A Breath of Relief: Inhaled Insulin as the Future of Diabetes Management

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Abstract: This review enlightens and focuses on the recent advancement for the Insulin delivery to show its hypoglycemic action [1]. Since from the decade the diabetes emerged as the most common metabolic disorder [2] observed in patient and the count of diabetes are increasing day by day due to change in the lifestyle. In the developed world, diabetes and obesity are reach epidemic proportion [3]. Diabetes relates to a long-term metabolic condition [4] where the blood glucose level rises above its normal value i.e.3.5 and 8mmol/liter (63 to 144mg/100ml) called as hyperglycemia. The major cause of diabetes is due to lack of insulin secretion by the β-cells of pancreas. Traditional methodology used for the management of diabetes [5] includes Oral hypoglycemic agent, subcutaneous injection or continuous infusion to control the blood glucose level. But this route of administration has several drawbacks as oral administration of drug results in breakdown in stomach hence there is loss of biopotency and the desired pharmacological action is not achieved; there is of lack patient compliance for subcutaneous route as it painful and burdensome for many patients. Due to patient incompliance it urges the formulator to pique their curiosity [6] towards the development of advanced route of administration with better patient compliance. The management of diabetes is complex process as there is general requirement of multiple risk-reduction programme along with glycemic control. After years of effort of research scientist and formulators "AFREZZA" (Human insulin) Inhalation powder was discovered to be a novel and effective route for insulin administration via inhalation route granted approval by the Food and Drug Administration in 2014. [7]

Keywords: Afrezza®, Inhaled insulin, Technosphere® technology, Diabetes mellitus, Pulmonary drug delivery, Glycemic control.

I. INTRODUCTION

Diabetes and obesity have surged to alarming levels in the developed world [8]. Diabetes is the seventh leading cause of mortality in United States. Diabetes was identified as most prominent metabolic chronic disorder observed in patient [9]. As per the WHO report in 1980 the global diabetic population increased from 108 million to 422 million by 2014[10]. Diabetes was found in around 8.5% of individuals 18 years and above in 2014[11]. The report also shows that in total, 1.5 million deaths were directly attributed to diabetes, with 48% occurring before the age of 70. The premature mortality rate from diabetes (deaths before 70) increased by 5%. from diabetes was reported in the year between 2000 and 2016[12]. In 2017 the investigated report states that around 9 million people was affected with type 1 diabetes (formerly referred to as insulin-dependent, juvenile, or childhood-onset) is marked by insufficient insulin production and necessitates daily insulin administration [13]. And more than 95% of people was affected with type 2 (formerly called as non-insulin dependent, or adult-onset) results from the body's ineffective use of insulin. Looking towards these records, facts and data consequently for more than 100 years, research on insulin and insulin resistance has been a key area of focus in medicine. [14]

