Novel Strategies for Nasal Drug Delivery with Chitosome Technology: A Review

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Abstract

The drug can be delivered specifically to the individual via intranasal administration, which also enhances site-specificity within the system and prevents systemic side effects.

In the current era, novel drug delivery systems are useful tools for targeting drug delivery without providing any harmful effects in nasal mucosa as well as the central nervous system.The primary challenges involving nasal delivery of drugs are the complicated structure of the nasal cavity, mucociliary clearance, degradation by the enzymes present there, and pathological conditions including rhinitis, the common cold, etc. using chitosome technology to enhance nasal absorption of drugs and bioavailability. So chitosan, the substance used to make chitosomes, involves liposomes to improve the stability and bioavailability. Chitosan's positive charge interacts with liposomes' negative charge to enhance controlled release. Because of their adhesive features, chitosomes can be used for targeted and long-lasting medication administration. They are able to compress drugs as well as active compounds and deliver them to a specific place in the body as long as a controlled release. In the article, an overview has been made of the most frequently used research methods, and the advanced applications in treatment.

Keywords:
Chitosomes, nasal drug delivery, chitosan, bioavailability, mucoadhesive drug delivery.
Kashyap, K., &Shukla, R. (2019).

1.Introduction

- **Overview of nasal drug delivery and its advamtages**

Overview of Nasal Drug Delivery

The process of administering pharmacological formulations via the nasal mucosa is known as nasal medication delivery. The nasal cavity's rich circulation promotes quick absorption into the systemic circulation, which makes it a useful route for both systemic and local treatments. (Benson et al., 2013).

Advantages of Nasal Drug Delivery

Fast Absorption and Action Start

Nasal administration of drugs allows for fast systemic circulation and speedy therapeutic effects. This is particularly useful for drugs like analgesics and antiemetics that need to take effect quickly. (Schäfer-Korting, et al., 2010).

The First-Pass Metabolism Bypass

By minimizing the first-pass metabolism that comes with oral treatment, nasal delivery increases the amount of the active drug that enters the circulation. This increases effectiveness and bioavailability of drugs. (Cohen et al., 2006).

Painless and Non-Invasive When nasal drug delivery is painless, patients tend to accept it more than injections. Better patient acceptance and compliance may result from this, especially in younger and older populations. (Khan et al., 2014).

Potential for Self-Administration
For chronic diseases requiring long-term care, nasal delivery systems' ease of self-administration and improved patient autonomy and convenience are especially useful. (Munder & Lichtenberg, 2015).

Formulation Versatility
For nasal delivery, a variety of dosage forms, such as solutions, suspensions, gels, and powders, can be created to meet the needs of different patient types and medication kinds. (Patel et al., 2016).

Decreased Infection Risk
Nasal medicine delivery is safer for patients with weaker immune systems since it is confined and has a reduced risk of systemic infections than intravenous methods. (Kumar et al., 2014).

- **Introduction to chitosomes and their significance in nasal drug delivery**

Definition of Chitosomes:

Chitosomes are new drug delivery vehicles that encapsulate therapeutic medicines using chitosan, a biopolymer made from chitin. Drug stability is improved and precious molecules are protected from deterioration by this encapsulation.

The potential of chitosomes to improve the delivery and effectiveness of several medicinal medicines is described by Mehta et al. (2015).

Special Features:
Chitosomes have important qualities including biocompatibility and biodegradability that make them appropriate for use in pharmaceutical applications, especially in nasal drug delivery, where safety is of the utmost importance.
The biocompatibility of chitosan and its advantageous interactions with biological tissues are covered by Mahmood and Ali (2015).

Advantages of Nasal Drug Delivery:
For the administration of drugs, the nasal route offers a number of benefits, especially for macromolecules with low oral bioavailability, such as proteins and peptides. Drugs can be administered through the nasal cavity for quick systemic absorption. Sinha et al. (2016).

Enhancement of Bioavailability:
Because chitosomes can make it easier for medications to pass through the nasal mucosa, they can greatly increase their bioavailability.Sinha et al. (2016).

Mucoadhesive Properties:
Chitosan has mucoadhesive qualities that help extend the duration of a drug's retention in the nasal cavity, guaranteeing greater absorption rates and better therapeutic outcomes.Prajapati et al. (2014).

