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DEVELOPMENT OF NILOTINIB-LOADED NANOSTRUCTURED LIPID CARRIERS FOR NOSE-TO-BRAIN DELIVERY IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a progressive neurological disorder characterized by cognitive deterioration, memory impairment, and changes in neuronal function. Nilotinib, a tyrosine kinase inhibitor, has attracted research interest because of its potential effects on cellular pathways associated with protein clearance and neurodegeneration. However, its clinical application in Alzheimer's disease remains investigational, and effective delivery to the brain continues to be an important challenge. The present research proposes the development of nilotinib-loaded nanostructured lipid carriers (NLCs) for intranasal nose-to-brain delivery. The formulation will be prepared using suitable solid and liquid lipids, surfactants, and an appropriate homogenization technique. Optimization will involve particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, and in vitro release. Nasal compatibility, mucoadhesion, and physical stability will also be investigated. The study will provide a formulation-development framework for subsequent preclinical evaluation of brain distribution, pharmacokinetics, and safety.

Keywords: Nilotinib, Alzheimer's disease, Nanostructured lipid carriers, Intranasal administration, Nose-to-brain delivery, Nanotechnology, Brain targeting.

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I. INTRODUCTION

Alzheimer's disease is a chronic neurodegenerative condition that progressively affects memory, cognitive abilities, behaviour, and the capacity to perform everyday activities. Its development involves complex pathological mechanisms, including amyloid-beta accumulation, abnormal tau phosphorylation, synaptic dysfunction, neuroinflammation, oxidative stress, and neuronal loss. These processes interfere with normal communication between neurons and contribute to progressive deterioration of brain function. The disease creates a substantial burden for patients, families, caregivers, and healthcare systems. Although currently available medicines may provide symptomatic benefits or modify selected disease-related pathways, there remains a need for additional therapeutic approaches that can address the biological processes associated with neurodegeneration.

Nilotinib is a small-molecule tyrosine kinase inhibitor approved for the treatment of specific forms of Philadelphia chromosome-positive chronic myeloid leukaemia. Its possible relevance to neurodegenerative diseases has been investigated because of its activity against kinase-related signalling pathways, including Abelson tyrosine kinase. Preclinical studies have suggested that modulation of these pathways may influence cellular processes involved in the handling of abnormal proteins, including amyloid-beta and tau. A small phase II clinical study also investigated the safety, tolerability, pharmacokinetics, and biomarker effects of nilotinib in individuals with mild-to-moderate Alzheimer's disease. However, that study was not designed or powered to establish clinical efficacy. Therefore, nilotinib must be considered an investigational candidate for Alzheimer's disease rather than an established therapy.

One of the major challenges in developing medicines for neurological disorders is the blood-brain barrier. This highly selective biological interface restricts the entry of many substances from systemic circulation into the brain. Although nilotinib has been detected in cerebrospinal fluid in clinical research, its brain exposure, distribution, and pharmacological effects remain important considerations. Conventional systemic administration may also expose patients to drug-related adverse effects outside the central nervous system. Intranasal administration has therefore attracted interest as a possible alternative delivery route. The nasal cavity contains olfactory and trigeminal neural pathways that may provide access to the central nervous system through neuronal and non-neuronal transport mechanisms. Nevertheless, nasal delivery is limited by mucociliary clearance, enzymatic activity, restricted administration volume, and the permeability characteristics of the nasal epithelium.

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Nanostructured lipid carriers are second-generation lipid-based nanoparticles developed using a combination of solid and liquid lipids. Their internal matrix can accommodate drug molecules and may provide improved drug incorporation, controlled release, and physical stability. NLCs are being investigated for intranasal delivery because their formulation properties can be adjusted according to the characteristics of the active pharmaceutical ingredient. The present research proposes the development and optimization of nilotinib-loaded NLCs for nose-to-brain delivery in the context of Alzheimer's disease. The formulation will be evaluated for particle size, PDI, zeta potential, entrapment efficiency, drug loading, release profile, nasal compatibility, and stability. Further preclinical investigations will be necessary to establish brain distribution, pharmacokinetic behaviour, and safety. The proposed work will therefore examine the feasibility of a lipid-based delivery platform rather than assume that intranasal NLC administration will improve the clinical effectiveness of nilotinib.

