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Review Article

An Overview on Pulmonary Insulin

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Abstract: Pulmonary insulin as an alternative to intravascular, intramuscular, and subcutaneous insulin administration, non-invasive insulin administration was created and implemented. It enters the lungs' alveoli through an as-yet-unidentified paracellular process, traverses the alveolar wall, and then circulates throughout the bloodstream. Inhaled insulin was divided into two categories based on its mechanism of action: 1. Rapid acting pulmonary insulin, which quickly disintegrates in the alveoli and circulates throughout the bloodstream as fine powder particles; and 2. slow acting pulmonary insulin. Recently, two technologies were developed: pulmosol powder technology, which employs a rapid drying procedure to make insulin particles of the right size and chemical stability, and AIR technology, which is a porous dry particle aerosol technology. Dry powders, liquid aerosols in cartridge-shaped inhalers, passive inhalers, Microprocessor-controlled inhalers, and liquid nebulizers were the various ways that inhaled insulin was delivered. Many studies have been conducted to examine various intrapulmonary delivery methods, and in January 2006, the US Food and Drug Administration authorized exubera, a dry powder passive inhaler, as the first pulmonary inhaled insulin. The pharmacokinetics of inhaled insulin, dosage guidelines, administration tools, benefits and drawbacks, and candidates for inhaled insulin administration are all discussed in this article.

Keywords: Insulin, Rapid acting, long acting, Pen injector, microencapsulation, Insulin pumps.

INTRODUCTION

The beta cells of the pancreas generate insulin, a polypeptide hormone, as a single chain consisting of three peptides, B, C, and A, in the following order: B-chain, C-peptide, A-chain. Insulin facilitates the movement of blood glucose into bodily cells, where it is processed to create energy. Unreasonably high blood glucose levels are a symptom of Diabetes Mellitus, a metabolic disease that develops when the body becomes resistant to insulin or is unable to manufacture insulin. There are two varieties of diabetes mellitus: type I and type II [1, 15].

Insulin was discovered in 1921 by scientists Banting and Best. Insulin is a hypoglycemic agent. Patients with type I and type II diabetes were first given the insulin hormone intramuscularly, then intravenously, and then subcutaneously, which significantly lowered blood sugar. For the treatment of diabetes, a variety of injectable insulin solutions are currently available. Insulin injection is still seen as a difficult and unpleasant process, despite advancements in the creation of smaller needles and patient-friendly Pen-injector devices to allow better tolerability of subcutaneous administration [2, 16].

The development of non-invasive insulin administration methods began as soon as insulin was introduced. Mucociliary clearance, proteolytic enzymes, digestive enzymes, and an acidic environment are all not barriers to insulin's pulmonary delivery. It is also believed that the lungs are ideally suited to absorb tiny peptides like insulin. Pulmonary insulin administration is facilitated by the lung's enormous surface area, excellent vascularization, ability for solute exchange, and ultrathin alveolar epithelia membrane [3, 4].

A lot of work has been done since 1925 to investigate different intrapulmonary delivery strategies for insulin. The first pulmonary inhaled insulin, Exubera, was approved by the US Food and Drug Administration in January 2006. You will find an outline of the pharmacokinetics, mechanism of action, and inhaled insulin in this article [3].

Methods of Insulin Administration

Parenteral pumps and subcutaneous injections are currently the only two available insulin delivery techniques. Next, in order to improve diabetes care gradually and lower invasiveness while increasing patient compliance, researchers are searching for different ways to provide medication. These approaches include capsules that inhale microspheres, insulin pumps in closed-loop administration devices, and oral forms utilizing microencapsulation techniques [5, 6].

Subcutaneous Insulin

This approach is the traditional method of administration. Owing to their high rates of absorption, the arms, thighs, buttocks, and belly (except from a 2-inch radius around the nave) are suggested injection locations. Preventing lipohypertrophy or lipoatrophy requires rotating the injection site. Syringes, pens, jet injectors, and pumps are used in this delivery mode.

Syringes

Needles used for insulin injections come in different lengths, and syringes are labeled in insulin units and can hold 0.3, 0.5, 1, or 2 milliliters of fluid. A doctor must periodically evaluate the patient's injection technique. Painful injections can be lessened by following certain recommendations, such as not using cold insulin, not moving the needle in a different direction, not using the same needle again, keeping the surrounding muscles calm, and puncturing the skin rapidly.