Versality of Encapsulation:
Chitosomes' medicinal uses are expanded by their ability to encapsulate a diverse range of pharmaceuticals, such as antiviral agents, antihistamines, and vaccine ingredients.Jain et al. (2020).

Controlled Release Kinetics:
By changing the kinetics of drug release from the chitosomes, chitosan makes it possible to create sustained and regulated release profiles that may be customized to meet particular therapeutic requirements.Mahmood and Ali (2015).

Overall Significance:
Chitosomes boost systemic absorption, extend residence time in the nasal cavity, shield sensitive therapeutic compounds from degradation, and greatly increase drug solubility.Bhardwaj et al. (2020).

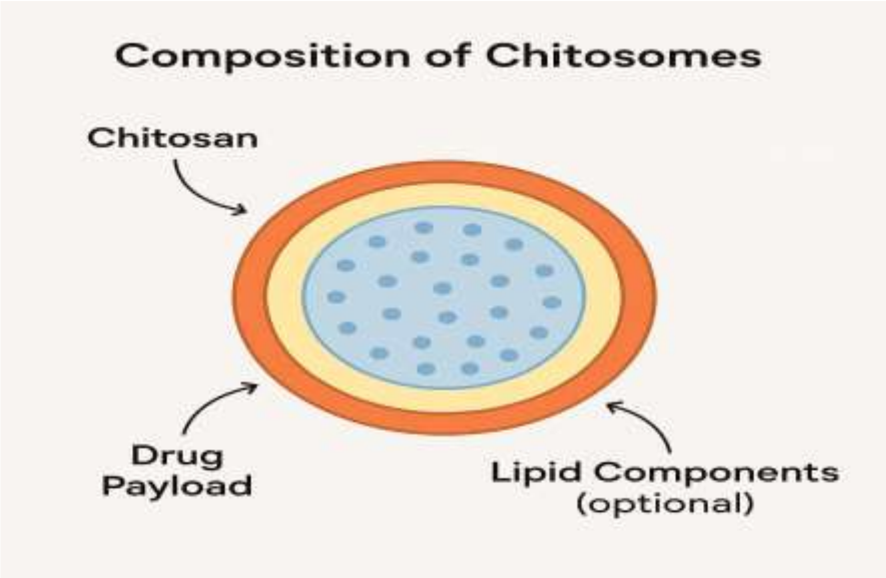
2. Composition and Structure of Chitosomes

- **Description of chitosan and its properties**

Description of Chitosan:

Chitosan is a biopolymer that is produced by deacetylating chitin, a naturally occurring polymer that is present in the cell walls of fungi and the exoskeletons of crustaceans like shrimp and crabs. Because of its distinct physicochemical characteristics, chitosan is known for its many uses in the food, medical, and agricultural sectors.(Rinaudo, 2006).

Chitosan chemical formula: Where "n" stands for the number of repeating units (degree of polymerization), chitosan's chemical formula is $(C_6H_{11}NO_4)_n$.



Characteristics of Chitosan –

Biocompatibility:
Chitosan is very biocompatible, which means the body can accept it well and has few negative consequences. For its uses in pharmaceuticals and drug delivery systems, this characteristic is essential.

Studies showing the beneficial interactions of chitosan with biological tissues have been undertaken by Lim et al. (2014), who have exhaustively documented the biocompatibility of chitosan.

Biodegradability:
Because chitosan is biodegradable, naturally occurring bacteria can break it down into non-toxic components. Because of this feature, it is an eco-friendly choice for a number of uses. According to testing by Tharanathan (2003), chitosan is biodegradable and breaks down into innocuous compounds, which adds to its safety in medicinal applications.

Mucoadhesive Properties-
Because of its potent mucoadhesive qualities, chitosan sticks to mucosal surfaces quite well. This characteristic increases the duration of a drug's retention in the nasal cavity and promotes its absorption.

By means of in vitro experiments, Prajapati et al. (2014) have illustrated the mucoadhesive properties of chitosan and how it might promote extended drug residence time.

Antimicrobial Activity:
Naturally antimicrobial, chitosan works well against a variety of bacteria and fungi. For its use in medication formulations and wound dressings, this is beneficial.
Proof of chitosan's antibacterial activity was presented by Rabea et al. (2003), who showed that it was effective against a range of harmful pathogens.

Solubility:
Because chitosan's amine groups are protonated in acidic environments, it can dissolve and create a variety of medicinal formulations, such as hydrogels and nanoparticles.
Muzzarelli (2010) described chitosan's solubility profile and investigated how pH affected the solubility and functional characteristics of chitosan.

