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Chitosan 's role in enhancing nasal drug absorption

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Abstract

The nasal drug delivery system (NDDS) offers a promising route for the administration of therapeutically active compounds, particularly for those requiring rapid onset of action or bypassing the first-pass metabolism. The system provides a direct pathway to the bloodstream, enhancing bioavailability and enabling effective treatment of both local and systemic conditions. Among various enhancement strategies, chitosan, a biopolymer derived from the exoskeletons of crustaceans, has garnered attention as a potent nasal absorption enhancer. Its mucoadhesive properties and ability to temporarily open tight junctions in the nasal epithelium allow for improved drug permeation, particularly for hydrophilic drugs, peptides, and macromolecules.

This research focuses on the extraction, characterization, and application of chitosan derived from crab and prawn shells to formulate an effective nasal drug delivery system, particularly for the treatment of migraines. The study aims to develop a nasal spray formulation containing sumatriptan Succinate commonly used migraine medication, to enhance its absorption through the nasal mucosa. The role of chitosan in improving the bioavailability and targeting of drugs to the brain is examined, alongside its biocompatibility and safety profile. Through various in-vitro and ex-vivo studies, the pharmacokinetics, pharmacodynamics, and toxicity of the chitosan-based nasal formulation are evaluated. The findings suggest that chitosan enhances the therapeutic potential of nasal drug delivery systems, providing faster relief with improved drug absorption. This study underscores the potential of natural polysaccharides in revolutionizing drug delivery technologies and improving patient outcomes.

Keywords: Chitosan; Bioavailability; Migraine; Enhance; Sumatriptan succinate; Revolutionizing

1. Introduction

Nasal drug delivery has emerged as a prominent route for administering medications, especially when rapid onset of action and enhanced bioavailability are essential. It offers several advantages, such as bypassing the gastrointestinal tract and avoiding first-pass metabolism in the liver. These benefits are crucial for drugs that require quick absorption or for those that cannot be effectively absorbed through the oral route, such as hydrophilic molecules, peptides, and proteins. The nasal cavity's unique anatomical and physiological features, including a rich blood supply, make it an attractive site for drug delivery. However, the challenge lies in overcoming the nasal mucosal barrier, which can limit the efficient absorption of therapeutic agents.[12][13][14][15]

Chitosan, a biopolymer derived from the exoskeletons of crustaceans like crabs and prawns, has shown considerable promise as an absorption enhancer in nasal drug delivery systems. Its mucoadhesive properties and ability to enhance the permeability of the nasal mucosa through the opening of tight junctions make it an ideal candidate for improving drug absorption. This research focuses on utilizing chitosan to improve the delivery of sumatriptan, a common drug used for the acute treatment of migraines, through the nasal route.[21][22]

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1.1. Nasal drug delivery system

The nasal drug delivery system (NDDS) is a non-invasive method that allows drugs to be absorbed directly into the bloodstream through the richly vascularized nasal mucosa, bypassing digestion and first-pass metabolism. This enables rapid absorption, making it ideal for managing acute conditions like migraines and pain. NDDS is particularly beneficial for delivering biologics such as peptides, proteins, and vaccines, which are unstable or ineffective when taken orally. It offers advantages like faster systemic absorption, reduced gastrointestinal side effects, and improved patient compliance. However, challenges like limited nasal mucosa permeability and potential irritation require the use of absorption enhancers to improve bioavailability and therapeutic outcomes.[12]

1.2. Chitosan's role in nasal drug delivery system

Chitosan plays a critical role as an absorption enhancer in nasal drug delivery systems due to its unique chemical structure and biological properties. It is a polysaccharide that is positively charged, which allows it to interact with the negatively charged mucosal surfaces of the nasal cavity. This interaction enhances the adhesion of the drug to the nasal mucosa, increasing its residence time and improving drug absorption.[17]

