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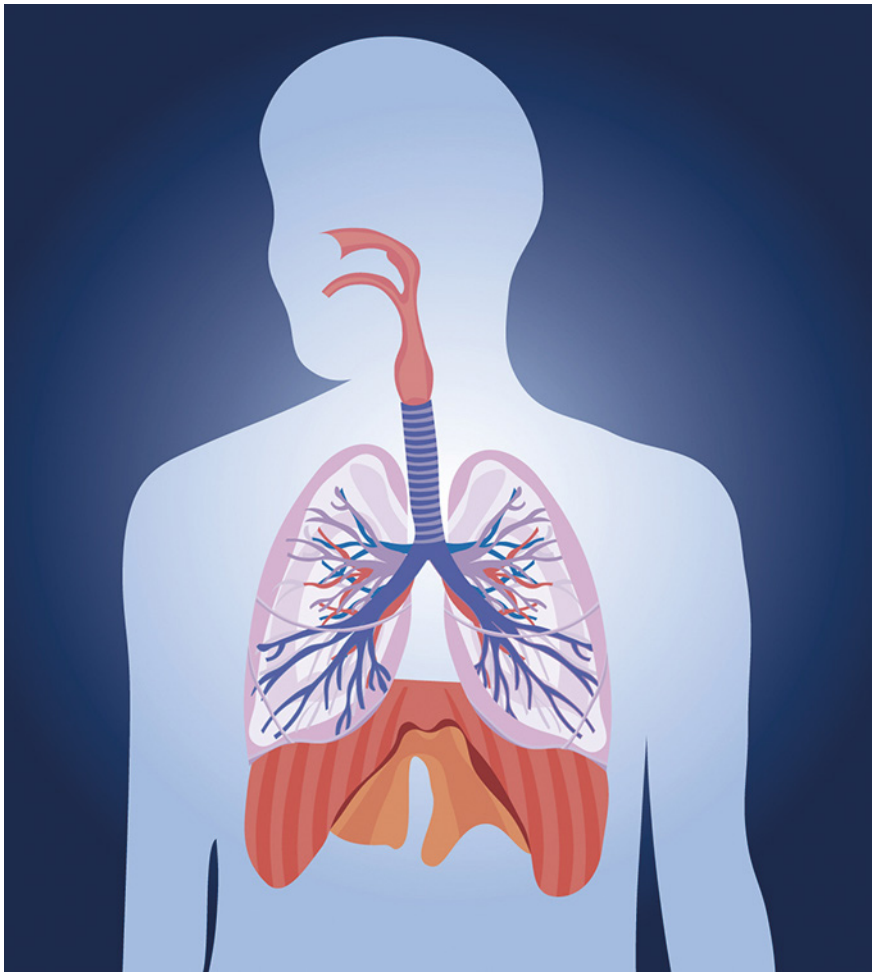
Inhaled Insulin

Past, Present, and Future Perspectives in the Treatment of Type 1 Diabetes

Inhaled insulin is presented as a promising alternative for the treatment of people with type 1 diabetes mellitus, especially in patients who have difficulties with multiple injections. This type of insulin, which is absorbed through the pulmonary epithelium, acts more quickly than traditional prandial insulins and seeks to imitate more precisely the physiological response that occurs after a meal.



Despite its potential, its clinical use has been limited by various factors: from technological and logistical challenges to regulatory limitations and lack of long-term studies.

This article analyzes the key aspects of this therapeutic option: the scientific bases supporting its development, its evolution, efficacy, safety profile, and current market situation. This global vision will allow for a better assessment of when inhaled insulin can represent a useful tool within individualized diabetes treatment.

PHYSICAL AND CLINICAL JUSTIFICATION OF THE INHALED ROUTE

The lung is an organ with a unique structure that makes it an effective route for the administration of medications with a systemic effect, such as insulin. Its large absorption surface, extremely thin epithelium, and the capillary network covering it allow certain substances to quickly pass into the bloodstream after inhalation.

This is especially relevant for drugs such as insulin, which are not well absorbed orally. Unlike subcutaneous insulins, which take longer to start acting, inhaled insulin reaches blood levels in just a few minutes. This behavior more closely resembles the natural pattern of insulin secretion that occurs after meals, making it very useful for controlling postprandial glycemia *(Table 1)*.

Furthermore, by not requiring needles, the inhaled route could improve quality of life and require treatment adherence in patients with needle phobia, adolescents, or people with poor diabetes control due to rejection of conventional treatment (1). »

» However, for it to work correctly, the medication needs to reach the deepest parts of the lung, avoiding its elimination by the mucociliary system or alveolar macrophages, and dissolve in the pulmonary fluid before crossing the respiratory epithelium ***(Figure 1)***. To achieve this, special formulations and devices have been developed that generate very small and well-distributed particles, optimizing their arrival at the alveoli and improving their bioavailability in the body (2).

