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An Investigation into In-Situ Nasal Gels for Enhanced Nasal Drug Delivery Systems

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Abstract: *The nasal cavity's rich blood supply significantly enhances drug absorption and bioavailability compared to other administration routes, making intranasal delivery highly desirable for systemic circulation. To prolong the retention time of in-situ gels on the nasal mucosa, biocompatible mucoadhesive polymers are employed in these drug delivery systems. In-situ nasal gels are administered as low-viscosity solutions that transform into gels upon contact with the nasal mucosa, minimizing first-pass metabolism, reducing enzymatic degradation, and preventing gastrointestinal ulcers. This controlled and sustained drug delivery system is particularly advantageous for drugs with poor oral bioavailability due to gastric irritation or extensive hepatic metabolism. Various stimuli-responsive polymers are used in gel formulations to enable precise control over drug release kinetics, based on gelation strength and viscosity. Given the limitations of oral drug administration, such as poor absorption and targeting difficulties, intranasal delivery offers a promising alternative. This review discusses the therapeutic advantages, nasal anatomy and physiology, challenges, opportunities, marketed products, and evaluation parameters for in-situ gel preparations in nasal drug delivery.*

Keywords: Polymer, in-situ drug delivery, formulation, mucoadhesion, metabolism, sustained release, nasal anatomy, bioavailability, transmucosal delivery, nasal gels

I. INTRODUCTION

Oral drug delivery is often the preferred method for administering medications. However, when systemic effects are required, the limited bioavailability of certain compounds has led to the exploration of alternative routes. The nasal mucosa has emerged as a critical pathway in transmucosal drug delivery, offering faster and more efficient drug absorption. Nasal drug delivery has demonstrated its potential, with many medications achieving better systemic bioavailability compared to oral administration. In this context, in situ gelation plays a key role. It involves the formation of a gel at the application site after the liquid formulation is applied, creating a semi-solid, mucoadhesive depot. This process enables effective delivery in liquid or solution form, further enhancing absorption through the nasal route.

II. NASAL DRUG DELIVERY

Nasal drug delivery involves administering medications through the nasal cavity, taking advantage of its unique anatomical and physiological characteristics for efficient absorption and rapid onset of action. The nasal cavity, with its rich network of blood vessels and mucosal tissues, provides a large surface area for drug absorption, while the mucociliary clearance mechanism helps regulate substance retention. This method offers several advantages, including rapid systemic absorption, bypassing first-pass metabolism, and being less invasive than injections, leading to improved patient compliance. Formulations for nasal delivery include liquid solutions, sprays, gels that transition upon contact with the mucosa, and inhalable powders.

However, challenges such as limited volume capacity, variability in absorption due to individual anatomical differences, and potential mucosal irritation can affect the effectiveness and tolerability of this route. Nasal drug

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delivery is well-suited not only for systemic applications, such as hormones and vaccines, but also for localized treatments of conditions like allergies and rhinitis. Recent advancements in formulation technologies, including nanoparticles and in situ gels, aim to improve drug stability, bioavailability, and patient experience, underscoring the ongoing potential of nasal delivery in various therapeutic contexts.

Advantages of In-Situ Nasal Gel:

- In-situ nasal gels enhance drug bioavailability by bypassing the first-pass metabolism typically associated with oral administration.
- These gels provide sustained and controlled drug release, resulting in prolonged therapeutic effects.
- The nasal route enables quicker drug absorption into the bloodstream, offering a faster onset of action compared to oral delivery.
- Nasal gels can target specific areas within the nasal cavity or reach systemic circulation, potentially increasing the efficacy of certain treatments.
- Avoiding the gastrointestinal tract reduces the risk of gastric irritation and ulcers, making it suitable for drugs that cause discomfort when taken orally.
- Nasal delivery is often more convenient and less invasive than methods like injections, leading to improved patient compliance.

Properties of In-Situ Nasal Gel:

- Balances flow and retention time within the nasal cavity.
- Enhances adherence to nasal mucosa, prolonging drug contact.
- Transitions from liquid to gel upon contact, triggered by temperature, pH, or ionic strength.
- Controls drug release rate and mechanism for sustained therapeutic effects.
- Should match the nasal environment (pH 5.5 to 6.5) to minimize irritation.
- Must be non-toxic and safe for nasal application.
- Maintains its properties under varying storage conditions.
- Should closely resemble body fluids to prevent irritation.
- Active ingredients need to be adequately soluble in the formulation.
- Influences absorption and potential irritation.
- Ensures uniformity, which affects patient acceptance.

