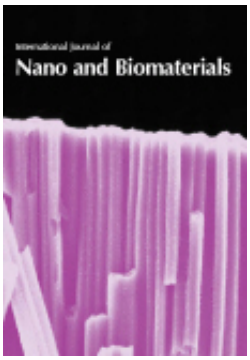

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Inhaled insulin: current steps towards diabetes treatment

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Abstract: Diabetes mellitus is among the most serious health challenges worldwide. Diabetes is a chronic condition that develops when the pancreas fails to adequately make or utilise insulin. 537 million individuals worldwide have diabetes, and in 2021, 6.7 million people will die from the diabetes. There are 90 million adult diabetics in India, and the disease claims 747 thousand lives per year. The act of taking in air and occasionally other substances into your lungs is known as inhalation. Common types of inhalers include nebulisers, dry powder inhalers, soft mist inhalers, and meter-dose inhalers. The body responds quickly and easily to inhalation therapy. The bloodstream is affected directly by the lung, and given its accessibility and extensive alveolar-capillary network for drug absorption, inhalational insulin is a desirable alternative to systemic administration of the hormone. The Food and Drug Administration (FDA) officially approved the inhaled insulin Afrezza. In comparison to other unsuccessful inhaled insulin forms, this new, faster-acting inhalable insulin has a different and safer pharmacokinetic profile.

Keywords: diabetes; inhalation; insulin; nanotechnology; future prospects; recent advances.

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1 Introduction

Diabetes is a chronic disease that develops when the pancreas either produces insufficient amounts of insulin or when the body uses its own insulin inefficiently (https://www.who.int/). In 2014, 8.5% of people over the age of 18 had diabetes. In 2019, 1.5 million deaths were directly related to diabetes, and 48% of these deaths occurred in those under the age of 70. Premature death rates linked to diabetes went up 5% between 2000 and 2016 (https://www.who.int/). One in ten adults between the ages of 20 and 79 (537 million) would have diabetes in 2021. This figure is projected to increase the 643 million by 2030 and to 783 million by 2045. More than 75% of diabetics live in low- and middle-income countries. One death due to diabetes will occur every 5 s by 2021 (http://www.idf.org/diabetesatlas). One in every eleven adults in Southeast Asia (SEA), or 90 million people, has diabetes. By 2030, there will be 113 million adults with diabetes, and by 2045, there will be 151 million. Diagnosis for more than one-third of adult diabetics is unknown (http://www.idf.org/diabetesatlas).

Other names for type 1 diabetes include insulin-dependent, juvenile, or childhood onset. When the pancreatic beta cells are destroyed by the immune system, it develops. Type 1 diabetes affects about 10% of all diabetics (https://www.idf.org/aboutdiabetes/type-1-diabetes.html). Another name for type 2 diabetes is adult-onset, non-insulin dependent. The beta cells in the pancreas are no longer producing insulin. About 90% of all instances of diabetes are type 2, making it the most prevalent kind (https://www.idf.org/aboutdiabetes/type-2-diabetes.html).

The American Diabetes Association claims that keeping blood sugar levels under control (i.e., 150 mg/dL fasting glucose or 7% A1C) is crucial for avoiding problems in diabetes individuals (Association, 2019). For instance, persistent hyperglycaemia has been connected to a variety of microvascular (such as eye, nerve, and kidney illness) and macrovascular (cardiovascular disease) issues (Association, 2019). Therefore, standard treatments for both types of diabetes often involve daily insulin administration (for example, by insulin pumps or subcutaneous injections) and frequent glucose monitoring. Nevertheless, inconsistent glucose monitoring and poor patient adherence, which are frequently caused by a variety of factors, such as discomfort and how time-consuming the procedure is can result in unpredictable insulin dosages and uncontrolled hyperglycemia, hypoglycemia, seizures, unconsciousness, or even death (Association, 2014; Schulman et al., 2014). The complexity of diabetes management is further increased in young people with diabetes due to developmental, psychological and caregiving problems (Streisand and Monaghan, 2014; Lemmerman et al., 2020).