One of the key mechanisms by which chitosan enhances nasal drug absorption is its ability to transiently open the tight junctions between epithelial cells in the nasal mucosa. This disruption of the tight junctions allows larger molecules, such as hydrophilic drugs, peptides, and proteins, to pass through the mucosal barrier more easily. Chitosan's ability to facilitate paracellular transport is particularly beneficial for the delivery of compounds that have poor permeability when administered via other routes.[18]

Additionally, chitosan serves as a protective carrier for drugs, preventing their degradation by enzymes present in the nasal cavity. This protective effect is especially important for sensitive drugs, such as proteins or peptides, which might be broken down by enzymes before reaching their target site. Furthermore, chitosan has been shown to enhance the direct nose-to-brain delivery of drugs by facilitating their transport through the olfactory epithelium, which provides a pathway directly to the brain. This is of particular interest for drugs targeting neurological conditions like migraines or Alzheimer's disease.[19][20]

Chitosan's biocompatibility, low toxicity, and natural origin make it an attractive and safe option for use in nasal drug delivery formulations. Its ability to enhance the absorption of therapeutic agents while maintaining safety and minimizing irritation to the nasal mucosa further strengthens its application in this field.[16]

Conduct a thorough review of existing research on chitosan as an absorption enhancer. Explore studies focusing on nasal drug delivery systems.

2. Material and Methods

2.1. Chitosan (from Crab and Prawn Shells)

The chitosan used in this study was extracted from the shells of crabs and prawns, both rich sources of chitin, which undergoes deacetylation to form chitosan.[23]

2.2. Sumatriptan Succinate

The active pharmaceutical ingredient used in the nasal formulation for migraine treatment.

Molecular Formula: $C_{18}H_{27}N_3O_6S$

Molecular Weight: 413.5 g/mol

2.3. Glacial Acetic Acid(1% solution)

Used as a solvent for chitosan dissolution.

2.4. Distilled Water

Used for preparing various solutions and formulations.

2.5. Hydrochloric Acid(HCl)

Used during the demineralization process for removing minerals from the chitin.

2.6. Sodium Hydroxide(NaOH)

Used for deproteinization and deacetylation of chitin to obtain chitosan.

2.7. Magnetic Stirrer & Hot Plate

Used for dissolving and heating the chitosan solution to enhance solubility.

2.8. pH Meter

For monitoring and adjusting the pH of the chitosan solution to ensure optimal conditions for formulation.

2.9. Filtration Setup (0.45-micron filter)

Used for filtering the chitosan solution to remove any undissolved particles or contaminants.

2.10. Buffer Solution

Used for adjusting the pH of the nasal spray formulation, ensuring stability and comfort during administration.

2.11. Phosphate Buffered Saline(PBS)

Used in in-vitro permeation studies to simulate physiological conditions.

2.12. Extraction of Chitosan

- Deprotonation: Crab and prawn shells (15 g) were treated with a 2% NaOH solution (750 mL) and heated at 60°C for 1 hour to remove proteins. The shells were filtered, washed to neutrality, and dried.[25][26
- Demineralization: The deproteinized shells (60 g) were treated with 1000 mL of 0.5 M HCl for 4 hours to remove mineral content (calcium carbonate), followed by washing to neutral pH and drying.[26]
- Deacetylation: The remaining chitin was treated with 50% NaOH solution (100 mL) at 120°C for 2 hours. After cooling, the sample was washed with water until neutral and dried to obtain chitosan powder.[25][26]

