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Design and Evaluation of Mucoadhesive Nasal Gel for Brain Targeting

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Abstract: *Mucoadhesive nasal gels have emerged as a promising strategy for efficient brain targeting of therapeutics, offering a non-invasive alternative to overcome the formidable challenge posed by the blood-brain barrier. This review highlights the anatomical advantages of the nasal cavity, examines the use of advanced polymers and nanoparticles for enhancing mucoadhesion and retention, and discusses formulation strategies that exploit the olfactory and trigeminal nerve pathways for direct nose-to-brain drug delivery. Special emphasis is placed on the design and evaluation of thermoreversible in situ gels, their physicochemical and mucoadhesive characterization, and comparative pharmacokinetic outcomes versus conventional routes. Recent studies demonstrate that mucoadhesive nasal gels significantly improve brain bioavailability and targeting efficiency while maintaining patient safety and tolerability. Limitations such as variability in nasal physiology, formulation irritancy, and scalability are also discussed. Overall, this review presents a comprehensive perspective on the advances, opportunities, and ongoing challenges in developing mucoadhesive nasal gels for targeted brain delivery of diverse therapeutics.*

Keywords: *Mucoadhesive*

I. INTRODUCTION

The delivery of therapeutic agents to the central nervous system (CNS) remains one of the most significant challenges in pharmaceutical development due to the restrictive nature of the blood-brain barrier (BBB). The intranasal route has emerged as a promising non-invasive strategy for brain-targeted drug delivery, offering direct access to the CNS through unique anatomical connections between the nasal cavity and brain structures. This approach, combined with mucoadhesive in situ gel formulations, represents an innovative platform that bypasses the BBB, enhances drug bioavailability, and minimizes systemic side effects. The development of mucoadhesive nasal gels for brain targeting addresses critical limitations of conventional oral and parenteral routes, including extensive first-pass metabolism, poor bioavailability of CNS-active drugs, and the need for invasive administration procedures.

Anatomical and Physiological Basis of Nasal Drug Delivery

The nasal cavity provides a unique opportunity for delivering pharmaceutical ingredients directly to the CNS through specialized neural pathways. The olfactory neuroepithelium represents the only region of the CNS that is not protected by the BBB and thus remains in direct contact with the external environment, creating a distinctive access port to the brain[1]. Following nasal administration, drugs can reach the CNS via three main pathways: the olfactory nerve pathway, which innervates the nasal olfactory epithelium and terminates in the olfactory bulb; the trigeminal nerve pathway, which innervates the respiratory and olfactory epithelium through its ophthalmic and maxillary branches, terminating in the brainstem and olfactory bulb; and the vascular pathway, which provides indirect delivery through systemic circulation[2].

The olfactory and trigeminal nerve pathways facilitate brain delivery through either slow intracellular axonal transport (hours to days) or fast perineural paracellular transport (minutes) from the submucosal space to the cerebrospinal fluid compartment[3][4]. Recent evidence suggests that intranasal drug delivery enables both small and large molecules to bypass the BBB via these neural pathways[5][6][7]. The direct nose-to-brain transport occurs through perineural and

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perivascular spaces associated with olfactory and trigeminal nerves, allowing solutes applied to the nasal epithelium to be transported to the olfactory bulb and brainstem before distribution to other CNS areas[8][9].

The nasal mucosa offers several advantages for systemic and brain-targeted drug delivery, including a large surface area (approximately 150-180 cm²), highly vascularized epithelium, relatively high permeability, avoidance of hepatic first-pass metabolism, and reduced enzymatic activity compared to the gastrointestinal tract[10][11][12]. However, the nasal route also presents challenges, particularly mucociliary clearance, which rapidly eliminates administered formulations from the nasal cavity with a half-life of approximately 20 minutes in humans[13]. This physiological protective mechanism significantly limits the residence time of conventional nasal formulations and necessitates the development of mucoadhesive delivery systems to prolong drug contact with the absorption site.