Since insulin and other macromolecular diabetes medications must be given subcutaneously due to the harsh environment of the gastrointestinal tract, patient compliance might be low (Heinemann, 2011). Additionally, this traditional method of insulin replacement therapy is ‘open loop’, which means that it relies on previous knowledge of the patient’s particular blood glucose profile in response to different meals and insulin treatments to predict insulin dosages (Pickup, 2012; Owens, 2002). By dynamically managing insulin levels with real-time data, several technologies have been created to solve the limitations of injectable therapy while lowering the treatment load placed on patients. To achieve these objectives, researchers are creating novel medicinal entities (Berenson et al., 2011), improving insulin pharmacokinetics (Mehanna, 2013), and enabling alternative routes of insulin administration (Owens, 2002).

Indeed, the numerous physical, chemical, and biological characteristics of nanoparticles and nanoscaled materials make them desirable for biomedical applications (Whitesides, 2003; LaVan et al., 2002). Small-molecule and big macromolecular (DNA, RNA, and proteins) therapies are both delivered by nanoparticles, which are also utilised to detect and track the development of disease (McNeil, 2011). For diverse biological purposes, new nanoparticulate drug delivery systems have been created, including liposomal nanoparticles, polymeric nanoparticles, solid lipid nanoparticles, and metallic nanoparticles (Veiseh et al., 2015).

1.1 Nanotechnology and diabetes diagnosis

For the accurate and timely detection of diabetes, nanotechnology can offer sensing technologies (Taguchi et al., 2014). To reduce the possibility of blood glucose levels dropping to unsafe levels, diabetes patients must independently do periodic checks (Duggan et al., 2017). For some people, especially the elderly and young children, doing this practise can be unpleasant and challenging (Bahendeka et al., 2019). The development of implantable and wearable sensing systems, which provide ongoing and accurate medical information, may be made possible by nanotechnology (Dias and Cunha, 2018). Utilising a microphysiometer or an implanted sensor are the two most popular techniques to use nanotechnology in the diagnosis of diabetes (Rauf et al., 2016). Multiwalled carbon nanotubes, which are electrically conductive, are used to construct the microphysiometer (Ramachandran et al., 2016). The two primary types of diabetes mellitus can now be differentiated using a microchip-based test, allowing for differential diagnosis (Mannino et al., 2019). Actually, this low-cost, portable diagnostic using a microchip can detect type-1 diabetes. Traditional methods for diagnosing diabetes are pricy, cumbersome, and only available in well-resourced medical facilities (Kahanovitz et al., 2017; Lagopati and Pavlatou, 2021)

1.2 Nanotechnology applications in monitoring

Using traditional glucose metres, which call for patients to physically ‘prick" themselves repeatedly throughout the day to observe changes in glucose levels, is the most widely used method of monitoring diabetes. Although tried and true, this method has a number of drawbacks, such as low patient compliance and inaccurate glucose readings caused by a range of variables, such as mealtimes, age, etc. (Association, 2019). Additionally, certain routine activities like sleeping or driving cannot be done when conventional glucose monitoring is being used. Due to the infrequent nature of traditional monitoring techniques, patients run the risk of serious consequences by missing potentially harmful glucose variations in between tests (Association, 2019; Schulman et al., 2014). Various efforts have been made over the past three decades to create a hassle-free way to monitor glucose levels. This concept eventually proved practical and gave rise to continuous glucose monitoring (CGM) devices, which can provide continuous glucose monitoring for up to 10 days (Edelman et al., 2018). Amperometric sensors that are implanted subcutaneously were a part of the initial generation of these devices. Depending on the level of glucose, these sensors create a detectable electric current (Hovorka et al., 2013). Even though they represent a development in CGM, these devices have a number of drawbacks, including

1 Lack of stability caused by signal lag and sensor drift

2 Requirement for weekly subcutaneous implantation and calibration procedures

3 High sensitivity to changes in a variety of physiological parameters, such as pH and temperature (Hovorka et al., 2013; Schmid et al., 2013).

Biosensors built with nanotechnology could be able to get beyond these restrictions. (Lemmerman et al., 2020)

1.3 Oral administration

The easiest way to maintain diabetes mellitus is thought to be oral insulin delivery (Shah et al., 2016). However, because lipid-bilayer cell membranes prevent the passage of hydrophilic medications like insulin into the bloodstream, the intestinal epithelium is thought to be a significant barrier to their absorption (Yang and Hinner, 2015). Gastric enzyme-based drug delivery systems guarantee that insulin is transferred to and degraded in the stomach (Patra et al., 2018). The active ingredient must be included in a protective matrix to shield it from the hostile environment of the stomach (Date et al., 2016; Lagopati and Pavlatou, 2021).