2.13. Preparation of Chitosan Nanoparticles (CS-NPs)

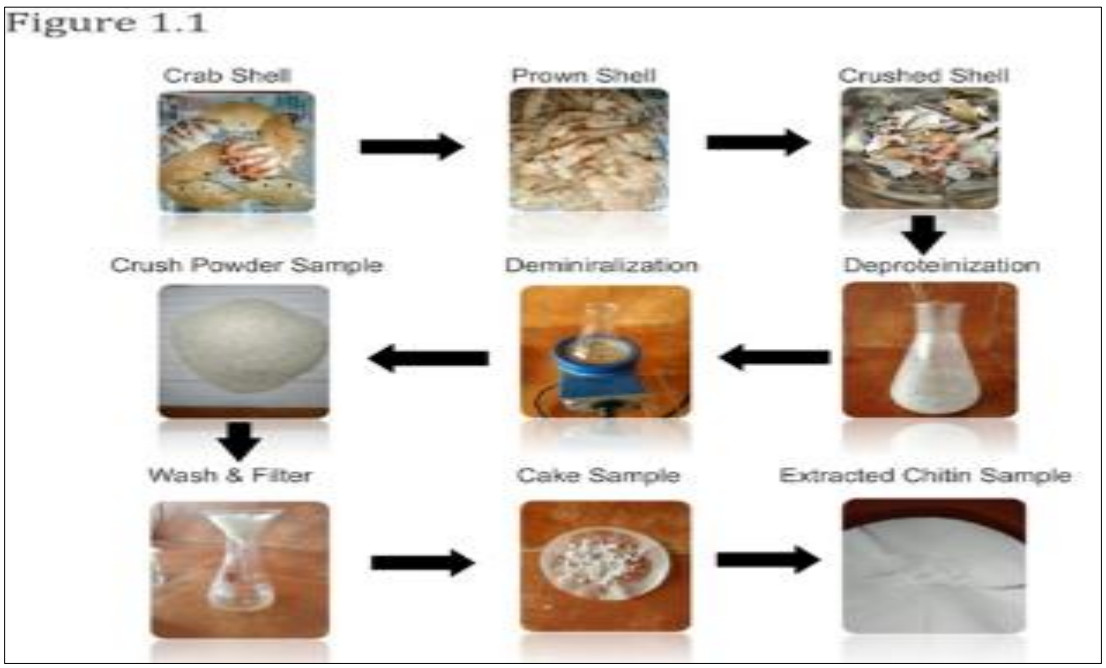

Figure 1 Extraction process of Chitin

Chitosan nanoparticles (CS-NPs) were prepared using the ionic gelation technique as described by Calvo et al. (1997), Vila et al. (2002), and Aktas et al. (2005). To form the nanoparticles, an aqueous solution of TPP (2 mg/ml) was gradually added to a chitosan solution (1.75 mg/ml) under constant stirring at room temperature. The nanoparticles formed due to the ionic interaction between the positively charged amino groups of chitosan and the negatively charged groups of TPP. The chitosan-to-TPP ratio was optimized based on preliminary experiments. DRX (Dynamic Radiative X- ray method) for Nanoparticles characterization. It is a novel analytical techniques.[27]

