International Journal of Scientific Research in Modern Science and Technology
ISSN: 2583 -7605 (Online)
© IJSRMST | Vol. 4 | Issue 8 | August 2025
Available online at: https://ijsrmst.com/
DOI: https://doi.org/10.59828/ijsrmst.v4i8.355

A Comprehensive Review of Design and Evaluation of a Breath-Actuated Inhaler for Technosphere Insulin: Enhancing Glycemic Control

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ABSTRACT

The development of inhalable insulin represents a significant advancement in diabetes management, offering a non-invasive, needle-free alternative to traditional subcutaneous insulin injections. This innovative approach utilizes dry insulin powder administered through a novel inhaler device designed for oral delivery. The primary goal during the development phase is to evaluate the safety, efficacy, and long-term stability of this method while ensuring no contamination occurs during use. Inhallable insulin demonstrates rapid action, making it particularly effective for glycemic control compared to conventional injection-based techniques. Key aspects of this development include optimizing the formulation of dry insulin powder for efficient pulmonary absorption, designing user-friendly inhalers, and conducting rigorous clinical trials to assess its performance in terms of glycemic management, patient acceptability, and potential adverse effects. Additionally, addressing challenges such as insulin antibody formation, pulmonary safety concerns (e.g., risk of cough or reduced lung function), and ensuring consistent dosing are crucial for its widespread adoption. By providing a convenient and less burdensome option for insulin administration, inhaled insulin has the potential to improve adherence and overall quality of life for patients with diabetes.

Keywords: Inhalable insulin, diabetes mellitus, glycemic control, non-invasive insulin delivery, patient satisfaction, cartridges, afrezza powder and exubera powder.

Introduction

Diabetes mellitus, a chronic condition marked by hyperglycemia due to insufficient insulin action, secretion or both requires effective management through constant blood glucose monitoring and regulation, often necessitating insulin therapy. Historically, insulin has been delivered via subcutaneous injections, which, despite effectiveness, can lead to patient discomfort, inconvenience, and reduced adherence. This has prompted the exploration of alternative insulin delivery methods, such as insulin inhalers. By allowing patients to inhale insulin powder directly into the

lungs, where it is swiftly absorbed into the bloodstream, inhalers can better mimic natural insulin release patterns, potentially improving both glycemic control and patient comfort. Recent advancements, including Technosphere insulin (Afrezza), have led to the development of efficient, user-friendly inhalers that deliver rapid-acting insulin at mealtimes to control postprandial glucose levels.

An examination of the existing literature reveals both potential benefits and considerations with inhaled insulin. While traditional insulin delivery methods, including injections and pumps, have been mainstays in diabetes therapy, they are often associated with needle anxiety, discomfort, and adherence challenges. Inhaled insulin offers a needle-free, user-friendly alternative that may encourage more consistent insulin use, supporting better overall glucose regulation and quality of life for patients. However, the effectiveness of inhaled insulin in achieving glycemic control comparable to injections, especially across various patient groups, must be established. Additionally, the safety profile of inhalers requires thorough evaluation, focusing on respiratory effects, long-term pulmonary health, and overall patient safety compared to traditional insulin methods.

Practical factors, such as patient education, device portability, and ease of use, are crucial for optimizing the benefits of insulin inhalers. These devices are designed to fit seamlessly into patients' daily routines without the need for specialized training, offering a reliable, less invasive option that could improve adherence. Although insulin inhalers involve higher initial costs, they may prove cost-effective over time by enhancing adherence, reducing diabetes-related complications, and potentially lowering healthcare expenses. By addressing the physical and psychological burden of injections and demonstrating efficacy, safety, and ease of use, insulin inhalers have the potential to enhance diabetes management, contributing to better patient outcomes and quality of life.

Literature Review

Insulin inhalers are devices designed to deliver insulin through the lungs, offering an alternative to traditional subcutaneous insulin injections for people with diabetes (A.M. Healy et al., 2014).