Using nanoparticles to administer insulin is a far more recent method. The therapeutic effectiveness of insulin is significantly influenced by the quantity of insulin and polymer. Studies conducted in vitro revealed that nanoparticles shield insulin from enzymatic breakdown. Polyalkylcyanoacrylate, polymethacrylic acid, and polylactic-co-glycolic acids are the primary polymers utilised in the formulation of nanoparticles. Additionally, naturally occurring polymers including chitosan, alginate, gelatin, albumin, lectin, and others are employed. Chitosan among them has a good penetration property. A nanoparticle containing chitosan dramatically lowers blood glucose levels in a diabetic rat model (Adams et al., 2005).

Poly (D,L-lactide-co-glycolide) PLGA based polymer nanoparticles or microparticles have been widely used as controlled drug delivery systems for molecules that are prone to degradation, such as peptides, proteins, antigens, hormones, and so on. Emulsions or the double-emulsion technique, solvent evaporation, or spray drying are some of the preparation techniques for these devices that have been used. To increase the therapeutic efficacy of these devices, certain preparation variables, including as release rates and encapsulation efficiency, should be improved (Mundargi et al., 2008).

Insulin enzymatic breakdown is prevented by poly(isobutylcyanoacrylate) nanocapsules, according to research by Aboubakar et al. According to a study, poly(isobutylcyanoacrylate) nanocapsules are crucial for the absorption of insulin and deliver the active form of the hormone when taken orally (Aboubakar et al., 2000).

Insulin liposomes were created and tested by Choudhari et al. Additionally, they assessed the formulation's results upon oral delivery. They came to the conclusion that this system had the same impact as 1 unit of subcutaneously delivered insulin (Choudhari et al., 1994; Verma et al., 2014).

2 Inhalation approach of insulin delivery

In comparison to the subcutaneous route, this method of administration offers a substantially quicker beginning of effect and less proteolytic enzyme breakdown. Inhaled insulin is absorbed through the mucosal membrane of the lungs (alveoli, approximate surface area 100 metre square). Exubera, human insulin (derived from ribosomal DNA) inhalation powder, has also received FDA (food and drug administration) approval for use in patients older than 6 years old and in adults.

i For people who are obese, it has been discovered that inhaled insulin absorption is unrelated to body mass index.

ii For smokers, a quicker beginning of action has been seen.

iii Greater maximum effect has been observed.

iv A greater effect on reducing total blood sugar has been seen.

v In asthmatic patients, it was discovered that absorption was 20% lower in the absence of bronchodilators than in nonasthmatic patients.

vi Systemic insulin concentrations have increased by a factor of two in those with COPD (chronic obstructive pulmonary disease).

vii Holding your breath at the conclusion of an inspiration does not increase the bioavailability of inhaled insulin.

viii Ten minutes before a meal, the dose is administered.

ix Exubera: Category C for pregnancy risk.

x Subcutaneous insulin: Category B for pregnancy risk (Cano-Cebrian et al., 2005; Laube, 2001; Exubra, 2006; Owens et al., 2003; Rave et al., 2005; Briggs, 2005).

Rapid-acting insulin analogues and inhaled insulin were examined by Leal et al. in the management of diabetes. They came to the conclusion that using fast-acting insulin analogues effectively controls elevated blood glucose levels. They came to the conclusion that it also lowers cardiovascular risk factors (Leal et al., 2007).

When exubera, or inhaled human insulin, is provided by young patients with insulin-dependent diabetes mellitus, Skyler et al. evaluated the safety of the pulmonary route. Exubera had no negative effects on lung function, they concluded (Skyler et al., 2008; Verma et al., 2014).

2.1 Inhaled as alternative to conventional insulin

One study found that inhaled insulin was effective in treating subcutaneous insulin resistance syndrome, a rare disorder caused by the fast breakdown of insulin in subcutaneous tissue. Research has shown that glycemic control, as measured by the mean HbA1c reduction from baseline to end point, was comparable across the groups receiving inhaled and conventional treatments. With the exception of cough, which appears to be less common and less severe with continuous usage, the number and type of adverse events recorded with inhaled insulin appear to be comparable to those described

with subcutaneous insulin (van Alfen-van der Velden et al., 2010; Mohanty and Das, 2017).