Insulin Pens

Cartridges are used in place of vials in these devices, which come in durable reusable forms and disposable versions. Insulin can be administered with low-dose pens in increments of half a unit. You may adjust the dosage by turning the pen's knob. When the pen's knob is fully down, it is advised to leave the needle in place for at least five seconds to ensure that the delivery is finished. In Europe, 80–90% of patients utilize them. Dosage calculations and tracking features are now available with "smart" pens.

Insulin Jet Injectors

Without using a needle, they inject insulin into the skin in a thin stream. Unlike injections, they distribute insulin across a greater region and at a fast speed (often >100 m/s) into the subcutaneous tissue of the skin.

Insulin Pump

It's a tiny, electronic gadget that inserts a thin tube under the skin to deliver insulin. It delivers insulin in a manner similar to how the body naturally produces it: a bolus at mealtime and a steady supply of basal insulin throughout the day and night. This therapeutic method is currently used by over a million people. It lowers the possibility of long-term problems by enhancing administration control. It is a component of closed-loop treatment systems, which link sensors that continuously monitor glucose levels with subcutaneous insulin infusion to produce an automatic response.

Oral Insulin

It has been a highly wanted goal ever since insulin was discovered. By boosting portal insulin concentration through intestinal absorption, it is the most amiable method of insulin administration and the one that most closely resembles physiological insulin delivery. Despite its inherent physical instability, oral insulin encounters several physiological obstacles, including GI tract degradation through chemical and enzymatic processes, inadequate oral absorption, and fast systemic evacuation. These factors culminate in reduced bioavailability and inadequate therapeutic impact. There is hope that the advancement of nanotechnology will boost its effectiveness. Insulin can be microencapsulated using a variety of nanoparticles made of biodegradable polymers, including liposomes, chitosan, alginate, mucin, yeast, and polymeric hydrogels.

Buccal Insulin

It avoids GI tract enzymatic breakdown and hepatic metabolism, increasing medication bioavailability while offering some of the benefits of oral insulin. Typically, mucoadhesive buccal films are used to present it. Because of the buccal mucosa's easy accessibility, high tissue permeability, high vascularization, and accelerated rate of cell development, high drug concentration-related cytotoxic effects are lessened. When compared to

subcutaneous injection, the rate of diffusion into buccal tissue for hydrophilic peptides like insulin is thought to be insufficiently quick. In order to improve trans buccal medication distribution, buccal delivery films typically need to be combined with permeation enhancers that work to relax epithelial cell connections.

Inhaled Insulin

It suggests that the pulmonary system is how insulin is absorbed. Small particles can be quickly absorbed into the systemic circulation thanks to the distant lung's huge, highly perfused surface area. Insulin that is inhaled avoids enzymatic breakdown in the gastrointestinal (GI) tract and hepatic metabolism, as well as invasive and painful treatments. For those who have respiratory issues, it could not work. The first successfully described alternative insulin delivery method was inhaled. It was not a commercial success, nevertheless, due to the expense and contraindications. A small inhaler device was used to provide an inhaled version of insulin in Technosphere's, which was approved by the FDA in 2014.This approach uses Technosphere's, which are carriers that are injected into the deep lung, to absorb an insulin formulation in the form of dry powder [6].

Classification of Pulmonary Insulin

Based on the mode of action of the Inhaled Insulin, they are broadly classified as the following [9].

Rapid-Acting Pulmonary Insulin

Long-Acting Pulmonary Insulin

Rapid-Acting Pulmonary Insulin

With today's technology, delivering insulin to the lung's alveolar gaps is a pretty simple process. The alveolar epithelium is highly permeable and vascularized, with a surface area of roughly 100 m^2. The peptide medicines are completely impermeable to the thickly layered mucosa of the upper airways and bronchial tree, although the absorption capacity of the alveolar surface varies.

Insulin taken in through the nose is quickly taken up by the alveolar capillaries and circulated throughout the bloodstream as a finely powdered substance. The particles contained in the powdered formulation have a diameter of less than 5 µm.

These particles disintegrate fast in alveoli due to their high solubility. Due to the particle's size, deep inhalations at a slow pace can effectively reach the deep lung.

While the smaller particles will be partially expelled, the larger particles have a higher chance of settling in the upper airway.

Compared to liquid aerosols, which contain only 1%–2% pure drug and 98% water, powdered aerosols can contain up to 95% pure drug. As a result, powder aerosols are far superior to liquid or nebulizer systems and can deliver five times the amount of medication in a single inhalation.

The process that produces particles of the proper size is known as "PULMOSOL POWDER TECHNOLOGY." This uses a quick drying method to produce insulin particles that are chemically stable. This system's insulin will be sold in blister packets that will remain stable for two years at room temperature [7, 8].