Formulation Strategies for Mucoadhesive Nasal Gels

Thermosensitive Polymers

Thermosensitive in situ gelling systems have gained significant attention for nasal drug delivery due to their ability to exist as low-viscosity solutions at room temperature, allowing easy administration, and then undergo sol-gel transition at nasal physiological temperature (32-34°C) to form a gel that resists rapid clearance[14][15][16][17]. Poloxamer 407 (Pluronic F127) is the most widely used thermoreversible gelling agent for nasal formulations due to its excellent thermosensitive gelling properties, water solubility, good drug release characteristics, low toxicity, and minimal irritation[18].

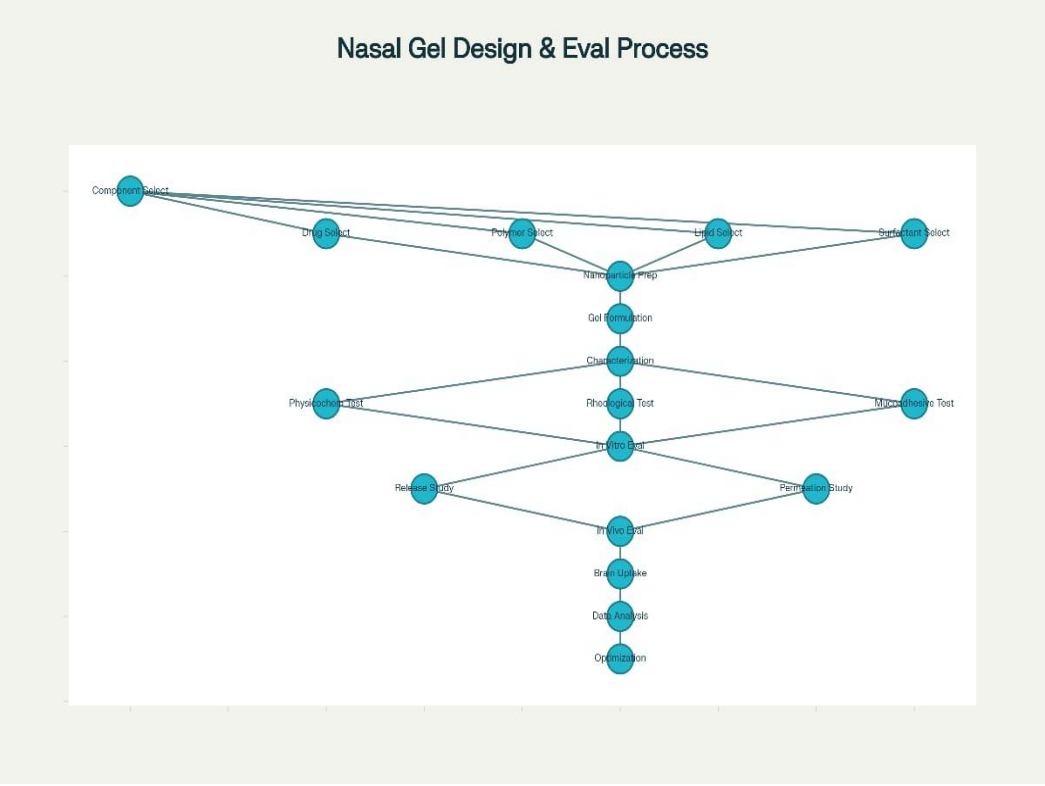

Fig. Flowchart of the design, formulation and evaluation of mucoadhesive nasal

Poloxamer 407 is an amphiphilic triblock copolymer consisting of polyoxyethylene-polyoxypropylene-polyoxyethylene units that undergoes temperature-dependent micellization and gelation[19][20][21]. At low temperatures, poloxamer molecules exist as unimers in aqueous solution, but as temperature increases, they form micelles due to dehydration of the hydrophobic polyoxypropylene blocks[22][23]. Further temperature increase leads to micelle packing and entanglement, resulting in gel formation. The gelation temperature of poloxamer 407 systems depends on polymer

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concentration, with typical concentrations ranging from 15-25% w/v to achieve gelation temperatures between 30-37°C suitable for nasal administration[24].