III. EVALUATION OF FORMULATION:

- **Physical Appearance:** The gel should be clear or slightly opalescent, with a uniform color and free from visible particulates.
- **pH Measurement:** The pH should align with the nasal mucosa (typically around 5.5 to 6.5) to minimize irritation.
- **Viscosity:** Viscosity is measured using a viscometer to ensure the gel has suitable flow properties for easy administration and retention in the nasal cavity.
- **Mucoadhesive Properties:** The gel's ability to adhere to nasal mucosa is assessed through tensile strength or other adhesion tests, ensuring prolonged contact time.
- **Drug Release Studies:** In vitro studies (e.g., Franz diffusion cells) are used to evaluate the drug release rate and mechanism over time.
- **Stability Studies:** The formulation undergoes accelerated stability testing under varying temperature and humidity conditions to assess its physical and chemical stability.
- **In Vitro Permeation Studies:** These studies examine drug permeability through nasal mucosa models to predict in vivo absorption.
- **Osmolality:** The gel's osmolality should be similar to physiological fluids to avoid irritation upon application.

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- **Thermal and Mechanical Properties:** The gel's stability and performance during storage and application are assessed by examining its response to temperature changes and mechanical stress.
- **Microbial Contamination Testing:** Testing for microbial contamination ensures the formulation is safe for use.
- **Patient-Centric Assessments:** Sensory evaluations, including taste, smell, and texture, help gauge patient acceptability, which is crucial for compliance.

IV. ANATOMY AND PHYSIOLOGY OF THE NASAL CAVITY:

The nasal cavity is an essential part of the respiratory system, serving not only as a pathway for airflow but also facilitating olfaction and providing a site for drug delivery. Its anatomical structure and physiological functions are designed to optimize these processes.

Anatomy

Structure:

- **Nasal Septum:** Divides the nasal cavity into two halves, composed of both cartilage and bone.
- **Turbinates (Conchae):** Three pairs of bony structures (superior, middle, and inferior) extend into the nasal cavity, increasing the surface area for air filtration and contact.
- **Nasal Mucosa:** The inner lining consists of a mucous membrane rich in blood vessels and glands, which produce mucus to help warm, humidify, and filter incoming air.
- **Sinuses:** The nasal cavity connects to the paranasal sinuses (frontal, maxillary, ethmoid, and sphenoid), which aid in air conditioning, reduce skull weight, and contribute to voice resonance.
- **Olfactory Region:** This upper portion of the nasal cavity contains olfactory receptors responsible for detecting smells.
- **Oropharynx Connection:** The nasal cavity connects to the oropharynx via the choanae, allowing airflow into the respiratory tract.

Physiology

- **Air Conditioning:** The nasal cavity warms, humidifies, and filters the air we breathe, protecting the lungs from cold, dry air, and trapping dust and pathogens.
- **Mucociliary Clearance:** Mucus produced by the nasal mucosa traps particles and pathogens. Cilia, tiny hair-like structures, move this mucus toward the throat for expulsion or swallowing, maintaining airway cleanliness.
- **Olfaction:** The olfactory epithelium detects odor molecules, transmitting signals to the brain for smell perception.
- **Immune Defense:** The nasal cavity contains immune cells and produces secretory immunoglobulin A (sIgA), which provides protection against infections.
- **Nasal Drug Delivery:** Due to its extensive blood supply and large surface area, the nasal cavity offers an effective route for drug absorption, enabling rapid systemic effects and bypassing the first-pass metabolism in the liver.

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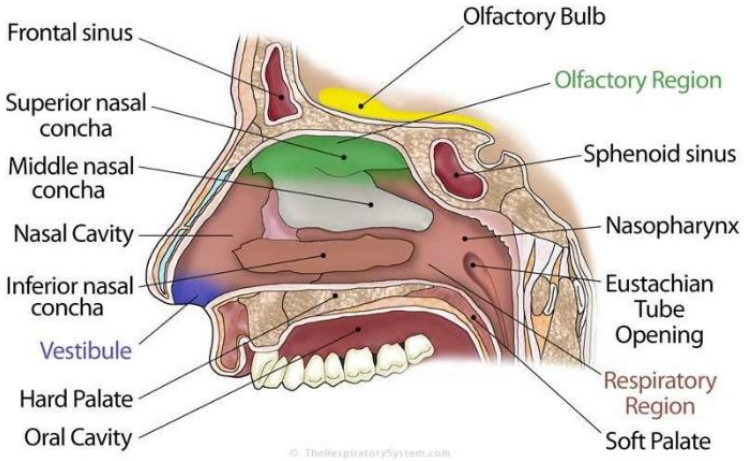