2.2 Inhaler for direct lung delivery system

The three primary forms of inhaled medicine delivery devices are nebulisers, pressurised metered-dose inhalers (MDIs), and dry powder inhalers (DPIs). Each category has unique benefits and drawbacks. An effective way to deliver a therapeutic agent for the treatment of disease is through aerosol delivery. A reliable drug dose and the correct size aerosol, ideally between 0.5 and 5 μm, are requirements for a successful drug delivery system. It should also preserve the chemical and physical stability of the medication formulation. The ideal breathing system must also be a lightweight, affordable device with few moving parts.

- Nebuliser
- Dry powder inhaler
- Metered dose inhaler.

2.2.1 Nebuliser

The jet and ultrasonic nebulisers use different amounts of force to turn each liquid into an aerosol. Depending on the model and the manufacturer, nebulisers can create droplets as small as 1 or as large as 5 μm. Since they do not require patient cooperation between inhalation and actuation, nebulisers are beneficial for children, the elderly, ventilated, non-conscious patients, or those who cannot utilise pMDI or DPIs. Nebulisers have the capacity to provide greater doses than the other aerosol devices, even if this will call for longer administration times. The following elements need to be tuned from the nebuliser's viewpoint in order to emit a precise and constant dose

- The amount of medication solution that has been loaded into the apparatus
- The medication solution's viscosity
- Low air pressure when using a jet nebuliser
- The mouthpiece, mask, or tubing that is utilised.

In non-optimised therapies, a sizeable portion of the nebuliser's emitted dose may be lost in the tubing, may remain as dead volume or in the case of nebulisers without vents, may be lost in the vicinity, exposing others to the aerosol. Lack of optimisation of these variables is the key factor contributing to dose variability a patient may encounter. Users of nebulisers suffer from the necessity of assembling and filling them with medication prior to each use. They need to be disassembled and cleaned if they're going to be used again. It could be difficult for an untrained young or old patient to adhere to all of these guidelines (Labiris and Dolovich, 2003; Ali, 2010).

2.2.2 Dry powder inhalers

Dry powder inhalers do not need propellant. The patient can administer the formulation very easily with the help of these compact, portable devices. Due to their solid shape and

rather stable chemical makeup, DPIs do not require cold chain storage. Over the past 20 years, DPI formulations have been developed employing particle engineering techniques such spray drying, lyophilisation, and super critical fluid technology. The influence of physicochemical properties of particulate systems, such as particle size, density, porosity, surface morphology, interparticle force, surface energy, etc., on the aerosol performance of DPIs have been widely investigated. Despite being essential to the inhalation product's quality and efficacy, the solid-state characteristics and physical stability of the powder formulations in DPIs are often ignored in the literature.

DPIs are preferred for their processing and stability since they are typically made as one phase, solid-particle blends. DPIs are a typical, inhaled dose type that is often employed. Nowadays, there are essentially two types of DPIs: those in which the drug is packaged in individual doses (capsules) (single dosage or unit-dose devices) and those that contain several doses in a foil blister or a reservoir of medication from which the doses are metered (multiunit and multidose devices (Shetty et al., 2020; Smola et al., 2008).

- **Challenges of dry powder inhaler**

The challenges with dry powder inhalers including nanoparticles include particle aggregation, proper powder production, reproducible powder filling, unit dose packaging, and the development of reliable aerosol dispersion and delivery systems. One of the main problems is the accumulation of particles. As a result, breaking up particles for those who inhale is more difficult.

2.2.3 Metered dose inhaler

The most often used inhalers to treat local respiratory conditions including COPD and asthma are pMDIs. The conventional pMDI's structural structure is composed of the canister, metering valve, actuator, and mouthpiece. The strong inert materials used to construct canisters can endure the high pressures necessary to maintain the propellant gas's liquid state. Canisters have been made from a variety of materials, including aluminium, stainless steel, glass, and plastic. Every time the gadget is turned on, the metering valve is made to deliver a precise amount of aerosol (20–100 μL). An inner valve between the canister and the metre chamber opens while the inhaler is not in use, allowing the liquid propellant-drug mixture to fill the chamber.