Film-Forming Capability: Chitosan is appropriate for applications involving controlled medication administration since it can form films and coatings. Stability and drug release characteristics can be improved by its capacity to generate stable films. Nair et al. (2013) conducted research that demonstrates the sustained release capabilities of chitosan films and demonstrates their potential for use in drug delivery systems.

- **Mechanism of chitosome formation and interaction with drug molecules**

Mechanism of Chitosome Formation:
Making the Chitosan Solution: To make a viscous solution, chitosan is dissolved in an acidic aqueous solution. The size of the chitosomes that form and the solubility of chitosan are both influenced by its molecular weight. (Bhatia & Reder, 2018).

Self-Assembly Process: Intermolecular interactions including hydrogen bonding, hydrophobic interactions, and ionic interactions cause chitosan molecules to self-assemble when a non-aqueous solvent (like ethanol) is added to the chitosan solution.(Zhang et al., 2020).

Encapsulation of Drug Molecules: Depending on their solubility characteristics, drug molecules may be integrated into the hydrophilic or hydrophobic portions of chitosomes during their self-assembly. A number of variables, such as the ratio of medication to chitosan and the conditions of production, affect the encapsulation efficiency. (Thanoo et al., 2019).

Stabilization: To improve their structural integrity and drug release patterns, chitosomes can be stabilized by adding functional groups, cross-linking agents, or surfactants. (Bhatia & Reder, 2018).

Interaction with Drug Molecules:

Medication Encapsulation: Chitosomes use chemical bonding or physical trapping to encapsulate medication molecules. Drug delivery requires that hydrophilic medications be located in the aqueous core and lipophilic drugs be located in the hydrophobic bilayers. (Zhang et al., 2020).

Controlled Release Mechanisms: Diffusion, swelling, or breakdown processes that are impacted by enzyme activity, pH, and ionic strength can all result in the release of drug molecules. (Thanoo et al., 2019).

Cellular Interaction: Chitosomes affect the efficient transport of the encapsulated medication by interacting with cellular membranes through adsorption or endocytosis after administration. (Bhatia & Reder, 2018).

3. Advantages of Chitosomes in Nasal Drug Delivery

- **Enhanced Bioavailability and Absorption**
  Chitosomes enhance the bioavailability of drugs by facilitating their absorption through the nasal membrane. The mucoadhesive properties of chitosomes allow for prolonged contact with the nasal epithelium, which can significantly improve drug permeability and absorption rates .(Jain et al., 2015). Additionally, the nano-sized particles can penetrate the tight junctions between epithelial cells more efficiently than larger drug particles.
- **Prolonged Retention Time in Nasal Mucosa**
  Chitosomes possess mucoadhesive properties that lead to their extended retention time within the nasal cavity. When chitosomes adhere to the mucosal surface, they significantly slow down the clearance of the drug, allowing for sustained release and prolonged therapeutic effects (Dhupar et al., 2019). This is vital for drugs requiring a longer duration of action or for steady-state release profiles.
- **Targeted Drug Delivery and Reduced Systemic Side Effects**
  Targeted drug delivery can be achieved by engineering chitosomes, which minimizes systemic distribution and permits the medication to accumulate preferentially in particular locations. Side effects frequently linked to systemic drug administration might be considerably decreased by this selective delivery (Huang et al., 2018). Enhancing therapeutic efficacy and safety can be achieved by targeting particular receptors on the nasal epithelium.

- **Preventing Enzymatic Drug Degradation**
  Chitosomes provide a practical way to shield medications from the enzymatic breakdown that frequently takes place in the nasal cavity. By encapsulating sensitive drug molecules, chitosan can protect them from hydrolytic enzymes and other biochemical agents found in the nasal environment, maintaining their effectiveness (Sattari et al., 2020¬).

- **Versatility in Encapsulating Various Types of Drugs**
  Chitosomes are adaptable delivery systems that can hold a variety of medicinal substances, such as proteins, peptides, nucleic acids, and tiny compounds. Their capacity to produce nanoparticles expands the range of applications in nasal medication administration by enabling the loading of hydrophilic and lipophilic medicines (Khan et al., 2019). Because of their adaptability, chitosomes can be used in a variety of therapeutic contexts, such as hormones, analgesics, and vaccinations.

