A Study to Develop a Device to Aid in the Administration of Corticosteroid Nasal Spray to Improve Efficacy

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Introduction

Allergic rhinitis and chronic rhinosinusitis represent conditions stemming from two pivotal pathophysiological factors: hypersensitivity reactions and inflammation. (Bjermer et al., 2019; Liva et al., 2021; Nur Husna et al., 2022) Patients afflicted with chronic rhinosinusitis experience symptoms that profoundly impact their quality of life. (Sapsaprang et al., 2015) Consequently, treatment guidelines consistently advocate for the utilization of intranasal corticosteroids (INC) in cases of severe disease or disruptive symptoms. (Bousquet et al., 2020; Dykewicz et al., 2020; Emeryk et al., 2019; Scadding et al., 2017) However, clinical evidence suggests that during episodes of nasal mucosal inflammation, tissue edema can hinder the comprehensive dispersion of INC particles into deeper nasal recesses, thus impeding their therapeutic reach to affected regions. (Abdelhafeez, 2022; Rollema et al., 2022; Sher & Ross, 2014) Conversely, presently available nasal spray formulations, particularly aqueous solutions commonly employed in Thailand, exhibit limitations in achieving efficient particle dispersion. Consequently, the effective delivery of INC is significantly contingent upon proper medication administration techniques, including bottle priming and synchronized inhalation during actuation. Literature reviews have divulged that many INC users frequently mismanage or inefficiently apply the medication, particularly during the actuation process. (Al-Rasheedi, 2023; May & Dolen, 2019) Common issues include improper alignment of the nasal spray nozzle, inadequate force exerted during actuation, and failure to synchronize inhalation with medication release, collectively contributing to suboptimal treatment outcomes.

In the contemporary landscape, there is ongoing development of a novel INC product, commercially known as OptiNose. (Chu, 2019; Djupesland et al., 2006; Leopold et al., 2019; Ov et al., 2023; Sindwani et al., 2019) This innovative product is characterized by a distinctive nozzle extension emanating from the medication container. It is complemented by specific usage instructions, involving concurrent oral inhalation to augment the force facilitating the delivery of INC particles into the nasal cavity. Literature reviews have unveiled the existence of randomized controlled trials (RCTs) demonstrating the efficacy of this novel mode of intranasal corticosteroid delivery. (Leopold et al., 2019; Ow et al., 2023) However, from a multifaceted perspective, it becomes evident that this product harbors certain limitations and issues necessitating further refinement.

For instance, the enhancement of product efficiency through user-generated airflow from oral exhalation may not allow precise control over force quality, acceleration, and velocity, consequently predisposing the potential for uneven particle dispersion in each instance of use. From a safety standpoint, the incorporation of oral airflow during application may introduce oral cavity microorganisms into the nasal passage, potentially precipitating secondary infections within the nasal, ocular, or aural systems, and even the lower respiratory tract. (Bomar et al., 2018; Dubourg et al., 2019) Additionally, this new product necessitates specialized medication administration techniques, thereby demanding that users acquire the requisite knowledge and skills to consistently achieve optimal results in practical application. Considering the aforementioned information, it becomes unequivocally apparent that the keystone of managing severe allergic rhinitis and chronic rhinosinusitis lies in the effective utilization of INC. Ensuring uniform dispersion of medication particles throughout the nasal cavity, and where appropriate, achieving their deposition into the deeper nasal recesses, is paramount to enabling INC to exert its therapeutic effects effectively. Thus, there is an imperative need for nasal spray formulations that facilitate efficacy. Furthermore, these formulations must prioritize both safety and user-friendliness in practical application by patients.
The objectives of this research endeavor are twofold: firstly, to investigate and develop a tool designed to facilitate comprehensive dispersion of INC particles throughout the nasal cavity, and secondly, to enable their deposition into the deeper nasal passages. This envisioned tool is expected to embody attributes prioritizing safety and user-friendliness in its practical application by patients.

Methods
This research study has received an exemption approval from the Ethics and Human Research Committee of Naresuan University, documented under the reference number P1-0086/2566.