Another exterior valve that separates the metre chamber from the outside air is closed at the same time. The outer valve opens as the inner valve shuts, releasing the metered drug-propellant mixture held in the chamber via the actuating aperture in an aerosol form as the patient presses the canister for dose actuation. The interior parts of the actuator are the spray nozzle (actuator orifice) and the expansion chamber, where the propellant discharged from the metering chamber expands and partially volatises as a result of the pressure drop. The performance of pMDIs is significantly influenced by the actuator's design. Smyth has shown that the actuator orifice, expansion chamber, orifice jet length, and spray pattern all have an effect on the size of the particles that are discharged. The dose counter on contemporary actuators indicates how many doses are still left (Smola et al., 2008; Thorat and Meshram, 2015).

2.3 Physiology of inhaling insulin

A novel way for diabetics to receive their insulin medication is by inhaling it into their lungs. The lung is a perfect organ for absorbing tiny molecules into the circulation because it possesses the same characteristics that make it so well-suited for gas exchange. The lung has a 130 cm^2 pulmonary alveolar surface area. Air enters roughly 300 million alveoli with each breath. Additionally, the alveolar lining cell is only 1–2 cm away from the pulmonary capillary lumen, which favours quick absorption into the bloodstream (Rosenstock et al., 2009).

The ratio of a molecule's molecular mass to its absorption through the alveolar-capillary interface is inverse. The extremely thin, vesiculated, permeable membrane easily absorbs small peptides like insulin (around 6000 Da). Because there are few mucociliary processes at the alveolar level molecules that reach it spend more time (Ryan et al., 2007).

Lower respiratory deposition of an aerosol or dry powder formulation is influenced by a number of factors. Particle size is highly affected for instance if particles are larger than 5 μm its deposit only in large airway and pharynx, typically 1–3 μm particles reach to the lower airway stable and alveoli. Deposition is also impacted by particle velocity. While flow rates of 15–25 L/min are appropriate for lower airway deposition, flow rates >35 L/min or 10 L/min will favour upper airway impaction. However, even under ideal conditions, only a small percentage of an aerosol or dry powder typically penetrates deeply into the lungs (Petrucci et al., 2009; Mohammed et al., 2016).

3 Anatomy of lung

The respiratory system's main organ is the lung. Lung anatomy is demonstrated in Each lung has several lobes. With three lobes, the right lung is slightly bigger than the left lung's two lobes. The pleura, a protective membrane, covers the lungs, which are housed in the thoracic cavity, or chest cavity. Human respiratory systems are primarily responsible for transferring oxygen from the atmosphere into the blood and eliminating carbon dioxide from the body. The human body really needs enough oxygen levels. For the most part, alveoli are in charge of gas exchange.

3.1 Alveoli

The lungs functional components, the alveoli, serve as the site of gaseous exchange. The body has the ability to alter the exchange of gases by altering the rate of breathing or by breathing more deeply. 12–20 breaths per minute constitute the usual respiratory rate. Tachypnoea refers to rapid breathing, it is a crucial indicator of respiratory illness. The amount of oxygen and carbon dioxide in the blood increase and decrease with faster breathing. Exercise can speed up breathing, as can respiratory conditions like asthma, bronchitis, and pneumonia. An alveolus is a collection of little sac-like structures at the tip of each bronchiole. About 300 million alveoli are present in each lung and capillary blood vessels surround each alveolus. The alveolar membrane allows oxygen and carbon dioxide to pass into blood vessels and vice versa. Between alveoli and capillary blood vessels, there is a constant exchange of gases. For quick gas exchange, the blood barrier between the pulmonary capillaries and the alveolar space is extremely thin. Inhalation

causes oxygen to permeate into the blood through the interstitial space and alveolar walls. Pulmonary alveolar cells come in various varieties. Pneumocytes of type I (or tiny type A) are membrane-bound, nonphagocytic cells. These 5 μm surface-lining epithelial cells have thin squamous cytoplasmic extensions that branch out from a central nucleus. The larger alveoli are type II cells, also known as type B or septal cells, which are linked to the basement membrane. These 10–15 μm tick epithelial pneumocytes are spherical, granular, and pneumocytes.