4**. Preparation Methods for Chitosomes**

- **Common Techniques such as Ionotropic Gelation, Solvent Evaporation, and Complex Coacervation**
  Ionotropic Gelation- In ionotropic gelation, chitosan nanoparticles are created by adding a cross-linking agent, usually divalent ions like calcium or aluminum, which react with the chitosan to create a gel-like structure. (Tavakkoli et al., 2019).
  Solvent Evaporation- The process of solvent evaporation involves dissolving chitosan in a volatile organic solvent, then allowing the solvent to evaporate to create nanoparticles. Drugs that are hydrophobic can be encapsulated using this method. (Patel & Mishra, 2021).
  Complex Coacervation- Chitosome production is the result of complex coacervation, which is the interaction of oppositely charged polymers. This technique preserves the integrity of the chitosomes while efficiently encapsulating a variety of medicinal substances. (Alves et al., 2020).

- **Factors Influencing Chitosome Stability and Effectiveness**
  Temperature, ionic strength, pH, and chitosan content are some of the variables that affect the stability and efficacy of chitosomes.
  pH: Because chitosan's solubility depends on pH, pH is important. Chitosan becomes protonated at lower pH values, which improves its solubility and drug-interaction capabilities.(Bourdon et al., 2020).
  Ionic strength -The interaction between the cross-linking agents and chitosan can be influenced by ionic strength. By strengthening electrostatic contacts, a higher ionic strength can make the chitosomes more stable. (Malik et al., 2019).
  Temperature: The gelation process can be affected by temperature; higher temperatures are frequently advantageous for increasing the effectiveness of active ingredient encapsulation.
  (Peppas & Santos, 2018).
  Concentration – Chitosan concentration is important because larger concentrations might cause aggregation or increased viscosity, which affects chitosome size and encapsulation effectiveness.

- **Quality Control and Characterization Methods**

  A variety of methods are used in chitosome quality control and characterisation to guarantee the stability, size distribution, and effectiveness of drug encapsulation.

  Dynamic Light Scattering: DLS is a popular technique for figuring out the size distribution of chitosomes, which is essential for forecasting their effectiveness and absorption. (Buchman et al., 2020).

  Fourier Transform Infrared Spectroscopy- By looking for particular vibration bands, Fourier Transform Infrared Spectroscopy (FTIR) is used to describe the chitosomes' chemical makeup and verify the existence of encapsulated medications.(Raha et al., 2021).

  Scanning Electron Microscopy - Scanning Electron Microscopy (SEM) offers comprehensive morphological data about the chitosomes' surface and shape, enabling an evaluation of their physical attributes.(Saad et al., 2020).

  Drug Encapsulation Efficiency - The amount of medicine retained within the chitosomes in comparison to the initial amount added can be determined using a variety of techniques, such as spectrophotometric analysis or ultrafiltration. (Huang et al., 2020).

5. Application of Chitosomes in Nsasal Drug Delivery

Because of their biocompatibility, capacity to increase permeability, and potential for targeted distribution, lipid-based nanoparticles called chitosomes which encapsulate chitosan are increasingly being used in nasal medication delivery. The particular uses of chitosomes in this situation are explained in more detail in the points that follow.

- **Management of Local Nasal Conditions (such as Sinusitis and Rhinitis)**

  The potential of chitosomes to carry medications straight to the nasal cavity to treat local ailments like sinusitis and rhinitis has been investigated. Chitosan's mucoadhesive qualities improve medication retention in the nasal mucosa, enabling longer-lasting therapeutic benefits. Studies have demonstrated that chitosomes can successfully encapsulate anti-inflammatory drugs, antibiotics, or antihistamines, offering localized treatment while reducing systemic exposure and potential negative effects (Mishra et al., 2020).

- **Systemic Delivery of Drugs via the Nasal Route**

  Systemic drug distribution can be accomplished non-invasively using the nasal route. Many systemic drugs can be effectively encapsulated in chitosomes, facilitating quick absorption into the bloodstream through the nasal mucosa. The first-pass metabolism that frequently lowers the bioavailability of medications taken orally is avoided by this technique. Numerous investigations have shown how chitosomal formulations can accelerate the pharmacokinetics of proteins and peptides, resulting in increased therapeutic efficacy. (Tiwari et al., 2021).