EVOLUTION OF INHALED INSULIN: FROM INITIAL ENTHUSIASM TO ITS WITHDRAWAL AND REAPPEARANCE AFTER FORMULATION IMPROVEMENTS (3, 4)

The history of inhaled insulin has been marked by promising advances but also by significant difficulties. The first commercial attempt was Exubera®, approved by the U.S. Food and Drug Administration (FDA) in 2006. It was a dry powder insulin for inhalation that generated great expectations, but its use in clinical practice was very limited. The device was bulky, its handling complex, and its cost high compared to injectable insulins. Furthermore, the need for periodic respiratory function controls and doubts about its pulmonary safety contributed to its poor acceptance. Finally, it was withdrawn from the market barely a year after its launch due to low sales.

Shortly after, in 2008, Pfizer issued a warning about a possible increased risk of lung cancer in smoking patients, which further heightened skepticism about this route of administration. As a consequence, most inhaled insulin projects were canceled, with only one exception.

Afrezza®, developed by MannKind, received the FDA approval in 2014. Although it shares some similarities with Exubera®, it incorporates significant improvements: a much smaller and simpler device, an optimized formulation, and more intuitive dosing based on international units instead of milligrams.

Its active ingredient is recombinant human insulin adsorbed onto technosphere microspheres, an inert excipient that facilitates its delivery to the deep lung. The particles, only 2–3 µm, rapidly release insulin after inhalation, allowing for efficient absorption. Currently, Afrezza® is indicated as prandial insulin for people with type 1 or type 2 diabetes, always in combination with basal insulin.

Despite these improvements, its commercialization remains limited. Currently, it is only available in some countries, such as the United States and Brazil. In Europe, the European Medicines Agency (EMA) has not authorized its use. The lack of approval in Europe has been linked to limited accumulated experience, the need for more long-term safety data, and the absence of a partner capable of integrating it into the European health care system.

PHARMACOKINETICS AND PHARMACODYNAMICS (5)

Inhaled insulin has a distinct pharmacoki- »

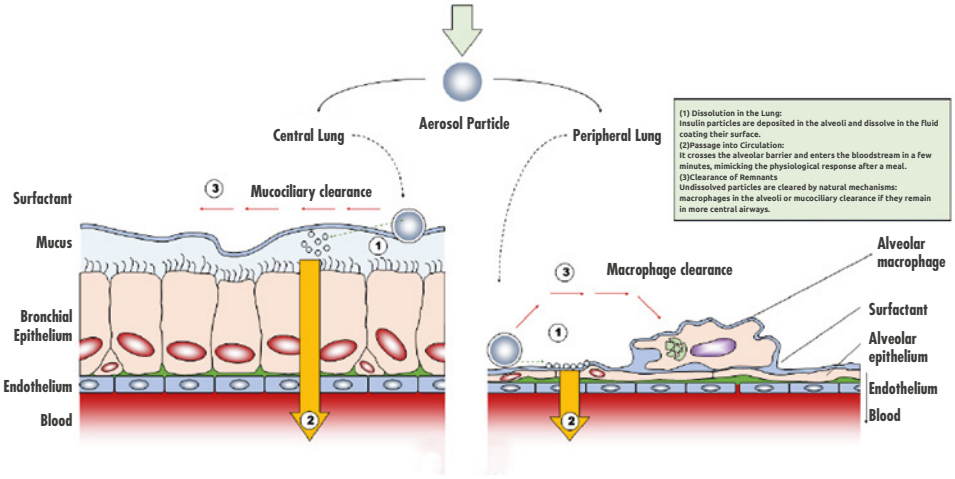


FIGURE 1. From inhalation to blood: the journey of insulin in the lung (Adapted from Ruge et al., with modifications)[3]

TABLE 1. Main Positive and Negative Aspects of Inhaled Insulin

» netic profile from subcutaneous insulins, with a faster onset of action and shorter duration *(Table 2)*.

Of note, there is no direct equivalence between subcutaneous and inhaled doses, so any change from one route to another must be conducted with individualized monitoring and adjustment to guarantee the safety and efficacy of the treatment.

CLINICAL OUTCOMES: GLYCEMIC CONTROL WITH INHALED INSULIN

In clinical trials, inhaled insulin has demonstrated comparable efficacy to injectable prandial insulins in people with type 1 diabetes mellitus, provided it is used in conjunction with basal insulin. Its faster action (between 7 and 15 minutes) and shorter duration allow for better control of post-meal glucose levels and reduce the risk of late hypoglycemias.
In comparative studies with subcutaneous insulins or placebo, technosphere inhaled insulin showed a smaller elevation of the post-meal glycemic peak and shorter exposure, which allows for greater flexibility in the timing of administration, even just at the beginning or end of a meal. This shorter action, however, may require adjusting basal insulin to avoid hyperglycemia.

Regarding the control of glycated hemoglobin (HbA1c), inhaled insulin has demonstrated non-inferiority vs usual prandial insulins. In addition, some studies have observed less weight gain (6, 8).

SAFETY AND TOLERABILITY

Although inhaled insulin is generally well tolerated, it can cause some respiratory effects related to its administration route. The most frequent is mild to moderate cough, which usually appears within the first few days into therapy and a few minutes after inhalation. Other symptoms, such as pharyngeal irritation or shortness of breath, are uncommon.