3.2 Breathing system of lung

The external intercostal muscles contract during inhalation, raising the rib cage. Additionally, the diaphragm descends, lowering the internal pressure in the thorax. The pleural membranes that attach the lungs to the thoracic wall allow them to expand outward and create internal negative pressure, which causes air to rush through the upper and lower airways (Lutfi, 2017; Patel et al., 2013).

Characteristics of lung absorption

- Large, highly vascularised area available for transcytosis
- Conducting airway 0.8 m^2 and Alveoli 80 m^2
- Alveoli highly permeable to many biologics; mostly small molecule and many macromolecules capable of absorption throughout the respiratory tract
- Relatively rapid, first-order absorption
- Less first pass metabolism and degradation in liver and gastrointestinal tract
- Only IAI and 4BI P450 isoenzymes reported in the human lung (Patel et al., 2013).

3.3 Pulmonary function in diabetes

Studies have shown that diabetic patients have lower forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) than non-diabetic people (Cooper et al., 1990; Sandler et al., 1986, 1987; Mori et al., 1992). The difference between the diabetic and non-diabetic groups in the Copenhagen City Heart Study (Lange et al., 2002) was 8%, which is comparable to the difference between a smoker and someone who has never smoked. It's unknown what caused the decline in lung function. Diabetes patients frequently have a high body mass index (BMI), which is linked to a decreased ventilatory capacity. A lower than expected lung function was linked to higher fasting glucose levels in the Framingham Heart Study (Walter et al., 2003).

EXUBERA: Adult patients with diabetes mellitus can use EXUBERA as a kind of treatment (Pfizer, 2008). Exubera should be used in individuals with Type 1 DM in conjunction with a long-acting insulin preparation to replace basal insulin in order to control post-meal glucose excursions. EXUBERA can be administered as a monotherapy, in conjunction with oral medicines, or in addition to long-acting insulin in individuals with Type 2 DM (Pfizer, 2008).

Type 2 DM is characterised by insulin resistance the authors feel that the most sensible course of action when using EXUBERA in combination with an oral medication is to

combine it with an insulin sensitiser (thiazolidinedione or metformin). Though its pharmacodynamic effect has been primarily demonstrated to diminish after 6 h, it is noteworthy that in several investigations of Type 2 DM, the use of EXUBERA as a monotherapy or in combination with an oral medication significantly lowered the FPG concentration EXUBERA has been demonstrated to significantly lower plasma glucose levels in both children and adolescents with Type 1 DM, even though its usage in these age groups has not been licenced (Pfizer, 2008; Defronzo, 1988, 2004). Patient contentment Subjects with Type 1 DM and Type 2 DM were randomised to receive either EXUBERA with ultralente, 2–3 doses of subcutaneous insulin with ultralente, or a mixed/split insulin regimen for a 12-week research by Rosenstock et al. (2004), which was followed by a 1-year open-label extension. Only 21% of patients who received subcutaneous insulin during the 12-week research elected to continue the regimen, compared to 85% of patients who received EXUBERA at same time. The EXUBERA group experienced higher patient satisfaction and compliance as well as long-lasting improvements on HbA1c levels. When inhaled insulin was offered as a treatment option, diabetic patients were three times more likely to select insulin therapy, according to a study assessing potential treatment options in people with Type 2 DM who were insufficiently managed (Freemantle et al., 2005; Jani et al., 2007).

AFREZZA: Another brand of inhaler with premeasured, fast-acting insulin is called Afrezza. The inhaled insulin, which was approved in 2014 (Figure 1), is intended to be used before to meals. Afrezza is intended for the treatment of type I and type II diabetes, like Exubera (but, thankfully, it comes in a much smaller size). For consistent blood glucose control throughout the day when used in the treatment of type I diabetes, patients will still need to utilise a long-acting insulin. Keep in mind that diabetic situations like diabetic ketoacidosis are not appropriate uses for inhaled insulin (DKA). Common side effects of Afrezza include sore throat, scratchy throat, coughing, and hypoglycemia. In general, people who smoke and those who have lung diseases should not use inhaled insulin. (https://canadianinsulin.com/articles/inhaled-insulin-brands/).