- **Potential for Brain Targeting (Nose-to-Brain Delivery)**
  Another promising method for treating neurological problems is nose-to-brain administration, which chitosomes may be able to accomplish. When administered nasally, medications can travel through the olfactory and trigeminal pathways, avoiding the blood-brain barrier (BBB). Chitosomes may help deliver neuroactive substances straight to the brain, according to research, which could be a treatment option for diseases including Parkinson's and Alzheimer's. This focused delivery reduces peripheral side effects while increasing medication concentration in the central nervous system. (Dhuria et al., 2010).

- **Use in Vaccine Delivery and Gene Therapy**
  A novel platform for nasal delivery of vaccinations and gene therapy drugs is provided by chitosomes. Because chitosan has immunomodulatory qualities that can boost the mucosal immune response, it can be used as an excipient in nasal vaccinations. Furthermore, chitosomes' capacity to encapsulate and shield nucleic acids holds potential for use in gene therapy. Recent research has demonstrated the promise of chitosomal formulations in the delivery of mRNA and DNA vaccines, demonstrating their capacity to elicit certain immune responses while reducing side effects.(Zhang et al., 2022).
  By taking advantage of chitosomes' special qualities, scientists are always looking into how they may enhance nasal medication delivery and expand their uses to other therapeutic domains.

6. Challenges and Limitations

Although chitosomes provide promising prospects for nasal drug administration, a number of obstacles and restrictions need to be overcome to enable their widespread use. Here is a detailed examination of the difficulties in developing and implementing chitosomes.

- **Variability in the Conditions of Preparation**
  Variability in chitosome preparation circumstances is one of the main problems with them, as it can have a big impact on their physicochemical characteristics like size, charge, and drug-loading ability. Inconsistent formulations may result from variations in variables such as temperature, chitosan concentration, solvent selection, and preparation technique (e.g., solvent evaporation, emulsification). For example, variations in the level of chitosan deacetylation can affect the stability and release characteristics of the medications that are loaded. Because of this diversity, it may be challenging to standardize chitosomal formulations for therapeutic use and to ensure consistency. (Mishra & Shukla, 2020).

- **Scalability and Manufacturing Challenges**

  There are several challenges in moving from laboratory-scale chitosome synthesis to large-scale manufacturing. In larger production systems, methods that perform effectively on a small scale may run into problems such insufficient mass transfer, heat transfer, or mixing. It might be difficult to achieve stability and homogeneity in particle size distribution over bigger batches. The viability of commercially feasible chitosome production can also be impacted by economic factors pertaining to the price of raw ingredients and scaling up processing equipment. Large-scale production may become more complex as a result of regulatory procedures that call for thorough analysis and validation of manufacturing processes.(Fathi et al., 2020).

- **Regulatory Considerations and Clinical Trials**

  Another major problem for chitosomal medication formulations is navigating the regulatory environment. Regulatory bodies need thorough safety, effectiveness, and toxicity data before they will approve new drug delivery methods. These assessments may be made more difficult by the intricacy of nanoparticle compositions, since chitosomes may behave differently in biological systems than their traditional pharmaceutical counterparts. The design of clinical trials for chitosome-based nasal drug administration may also call for creative methods to evaluate safety and effectiveness because of the particular pharmacokinetics and dynamics involved. Regulators might request solid evidence regarding the formulation's stability and repeatability over time, which would make the approval procedure even more difficult. (Patel & Jani, 2021).

  In conclusion, even though chitosomes have the potential to improve nasal drug delivery, a number of obstacles stand in the way of their development and use, including as inconsistent preparation conditions, issues with scaling and manufacturing, and regulatory barriers. In order to move chitosomal formulations from the laboratory to clinical practice and guarantee their safe and efficient application in therapeutic interventions, these problems must be resolved.

7. Future Directions and Research Opportunities

There are many opportunities for study and innovation in the rapidly developing field of chitosome application in nasal medication delivery. The research prospects and possible future directions that could further improve the usefulness of chitosomes in pharmaceutical applications are outlined in the sections that follow.

- **Technological Advancements in Chitosomes**

  Future developments in chitosome technology are probably going to concentrate on improving their performance and physicochemical characteristics. This could involve the creation of innovative formulation methods to produce chitosomes with enhanced drug loading, stability, and targeted delivery properties. To improve mucus penetration and cellular uptake, researchers are looking into the usage of cutting-edge materials like lipid-coated chitosomes or hybrid nanoparticles. Furthermore, the addition of stimuli-responsive components may enable the regulated release of medicinal substances in reaction to particular environmental cues. (Sebastiao et al., 2021).