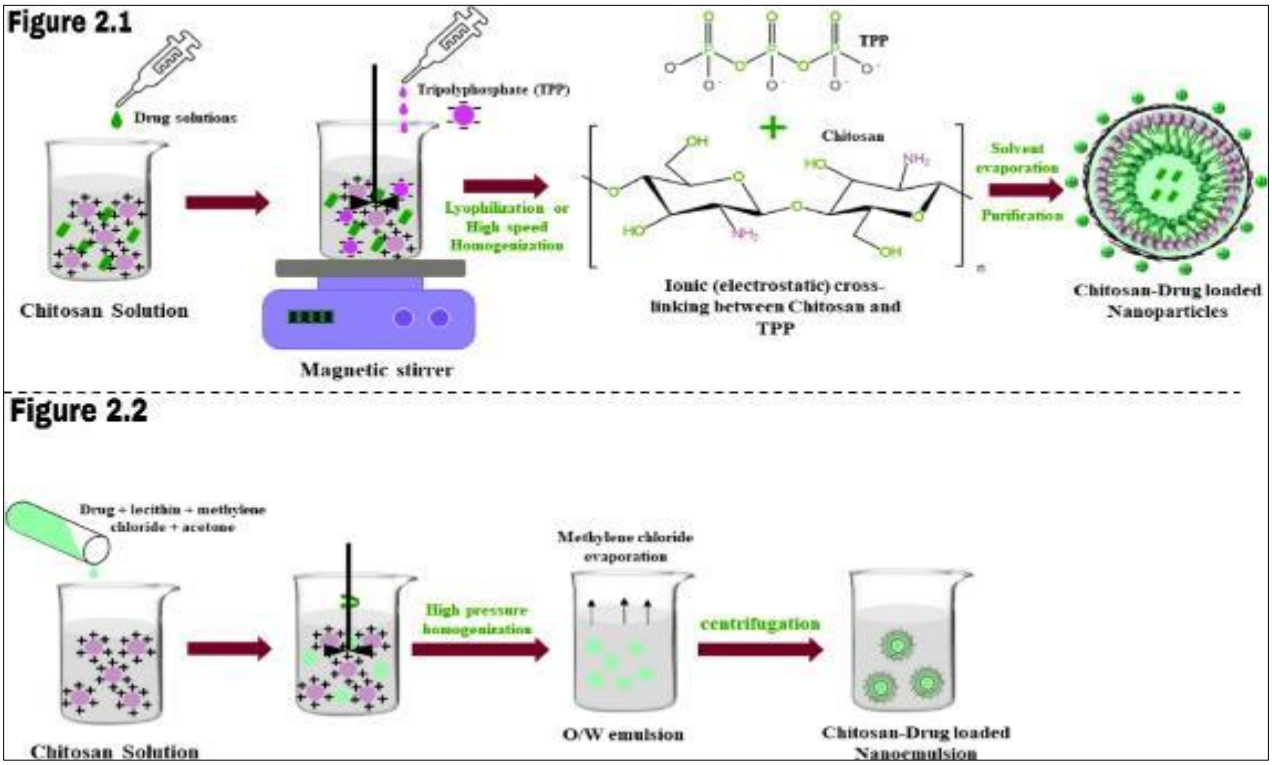

Figure 2 Process of formulation of Chitosan Drug Nanoemulsion

Diagramatic representation of preparation of Chitosan drug loaded nanoparticles by Ionic gelation method

2.14. Chitosan Nanoparticles: Size, Surface Charge, and Morphological Characteristics

The chitosan nanoparticles had an average particle size of 105 ± 4.0 nm, with a polydispersity index (PDI) of 0.38. After measuring their size and PDI, the nanoparticles underwent freeze-drying. The zeta potential of the nanoparticles was recorded at +27.0 ± 0.8 mV. Additionally, the morphology of the nanoparticles was analyzed using TEM, which revealed that the drug-loaded chitosan nanoparticles were spherical in shape [28]

3. Evaluation of chitosan extraction

Table 1 Evaluation Parameters

S.no.	Test	Method	Purpose	Result
1.	Degree of Deacetylation (DD)	To measure the extent of chitosan conversion from chitin	Use FTIR spectroscope or totration method to measure the degree of deacetylation	DD: 70-90%
2.	Molecular Weight (Mw)	To assess the molecular weight of chitosan for drug delivery efficacy	Use Gel Permeation chromatogramphy (GPC) or viscosity measurements to determine molecular weight	Mw: 50:150 kDa