Fig. 1: Anatomy of Nasal cavity

V. MECHANISM OF DRUG ABSORPTION

In the initial phase of nasal drug absorption, the drug must first move from the nasal cavity into the mucus layer. Small, uncharged molecules can pass through this mucus layer relatively easily, while larger or charged drugs encounter more difficulty. Mucin, the main protein in mucus, binds to solutes, hindering their diffusion and reducing their movement. Additionally, the properties of the mucus layer, such as its viscosity and composition, can be affected by environmental factors like temperature and pH changes, further influencing drug absorption.

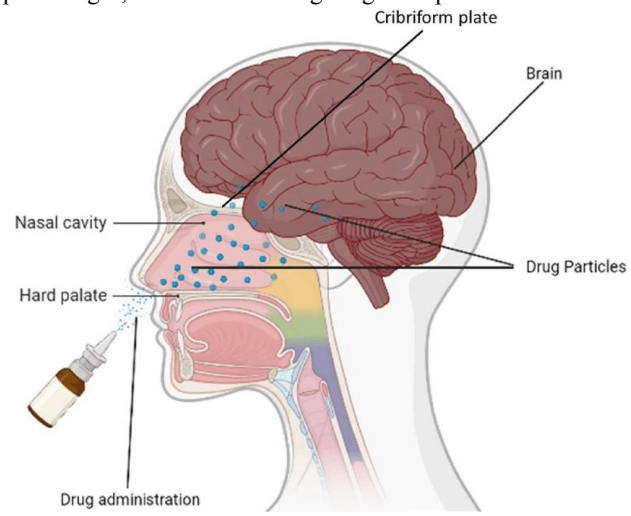

Fig. 2: Mechanism of drug absorption through nasal route

VI. CHALLENGES AND OPPORTUNITIES FOR NASAL DELIVERY SYSTEMS:

Challenges:

- **Limited Volume Capacity:** The nasal cavity can only hold small liquid volumes (50-200 µL), restricting the dosage for certain drugs.
- **Variability in Absorption:** Anatomical differences, mucosal conditions, and mucus presence can lead to inconsistent drug absorption and therapeutic outcomes.
- **Mucosal Irritation:** Some formulations may cause irritation or discomfort, reducing patient compliance.

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- **Drug Stability:** Nasal formulations can face stability issues due to environmental factors like temperature and humidity, potentially affecting their shelf life and efficacy.
- **Mucociliary Clearance:** The nasal cavity's natural defense mechanism clears mucus, limiting drug retention time and reducing effectiveness.
- **Regulatory Hurdles:** The regulatory process for new nasal drug delivery systems can be complex, affecting the time to market and approval.

Opportunities:

- **Enhanced Bioavailability:** Nasal delivery can improve the bioavailability of drugs that are poorly absorbed or heavily metabolized in the liver when taken orally.
- **Rapid Onset of Action:** Nasal delivery allows quick absorption into the bloodstream, offering fast therapeutic effects, particularly beneficial for emergency treatments.
- **Innovative Formulation Technologies:** Advances like nanoparticles, in-situ gels, and permeation enhancers can improve drug stability, absorption, and patient comfort.
- **Targeted Delivery:** Nasal systems can target the central nervous system or specific body areas, improving treatment effectiveness, especially for neurological disorders.
- **Increased Patient Compliance:** The non-invasive nature of nasal delivery, combined with user-friendly devices, can boost patient adherence to treatment regimens.

VII. METHODS OF FORMULATION OF IN SITU NASAL GEL:

Cold Method:

In this technique, the product and a specified amount of double-distilled water are mixed and refrigerated overnight at 4°C. The in-situ gelling polymer is then gradually added to the mixture while stirring continuously. The mixture is kept in the refrigerator until a clear solution forms, and the final volume is adjusted. This method is well-suited for gelling polymers such as poloxamer, chitosan, or Carbopol. Poloxamer remains in solution at low temperatures but transitions to a gel at nasal temperatures due to reduced solubility of its propylene oxide chain as the temperature increases. Similarly, chitosan stays in solution at low temperatures, with its hydrophobicity increasing as the temperature rises, promoting gel formation.