- **Potential for Combination Therapies**
  Chitosome use in combination therapies has a lot of promise, especially for conditions that call for complementary and alternative ways to treatment. For example, treating local illnesses like chronic rhinosinusitis may benefit from the co-delivery of antibiotics and anti-inflammatory drugs using chitosomes. Furthermore, a powerful therapeutic approach for the treatment of cancer may be offered by combining immunomodulatory medications with chemotherapeutic medicines in a single chitosomal formulation. Investigating the ideal proportions and combinations of these substances within chitosomes could result in sophisticated treatments that more effectively handle complicated medical conditions.(Khan et al., 2020).

- **Ongoing Research and Development Efforts**
  Chitosome research and development activities are progressing quickly. Understanding how chitosomes interact with biological barriers is essential to improving their design, and this is the focus of several studies. Surface changes, like functionalization with targeting ligands or mucoadhesive compounds, are being studied to improve the biodistribution and effectiveness of medicinal medicines administered through the nasal route. The potential of chitosomes to transport a wider variety of therapeutic payloads, such as biologics and RNA-based therapies, is also being investigated; this will be crucial in the developing field of customized medicine. (Morris et al., 2022).

- **Future Prospects in the Field of Nasal Drug Delivery**
  With the ongoing research on chitosomal formulations, the field of nasal medicine delivery is expected to increase significantly. Given the recent developments in mRNA vaccine technology, chitosomes may eventually become the norm for nasal vaccine delivery. More academic-industry partnerships to further translational research and clinical applications that leverage the special benefits of chitosomes are also among the opportunities. More research in this field is necessary since the nose-to-brain delivery method is becoming more widely recognized as a potential treatment for neurological illnesses. (Patel et al., 2021).

In summary, chitosomes in nasal medication administration have a bright future ahead of them, full of chances for combination therapy, technological developments, continued study, and major breakthroughs in clinical applications. Chitosomes may become a key component in the creation of successful treatment plans for a range of illnesses if the current issues are resolved and fresh knowledge is utilized.

8. Conclusion

- **Summary of Key Points**
  As innovative chitosan-containing nanocarriers, chitosomes have shown great promise for use in nasal medication delivery. They can be used for systemic medication delivery as well as the treatment of local ailments including sinusitis and rhinitis because of their mucoadhesive qualities, which improve retention and absorption of therapeutic drugs. Chitosomes also provide great prospects for distribution from the nose to the brain, allowing tailored treatments for neurological conditions by avoiding the blood-brain barrier. Additionally, their usefulness encompasses the delivery of vaccines and gene therapy, underscoring their adaptability in tackling a variety of health issues. (Mishra et al., 2020; Tiwari et al., 2021; Zhang et al., 2022).

  Regulatory landscape navigation, production scalability, and variation in preparation conditions are some of the obstacles that still need to be overcome despite their potential. To overcome these obstacles, creative approaches are needed, like investigating novel formulation methods and comprehending the intricate relationships between chitosomes and biological systems (Fathi et al., 2020; Patel & Jani, 2021). These obstacles must be addressed by ongoing research in order to standardize chitosomes for use in clinical settings (Morris et al., 2022).

- **The Promising Future of Chitosomes in Revolutionizing Nasal Drug Delivery**
  Chitosomes in nasal medication administration have a very bright future ahead of them, since they have the potential to revolutionize therapeutic approaches in a number of medical fields. Drug delivery efficiency and specificity may be improved by chitosome technology advancements such adding stimuli-responsive components and investigating hybrid formulations (Sebastiao et al., 2021). Their use in combination medicines may also open the door to more potent treatments that address complex illnesses.

  Chitosomes are anticipated to be crucial to future vaccine production as research progresses, particularly with regard to new dangers like pandemics, as evidenced by recent achievements in mRNA vaccine delivery (Zhang et al., 2022). Chitosomes' significance in clinical practice may also be further cemented by the possibility that their incorporation into personalized medicine may enable customized treatments. (Khan et al., 2020; Patel et al., 2021).

  As a result of continued research and technology developments in chitosome formulations, nasal drug delivery may see major breakthroughs that improve patient outcomes and therapeutic efficacy for a range of illnesses.

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