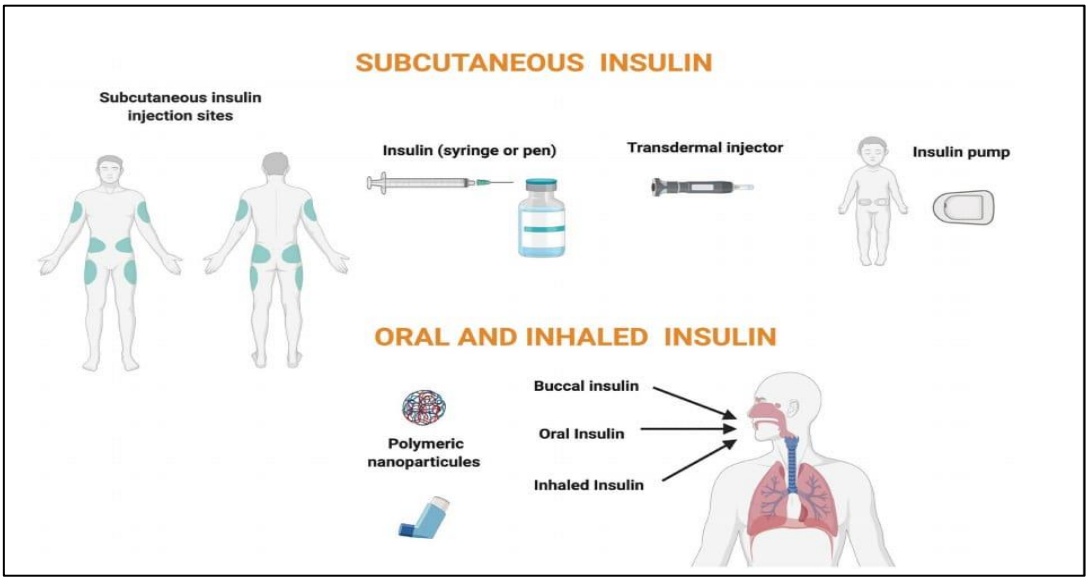

Fig 1: Classification of insulin

Long-Acting Pulmonary Insulin

It was observed in one investigation that a porous aerosol particle containing 80% poly and 20% insulin showed persistent release of insulin into the blood over several days. The inhaled particles had an 87% bioavailability compared to the subcutaneous injection. Regretfully, this trial's dose requirements were extremely high.

The term "AIR technology" refers to a novel, porous dry-particle aerosol technology that was recently invented. The pharmacokinetic characteristics of the long-acting AIR insulin are comparable to those of human insulin. Particle sizes of 1-3 μm and a low density of less than 0.1 g/ml are used in this technology. It is straightforward and inexpensive to aerosolize these particles using an inhalation device. The AIR inhaler gadget resembles a regular marker pen in both size and design [9].

Pharmacokinetics

A number of variables influence how well inhaled insulin is delivered to the lungs. These consist of the breathing pattern, the size of the aerosol's particle particles, and the inhaler's efficiency. The percentage of medication released from the inhaler by correct inhalation determines the inhaler's efficiency, which can range from 20 to 30% for liquid nebulizers to 80 to 95% for dry powder inhalers [5].

Aerodynamic diameters of 1 to 3 mm are ideal for deep alveolar deposition; larger particles, particularly those larger than 10 mm, are deposited mainly in the upper airways or oropharynx, while smaller particles are mainly exhaled. Aerodynamic diameters are a function of geometric diameter and mass density. The ideal way to inhale the aerosol is to slowly inspire while using a big tidal volume.

For inhalation therapy to be effective, pulmonary function must be adequate. Enhancing the alveolar region's collecting efficiency can be achieved by holding your breath for two to six seconds at the end of inspiration. However, forced inspiration causes particle loss in the Oro laryngeal area and negatively impacts alveolar deposition. Though the precise mechanism is still unclear, insulin is most likely transported over the alveolar wall by a paracellular process.

It's likely that a paracellular mechanism carries insulin across the alveolar wall, however the precise mechanism is yet unclear. Research suggests that approximately 20–40% of the insulin deposited in the lungs makes it into the bloodstream. The remainder leaves the lung by the mucociliary escalator or is biodegraded in the cytosol. Both acute and long-term smoking improves insulin absorption.