Hot Method:

This method is used for gelling polymers like gellan gum or pectin. At elevated temperatures, gellan gum chains dissolve in water, adopting a random coil structure with enhanced segmental mobility. When the gellan gum solution cools in the presence of ions such as K+ or Ca2+, a sol-gel transformation occurs. Likewise, pectin requires high temperatures for demethoxylation, which is essential for dissolving or preparing a pectin solution.

TRIGGERED IN SITU GELLING FORMATION:

Temperature-Triggered In-Situ Gel:

Certain polymers exhibit significant physical and chemical changes in response to minor environmental shifts, known as stimuli-responsive polymers. These materials can detect stimuli, assess their intensity, and modify their chain conformation accordingly. Temperature-sensitive polymers are among the most extensively studied in drug delivery due to their ease of temperature control in both in vitro and in vivo settings. In this system, gelation occurs with temperature changes, facilitating sustained drug release. These hydrogels remain in liquid form at room temperature (20 to 25°C) and transition to gel upon contact with body fluids at temperatures ranging from 35 to 37°C. Utilizing biomaterials that transition from sol to gel in response to temperature increases offers an effective strategy for in situ gel formation. The optimal temperature range for such systems aligns with ambient and physiological conditions, enabling clinical manipulation without the need for external heat sources beyond body temperature.

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pH-Triggered In-Situ Gel:

Another physiological trigger for in situ gel formation is pH. Polymers in this category contain acidic or basic groups capable of accepting or releasing protons in response to environmental pH changes, making them pH-sensitive. Many pH-sensitive polymers, particularly those with anionic groups, are derived from polyacrylic acid (PAA), such as Carbopol® and its derivatives.

Ion-Activated In-Situ Gel:

In this gelation type, polymers undergo phase transitions in the presence of specific ions. For instance, gellan gum, an anionic polysaccharide, transitions from sol to gel in the presence of monovalent and divalent cations, such as Ca^{2+}, Mg^{2+}, K^{+}, and Na^{+}, which are found in nasal secretions.

POLYMERS USED FOR IN SITU GELLING SYSTEM PREPARATION:

Polymer for pH In Situ Gelling System:

Carbopol:

Carbopol polymers are known for their excellent water absorption properties. With a pKa of 6.0, they can swell in water by up to 1000 times their original volume and can increase their diameter tenfold, forming a gel at pH levels between 4.0 and 6.0. These high molecular weight derivatives of cross-linked polyacrylic acid possess strong mucoadhesive characteristics. The incorporation of cellulose can reduce the polymer concentration while enhancing gelling properties. Commonly used variants include Carbopol 934 and Carbopol 841.

The mucoadhesive nature of Carbopol is attributed to electrostatic interactions, hydrophobic interactions, and hydrogen bonding. As an acidic polymer, the carboxylic groups within its structure partially dissociate when dispersed in water, resulting in a spiral conformation. Being a pH-sensitive polymer, an increase in solution pH leads to swelling of the polymer. The gelling effect is activated in two stages: first, through neutralization achieved by adding sodium hydroxide, potassium hydroxide, or triethanolamine.

Polymer Used in Temperature-Sensitive In-Situ Gelling System:

Poloxamer:

Poloxamer is a water-soluble tri-block copolymer made up of two polyethylene oxide segments and one polypropylene oxide segment in an ABA configuration. Known as Pluronic, it exhibits excellent thermal setting properties that enhance drug retention time. Poloxamer serves as both a gelling agent and a solubilizing agent, resulting in a colorless, transparent gel. It is available in various molecular weights, each possessing distinct gelling properties based on the ratio and arrangement of the hydrophobic and hydrophilic chains.

At room temperature (25°C), Poloxamer acts as a viscous liquid, but when heated to body temperature (37°C), it transforms into a transparent gel. In solution, it forms small micellar subunits at lower temperatures, and an increase in temperature leads to higher viscosity and swelling, resulting in the formation of a large micellar cross-linking network.

Polymer Used in Ion-Sensitive In-Situ Gelling System:

Sodium Alginate:

Sodium alginate, derived from brown algae, is a salt of alginic acid and is characterized as a linear block polysaccharide. It consists of two types of monomers: β-D-mannuronic acid and α-L-glucuronic acid, connected by 1,4-glycosidic linkages. Sodium alginate is non-toxic and biodegradable, making it suitable for various applications. Its carboxylic groups contribute to its strong mucoadhesive properties.