While poloxamer 407 alone can provide thermosensitivity, its gelation temperature is often too low or too high at practical concentrations, and the resulting gel may lack sufficient mechanical strength and mucoadhesive properties. To address these limitations, poloxamer formulations are frequently combined with poloxamer 188, which helps modulate gelation temperature and improve gel strength. The incorporation of poloxamer 188 at concentrations of 2-5% w/v alongside poloxamer 407 allows fine-tuning of the gelation temperature while maintaining acceptable viscosity in the sol state[25].

Mucoadhesive Polymers

Mucoadhesion is critical for prolonging the residence time of nasal formulations at the absorption site, thereby enhancing drug bioavailability and brain targeting efficiency[26]. Mucoadhesive polymers interact with the mucus layer through various mechanisms, including hydration of polymer chains, intimate contact and entanglement with mucin fibers, formation of labile bonds such as disulfide bridges, electrostatic attractive forces, hydrophobic interactions, and hydrogen bonding[27].

Hydroxypropyl methylcellulose (HPMC) is extensively used as a mucoadhesive polymer in nasal gel formulations due to its excellent biocompatibility, non-toxicity, and ability to enhance viscosity and mucoadhesion[28]. HPMC grades such as K4M, K15M, and K100M differ in molecular weight and viscosity, with higher grades providing greater mucoadhesive strength but potentially slower drug release[29]. Typical HPMC concentrations in nasal gel formulations range from 0.2-1.0% w/v, balancing mucoadhesive properties with acceptable sol viscosity for administration[30].

Carbopol (polyacrylic acid) represents another widely used mucoadhesive polymer that exists as a coiled structure at low pH and swells significantly at higher pH due to ionization of carboxyl groups[31]. Carbopol 934P and Carbopol 940P are commonly employed in nasal formulations at concentrations of 0.1-0.5% w/v to enhance mucoadhesion without excessively increasing the initial solution viscosity. The combination of carbopol with thermosensitive poloxamers creates a synergistic effect, providing both pH-triggered and temperature-triggered gelation along with enhanced mucoadhesive properties.

Chitosan, a cationic polysaccharide derived from chitin, has emerged as a particularly promising mucoadhesive agent for nasal drug delivery due to its biocompatibility, biodegradability, inherent mucoadhesiveness, and ability to transiently open epithelial tight junctions, thereby enhancing drug permeation[32][33]. Chitosan exhibits a positive charge at nasal physiological pH (5.5-6.5), facilitating electrostatic interaction with the negatively charged sialic acid residues of mucin glycoproteins. Furthermore, chitosan has been shown to inhibit efflux transporters and enzymatic degradation, contributing to improved drug bioavailability. Chitosan concentrations in nasal gel formulations typically range from 0.1-0.5% w/v to provide mucoadhesion without causing excessive viscosity or potential nasal irritation[34].

Nanocarrier-Based Gel Systems

The incorporation of drug-loaded nanoparticles into mucoadhesive in situ gel matrices represents an advanced strategy that combines the advantages of nanosystems with prolonged nasal residence time[35][36][37]. Nanocarrier systems, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, liposomes, ethosomes, and bilosomes, offer several benefits for nasal brain targeting: protection of encapsulated drugs from enzymatic and chemical degradation, enhanced drug solubility and stability, controlled drug release kinetics, improved cellular uptake and mucosal permeation, and the ability to traverse neural pathways to reach the brain[38][39][40].

Solid lipid nanoparticles and nanostructured lipid carriers have been extensively investigated for nose-to-brain delivery due to their biocompatibility, biodegradability, protection of labile drugs, controlled release properties, and enhanced brain uptake[41]. SLNs are typically prepared using solid lipids such as glyceryl monostearate, stearic acid, or compritol, while NLCs incorporate both solid and liquid lipids to create an imperfect crystal lattice that accommodates higher drug loading and reduces drug expulsion during storage. Preparation methods include hot homogenization, ultrasonication, microemulsion, and solvent emulsification-evaporation techniques[42].