When a typical insulin dose is inhaled, smokers' peak insulin levels are more than three times greater, which might cause hypoglycemia. In nonsmokers, the bioavailability of inhaled insulin is between 8 and 12% under ideal circumstances. Insulin that is breathed is quickly absorbed. Subcutaneous short-acting insulin analogs and subcutaneous regular insulin have identical half-lives when it comes to reaching maximal insulin concentration and the glucose-lowering action.

Four to six hours is the duration of action for inhaled insulin, which is marginally longer than that of its short-acting counterparts and somewhat shorter than that of conventional insulin given subcutaneously. Insulin that is inhaled is appropriate for use during meals due to its pharmacokinetic properties.

It appears that neurofibrillary tangles and senile plaques are the primary neuropathological characteristics of AD. As the disease worsens, the senile plaques appear to start in brain regions linked to cognition before spreading to other cortical areas. Among other things, the senile plaques are made up of insoluble deposits of amyloid-β-Peptides (AB), which are a piece of the amyloid precursor protein (APP) [5].

Table 1: Types and trade names of inhalers available in market

Type of product and inhaler	Trade name
Dry powder Passive inhaler	Exubera®
Liquid aerosol Microprocessor-controlled inhaler	AERx® iDMS
Dry powder Passive inhaler	HIIP®
Liquid aerosol Passive inhaler	Aerodose®
Dry Powder microparticules Passive inhaler	Technosphere®
Dry powder Electromechanical inhaler	Spiros®
Dry powder	Microdose DPI®
Coated dry particles	Bio-Air®
Liquid aerosol	Alveair®

DOSES

It is not possible to compare the dosage of inhaled insulin to that of injected liquid insulin. There are three dose options available for Afrezza's inhaled insulin: four, eight, and twelve units. Most people think this equates to four units, such as an injection of

Humalog or Novolog. Which seems completely unfeasible in terms of T1D management. It's entirely distinct! Additionally, the way it operates makes it impossible to propose an exact X = X comparison between injectable insulin and Afrezza [13].

The following is general advice on how much Afrezza to take at first:

> About 2-2.5 units of rapid-acting Novolog, Humalog, etc. are contained in a 4-unit cartridge. Eight cartridges equal about five to eight units of fast-acting Novolog, Humalog, etc. A 12-unit cartridge is equivalent to about 12 quick-acting Novolog, Humalog, etc. units [13].

Exubera is the most extensively studied inhaled pulmonary insulin system. It is a dry- powder formulation with ordinary insulin (around 60%) and stabilizers, mostly mannitol, packaged in blisters containing 1 or 3 mg of insulin, which contains 28 or 84 units of insulin, respectively [5]. 1 mg of Exubera is equivalent to about three subcutaneous insulin units. At the beginning of the trial, the average daily dose of inhaled insulin varied from 9.6 to 12.4 mg; it thereafter climbed slightly to 10.8 to 14.2 mg. After six weeks of treatment, the average daily dose of inhaled insulin was 15.6 mg, and after 24 weeks, it was 16.6 mg. Inhaled insulin did not seem to cause weight gain, while the subcutaneous insulin regimen did appear to cause an almost 1.5 kg increase in weight. The AERx iDMS delivery system was created as a tool for administering liquid insulin aerosols sublingually. With breath activation, the insulin inhaler releases insulin only when inspiratory flow is enough, minimizing intra-subject variability brought on by patient technique. The insulin is supplied in strips, each of which has about one subcutaneous unit's worth of insulin. Human inhaled insulin powder (HIIP) is available in two dose strengths of 0.9 mg and 2.6 mg, which are equivalent to 2 and 6 units of subcutaneous insulin, respectively. Future developments may involve the production of a sustained-release formulation. Large porous particles of low mass that consist of a biodegradable polymer matrix that contains fast-acting human insulin were developed through advanced inhalation research [5].

Admelog Infusion: U-100, or 100 units/mL, is offered as:
10 mL vials for numerous doses
3-milliliter multiple-dose vials
3 mL for a single patient.
Pens prefilled with SoloStar [11]

Adlyxin: 50 mcg/mL in a green prefilled pen with a capacity of 3 mL (for 14 pre-set dosages, 10 mcg per dose).

100 mcg/mL in a 3 mL prefilled pen in burgundy (for 14 pre-set dosages, 20 mcg each).

For 14 days, start at 10 mcg once daily. Increase the dosage to 20 mcg once daily starting on Day 15 and deliver it once daily no later than one hour before the first meal of the day [12].

Devices
Device Type: Inhalable Insulin
Refusable Disposable: Disposable (Single dose only) [10].