II. FORMULATION DESIGN AND PREPARATION OF NILOTINIB-LOADED NANOSTRUCTURED LIPID CARRIERS

The initial stage of formulation development will involve the selection of suitable pharmaceutical excipients for preparing nilotinib-loaded nanostructured lipid carriers. The selection of solid and liquid lipids will be based on drug solubility, compatibility, melting characteristics, safety, and formulation stability. A solid lipid will provide the structural framework of the nanoparticle, while the liquid lipid will create imperfections in the lipid matrix and may improve the capacity for drug incorporation. Candidate solid lipids may include glyceryl monostearate, stearic acid, or other pharmaceutically acceptable materials. Medium-chain triglycerides or other suitable oils may be screened as liquid lipid components. The final combination will be selected after conducting preliminary solubility and compatibility investigations.

Nilotinib has limited aqueous solubility, making the selection of an appropriate lipid environment particularly important. Preliminary solubility studies will be performed to identify lipid materials capable of dissolving or dispersing the drug during the preparation process. The solubility of nilotinib in different solid and liquid lipids will be examined under controlled conditions. Drug-excipient compatibility may be evaluated through Fourier-transform infrared spectroscopy and differential scanning calorimetry. These techniques may help identify changes in characteristic functional groups or thermal behaviour that could indicate possible interactions. The results will support the selection of suitable excipients and help determine whether the drug can be incorporated into the proposed lipid matrix without undesirable changes.

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The NLCs may be prepared using hot homogenization followed by high-pressure homogenization or another suitable emulsification technique. In the hot homogenization approach, the selected solid lipid will be heated above its melting temperature and mixed with the liquid lipid. Nilotinib will be incorporated into the lipid phase under conditions selected to maintain drug stability and adequate dispersion. An aqueous phase containing an appropriate surfactant will be prepared separately and heated to a temperature compatible with the lipid phase. The two phases will then be combined under controlled mixing to form a coarse emulsion. Homogenization will reduce the size of the dispersed lipid droplets, and subsequent cooling will allow the lipid phase to solidify into nanostructured carriers.

Different formulation batches will be developed by changing the relative concentrations of solid lipid, liquid lipid, surfactant, and nilotinib. These variables may influence particle size, entrapment efficiency, drug loading, and drug-release characteristics. A suitable balance between the solid and liquid lipid fractions will be necessary to maintain a stable matrix while providing adequate drug incorporation. Surfactant concentration will also be optimized to prevent aggregation and improve dispersion stability. Excessive surfactant, however, may affect nasal compatibility and should be avoided. The selection of excipient concentrations will therefore be based on systematic screening and experimental evaluation.

The manufacturing process will be controlled through parameters such as homogenization speed, processing time, temperature, and cooling conditions. These variables can influence the size distribution and physical characteristics of the resulting nanoparticles. Insufficient homogenization may produce larger particles and a broader size distribution, whereas excessive processing may increase energy input and potentially affect drug stability. The preparation conditions will be documented for each batch to support reproducibility. The use of a standardized procedure will also help distinguish the effects of formulation composition from the effects of manufacturing conditions.

The prepared dispersions will undergo preliminary evaluation for appearance, homogeneity, precipitation, aggregation, and phase separation. Formulations showing visible instability or poor dispersion characteristics will not be selected for further development. Suitable batches will be stored in appropriately selected containers and subjected to detailed physicochemical characterization. The formulation-development stage will be considered successful when it produces reproducible nilotinib-loaded NLCs with acceptable drug incorporation and physical characteristics. The selected formulation will then proceed to optimization and intranasal

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performance evaluation.

III. OPTIMIZATION AND PHYSICOCHEMICAL CHARACTERIZATION OF NILOTINIB-LOADED NLCS

The optimization of nilotinib-loaded NLCs will involve the systematic evaluation of formulation and process variables that influence the quality of the final product. Experimental design methods, including factorial design or response surface methodology, may be used to study the effects of selected independent variables. These may include solid lipid concentration, liquid lipid concentration, surfactant concentration, and homogenization conditions. The dependent responses may include particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, and in vitro drug release. Statistical analysis will help identify the relative contribution of each variable and the interactions between formulation components.