Systematic Review
The databases utilized for this search encompass both published and unpublished sources. The medical electronic databases of international significance employed include PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, ScienceDirect and Open Gray. The search was conducted using a set of specific keywords, Medical Subject Headings (MeSH), and Boolean operators to retrieve relevant data. The keywords and Boolean operators used in the search queries were as follows: (“intranasal corticosteroids” OR “INC”) AND (“device”) AND (“develop” OR “development”), (“intranasal corticosteroids” OR “INC”) AND (“device”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“develop” OR “development”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”), (“intranasal corticosteroids” OR “INC”) AND (“administration”) AND (“technique”) AND (“develop” OR “development”) AND (“efficacy”).

The criteria for the inclusion of documents in the research are twofold:
1. The documents must pertain to clinical research in the form of randomized controlled trials (RCTs), quasi-experimental studies, or observational studies in both human subjects and in vitro, in vivo, ex vivo, or artificial neural networks.
2. The documents should relate to the medical practices and guidelines for the treatment of allergic rhinitis (AR) established by medical institutions, both in Thailand and internationally. These documents should address aspects such as the efficacy, safety, collaboration, or convenience of using methods, tools, and supplementary equipment to facilitate the comprehensive and particle-wide drug delivery of intranasal corticosteroids (INC). This comprehensive delivery should include access to deeper nasal regions, such as the middle or superior turbinate, within the nasal cavity.

The quality assessment of research studies involved two independent pharmacy student researchers, who followed Cochrane guidelines. In instances of discordant evaluations, a third experienced pharmacist researcher was consulted to reach a consensus. Quality assessments employed Cochrane Risk of Bias Version 2 (ROB-2) for randomized controlled trials (RCTs) and quasi-experimental studies, and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) for observational studies. Evaluation criteria for in vitro, in vivo, ex vivo, or artificial neural network studies encompassed clear research objectives, transparent experimental methodologies, ethical sourcing of materials, appropriate statistical methodologies, and unbiased interpretation of findings. For treatment guidelines and quality assessment, the AGREE II tool was applied. Research that demonstrated “low risk of bias in all domains” passed the quality assessment. Data extraction was carried out independently by two researchers, with a third researcher resolving discrepancies, applying criteria such as accurate drug delivery (≥80%), objective outcome measures, and research relevance for clinical application. Data extraction was conducted by two researchers who independently reviewed research articles that had undergone quality assessment. They extracted relevant data from these studies and recorded it in a summary table outlining the “Technical Requirements for Supplementary Devices Facilitating Comprehensive Intranasal Corticosteroid (INC) Drug Delivery Throughout the Nasal Cavity, Including Access to Deep Nasal Regions, such as the Middle or Superior Turbinate.” In cases where there were discrepancies in their assessments, a third researcher was engaged to participate in decision-making. The criteria for considering data as significant included:
1. Devices or methods that demonstrated superior drug management efficiency,
2. Outcome measures that presented objective research data, and
3. Research conducted in either patient populations or healthy volunteers that yielded results facilitating proper drug management, exhibiting statistically significant differences, and practical clinical applicability.

The development of supplementary tools was initiated through a collaborative brainstorming process involving a panel of experts from various disciplines, including one physician each from specialties such as orthopedics, sports medicine, general internal medicine, and pediatrics, a group of pharmacists comprising those with expertise in orthopedics, sports medicine, and community pharmacy with over five years of experience, engineers specialized in mechanical engineering,
and experts in product and packaging design. This expert panel engagement took the form of individual online interviews using open-ended questions, focusing on two key aspects: 1) The specific attributes required for a supplementary device to efficiently deliver intranasal corticosteroid (INC) particles throughout the nasal cavity and access deep nasal regions like the middle or superior turbinate, and 2) The essential components and operational configurations necessary to ensure optimal performance, safety, ease of use for all individuals, and cost-effectiveness for mass accessibility, targeting both pharmacy professionals and the general public. Researchers provided a platform for experts from each domain to express their insights freely and concluded the brainstorming sessions upon achieving data saturation or no further additional comments from experts. The researchers meticulously organized and analyzed all the compiled information to distill key themes and perform a comprehensive content analysis. Moreover, they were vigilant in controlling potential recall bias that might arise from individual experts’ experiences or perspectives in offering opinions on diverse approaches to device development. This process was especially significant in enabling medical and pharmacy professionals to contemplate their recent experiences in recommending drug management for patients. Subsequently, all data were systematically categorized into key considerations and subjected to thorough thematic analysis. The data extraction process involved two researchers independently summarizing and synthesizing information obtained from expert brainstorming sessions and the extraction of pertinent research findings. Subsequently, the researchers recorded key data points in the preliminary draft of the “Technical Requirements for the INC Drug Delivery Device Version 1” table. In cases of discrepant opinions, a third researcher was consulted to make a final decision. The criteria for considering data as crucial were twofold:

1. Consensus among experts, with over 80% agreement, on the efficacy, safety, and practicality aspects of the device’s real-world application, and
2. Data deemed significant by patients, including factors related to convenience, pain avoidance during drug administration, ease of use, among others.