The arrangement of alginate monomers results in alternating blocks of mannuronic (M) and glucuronic (G) acids. The G-block segments interact with calcium ions, facilitating the formation of a homogeneous gel. The mechanical strength and porosity of the resulting hydrogel depend on the G ratio and the type of cross-linker used.

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Synthetic Polymers:

N-Isopropyl Acrylamide Copolymers:

These non-biodegradable polymers exhibit a lower critical solution temperature (LCST) of approximately 32°C, causing them to collapse in water and form cross-linked gels.

PEG/PLGA Block Copolymers:

This innovative approach combines thermal gelation with biodegradability and low toxicity, designed for injectable gel devices that offer enhanced safety and extended gel formation duration.

VIII. EVALUATION OF NASAL IN-SITU GELS

The evaluation of nasal in-situ gels is crucial to ensure their safety, efficacy, and suitability for clinical applications. Several parameters must be assessed, including:

- **Physical Appearance:** The gel should be clear or slightly opalescent, with uniform color and no visible particulates, indicating a homogeneous formulation.
- **pH Measurement:** The pH of the gel should be compatible with nasal mucosa (typically around 5.5 to 6.5) to minimize irritation upon administration.
- **Viscosity:** The viscosity of the gel is measured using a viscometer to ensure appropriate flow characteristics for administration and retention within the nasal cavity.
- **Mucoadhesive Properties:** The gel's ability to adhere to the nasal mucosa can be evaluated through tensile strength tests or other adhesion tests, ensuring prolonged contact time and effective drug delivery.
- **Drug Release Studies:** In vitro release profiles are assessed using techniques such as Franz diffusion cells to determine the rate and mechanism of drug release over time.
- **Stability Studies:** The formulation undergoes accelerated stability testing under various temperature and humidity conditions to evaluate its physical and chemical stability over time.
- **In Vitro Permeation Studies:** These studies assess the permeability of the drug through the nasal mucosa using models that simulate nasal tissue, providing insights into potential in vivo absorption.
- **Osmolality:** The osmolality of the gel should be close to that of physiological fluids to prevent irritation during administration.
- **Thermal and Mechanical Properties:** Evaluating the gel's response to temperature changes and mechanical stress helps assess its stability and performance during storage and application.
- **Microbial Contamination Testing:** Formulations must be tested for microbial contamination to ensure safety for use.
- **Patient-Centric Assessments:** Sensory evaluations regarding taste, smell, and texture can provide insights into patient acceptability, which is crucial for treatment compliance.

IX. DRUG-POLYMER INTERACTION STUDY AND THERMAL ANALYSIS

1. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy is employed to investigate drug-polymer interactions by analyzing the chemical bonds and functional groups present in the formulation. The KBr pellet method is commonly used to prepare samples, allowing for the assessment of the nature of the interacting forces between the drug and polymer components. This technique can identify specific interactions, such as hydrogen bonding or ionic interactions, which may affect the drug's stability and release profile.

2. Thermogravimetric Analysis (TGA)

Thermogravimetric analysis assesses the thermal stability and composition of the hydrogel by measuring weight changes as a function of temperature. TGA can help determine the percentage of water in the hydrogel, which is crucial for understanding its physical properties and performance in drug delivery applications.

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3. Differential Scanning Calorimetry (DSC)

DSC is utilized to identify thermal properties by comparing the thermograms of the gel with those of the pure active ingredients. This analysis helps in understanding the melting points, glass transition temperatures, and other thermal characteristics of the formulation, providing insights into the stability and interactions within the gel.

4. Gelling Capacity

To evaluate the gelling capacity of in-situ ophthalmic products, the gel is mixed with simulated tear fluid in a ratio of 25:7 (25 µL of gel to 7 µL of tear fluid). Gelation is assessed visually by measuring the time taken for the gel to form and the duration for its dissolution, providing valuable information on its performance in physiological conditions.

5. Sterility Testing

Following the guidelines set forth by the IP 1996, sterility testing is performed by incubating the formulation in fluid thioglycolate medium at 30 to 35°C for 14 days to check for bacterial growth. Additionally, the formulation is incubated in soybean casein digest medium at 20 to 25°C to detect fungal growth. This ensures that the product is safe for use in clinical settings.

