMAL IN SITU GELS

The development of Donepezil-Resveratrol-loaded liposomal in situ gels requires the careful selection of suitable pharmaceutical ingredients, carrier materials, and gel-forming polymers. The primary objective of formulation development will be to prepare a stable liposomal system capable of incorporating both therapeutic agents and maintaining their pharmaceutical properties during intranasal administration. Donepezil hydrochloride will be selected as the cholinergic therapeutic agent, whereas Resveratrol will be incorporated as a complementary antioxidant compound. Their combination will be investigated to explore the possibility of addressing different pathological mechanisms associated with cognitive impairment. The selection of appropriate excipients will play an important role in determining the stability, encapsulation, drug release, and nasal compatibility of the developed formulation.

Liposomes will be selected as the primary drug delivery carriers because of their phospholipid-based structure and ability to incorporate hydrophilic and lipophilic substances. Phosphatidylcholine, cholesterol, and other suitable pharmaceutical-grade lipids may be employed during formulation development. Phosphatidylcholine will provide the principal bilayer structure, whereas cholesterol will help regulate membrane rigidity and reduce premature leakage of encapsulated drugs. The lipid composition will be optimized to achieve appropriate vesicle characteristics and satisfactory drug encapsulation. The ethanol injection method or thin-film hydration technique may be used for liposome preparation. During thin-film hydration, the selected lipid components will be dissolved in an appropriate organic solvent, followed by solvent evaporation to obtain a thin lipid film. The film will subsequently be hydrated with an aqueous phase containing the appropriate drug component under controlled conditions.

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The prepared liposomal dispersion will undergo size reduction using sonication or extrusion techniques to obtain relatively uniform vesicles. These procedures will help control particle size and improve formulation homogeneity. The concentration of phospholipids, cholesterol, drug-to-lipid ratio, hydration conditions, and processing parameters will be systematically optimized. Since Donepezil and Resveratrol possess different physicochemical characteristics, their incorporation into the liposomal system will require careful consideration of their respective locations within the vesicular structure. Donepezil hydrochloride may predominantly associate with the aqueous compartment, whereas Resveratrol may interact with the lipid bilayer. Their combined encapsulation efficiency and compatibility will therefore require individual analytical assessment.

After liposome preparation, the optimized vesicular dispersion will be incorporated into a suitable in situ gelling vehicle. Poloxamer 407 may be selected as the principal thermosensitive polymer because it can form a gel when exposed to physiological temperatures. Poloxamer 188 may be incorporated in appropriate proportions to modify gelation temperature and viscosity. Alternatively, gellan gum may be considered for ion-sensitive gel formation in response to electrolytes present in nasal secretions. The polymer concentration will be adjusted to obtain a formulation that remains sufficiently fluid during administration and undergoes gelation under nasal physiological conditions. The selection of polymers will also consider their compatibility with liposomes and the stability of the encapsulated therapeutic agents.

The preparation process will involve the gradual addition of the optimized liposomal dispersion into the previously prepared polymeric solution under controlled stirring conditions. For thermosensitive gel development, the cold preparation technique may be used to ensure complete polymer hydration and uniform dispersion. The formulation will be maintained under refrigerated conditions during preparation, where required, to prevent premature gelation. Appropriate pharmaceutical-grade buffers may be used to maintain nasal-compatible pH. The resulting formulation will be examined for appearance, homogeneity, clarity, phase separation, and physical stability. Particular attention will be given to avoiding excessive viscosity because the formulation must remain suitable for nasal administration.

Optimization of the formulation will involve evaluating the effects of lipid concentration, cholesterol ratio, polymer concentration, and drug loading on important formulation characteristics. A quality-by-design approach may be adopted to identify critical material attributes and process parameters. Experimental design techniques, such as factorial design or

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response surface methodology, may help establish relationships between formulation variables and measurable responses. The optimized formulation will be selected based on suitable vesicle size, acceptable encapsulation efficiency, controlled drug release, appropriate gelation temperature, and satisfactory nasal compatibility. Thus, the proposed formulation development process will establish the foundation for producing a reproducible liposomal in situ gel with potential applications in intranasal brain-targeted delivery.

III. PHYSICOCHEMICAL CHARACTERIZATION AND EVALUATION OF FORMULATION

The physicochemical characterization of the developed Donepezil-Resveratrol liposomal in situ gel will be essential for determining its pharmaceutical quality, structural properties, and suitability for intranasal administration. The prepared liposomes will initially be examined for particle size, polydispersity index, zeta potential, morphology, and entrapment efficiency. Particle size will be determined using dynamic light scattering, which provides information about the average hydrodynamic diameter of vesicles. A relatively uniform particle-size distribution will be desirable because it may contribute to consistent formulation behaviour and reproducible drug delivery. The polydispersity index will be measured to evaluate the distribution of vesicle sizes. A lower value will generally indicate a more homogeneous liposomal population.