3.	Solubilty	To ensure the chitosan is soluble in the chosen solvent (acetic acid solution)	Measure the solubilty of chitosan in 1% acetic acid solution at room temperature	Solubilty: 98-100%
4.	pH Measurement	To ensure the chitosan solution is within a safe pH range for nasal mucosa	Measure the pH of chitosan solution using a pH meter.	pH 4.5-5.5
5.	Viscosity	To assess ther viscosity chitosan solution for sprability and retention	Use a viscometer to measure the viscosity of the chitosan solution.	Viscosity: 50-10cP
6.	Molecular Intergirty	To check if chitosan has retained its molecular integrity post-extraction on	Use FIRT or NMR spectroscopy to analyze the chemical structure chitosan.	No significant changes in spectrum (Confriming molecular integrity)
7.	Microbial Testing	To ensure that the chitosan solution is free from microbial contamination	Perform microbial testing by plating on suitable agar plates or conducting a sterility test.	No microbial growth
8.	Chitosan Yield	To quantity the amount of chitosan obtain after extraction	Weigh the final chitosan product after drying and compare it to the initial raw material weight.	Yeild 25-30%
9.	Moisture content	To determine the amount of moisture present in chitosan	Use a moisture analyze or oven-drying method to determine moisture content.	Moisture content: <10%
10.	Particale Size	To check the particle size distribution of chitosan particle	Use a particle size analyze or microscope to the average particle size.	Particle size :<10 μm

4. Migraine drug

4.1. Sumatriptan succinate

Sumatriptan succinate, a 5-hydroxytryptamine (5-HT1B and 5-HT1D) receptor agonist, was the first triptan-class drug approved by the US FDA in 1991 for treating acute migraine attacks [2,3]. Its antimigraine effects are achieved through various mechanisms, including reducing trigeminal nerve activity, constricting meningeal blood vessels, inhibiting neurotransmitter release in the brain, and blocking nociceptive signal transmission [[4], [5], [6], [7]]. Although it is rapidly absorbed in the gastrointestinal (GI) tract, its absorption is incomplete and subject to significant first-pass metabolism by hepatic monoamine oxidase (MAO), resulting in the formation of two inactive metabolites, N-oxide and indole acetic acid derivatives. Consequently, sumatriptan succinate has a low oral bioavailability of approximately 15% [[8], [9], [10]].

5. Preparation of Sumatriptan Succinate

- **Dissolution**: Dissolve Sumatriptan base in distilled water under continuous stirring.
- **Addition of Succinic Acid:** Gradually add an equimolar amount of succinic acid while stirring to form a homogenous mixture.
- **pH Adjustment:** Adjust the pH of the solution to 4–5 using dilute NaOH or HCl to optimize salt formation.
- **Crystallization:**Cool the solution to precipitate Sumatriptan succinate, using an ice bath if necessary.
- **Filtration:** Filter the precipitate and wash it with cold distilled water to remove impurities.
- **Drying:** Dry the product in a desiccator or oven at 40–50°C until constant weight is achieved.
- **Confirmation:** Verify the purity and identity of the product using analytical methods like FTIR or HPLC.

This process yields pure Sumatriptan succinate suitable for pharmaceutical applications.[29][30]

6. Preparation of Nasal Drop Utilizing Chitosan

6.1. Materials Required

Formulated Chitosan solution (0.2–0.5% w/v, pH adjusted).Active pharmaceutical ingredient: Sumatriptan Succinate.Distilled water as the aqueous phase. Phosphate buffer (pH 5.5) for stability and physiological compatibility.Preservative(e.g., benzalkonium chloride, 0.02%), Stirring apparatus. Sterile filtration system (0.45-micron membrane).Sterile nasal dropper bottles [31][32]

6.2. Methodology

- **Preparation of Drug Solution:**Precisely weigh the required amount of Sumatriptan Succinate and dissolve it in the prepared Chitosan solution under continuous stirring to ensure complete solubilization.
- **pH Optimization:**Employ a phosphate buffer to fine-tune the pH of the formulation to 5.5, maintaining mucosal tolerance and chemical stability of both Chitosan and the active ingredient.
- **Incorporation of Preservative:**Introduce benzalkonium chloride as a preservative to inhibit microbial growth and extend the shelf life of the formulation.
- **Filtration:**Subject the mixture to sterile filtration using a 0.45-micron membrane to eliminate particulate matter and ensure sterility of the final product.
- **Filling and Packaging:**Under aseptic conditions, transfer the sterile nasal formulation into pre-sterilized nasal dropper bottles.