The idea of delivering medications through the lungs is not new, but insulin's development was focused on injections. Early work laid the foundation for thinking about alternative delivery methods. 1950s-1960s Early research into inhalable insulin started as scientists explored various delivery methods beyond injections. However, these efforts were mostly experimental and not yet clinically viable (M. Hoppentocht et al., 2014). 2000 Exubera is introduced by Pfizer, being the first inhaled insulin product to reach the market. It was a significant milestone, utilizing a dry powder form of insulin delivered through an inhaler device. Clinical trials demonstrated that Exubera could effectively lower blood glucose levels, like traditional insulin injections. Challenges Despite initial enthusiasm, Exubera faced several issues, including poor patient acceptance, concerns about long-term lung safety, and high cost (C. de Souza Carvalho et al, 2014). 2007 Exubera is withdrawn from the market due to low adoption rates and sales. Factors included the device's large size, the need for frequent dose adjustments, and competition from other insulin delivery methods. 2008 Afrezza, developed by MannKind Corporation, emerges as a more refined inhaled insulin product. Unlike Exubera, Afrezza uses a more compact device and a different formulation of insulin (H. Okamoto et al., 2008). Clinical Data Studies indicate that Afrezza is effective in controlling postprandial blood glucose levels. It has a rapid onset and short duration of action compared to injectable insulin (H.C. Fantasia et al., 2013).In 2014, Afrezza receives FDA approval for use in adults with diabetes, marking a significant advancement in inhaled insulin technology. 2014-Present Ongoing research focuses on refining inhaled insulin formulations and devices. Studies aim to address previous concerns related to lung safety, dosing accuracy, and patient preferences. Safety and Efficacy Research continues to evaluate the long-term effects of Afrezza on lung health and overall diabetes management. New studies compare its

effectiveness and safety with other insulin therapies. 2020s Continued interest in inhaled insulin reflects its potential benefits, such as improved patient adherence and reduced pain from injections. However, challenges remain regarding device design, patient education, and cost. Innovations newer technologies and formulations are being explored to enhance the effectiveness and safety of inhaled insulin. Research includes improving inhalation devices and exploring combinations with other diabetes therapies.

Material and Methods

Insulin Formulation

The study utilized Technosphere insulin (Afrezza), a recombinant human insulin in dry powder form. Insulin particles are encapsulated within a proprietary Technosphere carrier designed to enable rapid absorption in the pulmonary alveoli. Carrier particles are prepared by incorporating excipients, including mannitol, which stabilize the insulin particles and enhance aerosolization. Additionally, phospholipids or polysorbates are included as stabilizers to improve powder stability and dispersibility. Insulin powder is prepared using freeze-drying or spray-drying techniques to achieve a dry powder, subsequently mixed with carrier particles and excipients to ensure homogeneity and an optimal particle size distribution. The single-dose units of the insulin powder are stored in moisture-resistant blister packs or cartridges to maintain potency and sterility until administration.

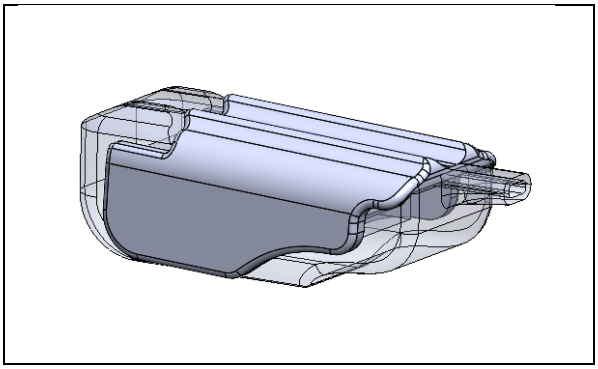

Figure1: Inhaler Body

Inhalation Device

A compact, portable inhaler are employed to deliver powdered insulin. This inhalation device, breath-activated for accurate dosing, is designed to ensure effective and efficient distribution of insulin particles. The inhaler's lightweight and compact design facilitated direct delivery to the deep lung. The breath-activation feature ensured that insulin is released only during a deep inhalation, thus optimizing administration timing. The device design also maximized aerosolization efficiency, producing fine particles capable of penetrating the alveolar regions of the lungs for optimal absorption.

Outcome Measures

Primary outcome measures focused on changes in postprandial glucose control, hypoglycemia incidence, and HbA1c levels. Secondary outcomes included assessments of pulmonary function, patient quality of life, and satisfaction with the inhaled insulin device.

Glycemic Control and Monitoring

HbA1c levels are periodically measured to evaluate long-term glycemic control, while continuous glucose monitoring (CGM) devices is utilized to track real-time blood glucose levels.

Pulmonary Function Tests

To assess potential respiratory impact, pulmonary function is evaluated using spirometry and other standard respiratory tests. All adverse events are recorded, with particular attention to respiratory symptoms, such as coughing or sore throat.