Zeta potential will be determined to assess the surface charge and colloidal stability of the prepared liposomes. Surface charge influences electrostatic interactions between vesicles and may affect their aggregation behaviour during storage. Liposomal morphology will be investigated using suitable microscopic techniques, such as transmission electron microscopy or scanning electron microscopy. These techniques will help examine vesicle shape, surface characteristics, and structural integrity. The entrapment efficiency of Donepezil and Resveratrol will be determined separately using a validated analytical procedure. Free and encapsulated drug fractions will be separated using an appropriate method, such as ultrafiltration or centrifugation. Drug concentration will subsequently be quantified using high-performance liquid chromatography or another validated analytical technique.

The gel-forming characteristics of the final formulation will also be investigated. Gelation temperature will be determined by gradually increasing the temperature of the formulation under controlled experimental conditions. The transition from liquid to gel will be recorded to establish whether the formulation undergoes gelation within the desired physiological temperature range.

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Gelation time will also be measured because rapid but controlled gel formation may improve nasal retention. Viscosity measurements will be performed using a suitable rotational viscometer or rheometer. The formulation should exhibit sufficient fluidity before administration and increased viscosity after gel formation. These characteristics will help determine its suitability for nasal application and prolonged residence within the nasal cavity.

The pH of the formulation will be measured using a calibrated digital pH meter. Maintaining an appropriate pH will be important for ensuring nasal compatibility and preserving the chemical stability of both therapeutic agents. Mucoadhesive properties will be examined using suitable experimental techniques to determine the interaction between the formulation and mucin or nasal mucosal surfaces. In vitro drug release studies will be performed using an appropriate diffusion-based experimental model under controlled temperature and physiological conditions. Samples will be collected at predetermined intervals and analyzed to determine the release profiles of Donepezil and Resveratrol. Different mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, may be applied to interpret the release mechanism.

Ex vivo permeation studies will be conducted using suitable nasal mucosal tissue, such as sheep nasal mucosa, following appropriate ethical and laboratory requirements. The study will help evaluate the ability of the formulation to facilitate drug transport across the nasal epithelial barrier. The amount of each drug permeating through the tissue will be quantified using a validated analytical method. Histopathological examination may be performed to investigate possible structural changes in the nasal mucosa following exposure to the formulation. Nasal ciliotoxicity assessment will also be important because ciliary movement plays a major role in normal mucociliary clearance and nasal protection. These evaluations will help establish preliminary nasal safety and formulation compatibility.

Finally, stability studies will be performed under suitable storage conditions in accordance with applicable pharmaceutical stability guidelines. The samples will be examined periodically for changes in particle size, polydispersity index, zeta potential, drug content, entrapment efficiency, pH, viscosity, and gelation characteristics. Drug degradation and possible leakage from liposomes will also be investigated. Compatibility between the drugs, lipids, and polymers will be assessed using techniques such as Fourier-transform infrared spectroscopy and differential scanning calorimetry. The results of these investigations will provide information regarding the physical and chemical stability of the formulation. Collectively, these characterization studies will help identify an optimized liposomal in situ gel suitable for subsequent biological and pharmacological

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investigations.

IV. BRAIN TARGETING POTENTIAL AND THERAPEUTIC SIGNIFICANCE

Intranasal administration provides an alternative approach for delivering therapeutic agents towards the central nervous system without depending entirely on systemic circulation. The nasal cavity contains specialized anatomical regions associated with olfactory and trigeminal nerve pathways, which may facilitate the movement of administered substances towards different brain regions. These pathways are particularly important in the development of pharmaceutical formulations intended for neurodegenerative disorders. Conventional oral administration of Donepezil involves gastrointestinal absorption and systemic distribution before the drug reaches the brain. Although the drug provides symptomatic benefits, its therapeutic distribution may be affected by pharmacokinetic limitations and adverse effects. Therefore, intranasal liposomal delivery may offer an alternative strategy for improving the availability of Donepezil at the intended site of action.

The liposomal carrier system may contribute to improved drug delivery through its phospholipid-based structure. Liposomes can protect encapsulated compounds from certain environmental influences and provide a platform for controlling drug release. Their small vesicular structure may facilitate interactions with nasal epithelial membranes, although actual transport depends on particle characteristics, surface properties, formulation composition, and biological barriers. The incorporation of Resveratrol may provide an additional therapeutic dimension because of its potential antioxidant and anti-inflammatory effects. Oxidative stress is considered an important contributor to neuronal injury and neurodegenerative processes. Resveratrol has been investigated for its ability to influence cellular antioxidant mechanisms, mitochondrial activity, and inflammatory signalling pathways. However, its clinical neuroprotective effectiveness remains under investigation.