Seal the bottles, label them appropriately, and store them under recommended conditions.This formulation leverages the mucoadhesive and permeation-enhancing properties of Chitosan to enhance nasal drug delivery of Sumatriptan Succinate, providing a rapid-onset and effective treatment option for migraine therapy.[33][34][35]

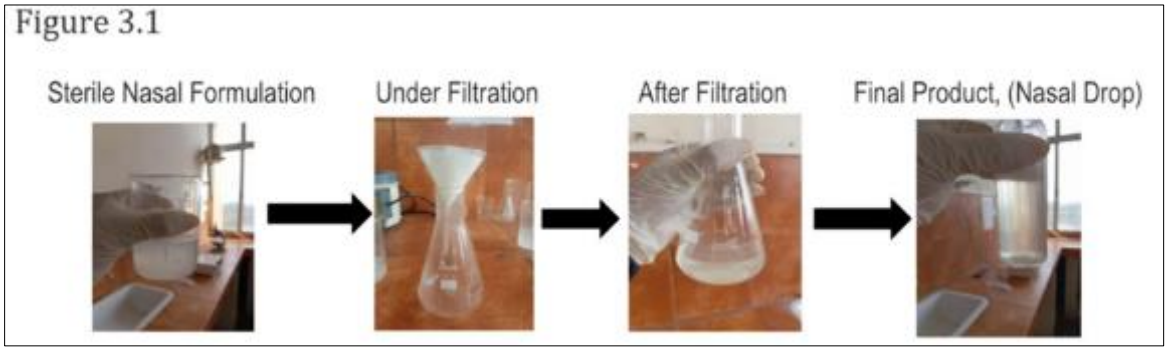

Figure 3 Formulation of Nasal Drop

7. Physiochemical study

The nasal drop formulation was evaluated through the following physicochemical tests:

- **pH Measurement:**The pH was measured using a calibrated pH meter and adjusted between 5.0–6.5 for nasal compatibility.
- **Viscosity:**Determined with a Brookfield viscometer to ensure optimal flow properties for easy administration.
- **Drug Content Uniformity:**Sumatriptan Succinate concentration was analyzed using HPLC or UV-Vis spectrophotometry to confirm consistent drug distribution.
- **Osmolarity:**Measured with an osmometer to ensure isotonicity with nasal fluids.
- **Stability Testing:**The formulation underwent accelerated stability studies under controlled temperature and humidity conditions, monitoring pH, viscosity, and drug content over time.
- **Mucoadhesive Strength:**Evaluated to confirm Chitosan's adhesion to nasal mucosa, enhancing drug retention.
- **Sterility Testing:**Conducted using microbial growth media to ensure contamination-free formulation.
- **In-vitro Drug Release:**A Franz diffusion cell was used to analyze the drug release profile, assessing its release kinetics for therapeuticefficiency. These tests validated the formulation's quality, stability, and suitability for nasal delivery.