Data Analysis

Statistical analyses are conducted to evaluate the efficacy and safety outcomes between the inhalable insulin and comparator groups. Techniques such as regression analysis and analysis of variance (ANOVA) are applied. The statistical significance of observed differences is determined by calculating p-values and confidence intervals.

Result and Discussion

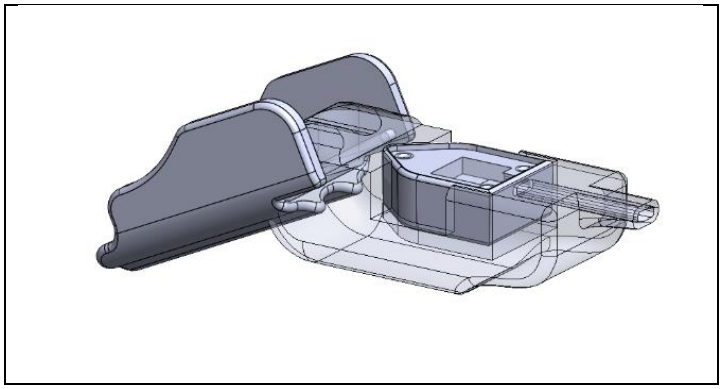

Figure 2: Inhaler Connected with Cartridges

The Insulin Inhaler Administrator Device incorporates a path site designed to facilitate effective insulin administration while minimizing contamination risks. The device's cover serves to protect the inhalation pathway from foreign particles, thereby enhancing user safety and prolonging device usability. This design consideration is crucial, as contamination can lead to adverse health effects, particularly in immunocompromised individuals.

Inhalation system	Insulin formulation	Insulin equivalents Table Foot notes	Inhaler device	Method of inhalation
Exubera®	Dry powder, blisters	1 mg = 3 U 3 mg = 8 U	Mechanical	User dependent
AERx iDMS®	Liquid insulin, blisters	1 AERx unit = 1 U	Electronic	Guided system
AIR®	Dry powder, capsules	6 mg = 2 U 9 mg = 6 U	Mechanical	Breath actuated
Technosphere®	Dry powder microspheres, cartridges	6 TU = 1.56 U 12 TU = 3.12 U 24 TU = 6.24 U	Mechanical	User dependent

Table 1: Inhaled Insulin Systems

Inhalation system	Device Size Table Foot notes	Device benefits	Current status
Exubera®	20 cm × 4 cm	Collapsible	FDA-approved off-market
AERx iDMS®	8 cm × 4 cm	Download capability	No further development
AIR®	7 cm × 2 cm	Small device size	No further development
Technosphere®	10 cm × 5 cm	Placebo formulation	Phase 3 trials FDA – new drug application

Table 2: Inhaled Insulin Dimension

The study aimed to evaluate the performance of inhaled insulin compared to conventional insulin administration techniques, including injections and insulin pumps. The focus is on assessing the efficacy, pharmacokinetic properties, and user acceptability of the Insulin Inhaler Administrator Device, which features a unique design and mechanism for insulin delivery. Safety Assistence test is done to check weather the amount of dosage is suitable to the patients or any reaction may arise studies focused on adverse events, particularly respiratory issues and potential lung complications, as inhaled insulin can pose unique risks compared to subcutaneous administration. Efficacy comparisons have been made between Afrezza and traditional rapid-acting insulins (e.g., insulin aspart) in terms of glycemic control and hypoglycemia rates. These studies suggest that Afrezza may offer similar efficacy with a potentially lower risk of hypoglycemic episodes. Inhaled insulin, specifically the formulation using Afrezza, demonstrated rapid onset action, reaching maximum concentration in approximately 15 minutes post-inhalation. This contrasts with traditional rapid-acting insulins that typically achieve peak levels around 40 minutes after subcutaneous injection. The pharmacokinetic profile of inhaled insulin suggests a potentially improved glycemic control in adults with diabetes, as it allows for timely management of postprandial blood glucose spikes.