Following this step, the researchers reconvened the expert panel for further consultation and reiterated the process. In this iteration, the researchers invited the same group of experts from the initial brainstorming session to provide additional feedback, highlighting any new insights or suggestions (if any) concerning the technical requirements for the device in each specific category. The data collected were then collated and summarized into a consolidated set of technical specifications for the INC drug delivery device in Draft 3.

The Design of Prototype Instruments
In this research endeavor, the prototype instrument employed is the OptiNose, which operates on the principle of simultaneously delivering nasal medication while utilizing oral exhalation to facilitate the dispersion of nasal spray particles in the form of aqueous solutions over a greater distance and breadth. Nevertheless, upon scrutinizing the configuration and operational principles of this apparatus, the research team has encountered several unresolved queries and identified certain limitations that warrant refinement. Pursuing such refinements is likely to enhance both the efficiency and safety of the device and ultimately lead to a significantly improved ease of use.

The underlying framework of thought has been employed to facilitate innovation, given empirical evidence suggesting its potential to foster novel ideas in situations characterized by limited time and resources. Topics examined using the OptiNose device prototype include:

1. Segmentation and Partitioning: This entails the redesign of the apparatus by segmenting the components to allow users to exhale into the device mouthpiece, thereby enhancing the dispersion of medication particles into the nasal cavity. Research has indicated that the act of exhaling from the mouth to the nose might increase the risk of infection transmission from the oral and throat regions to the nasal passages, ears, and eyes. Since all four of these bodily areas are interconnected, the next level of risk involves the potential for medication dissolution and partial volatilization due to the higher temperature of exhaled breath, potentially affecting the dispersion of medication before reaching the target site. The final dimension of risk is associated with the variability in pressure and flow rate of exhaled breath from individual patients during actual device usage. Furthermore, patients must be trained to operate the device proficiently, ensuring consistent pressure and flow rate during each use.

2. Augmenting Quantity and Functionality: Redesign involves incorporating external air sources with known pressure and flow rate into the design to replace the use of exhaled breath.

3. Interconnecting Components: The redesign includes an approach that combines the actuation of the medication spray with the release of external air simultaneously. Employing the framework as described above, researchers have developed a prototype instrument ready for testing the efficacy of its operation in subsequent laboratory experiments.

Efficacy Assessment
The prototype instrument’s efficacy was assessed in a laboratory setting. Prior to conducting the experiments, consultations were held with expert allergists, otolaryngologists, and pharmacists specialized in the intricacies of medication administration techniques and optimal sites for the placement of medication-receiving surfaces within the nasal and throat anatomical models. Brainstorming sessions with these healthcare professionals yielded two key findings:

1. Medication Administration Simulation: It was recommended that medication administration mimic standard nasal spray procedures, with the addition of externally supplied air with known pressure and flow rate.
2. Optimal Medication-Receiving Sites: It was determined that the medication-receiving surfaces should be strategically positioned at the inferior turbinate, middle turbinate, superior turbinate, and nasopharynx. This
placement aims to encompass the pathophysiology of conditions such as allergic rhinitis and cater to the various severity levels of the disease.

3. The medication solution was transformed into a colored solution, which was adjusted to match the density of the standard nasal spray solution. This modification was undertaken with the specific purpose of enabling clear visualization and identification of the distribution of the solution, as well as the extent of its deposition at various sites.

**Figure 1:** The prototype instrument and the methodology employed for performance testing (NU_Nasal delivery Aid, NUNA).

**Note:** The tool is currently undergoing the patent application process, and therefore, its configuration cannot be disclosed.