6. Accelerated Stability Studies

Accelerated stability testing involves storing the formulation in amber-colored vials sealed with aluminum foil to protect against light degradation. According to ICH guidelines, these studies are conducted at 40 ± 2°C and 75 ± 5% relative humidity (RH) to evaluate the short-term stability of the formulation.

7. In Vitro Drug Release Study

For in situ preparations intended for nasal or ocular administration, in vitro drug release tests are conducted using a plastic dialysis cell. This cell consists of two half-cells: a donor compartment containing the formulation and a receptor compartment containing the release medium, separated by cellulose membranes. The cell is placed in an incubator with horizontal shaking. At regular intervals, samples from the receptor solution are withdrawn and replaced with fresh media. The samples are then analyzed using appropriate analytical methods to assess the drug release profile over time.

X. APPLICATIONS OF IN SITU DRUG DELIVERY SYSTEMS:

1. Oral Drug Delivery System

Natural polymers such as pectin, xyloglucan, and gellan gum are employed in in situ forming oral drug delivery systems. Pectin gelation typically occurs in the presence of H^+ ions, with divalent ions like calcium necessary for forming gels that act as drug delivery vehicles. For example, paracetamol has been formulated into an oral in situ gelling system using pectin to achieve sustained release.

2. Ocular Drug Delivery System

In ocular applications, natural polymers such as gellan gum, alginic acid, and xyloglucan are commonly used. Various compounds, including antimicrobials and anti-inflammatory agents, are utilized to manage intraocular pressure in glaucoma patients. Conventional delivery systems often struggle with poor bioavailability due to rapid elimination by tear fluid. In situ gels effectively address this issue; for instance, gellan's aqueous solution transitions to a gel state upon contact with tear fluid, thereby enhancing retention time and improving drug release compared to traditional eye drops .

3. Nasal Drug Delivery System

An in situ gel formulation for the nasal delivery of mometasonefuroate has been developed to treat allergic rhinitis. Polymers like xanthan gum and gellan gum are incorporated into these gel systems. Animal studies using allergic rhinitis models demonstrated that the in situ gel significantly reduced nasal symptoms in sensitized rats, showing greater efficacy than the marketed Nasonex formulation (mometasonefuroate suspension 0.05%).

4. Rectal Drug Delivery System

In situ gels also show promise for rectal and vaginal drug delivery applications. Research by Miyazaki et al. focused on xyloglucan-based thermoreversible gels for the rectal delivery of indomethacin.

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5. Vaginal Drug Delivery System

A mucoadhesive, thermosensitive vaginal gel containing a clotrimazole-β-cyclodextrin complex has been developed for treating vaginitis, demonstrating improved therapeutic effectiveness and patient compliance. Pluronic F-127 was used as the in situ gel-forming polymer, along with mucoadhesive agents such as Carbopol 934 and hydroxypropyl methylcellulose to prolong the residence time at the application site.

6. Injectable Drug Delivery System

For tumor treatment, a novel injectable thermosensitive in situ gelling hydrogel has been created. This formulation comprises a chitosan solution that is neutralized with β-glycerophosphate, allowing for localized and sustained drug delivery.

XI. CONCLUSION

The exploration of in-situ nasal gels represents a significant advancement in the field of nasal drug delivery systems. These gels offer a promising approach to enhance the bioavailability and therapeutic efficacy of various medications administered through the nasal route. By utilizing stimuli-responsive polymers, in-situ gels can provide controlled drug release while ensuring prolonged retention within the nasal cavity.The advantages of in-situ nasal gels, such as improved patient compliance, rapid onset of action, and the ability to bypass first-pass metabolism, make them an attractive alternative to traditional nasal formulations. Furthermore, the incorporation of natural and synthetic polymers has expanded the possibilities for developing customized formulations tailored to specific drug characteristics and therapeutic needs.However, challenges remain in optimizing formulation parameters, ensuring stability, and addressing variability in absorption due to individual anatomical differences. Continued research and innovation in formulation technologies, coupled with thorough preclinical and clinical evaluations, are essential to overcome these obstacles.Overall, in-situ nasal gels hold significant potential for revolutionizing nasal drug delivery, paving the way for more effective and patient-friendly therapeutic options in the management of various conditions, from chronic diseases to acute emergencies. As the field progresses, it will be crucial to translate these innovations into practical applications that can benefit patients and improve healthcare outcomes.

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