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The optimal particle size for nasal brain targeting appears to be in the range of 100-300 nm, balancing sufficient mucus penetration with adequate cellular uptake and neural transport [43]. Particles below 500 nm can squeeze through the non-viscous aqueous pores within the entangled mucin network, enhancing interaction with the epithelium. Surface charge also significantly influences nanoparticle fate in the nasal cavity; positively charged nanoparticles exhibit enhanced mucoadhesion through electrostatic interaction with negatively charged mucus, while neutral or slightly negative particles may demonstrate better mucus penetration [44][45].

Characterization and Evaluation Methods

Physicochemical Characterization

The comprehensive physicochemical characterization of mucoadhesive nasal gels is essential to ensure product quality, stability, and performance. Critical parameters include pH, which should be maintained between 5.5 and 6.5 to match nasal physiological conditions and avoid mucosal irritation. pH measurement is typically performed using a calibrated digital pH meter at room temperature. Gelation temperature is determined using the visual tube inversion method, where formulations are placed in test tubes and gradually heated in a water bath, with the temperature at which the formulation no longer flows upon inversion recorded as the gelation temperature .Optimal gelation temperatures for nasal application range from 30-37°C, ensuring the formulation remains liquid at room temperature for easy administration but rapidly gels upon contact with the warmer nasal mucosa[46].

Drug content determination ensures uniform distribution and accurate dosing of the active pharmaceutical ingredient. Samples are typically diluted with appropriate solvents, filtered, and analyzed using validated spectroscopic (UV-visible spectrophotometry) or chromatographic (HPLC) methods. Drug content should generally be within 95-105% of the theoretical value to ensure dosing accuracy.Viscosity measurement provides critical information about the formulation's flow properties and patient acceptability. Rheological studies are conducted using viscometers or rheometers at both storage temperature (25°C) and nasal physiological temperature (34-37°C)[47]. Mucoadhesive nasal gels typically exhibit non-Newtonian pseudoplastic (shear-thinning) flow behavior, facilitating administration while providing adequate gel strength after application [48].

For nanoparticle-loaded gel formulations, additional characterization is required for the nanocarriers. Particle size, polydispersity index (PDI), and zeta potential are measured using dynamic light scattering and electrophoretic light scattering techniques. Particle sizes of 100-300 nm with PDI values below 0.3 indicate uniform, monodisperse formulations suitable for nasal delivery. Zeta potential values greater than ±20 mV suggest adequate electrostatic stability to prevent aggregation. Encapsulation efficiency and drug loading are determined by separating free drug from nanoparticles through centrifugation or ultrafiltration and quantifying drug content in both fractions [49].

Mucoadhesive Strength Assessment

Mucoadhesive strength quantifies the force required to detach the gel formulation from nasal mucosa, providing a direct measure of residence time potential. The most common method employs a texture analyzer or modified physical balance with nasal mucosa (typically from sheep, goat, or porcine sources) mounted between two chambers. The gel is applied to the mucosal surface, allowed to hydrate, and then subjected to a controlled tensile force until detachment occurs. Mucoadhesive force is expressed in dynes/cm² or Newtons, with higher values indicating stronger mucoadhesion and potentially longer residence time. Formulations with mucoadhesive strength exceeding 1000 dyne/cm² are generally considered suitable for nasal application.

Gel strength is assessed to ensure the formulation maintains sufficient structural integrity after gelation to resist drainage from the nasal cavity. This parameter is typically measured using a texture analyzer with a cylindrical probe penetrating the gel at a constant rate, with the force required for penetration recorded [50]. Alternatively, gel strength can be evaluated through the time required for a specific weight to sink a defined distance through the gel matrix. Adequate gel strength ensures the formulation remains in contact with the nasal mucosa for extended periods, facilitating sustained drug release and absorption [51].

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In Vitro Drug Release Studies

In vitro drug release studies provide critical information about the formulation's ability to deliver the drug over time and help predict in vivo performance. The most widely used method employs Franz diffusion cells with a dialysis membrane (typically cellulose or PVDF with MWCO 12-14 kDa) separating the donor compartment containing the gel from the receptor compartment containing phosphate buffer (pH 6.4) or simulated nasal fluid at 34-37°C.The receptor medium is continuously stirred and sampled at predetermined intervals, with sink conditions maintained throughout the study. Drug release profiles are analyzed using mathematical models including zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell equations to elucidate release mechanisms[52].