**Outcome and Data Collection**

The primary outcome of interest in this research pertains to the contact of medication particles with adhesive sheets pre-designated to represent the positions of the middle turbinate, superior turbinate, and nasopharynx. The decision to exclude the inferior turbinate position from data collection was made because it is a location where contact with medication particles is assured. Consequently, data collection at this position would not yield significant practical insights when compared to the other designated positions. The positioning of the adhesive sheets was consistently maintained at their predefined locations throughout all test repetitions. Data acquisition was conducted using video and photographic recording methods, with the camera angle fixed at the same position during the entire duration of testing. Testing procedures were repeated 100 times, and the recorded results were categorized as either contact or non-contact with the pre-designated adhesive sheets.

**Statistical Analysis**

Statistical inference was employed to analyze central tendencies from a dataset consisting of 100 test repetitions. The results were reported as mean values ± standard deviations of medication particle contacts with various positions within the nasal cavity. Additionally, a mode analysis was conducted.
Following a systematic review, it was noted that there were only four research studies directly related to OptiNose. Therefore, the researchers refrained from providing a comprehensive literature review, as it might introduce bias due to the limited available research. Nevertheless, the researchers will incorporate OptiNose as a tool for designing future prototype devices.

**The Prototype**

The prototype instrument, as depicted in Figure 1, operates by utilizing clean external air. In practical use, a filter is positioned at the air outlet to prevent the ingress of foreign particles or contaminants into the nasal cavity. The selected pressure and flow rate settings are 10cm H$_2$O and 10cm H$_2$O/second, respectively. Stabilize air pressure and velocity to a constant level using a manometer as a measuring instrument. These settings were chosen based on a unanimous consensus among the research team that they represent a balance between providing sufficient force to introduce medication particles into the nasal cavity, particularly during inflammation, and avoiding excessive force that might result in discomfort or adverse effects within the nasal cavity. This balance is crucial to ensure that medication particles can be dispersed both widely and deeply within the nasal cavity. Figure 2 illustrates an example of the contact of the test medication particles with the adhesive sheets. It is evident from the findings that there was contact observed in three specific areas, namely the inferior turbinate, middle turbinate, and superior turbinate positions. Conversely, there was no observed contact of the test medication particles at the nasopharynx position.

**The Efficacy in Laboratory Testing**

In the testing of the actuation of a nasal spray bottle under an external pressure of 100 repetitions, it was observed that upon repeating the test 75 times, the results consistently exhibited a unidirectional dispersion pattern. Specifically,
the test substance particles were found to disperse uniformly throughout the nasal cavity, with particles adhering to the inferior turbinate, middle turbinate, and superior turbinate regions. However, no test substance particles were detected in the nasopharynx region. Consequently, the researchers temporarily halted the research activities and made slight modifications to the research methodology, including the removal of an adhesive patch, as it was speculated to potentially obstruct the dispersion of particles to the nasopharynx region. Subsequently, an additional 25 repetitions of the test were conducted to complete a total of 100 repetitions. Nevertheless, the results remained consistent with those depicted in Figure 3.

![Image: The contact of the test medication particles without the adhesive sheets](image3)

**Figure 3:** The contact of the test medication particles without the adhesive sheets

**Discussion**

Currently, medical observational evidence consistently points to the efficacy and safety of intranasal corticosteroids in the treatment of allergic rhinitis. However, a practical challenge arises in the administration of these medications. They require specialized techniques for drug delivery, potentially rendering certain patients unable to achieve targeted drug delivery to the specific site of action efficiently. Moreover, in cases of severe disease or complications such as nasal polyposis, inflammation of the nasal cavity structures can hinder the dispersion of the drug, particularly in the regions of the middle turbinate and superior turbinate. (Bjermer et al., 2019; Liva et al., 2021; Nur Husna et al., 2022) Hence, it is imperative that innovative methods or technologies are explored to facilitate the effective delivery of intranasal corticosteroid particles, especially in the form of aqueous solutions, to the afflicted areas. This holds the potential to significantly enhance treatment outcomes.