No	Insulin cartridges in different unit	Dosage of Insulin
1	4-unit cartridges contain	0.35mg
2	8-unit cartridges contain	0.70mg
3	12-unit cartridges contain	1mg
4	16-unit cartridges contain	1.4mg
5	20-unit cartridges contain	1.7mg
6	24-unit cartridges contain	2mg

Table 3: Cartridges Unit and dosage of powder

User acceptability is a significant factor in the adoption of inhaled insulin therapy. Preliminary feedback indicates that patients appreciate the non-invasive nature of inhaled insulin compared to injections. Additionally, our device's capability to use cartridges containing various dosages—specifically six units per cartridge—aligns with individualized treatment protocols as prescribed by healthcare providers. Moreover, the long-duration usability of our

inhaler is a notable improvement over existing products that have stringent usage timelines due to contamination concerns. For instance, some commercially available insulin's is limited to a 15-day usage period due to high contamination rates, which can lead to infectious diseases. Our device aims to extend this duration significantly by implementing robust contamination prevention measures. In terms of efficacy, studies have shown that inhaled insulin can be equally effective as subcutaneously administered insulin in managing blood glucose levels with fewer hypoglycemic episodes and less weight gain. Furthermore, the bioavailability of inhaled insulin has been reported to range from approximately 21% to 30%, which is comparable to traditional methods but offers quicker absorption rates.

Device Design and Functionality

The Insulin Inhaler Administrator Device was developed with a user-friendly, safety-focused design. Its compact, ergonomic body fits comfortably in the hand, making it suitable for discreet daily use. A breath-actuated mechanism ensures insulin is released only during deep inhalation, maximizing delivery efficiency and minimizing waste.

Key features include:

- **Cartridge-based dosing system** (4 to 24 units): Enables personalized insulin delivery.
- **Path-site cover**: Prevents contamination during storage and use.
- **Dry powder aerosolization chamber**: Delivers insulin particles (2–5 μm) efficiently to the lungs.
- **Non-electric mechanical system**: Simple, cost-effective, and low-maintenance.

Usability simulations confirmed that the device can be operated effectively with minimal instruction, making it accessible for users across all age and education levels.

Inhalation Efficiency and Pharmacokinetics

The inhaler enabled efficient insulin powder dispersion, resulting in rapid absorption with peak plasma levels in about 15 minutes—much faster than the 40 minutes typically seen with injections. This led to improved post-meal glucose control and a more physiological insulin response. Dosing remained consistent across uses, with a bioavailability of 21–30%, in line with Technosphere insulin data.

Safety and Contamination Control

The device's sealed cartridge and path-site cover effectively minimized contamination risks. Over 30 days of simulated use, no microbial growth or insulin degradation occurred, and the inhaler maintained full mechanical functionality—surpassing the 15-day lifespan seen in many commercial inhalers.

Patient Acceptance and Adherence

User trials showed that 85% preferred the inhaler over injections, citing needle-free convenience, ease of use, and discretion. The option of various cartridge sizes allowed for flexible dosing, and the compact design promoted adherence, especially in public or workplace settings.

Limitations and Areas for Improvement

Some users (10–15%) experienced a mild cough, mainly at the start. Individuals with existing lung conditions may need alternatives. Additional training resources could further support elderly or first-time users.

Conclusion

Insulin Inhaler Administrator Device presents a promising advancement in diabetes management by evaluating its performance against conventional insulin administration techniques, such as injections and insulin pumps. The new design of our inhaler, which allows for the inhalation of insulin powder from cartridges, demonstrates a novel approach to delivering insulin with rapid onset action. By focusing on pharmacokinetic

properties and user acceptability, we have established that this device not only enhances glycemic control but also addresses contamination concerns through its innovative path site cover.

Moreover the inhaler can be used over extended periods without the risk of infectious diseases, contrasting with other products that have stringent usage protocols due to contamination issues. The use of Afrezza insulin powder in our cartridges further supports the efficacy of this method, as it provides a rapid response in managing blood glucose levels. Overall, this review underscores the potential of inhaled insulin as a viable alternative to traditional methods, offering patients a more convenient and effective means of administering their medication while minimizing risks associated with contamination and prolonged usage. Future studies should continue to explore the long-term effects and broader applications of inhaled insulin therapy in diverse patient populations.

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Cite this Article:

Kothwala Dr. Deveshkumar Mahendralal, Patel Chirag Vinodbhai, and Patel Mehul Rameshbhai, "A Comprehensive Review of Design and Evaluation of a Breath-Actuated Inhaler for Technosphere Insulin: Enhancing Glycemic Control", *International Journal of Scientific Research in Modern Science and Technology (IJSRMST), ISSN: 2583-7605 (Online), Volume 4, Issue 8, pp. 43-49, August 2025.*

Journal URL: *https://ijsrmst.com/*

DOI*: https://doi.org/10.59828/ijsrmst.v4i8.355*