The Korsmeyer-Peppas model is particularly useful for characterizing drug release from polymeric matrices, with the release exponent (n) indicating the transport mechanism: $n \leq 0.43$ suggests Fickian diffusion, $0.43 < n < 0.85$ indicates anomalous (non-Fickian) transport involving both diffusion and polymer relaxation, $n = 0.85$ represents Case II transport (polymer relaxation), and $n > 0.85$ indicates super Case II transport. Ideal nasal gel formulations should demonstrate controlled release over 6-12 hours, providing sustained drug levels while the formulation remains in the nasal cavity [53].

Ex Vivo Permeation Studies

Ex vivo permeation studies using excised nasal mucosa provide more biorelevant data than in vitro release studies by incorporating the biological barrier. Nasal mucosa is typically obtained from freshly slaughtered animals (sheep, goat, or porcine) and used immediately or stored frozen at -20°C for short periods . Modified Franz diffusion cells are employed with the nasal mucosa mounted between donor and receptor compartments, with the epithelial side facing the donor . The gel formulation is applied to the mucosal surface, and the receptor compartment (typically containing phosphate buffer pH 6.4 or simulated nasal fluid) is maintained at 34-37°C with continuous stirring. [54]

Samples from the receptor compartment are analyzed at regular intervals to determine cumulative drug permeation. Key parameters calculated from permeation data include cumulative amount permeated (Q), steady-state flux (Jss, typically in µg/cm²/h), permeability coefficient (Kp, in cm/s), and enhancement ratio compared to control formulations. The flux is determined from the slope of the linear portion of the cumulative amount permeated versus time plot, while the permeability coefficient is calculated by dividing flux by the initial drug concentration. Mucoadhesive gel formulations typically demonstrate significantly higher permeation parameters compared to simple drug solutions due to prolonged contact time and potential permeation enhancement effects of formulation excipients.[55]

To ensure tissue viability during extended permeation studies, novel approaches have been developed, including the use of Krebs-Henseleit buffer solution in the receptor compartment to supply glucose to the tissue, thereby maintaining metabolic activity throughout the experiment. Histopathological examination of mucosal tissue following permeation studies is critical to assess potential damage or irritation caused by the formulation. [56]

In Vivo Pharmacokinetic and Biodistribution Studies

In vivo studies in animal models provide the definitive assessment of nasal gel formulations for brain targeting by quantifying drug levels in plasma and brain tissues following intranasal and intravenous administration. Rodent models, particularly rats and mice, are most commonly used, with formulations administered to anesthetized animals using micropipettes or specialized nasal delivery devices. Animals are typically sacrificed at predetermined time points (ranging from 15 minutes to 24 hours), and blood samples are collected via cardiac puncture while brain tissue is harvested, homogenized, and processed for drug quantification.[57]

Drug concentrations in plasma and brain homogenates are measured using validated analytical methods, most commonly high-performance liquid chromatography (HPLC) with UV, fluorescence, or mass spectrometry detection. Pharmacokinetic parameters including maximum concentration (Cmax), time to maximum concentration (Tmax), area under the concentration-time curve (AUC), elimination half-life (t1/2), and mean residence time (MRT) are calculated using non-compartmental or compartmental analysis.[58]

Critical to nose-to-brain delivery assessment is the calculation of brain targeting parameters that quantify the efficiency of direct neural transport versus systemic circulation pathways. The drug targeting efficiency (DTE%) is calculated as:

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DTE% = [(AUC brain/AUC blood) intranasal / (AUC brain/AUC blood) intravenous] × 100

where values exceeding 100% indicate superior brain targeting via the intranasal route compared to intravenous administration.