After conducting an extensive review of the available medical literature, it has become evident that there are devices, exemplified by OptiNose, equipped to effectively tackle these identified challenges. Additionally, a substantial body of scholarly research has demonstrated improvements in disease symptom management resulting from their implementation. (Chu, 2019; Djupesland et al., 2006; Leopold et al., 2019; Ow et al., 2023; Sindwani et al., 2019) In a seminal investigation conducted by Messina and research team (Messina et al., 2019), a comprehensive evaluation was undertaken to assess the systemic bioavailability of OptiNose. This inquiry involved a comparative analysis of the pharmacokinetic characteristics associated with a single dose of fluticasone, administered via three distinct delivery apparatuses: OptiNose, Flonase® (a fluticasone propionate inhalational nasal spray), and Flovent® HFA (a fluticasone propionate inhalational aerosol). The outcomes of this study unequivocally establish that intranasal doses of OptiNose (372 μg) and Flonase® (400 μg) are unambiguously non-bioequivalent. It is essential to emphasize that systemic exposure is remarkably limited across all assessed products. To provide further clarity, systemic exposure levels are conspicuously elevated when employing OptiNose in comparison to Flonase®, yet significantly diminished when juxtaposed with Flovent® HFA, both at the 440 μg and 220 μg dosage levels, as discerned through dose normalization methodologies. The findings of this study are in accordance with Chu’s review article, which discusses the treatment of severe complications in allergic rhinitis, a condition that can affect both children and adults. Treatment necessitates achieving local and systemic drug delivery, and OptiNose serves as an innovative drug delivery device designed to facilitate deeper drug penetration, reaching the affected nasal regions.

However, the available safety data remains notably sparse, particularly in terms of reports on post-use complications over prolonged periods, even though the drug delivery devices carry inherent risks that may lead to adverse events. Another noteworthy gap in the research landscape pertains to the absence of studies elucidating the consistency of pressure and flow rates achievable by such devices, as well as their implications on treatment efficacy.

This study employed OptiNose as a prototype to advance our understanding and innovation in drug delivery and create a new method called NUNA, figure 1. The research findings have illuminated that when controlling the pressure and flow rate of air responsible for propelling the drug particles, an optimised parameter can facilitate the targeted drug delivery to deeper disease sites, leading to a broader dispersion of drug particles. This observation underscores the potential influence of air pressure and flow rates as factors contributing to improved clinical outcomes. Nevertheless, it is important to note that this research serves as an initial exploration and necessitates further investigation and development. For instance, future endeavors may involve experimental manipulations involving adjustments to air pressure and flow rates, alterations in airflow patterns, and the execution of clinical trials on definitively diagnosed patients at specific sites of interest. Subsequently, a prospective cohort study design could be implemented to address the question of whether air pressure and flow rates indeed lead to improved disease manifestations. This study would require comprehensive measurements of both final clinical outcomes and pertinent biomarkers to provide a thorough and comprehensive assessment.

The NUNA innovation necessitates ongoing research and development. From a researcher’s perspective, essential attributes include the ability to control both the pressure and airflow rate entering the nasal cavity while allowing for
flexible adjustments to suit the individual patient’s condition. Furthermore, there may be a need to incorporate additional features, such as a small-sized camera for nasal cavity examination, a guidance system to control airflow direction for precise drug delivery, an air filtration system to ensure clean air enters the nasal cavity, and a system for spraying 0.9% normal saline to moisten the nasal mucosa before medication administration, among others.

This research still bears several significant limitations, which could potentially impact the quality of the study. For instance, it is conducted within a laboratory setting, where participants are represented by artificial models lacking the physiological complexity of actual human subjects. The primary objective achievable in this context is merely the observation of whether the test substance particles reach the anatomical regions of interest. It is important to acknowledge that outcomes observed in human experimentation may yield either congruent or disparate results. Nevertheless, the findings of this research serve as a steppingstone to generate novel research questions and future research directions. Subsequently, further investigations will be required to bridge the gap between laboratory-based experimentation and clinical applications, where human subjects are involved. These forthcoming studies will contribute to a more comprehensive understanding of the subject matter.

**Conclusion**

A potential approach identified in this research to enhance the effectiveness of intranasal corticosteroids involves the utilization of external air pressure and appropriate flow rates to facilitate the dispersion of drug particles throughout the nasal cavity, ensuring their access to anatomical regions commonly associated with disease pathogenesis and challenging to reach with therapy, such as the middle turbinate and superior turbinate. However, it is crucial to emphasize that this study does not constitute human experimentation, and further research endeavors are warranted to explore this avenue thoroughly.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**