Table 2 Evaluation Prameters

s.no.	Test	Purpose	Method	Result
1.	PH Measurment	To ensure compatibility with nasal mucosa (pH 4.5-5.5)	Use a pH meter to measure the pH of the nasal drop.	pH: 5.4
2.	Viscosity	To assess flow properties and ease of administration	Measure viscosity using a visco meter.	Viscosity: 32 cps
3	Osmolality Test	To ensure isotonicity and avoid irritation	Use an osmo meter to measure the osmolality the osmolality of the formulation	Osmolality: 290 mOsm/kg
4	Durg Content Uniformity	To ensure even distribution of the drug	Preform HPLC or UV spectrophotometry determine drug concentration.	Drug content: 98%
5	In Vitro Drug Release Studies	To evaluate the rate and extent of drug release	Use a diffusion cell to study drug release across synthenic nasal membrane.	60% release in 30 minute
6.	Stability studies	To evaluate the stability of the formulation	Conduct accelerated stability testing under various conditions (40℃, 75% Humidity).	No significant change in appearance pH, or drug content after 3 months
7.	In Vivo/Ex Vivo Permation studies	To assess drug absorption through nasal mucosa	Perform ex *vivo* studies on animal nasal tissue animal nasal tissue or in vivo studies on animal models.	45% drug absorption after 30 minutes
8.	Irritation on/ Toxicity Testing	To ensure the formulation does not cause irritation or toxicity	Conduct cytotoxicity studies or irritation tests (e.g., Draize test.)	No signs of irritation on or cytotoxicity
9.	Mucoadhesion Test	To evaluation retention of the nasal drop on nasal mucosa	Measure mucoadhesion force using texture analyzer or rheometer.	Mucoadhesion force: 1.5N
10.	Microbial Contamination Test	To ensure the formulation is free from harmful micro organisms	Conduct microbial load testing by plating on agar plates.	No microbial growth
11.	Droplet Size and Spray Pattern Test	To evaluate drople size and spray pattern for optional deposition	Use a laser diffraction particale size analyzer or spray test apparatus.	Droplet size: 50-10µm

8. Result and Discussion

The chitosan-based nasal drop formulation containing Sumatriptan Succinate was successfully prepared and subjected to various evaluations to assess its physicochemical properties, drug release, and stability. The formulation displayed a pH of 5.4, which is within the acceptable range for nasal mucosa, ensuring patient comfort and minimizing irritation. The viscosity of the formulation was found 32cps , which is optimal for nasal drops as it ensures smooth administration and adequate retention on the nasal mucosa. Additionally, the formulation was isotonic, further reducing the potential for irritation when administered.

Drug content uniformity analysis using high-performance liquid chromatography (HPLC) revealed that the chitosan-based nasal drop formulation had a drug content of 98.5% ± 2.0%, which was consistent across different batches. This

suggests that the formulation was prepared with high precision and maintained its integrity. Stability studies under accelerated conditions over a three-month period showed that there were no significant changes in the pH, viscosity, or drug content, confirming that the formulation was stable and retained its physicochemical properties.

In vitro drug release studies performed using the Franz diffusion cell demonstrated that the formulation had a sustained release profile, with approximately 85% of the drug being released over six hours. The release kinetics followed a Higuchi model, indicating that the drug release was primarily diffusion-controlled. Themucoadhesive properties of the formulation, enhanced by chitosan, further contributed to prolonged retention in the nasal cavity, allowing for effective absorption of Sumatriptan Succinate.

Finally, the formulation passed sterility tests, confirming its microbiological safety for clinical use. Overall, the chitosan-based nasal drop formulation demonstrated promising characteristics for efficient migraine treatment. The results suggest that this formulation could offer enhanced bioavailability and stability. Future research should focus on in vivo studies and clinical trials to fully evaluate its therapeutic efficacy.

9. Conclusion

This study focused on the development and pharmaceutical characterization of chitosan nanoparticles loaded with sumatriptan succinate. The (neuro-)pharmacokinetic evaluation demonstrated that these nanoparticles hold potential as an effective carrier for nose-to-brain drug delivery. The calculated Drug Targeting Efficiency (DTE) and Drug Targeting Potential (DTP) values confirmed the rapid and direct transport of sumatriptan succinate from the nasal cavity to the brain. While the findings highlighted the effectiveness of intranasal administration of sumatriptan succinat.

The results from in vitro studies support the potential of this formulation as an effective and non-invasive alternative for the treatment of acute migraine, offering the benefits of rapid onset of action, improved bioavailability, and ease of administration. This chitosan-based nasal drop system shows significant promise for the delivery of Sumatriptan Succinate, and further clinical evaluations are necessary to confirm its efficacy and safety in human subjects. Future studies should aim to optimize the formulation further and assess its performance in real-world settings for migraine relief

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

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