The combination of Donepezil and Resveratrol may be explored as a complementary therapeutic approach. Donepezil primarily acts through inhibition of acetylcholinesterase, thereby increasing acetylcholine availability in neuronal synapses. This mechanism supports cholinergic neurotransmission, which is important for learning and memory. Resveratrol may influence other biological mechanisms associated with neuronal damage, including oxidative stress and neuroinflammation. Combining these agents in a single delivery system may therefore provide opportunities to investigate their complementary effects. Nevertheless, the possibility of

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pharmacological interactions, appropriate drug ratios, and the contribution of each component must be carefully examined through experimental studies. The combination should not be considered clinically superior to existing treatments without supporting evidence.

The in situ gelling system may further improve intranasal delivery by increasing formulation residence time within the nasal cavity. Conventional liquid nasal preparations may be rapidly removed through mucociliary clearance, reducing the period available for drug absorption. Following administration, the liquid formulation may undergo gel formation under physiological nasal conditions. This transition may reduce rapid drainage and provide a controlled environment for the release of liposomal vesicles. The polymeric gel matrix may also help maintain the physical distribution of liposomes within the formulation. However, the gel should not become excessively viscous because this may interfere with nasal spreading, drug diffusion, and patient acceptability. Therefore, appropriate optimization of polymer concentration and gelation characteristics will be necessary.

The brain-targeting potential of the optimized formulation will be investigated through appropriate in vivo pharmacokinetic and biodistribution studies. Experimental animals may be used following institutional ethical approval and established animal welfare guidelines. Drug concentrations in plasma and different brain regions will be measured at predetermined time intervals following intranasal administration. Comparative groups may include free drug solution, liposomal formulation, liposomal in situ gel, and an appropriate reference treatment. Pharmacokinetic parameters, including maximum concentration, time to maximum concentration, and area under the concentration-time curve, will be determined. Drug targeting efficiency and direct transport percentage may also be calculated using established pharmacokinetic approaches. Behavioural assessments, including suitable memory and learning tests, may provide additional information about the pharmacodynamic performance of the formulation.

The proposed system may have considerable pharmaceutical significance because it integrates a dual-drug approach, liposomal encapsulation, and nasal in situ gel technology. Nevertheless, successful brain delivery will depend on several factors, including nasal deposition, epithelial permeation, drug stability, release kinetics, and the ability of the formulation to maintain acceptable nasal safety. Long-term toxicity, repeated-dose tolerability, immunological responses, and potential systemic exposure must also be examined. Future investigations should include detailed mechanistic studies and appropriately designed preclinical evaluations before clinical translation. Thus, Donepezil-Resveratrol liposomal in situ gels may represent a promising research

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direction for developing alternative brain-targeted delivery systems for cognitive dysfunction associated with neurodegenerative disorders.

V. CONCLUSION

The proposed development of Donepezil-Resveratrol-loaded liposomal in situ gels represents a promising pharmaceutical approach for intranasal brain-targeted drug delivery. The combination of Donepezil and Resveratrol may provide complementary pharmacological effects through cholinergic enhancement and antioxidant mechanisms. Their incorporation into liposomal carriers may improve drug protection, encapsulation, and controlled release characteristics. Furthermore, the use of an appropriate in situ gelling polymer may increase nasal residence time and reduce premature elimination through mucociliary clearance. These formulation characteristics may contribute to improving the overall performance of the developed intranasal delivery system.

The physicochemical characterization of the formulation will provide important information regarding particle size, polydispersity, zeta potential, entrapment efficiency, gelation temperature, viscosity, and drug release behaviour. Ex vivo nasal permeation studies and preliminary mucosal safety investigations will help determine its suitability for intranasal administration. Stability assessment will also be necessary to establish the compatibility of the drugs, lipids, and polymeric materials during storage. Appropriate optimization of these parameters will be essential for obtaining a uniform, stable, and reproducible formulation.

The proposed liposomal in situ gel may provide an opportunity to investigate direct nose-to-brain transport and improve the distribution of therapeutic agents within brain tissues. Comparative pharmacokinetic and pharmacodynamic studies will be necessary to determine whether the developed formulation offers advantages over conventional drug administration. Particular attention should be given to the individual contribution of Donepezil and Resveratrol, their possible interactions, and their effects on cognitive functions. Detailed preclinical investigations will also be required to evaluate repeated-dose safety and long-term tolerability.

Overall, the developed formulation may establish a useful foundation for further research into combination-based intranasal delivery systems for neurodegenerative disorders. Its potential benefits will depend on successful formulation optimization, biological compatibility, and demonstrated therapeutic effectiveness. Although the approach offers encouraging pharmaceutical possibilities, clinical benefits cannot be established without appropriate experimental and clinical evidence. Further investigations may help determine its applicability as an alternative delivery

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platform for supporting cognitive function and improving the management of Alzheimer's disease.

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