The direct transport percentage (DTP%) estimates the fraction of drug reaching the brain through direct nose-to-brain pathways:

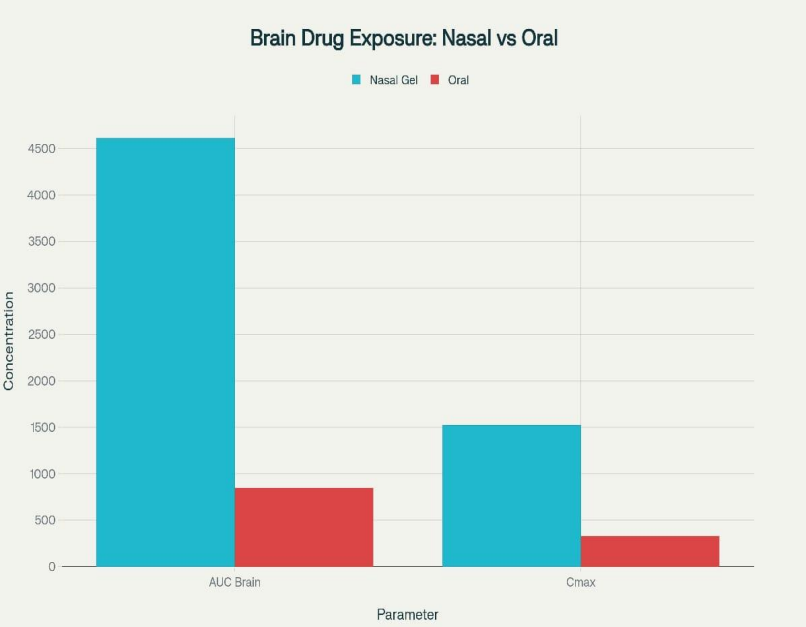
$$DTP\% = [(Bin - Bx) / Bin] \times 100,$$

Where , Bin is the brain AUC following intranasal administration and Bx is the fraction accounting for drug that crossed the BBB from systemic circulation.

Bx is calculated as:

$$Bx = (Biv / Piv) \times Pin,$$

where Biv and Piv are brain and plasma AUC after intravenous administration, and Pin is plasma AUC after intranasal administration.



Graph .1. Comparison of brain drug exposure (AUC,Cmax) via Intranasal Gel vs oral administration

Positive DTP values up to 100% confirm the contribution of direct neural pathways to brain drug delivery.The brain/blood concentration ratio provides additional insight into preferential brain accumulation, with ratios greater than unity indicating enhanced brain distribution.

Drug targeting index (DTI), calculated as the ratio of brain-to-blood AUC after intranasal administration divided by the same ratio after intravenous administration, offers another measure of targeting efficiency, with values above 1.0 demonstrating preferential brain delivery.

Biodistribution studies examining drug levels in multiple organs (brain regions, liver, kidney, heart, lungs, spleen) help assess selectivity of brain targeting and potential off-target accumulation. Regional brain distribution analysis, evaluating drug concentrations in olfactory bulb, cerebrum, cerebellum, hippocampus, striatum, and brain stem, provides mechanistic insights into the neural pathways involved in nose-to-brain transport.[59]

Pharmacodynamic and Toxicity Evaluation

Pharmacodynamic studies complement pharmacokinetic data by assessing the therapeutic efficacy of nasally administered formulations in disease models. For neurological disorders, disease-specific animal models are employed, such as 6-hydroxydopamine or MPTP-induced Parkinson's disease models, haloperidol-induced catalepsy,

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streptozotocin-induced Alzheimer's disease models, and pentylenetetrazol-induced seizure models. Behavioral assessments relevant to the specific disease are conducted, including locomotor activity measurement, rotarod performance, catalepsy tests, cognitive function tests (Morris water maze, novel object recognition), and seizure frequency and intensity scoring.

Biochemical markers in brain tissue provide additional evidence of therapeutic effect and mechanistic insights. Common assessments include neurotransmitter levels (dopamine, serotonin, norepinephrine), enzyme activity (monoamine oxidase, acetylcholinesterase, catalase), oxidative stress markers (malondialdehyde, reduced glutathione, superoxide dismutase), and inflammatory mediators (IL-1β, IL-6, TNF-α.