The Afrezza experience to date

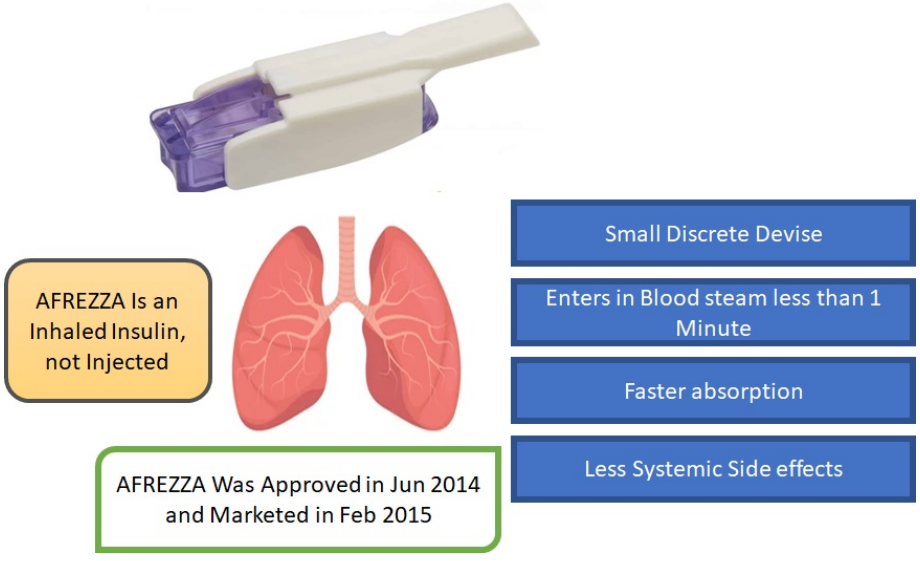
Although Exubera's commercialisation ultimately failed, inhaled insulin innovation persisted, and in 2014, Afrezza was introduced. The AFFINITY-1 research found that significantly fewer patients experienced hypoglycemia and that Afrezza's A1C decrease was noninferior to insulin as part in type 1 diabetic patients taking basal insulin (Bode et al., 2015). The AFFINITY-2 research verified that the addition of prandial Afrezza to individuals with type 2 diabetes who were uncontrolled on oral medications was successful, dramatically decreasing A1C (P 0.0001) (Rosenstock et al., 2015).

It indicates that Afrezza has significant advantages over Exubera. Its distribution method is compact, stylish, dosed in units, and includes a straightforward dosing conversion chart, in contrast to Exubera's delivery method, which was bulky, unwieldy, and dosed in milligrammes. Afrezza's changes enable a more discrete administration technique and a dose schedule that is simpler to understand for both prescribers and patients.

The safety profile of Afrezza, however, is similar to that of Exubera, with a loss in pulmonary function and a modest rise in lung cancer incidence. The FDA mandated a risk assessment and mitigation strategy and a 'black-box" warning advising patients of an elevated risk of acute bronchospasm in those with chronic lung illness as a result of fresh

concerns raised following the approval of Afrezza (2014). Patients in the Afrezza cohort were also shown to have higher rates of diabetic ketoacidosis.

Figure 1 Inhaled insulin AFREZZA for control of diabetes (see online version for colours)



4 Patents

A formulation of breathed insulin that improves the absorption of insulin in the lower respiratory tract was created by Backstorm et al. This is accomplished by using a powdered formulation (Backstorm et al., 2003). A dry powder insulin formulation that allows for quick alveolar absorption was created by Patton et al. (1999). A technique and a tool were created by Gonda et al. that do not require injecting insulin. The rate of absorption of insulin was accelerated when aerosolised monomeric insulin was administered via inhalation. Measure the inspiratory flow using the electronic sensor built into this device (Gonda and Rubsamen, 1999).

5 The Future of inhaled insulin

Although Exubera drawbacks, such as the size of the inhaler and convenience of use, have been addressed by Afrezza® and 501 insulin, it is now obvious that inhaled insulin will not sell itself and that other significant obstacles must be overcome to reach a wider patient population. Aerami Therapeutics is initially seeking a partner for 501 insulin in order to advance through phase 3 and submit an application for market approval. If this inhaled insulin does make it to the market, it will nevertheless face the same challenges as Exubera® and Afrezza®. Pricing and reimbursement will be crucial, and there are still some questions about the long-term safety of inhaled insulin, as well as safety considerations including the requirement for pulmonary function tests (https://blog.profil.com/blog/rollercoaster-life-of-inhaled-insulin).