Particle size will be determined using dynamic light scattering. This parameter is important because it influences the surface area, physical behaviour, and release characteristics of the nanoparticle dispersion. A relatively small and reproducible particle-size distribution may be desirable for developing a stable intranasal formulation. However, particle size alone cannot establish the ability of NLCs to reach the brain. The relationship between particle characteristics, nasal deposition, mucosal interaction, and brain distribution will require further experimental investigation. The selected formulation will therefore be assessed using particle size together with other physicochemical and biological parameters.

The polydispersity index will be measured to evaluate the uniformity of the nanoparticle population. A lower PDI generally indicates a narrower particle-size distribution, while a higher value may suggest heterogeneity or aggregation. Zeta potential will be measured to assess the surface charge of the prepared NLCs. Surface charge may influence particle-particle interactions and dispersion stability. Nevertheless, the stability of lipid nanoparticles also depends on surfactant characteristics, steric stabilization, lipid composition, and storage conditions. Therefore, the PDI and zeta potential values will be interpreted alongside particle size and stability observations rather than being treated as independent indicators of formulation quality.

Entrapment efficiency will be evaluated to determine the proportion of nilotinib incorporated into the lipid carriers. Free drug will be separated from the nanoparticle dispersion using a suitable validated method, such as ultrafiltration or centrifugation, depending on the characteristics of the formulation. The amount of unentrapped drug will be quantified using a validated high-

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performance liquid chromatography method. Entrapment efficiency will be calculated by comparing the amount of incorporated drug with the total amount initially added. Drug loading will also be calculated to determine the quantity of nilotinib associated with the nanoparticle mass. These parameters will help identify formulations that provide adequate drug incorporation and consistent batch performance.

Morphological characterization will be carried out using suitable imaging techniques, such as transmission electron microscopy or scanning electron microscopy. These techniques may provide information about particle shape, surface appearance, and aggregation. Differential scanning calorimetry and X-ray diffraction may be used to investigate the thermal behaviour and physical state of the drug and lipid components. Changes in the characteristic thermal peaks or diffraction patterns may provide evidence of altered crystallinity or drug distribution within the lipid matrix. These findings will be interpreted carefully because the absence of a distinct crystalline drug peak does not, by itself, establish complete molecular dispersion or chemical compatibility.

The optimized formulation will be selected by considering all major quality attributes rather than relying on a single response. A batch with high entrapment efficiency may still be unsuitable if it exhibits excessive particle size, poor uniformity, inadequate stability, or an undesirable release profile. A predefined optimization strategy will therefore be used to identify a balanced formulation. The selected NLCs will undergo further testing for drug release, nasal compatibility, mucoadhesive behaviour, and stability. The overall objective will be to obtain a reproducible formulation with suitable physicochemical properties for subsequent preclinical investigation.

IV. IN VITRO EVALUATION, NOSE-TO-BRAIN POTENTIAL, AND SAFETY ASSESSMENT

In vitro drug-release testing will be conducted to investigate the release behaviour of nilotinib from the optimized NLC formulation. A suitable diffusion-based method, such as a dialysis membrane system, may be selected after confirming its suitability for the drug and formulation. The study will be performed under controlled temperature and agitation conditions using an appropriate release medium. Samples will be withdrawn at predetermined time intervals and replaced with fresh medium to maintain suitable sink conditions. The amount of nilotinib released will be determined using a validated analytical method. The cumulative percentage of drug release will be calculated and compared with an appropriate control containing unencapsulated nilotinib.

The release data may be analysed using mathematical models, including zero-order, first-order,

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Higuchi, and Korsmeyer-Peppas equations. These models may help describe the observed release pattern and provide an indication of whether diffusion or other formulation-related processes contribute to drug release. The mathematical model with the most appropriate statistical fit may be selected for describing the data. However, the model should not be interpreted as definitive proof of a particular release mechanism. The lipid composition, drug distribution, particle structure, and interaction with the release medium may all influence the observed profile.

Nasal compatibility will be an essential consideration because the formulation is intended for administration through the nasal cavity. The pH, osmolality, viscosity, and other relevant physical characteristics will be evaluated to determine whether the formulation is suitable for nasal application. In vitro cytotoxicity studies may be performed using an appropriate nasal epithelial cell model. Cell viability and morphological changes will be assessed following exposure to different concentrations of the formulation. The study may also examine relevant indicators of cellular injury or inflammatory responses. These investigations will provide preliminary evidence of biological compatibility but will not replace comprehensive toxicological studies.