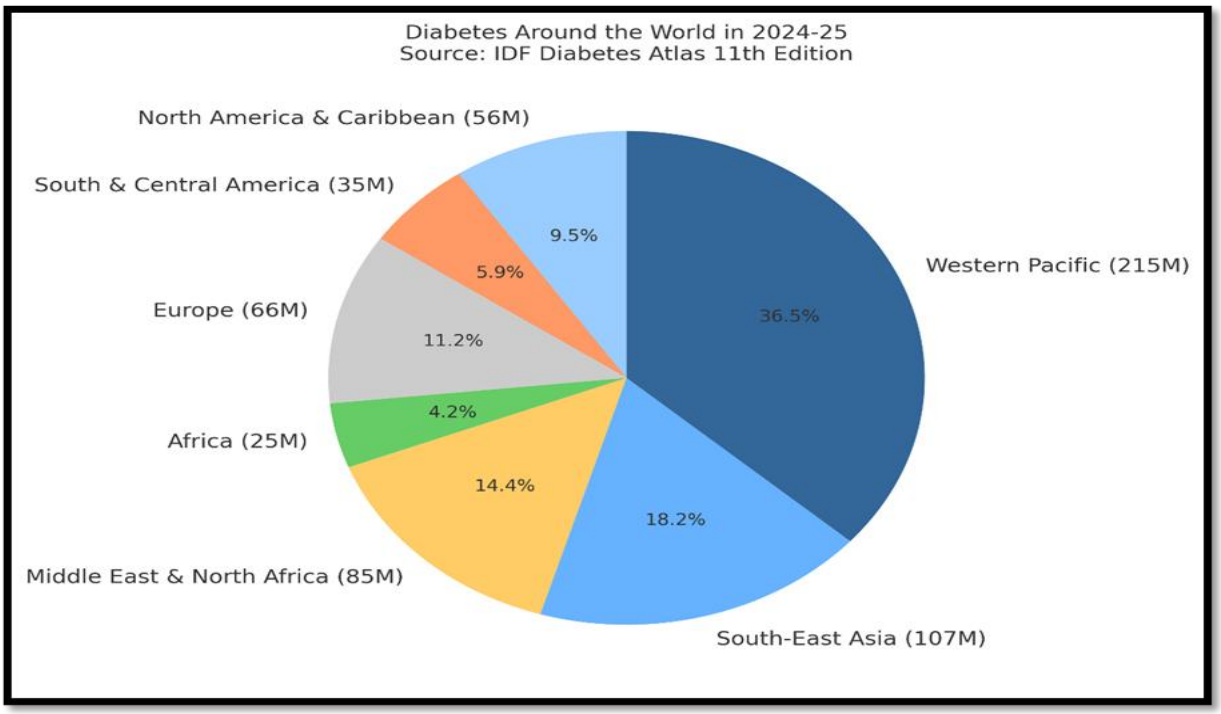

Figure 1Diabetes Around the World in 2024-25.

Diabetes mellitus is a persistent metabolic disorder [15] where the blood glucose level hikes to its normal range i.e. hyperglycemia (fasting plasma glucose ≥ 126mg/dL and /or ≥ 200mg/dL, 2 hours after 75g oral glucose).

Other complication associated due to the diabetes mellitus is glycosuria, hyperlipidemia, negative nitrogen balance and occasionally associated with ketonaemia.[16] A predominant pathological change has also been reported such as change in thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation leading to vascular complications such as early atherosclerosis, narrowing of the lumen, sclerosis of glomerular capillaries, retinopathy and peripheral vascular insufficiency.[17]

Looking toward the complication associated with diabetes mellitus the diabetes management is complex process as there is general requirement of multiple risk-reduction programme along with glycemic control. [18]

Causes of diabetes mellitus:

The major causes of diabetes mellitus were found to be lack of insulin secretion by the β-cells of pancreas. The factors associated with insulin secretion that causes diabetes mellitus are as follow:

- Down regulation of insulin
- Excess of hyperglycemic hormones
- Genetic and environmental factors
- Impaired insulin secretion

Other leading cause for causing diabetes is level of glycosylated hemoglobin, change in behavioral pattern, dietary pattern as well as change in lifestyle. The glycosylated hemoglobin (HbA1c) concentration is a key indicator of protein glycosylation, showing the glycemic state in the preceding timeframe of 2-3 months [19]. The sufficient control of glycosylated hemoglobin (HbA_{1c}) level has proven to reduce diabetes –associated mortality by decreasing chronic complication. The facts show reduction by 1% in HbA_{1c} level results in 35% reduction in diabetes related microvascular complication, which includes diabetic neuropathy, retinopathy and neuropathy.

Goals and diagnostic criteria by the American Diabetes Association (ADA)

- A fasting plasma glucose (FPG) level of 126mg/dL (7.0 mmol/L) or greater, or
- A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or above during a 75g oral glucose tolerance test(OGTT), or

- A random plasma glucose of 200 mg/Dl (11.1 mmol/L) or more in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or
- Based on a 2013 position statement on standard care for diabetes a glycosylated hemoglobin A_{1c} (HbA_{1c}) level should be of <7% for adult with diabetes. [20]

According to the ADA, the severity of this goal may need to be monitored and adapted with reference to the following factors [21]

- Patient duration of diabetes
- Known cardiovascular or advanced microvascular complication
- Comorbidities
- Age
- Other patient-specific factors

Goals & Diagnostics Criteria by American Association of Clinical Endocrinologists (AACE).

Based on a 2013 position statement on standard care for diabetes a glycosylated hemoglobin A_{1c} (HbA_{1c}) level should be of <7% for adult with diabetes, an HbA1c target of <6.5% is recommended by the American Association of Clinical Endocrinologists (AACE) for the majority of type 2 diabetes patients [22], acknowledging that this goal may be aggressive for some patient and not aggressive enough for other patient such as younger patient for whom a lower target may prevent later complication.

Goals:

Antihyperglycemic pharmacotherapy should aim to

- Avoid hypoglycemia
- Accomplish both clinical and biochemical glucose targets
- Reduce or avoid increasing cardiovascular risk
- Assist with weight loss and minimize weight gain in patient who is obese.