Recent improvements to injection comfort and to speed up the absorption of subcutaneous insulin were made concurrently with discoveries in inhaled insulin (https://blog.profil.com/blog/the-need-for-speed, https://blog.profil.com/blog/insulin-injection-recent-improvements-and-alternatives). In particular for some persons with type 1 diabetes, automated insulin delivery is developing toward systems requiring less manual intervention (https://www.diabettech.com/uncategorized/more-commercial-aid-systems-what-do-the-trials-tell-us/). Future mealtime insulin products, both injectable and non-injectable, now have higher standards to meet. Predicting the future course of inhaled insulin is therefore difficult given the rollercoaster ride it has experienced thus far. Despite this, there is a sizable global market for insulin, and there will be a rising desire for a straightforward, quick, and painless alternative. Because of this, inhaled insulin will likely last a little longer.

6 Recent advances in insulin therapy

When compared to conventional commercial inhaler devices, the first generation of novel insulin delivery systems, such as the first Inhale® and AERx® systems, were notable for being able to deliver insulin to the lungs with the efficiency and dependability required. Inhale Therapeutics (Palo Alto, CA) and Pfizer Inc. jointly developed the Inhale® system, and Aradigm Corporation (Hayward, CA) and Novo Nordisk jointly developed the AERx® system, which entered first clinical trials of inhaled insulin in the mid-1990s (Valente et al., 2003). Dance 501 inhaled insulin is a brand-new liquid human insulin formulation that is administered by a tiny, portable aerosol device (Aerami Therapeutics). This insulin is reportedly prepared to begin phase 3 trials, according to the company website. The comparative biopotency to subcutaneous RAI is 13% (https://aerami.com/#pipeline). When compared to lispro insulin, data presented at the 2019 Diabetes Technology Meeting in people with T2D showed a linear dose relationship and a quicker onset of action (Zijlstra et al., 2019a) similar findings were also presented at the 2019 American Diabetes Association Scientific Sessions in adults with T1D (Zijlstra et al., 2019b; Wilson and Castle, 2020).

Apart from this some recent advances in novel Inhaled insulin therapy for diabetes include are summarised in Table 1.

Table 1 Newer inhaled insulin formulations and details of their respective experimental results

Formulation	*Experimental model*	*Results*	*References*
Insulin + HA dry powder + (Zn2+ or HPC)	In vivo (beagle dogs)	In comparison to spray-dried pure insulin, the addition of Zn2+ and HPC increased the mean residence time by >9 and >7 fold, respectively	Khafagy et al. (2007) and Surendrakumar et al. (2003)
Insulin/liposome	In vivo (alloxan-induced diabetic rats)	Uniformly dispersed throughout the lung. Longer medication retention periods Hypoglycaemic effect	Khafagy et al. (2007) and Huang and Wang (2006)

Table 1 Newer inhaled insulin formulations and details of their respective experimental results (continued)

Formulation	*Experimental model*	*Results*	*References*
Insulin + H-MAP	In vivo (rats)	Effect that is dose-dependent and peaks at 16 mg/kg H-MAP and 1.3 U/kg insulin In comparison to the same dose of insulin alone, at maximal doses, relative bioavailability rose by >2.5 times, maximum insulin concentration by 2 times, and blood glucose was reduced by 2 times	Suarez et al. (2001) and Ahmad et al. (2014)

7 Summary and conclusions

Diabetes is a serious global health issue. With good Blood Glucose control and comprehensive diabetes medication, the risk of micro-vascular problems and cardiovascular disease is decreased. Insulin resistance and unregulated Blood Glucose control are known risk factors for these conditions. The majority of patients do not attain optimal Blood Glucose control despite the availability of a variety of medicines for regulation. A novel, risk-free way to administer insulin, inhaled insulin may improve patient adherence to their insulin medication, enabling patients to achieve optimal glycemic control and possibly lowering their risk of cardiovascular problems. Diabetes, however, is a chronic condition that calls for ongoing treatment. Long-term studies are still necessary to confirm the ongoing effectiveness and safety of this novel diabetic treatment.

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