Histopathological examination of brain tissue sections stained with hematoxylin and eosin or specialized neuronal stains allows visualization of neuroprotective effects and assessment of potential formulation-induced toxicity. Safety evaluation of nasal formulations includes assessment of nasal mucosal toxicity through histopathological examination of nasal tissue following acute (single dose) and chronic (repeated dose) administration. Parameters evaluated include epithelial integrity, presence of inflammation, edema, vascular congestion, and ciliary function. Mucus production and ciliary beat frequency can be assessed using specialized microscopy techniques [60].

Systemic toxicity studies examine hematological parameters (complete blood count, differential white blood cell count), clinical biochemistry (liver function tests, kidney function tests, electrolytes), and body weight changes. Long-term stability studies following ICH guidelines (Q1A) assess formulation stability under accelerated (40°C ± 2°C/75% RH ± 5% RH) and long-term (25°C ± 2°C/60% RH ± 5% RH) storage conditions over 3-6 months [61].

Clinical Applications and Future Perspectives

Mucoadhesive nasal gels for brain targeting have demonstrated significant potential for treating a wide range of CNS disorders. For neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis, nasal delivery offers the possibility of delivering neuroprotective agents, neurotransmitter precursors, and anti-inflammatory drugs directly to affected brain regions while minimizing systemic exposure. Clinical trials have explored intranasal insulin for Alzheimer's disease, oxytocin for autism and psychiatric disorders, and davunetide for cognitive impairment.[62]

In the treatment of acute neurological conditions such as migraine, seizures, and stroke, the rapid onset of action achievable through nasal delivery provides significant therapeutic advantages. Several triptan formulations for migraine have received regulatory approval for nasal administration, validating the clinical feasibility of this route. Brain tumors represent another potential application, with nasal delivery offering a non-invasive means of delivering chemotherapeutic agents, targeted therapies, and nanocarrier systems directly to tumor sites.[63]

Despite significant progress, several challenges remain to be addressed for successful clinical translation of mucoadhesive nasal gels for brain targeting. Inter-individual variability in nasal anatomy, mucociliary clearance rate, and disease state can affect formulation performance and necessitates careful clinical evaluation. Development of patient-appropriate nasal delivery devices capable of depositing formulations in the olfactory region is critical for maximizing direct brain delivery. Most conventional nasal spray devices deposit primarily in the respiratory region, limiting olfactory pathway utilization. Advanced devices such as the ViaNase atomizer, Precision Olfactory Device, and Exhalation Delivery Systems have been developed specifically for olfactory deposition[64].

Regulatory considerations for nasal formulations intended for brain targeting require demonstration of both local tolerability and evidence of brain-specific pharmacokinetics and pharmacodynamics. This may involve specialized clinical trial designs incorporating neuroimaging techniques, CSF sampling, or pharmacodynamic biomarkers to confirm brain delivery and therapeutic effect. Long-term safety evaluation is particularly important for chronic CNS conditions requiring extended treatment duration.[65]

II. CONCLUSION

The development of mucoadhesive nasal gels for brain targeting represents a transformative approach to CNS drug delivery that addresses the fundamental challenge posed by the blood-brain barrier. By exploiting the unique anatomical

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connections between the nasal cavity and brain, these formulations enable direct neural transport of therapeutic agents while avoiding systemic circulation and first-pass metabolism. The integration of thermosensitive and mucoadhesive polymers creates an elegant solution that is easily administered as a liquid but rapidly forms a gel in situ to prolong residence time at the absorption site. The further incorporation of nanocarrier systems provides additional advantages of drug protection, controlled release, enhanced permeation, and targeted delivery.

Comprehensive evaluation methodologies encompassing physicochemical characterization, rheological analysis, mucoadhesive strength assessment, in vitro release studies, ex vivo permeation studies, and in vivo pharmacokinetic and pharmacodynamic assessments provide the necessary evidence to validate these formulations. The calculation of brain targeting parameters including drug targeting efficiency, direct transport percentage, and drug targeting index allows quantitative assessment of nose-to-brain delivery superiority over conventional routes. As research continues to elucidate the mechanisms of nasal brain targeting and optimize formulation parameters, mucoadhesive nasal gels hold tremendous promise for revolutionizing the treatment of neurological disorders, offering patients non-invasive, effective, and targeted therapeutic options that were previously unattainable through conventional drug delivery approaches.

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