Fig. 2: Inhalable Insulin [10]

Device Type : Insulin Pen [11]
Reusable Disposable : Reusable [11]

Fig 3: Inhaled Insulin [11]

Device Type : Médicine Pen [12]
Reusable Disposable : Disposable [12]

Fig 4: Medicine Pen [12]

Candidates for Inhaled Insulin

Selecting the best insulin delivery system for a given person involves many considerations. Inhaled insulin might be a beneficial choice for those who:
Do you dislike needles or injections?
Wish to use a less intrusive, more convenient way to deliver insulin?
Wish to promptly regulate their post-meal blood sugar levels
Are you seeking for an insulin to take in relation to exercise?

Are 18 years of age or older and have either Type 1 or Type 2 diabetes (inhaled insulin is not currently licensed for use in children).

It's important to remember that those with lung conditions like asthma or chronic obstructive pulmonary disease (COPD) or those who smoke should not use inhaled insulin. For further information, see the Afrezza website. [14]

Advantages of Inhaled Insulin

Some users of inhaled insulin list the following as their main benefits over regular insulin injections:

Convenience: Using inhaled insulin doesn't require syringes or needles, and it's a simple process. Unlike insulin injections, it doesn't need to be prepared as much and can be given quietly.

Faster Acting: Compared to injectable insulin, inhaled insulin acts more quickly since it is swiftly absorbed into the bloodstream. "It can start lowering blood sugar levels within about 12 minutes, and it passes from your lungs to your bloodstream in less than a minute," the maker claims. People who need to swiftly control their blood sugar levels, such those who don't always take their pre-boluses, may find great benefit from this.

Depending on the dosage, inhaled insulin also leaves the body quickly—between 1.5 and 3 hours. This characteristic helps those who engage in physical activity by reducing the likelihood of insulin stacking.

More Comfortable: Not everyone is a good fit for needles. Injectable pain or discomfort is a common complaint among diabetics, which can make it challenging to control their condition. Their quality of life can be enhanced with inhaled insulin since it eliminates the need for injections.

- A large absorption surface area
- Excellent bioavailability is ensured by perfused epithelial cells.
- A thin, highly permeable barrier
- Hepatic and enzymatic metabolism are mostly circumvented
- Effective, non-invasive path

For those with specific kinds of disability, inhaled insulin may also be a more convenient way to deliver the drug.

Disadvantages of Inhaled Insulin

Limited Brand Options: As of right now, Afrezza is the only kind of inhaled insulin that is sold on the market. As a result, individuals with diabetes

might not have as much freedom and choice as they would while using injectable insulin.

Restricted Dosing alternatives: Insulins that can be inhaled have set doses, unlike other alternatives. There are currently color-coded 4-, 8-, and 12-unit cartridges available for inhalable insulin. The user can switch up the cartridges if necessary to get the recommended dosage.

Cost: Some people may find inhaled insulin prohibitively expensive compared to injectable insulin. It's vital to confirm with your insurance company whether inhaled insulin is covered as coverage may differ.

On the other hand, manufacturers often provide affordability initiatives that might help individuals reduce their expenditures. As of the time this article was published, qualifying commercially insured patients could spend as little as $35 per month (there are, of course, limitations) with the Afrezza Savings Card. For the most recent deals, visit Danatech's Afrezza product page.

Adverse Effects: As with all insulins, there may be adverse reactions. Shortness of breath, coughing, sore throats, and hypoglycemia are among the side effects of inhaled insulin. Although the final three side effects are usually not so bad, some people may experience more severe symptoms [5, 14].

CONCLUSION

Insulin delivered via the lungs offers more than just a promising treatment for diabetes mellitus. For both type 1 and type 2 diabetes mellitus, inhaled insulin appears to be at least as effective as the traditional regimen of subcutaneous insulin and/or oral glucose-lowering medications. The key advantages of this novel medication are its non-invasive mode of delivery and its enhanced metabolic regulation. The type of propellants utilized, air flow velocity, particle size and velocity, drug deposition into the neck, and the size of the bronchial tree all affect the different processes of deep-lung deposition and adsorption of insulin. These elements in turn rely on respiratory mechanics and fluxes as well as the pulmonary delivery systems that are employed. Due to pulmonary anatomy and physiology as well as the absence of needles, inhaled insulin has a number of advantageous features. Studies on pharmacokinetics and pharmacodynamics have revealed a time-action profile appropriate for insulin use throughout the meal. In terms of time-action profiles and rates of hypoglycemia, inhaled insulin may be better than subcutaneous rapid-acting insulin analogs. It also appears to be safe and effective when compared to other prandial insulin treatments.

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