A slight decrease in forced expiratory volume (FEV) has been described, generally transient. Although it is not usually clinically relevant, it is recommended to perform a baseline spirometry before starting treatment and monitor its evolution if long-term treatment is maintained. This need for follow-up can represent an additional burden for patients and the health care system.

For these reasons, inhaled insulin is contraindicated in people with chronic lung diseases, such as asthma or COPD, as well as in smokers. In ex-smokers or patients with a history of mild respiratory issues, its use must be evaluated individually and always with adequate clinical follow-up.

Regarding metabolic safety, studies show a similar or even lower incidence of hypoglycemia than with injectable prandial insulins, especially in the late postmeal period, thanks to its shorter action (7, 8).

PRACTICAL USE OF INHALED INSULIN: ADMINISTRATION, STORAGE, AND MANAGEMENT

Currently, the only inhaled insulin marketed worldwide is presented as a dry powder in pre-filled cartridges that are administered via a reusable pocket inhaler. Although its handling is simple, it is essential to follow a proper inhalation technique to ensure its effectiveness.

The insulin is contained in fixed-dose cartridges of 4, 8, and 12 units, which can be combined to achieve the necessary dose.

Insulin should be inhaled at the beginning of meals, and in some cases, it may be necessary to repeat the dose one or two hours later, depending on the glycemic response.

The inhaler should be kept at room temperature and replaced every 15 days from its first use. Cartridges should be stored refrigerated until opened. Once out of the refrigerator, they can be used for up to 10 days if they remain in their blister pack or 3 days if they have been removed from it. Before use, it is recommended to leave them at room temperature for about 10 minutes to improve tolerance. »

	ADMINISTRATION ROUTE	ONSET OF EFFECT (MINUTES)	PEAK EFFECT (HOURS)	DURATION OF EFFECT (HOURS)
RAPID-ACTING INSULINS				
REGULAR INSULIN (ACTRAPID®, HUMULIN®)	Intravenous or Subcutaneous	30	1.5-3.5	7-8
ULTRA-RAPID-ACTING INSULINS				
LISPRO (HUMALOG®)	Subcutaneous	15	0.5-1.25	2-5
ASPART (NOVORAPID®)	Subcutaneous	10-20	1-3	3-5
GLULISINE (APIDRA®)	Subcutaneous	10-20	1	6
TECHNOSPHERE (AFREZZA®, USA AND OTHERS)	Inhaled	7-15	1	2-3

TABLE 2. Pharmacokinetic characteristics of the main marketed rapid and ultra-rapid insulins.

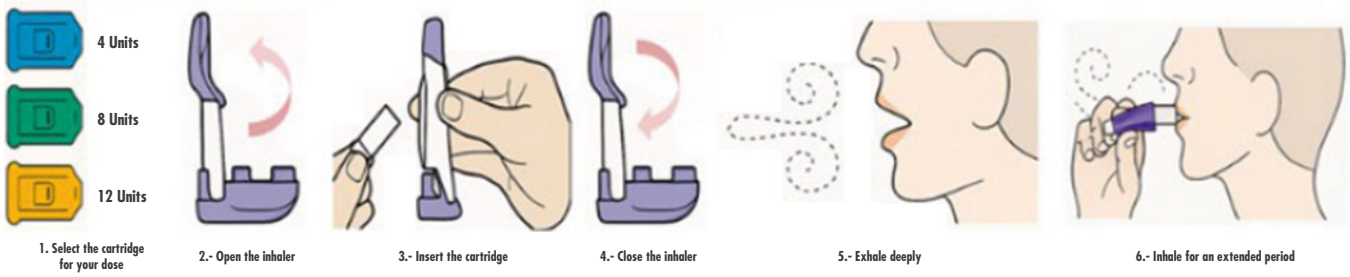


FIGURE 2. How to use inhaled insulin

» For administration, insert the insulin cartridge into the device, close it, exhale completely away from the inhaler, and inhale deeply and sustainedly. After inhalation, it is advisable to hold your breath for a few seconds. Adequate patient training is key to ensuring correct use ***(Figure 2)***.

BARRIERS AND FUTURE PERSPECTIVES (4, 9)

Beyond its current limitations, inhaled insulin raises new questions about the future of insulin therapy. Its development responds to an unmet need: to have insulin formulations that are more physiological, flexible, and better accepted by patients. In this sense, the inhaled route continues to be an option with potential, especially if progress is made towards more stable, affordable, and easy-to-use formulations.

Inhaled insulin represents a relevant innovation, not so much because of its widespread impact, but because of what it proposes in terms of diversifying therapeutic options and adapting to individual needs.

In this context, its role should not be considered a universal alternative, but rather a complementary option for patients with specific needs: ultra-rapid action, aversion to injections, or unpredictable eating patterns. However, to consolidate itself as a valid alternative, it will be essential to generate solid evidence on its clinical impact and its repercussion on quality of life. D

CONCLUSIONS

Inhaled insulin offers a complementary option for individualizing diabetes treatment, especially in selected patients. Although it can improve the therapeutic experience, its use is still limited by scarce international availability, which conditions its actual clinical application.

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