The mucoadhesive properties of the formulation may be examined to understand its interaction with nasal mucus. Suitable in vitro methods may be used to evaluate the interaction between NLCs and mucin. A mucoadhesive polymer may be considered if the initial formulation demonstrates insufficient retention, but its inclusion should be carefully optimized. Excessive viscosity or strong mucoadhesion may interfere with spreading, administration, and drug release. The formulation must also account for mucociliary clearance, which is a natural protective mechanism of the nasal cavity. Therefore, improved nasal residence time should be assessed together with epithelial compatibility and the possible effects on normal mucociliary function.

The potential for nose-to-brain delivery will require further investigation beyond routine in vitro characterization. Appropriate animal studies may be designed to compare intranasal administration of nilotinib-loaded NLCs with suitable control formulations and administration routes. Pharmacokinetic analysis should determine nilotinib concentrations in plasma and relevant brain regions at predefined time points. Parameters such as maximum concentration, time to maximum concentration, and area under the concentration-time curve may be calculated. Brain targeting efficiency and drug targeting indices may also be evaluated using clearly defined methods. Such studies will help determine whether the intranasal formulation increases brain exposure relative to systemic exposure. Animal findings, however, cannot be directly assumed to predict human nose-to-brain delivery because nasal anatomy and physiology differ between species.

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Stability and safety evaluations will be required before considering further development. The optimized NLC formulation will be stored under selected temperature and humidity conditions, and samples will be examined at predetermined intervals for appearance, particle size, PDI, zeta potential, pH, drug content, entrapment efficiency, and signs of aggregation or precipitation. Stability-indicating analytical methods will be used to monitor possible drug degradation. Further toxicological investigations should examine local nasal irritation, systemic exposure, organ-related toxicity, and other relevant safety outcomes. Since nilotinib is associated with clinically important safety considerations, including cardiovascular and metabolic risks, its use for a new indication and delivery route would require careful evaluation. The proposed formulation must therefore undergo rigorous preclinical assessment before any clinical application can be considered.

V. CONCLUSION

The proposed research focuses on the development and optimization of nilotinib-loaded nanostructured lipid carriers for intranasal nose-to-brain delivery in the context of Alzheimer's disease. Nilotinib has attracted scientific interest because of its potential influence on kinase-related cellular pathways involved in neurodegeneration and protein handling. Nevertheless, its use in Alzheimer's disease remains investigational, and the available clinical evidence does not establish it as an effective treatment. The development of an alternative delivery system may help investigate its formulation properties and possible distribution within the central nervous system. Intranasal administration is of particular research interest because it may provide access to olfactory and trigeminal pathways while reducing dependence on systemic circulation.

Nanostructured lipid carriers may provide a suitable platform for incorporating nilotinib because their matrix contains both solid and liquid lipids. The composition of this matrix can be adjusted to influence drug incorporation, particle size, release behaviour, and physical stability. The proposed preparation methods, including hot homogenization and high-pressure homogenization, will support the development of different formulation batches. Systematic optimization will be necessary to determine the influence of lipid concentration, surfactant level, and processing conditions on the final product. The selection of the optimized formulation should consider particle size, PDI, zeta potential, entrapment efficiency, drug loading, and stability together.

The proposed evaluation will include physicochemical characterization, in vitro drug-release testing, nasal compatibility, mucoadhesive assessment, and stability studies. These investigations will provide preliminary evidence regarding the quality and suitability of the formulation for

intranasal administration. However, in vitro findings cannot establish direct brain delivery or therapeutic effectiveness. Further research should include pharmacokinetic studies, brain biodistribution, nasal tissue evaluation, and comprehensive toxicological assessment in appropriate preclinical models. Particular attention should be given to the safety profile of nilotinib, the dose delivered through the nasal route, and the possibility of systemic exposure.

Overall, the proposed work will provide a formulation-development framework for investigating nilotinib-loaded NLCs as a potential nose-to-brain delivery system. The research may contribute to understanding how lipid composition and nanoparticle characteristics influence the delivery of an investigational drug candidate. Future studies should establish reproducibility, long-term stability, brain exposure, and safety before considering clinical translation. Any potential role of this formulation in Alzheimer's disease must be established through appropriately designed clinical trials. Thus, the proposed system represents an experimental pharmaceutical approach and should not be regarded as an approved or proven treatment for Alzheimer's disease.

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