Looking towards all the facts and data provide by the WHO related to increasing number of diabetes cases, mortality rates complication associated with diabetes consequently for more than 100 years, the exploration of insulin, insulin resistance, and strategies for managing diabetes has remained central to medical research.[23]The medical science and medical research aims for the betterment of life of patient by introduction of advance technology and novel techniques for management of such disease and disorder with improved patient compliance, safety , efficacy and minimal toxicity.

Insulin:

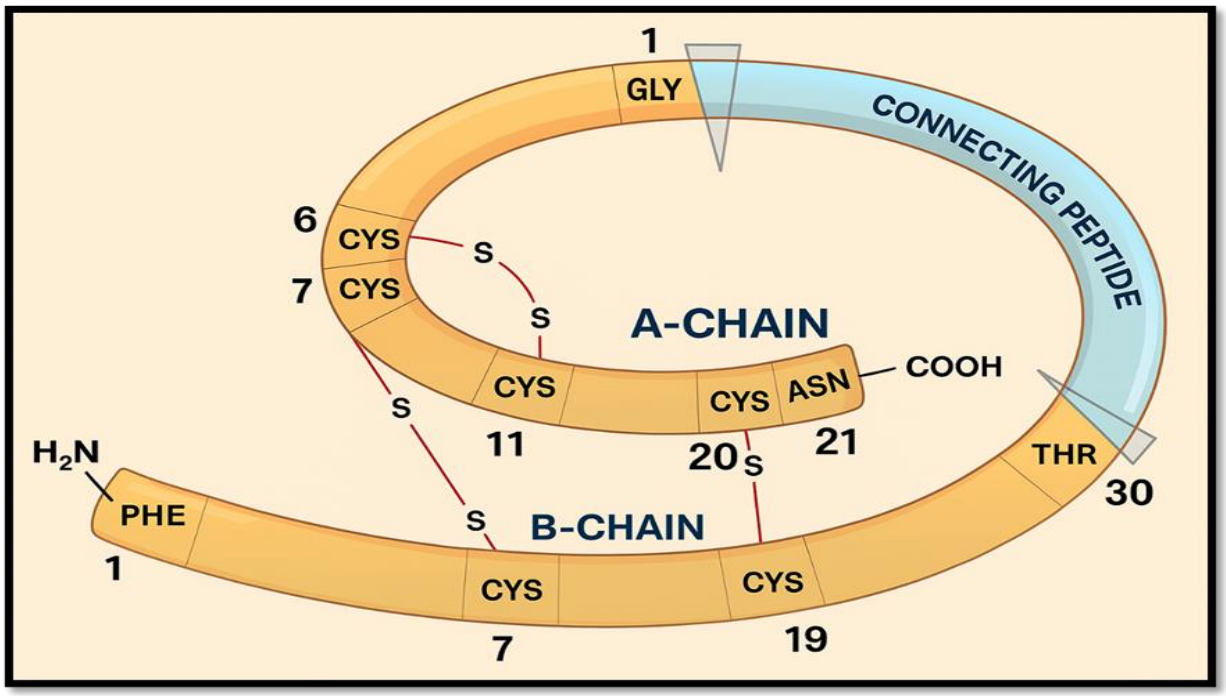

Figure 2 Structure of Insulin.

The increased level of blood glucose in body is majorly governed by the insulin secretion by the β-cells of pancreas. Insulin was first discovered by Banting and Best in 1921 [24]. They both have demonstrated the hypoglycemic effect of a pancreas extract prepared after the degeneration of the exocrine portion caused by the ligation of the pancreatic duct [25]. The crystalline form of insulin was firstly obtained in year 1926, whereas the chemical structure of insulin was fully worked out in 1956 by Sanger.

Insulin is made up of two polypeptide chains with a total of 51 amino acids. [26] The A-Chain has 21 amino acids while the B-chain has 30 amino acids.

Action of Insulin:

The high blood glucose level in body is regulated by the in insulin secreted by the β-cells of pancreas. Insulin's overall effects are to dispose meal derived glucose, amino acids, fatty acid and facilitate fuel storage [27].

- The transport of glucose across the cell membrane is facilitated by insulin.
- Insulin inhibit gluconeogenesis in liver
- Insulin inhibit lipolysis in adipose tissue
- Insulin enhance transcription of vascular endothelial lipoprotein lipase
- Insulin facilitates amino acid entry into muscles and most other cells

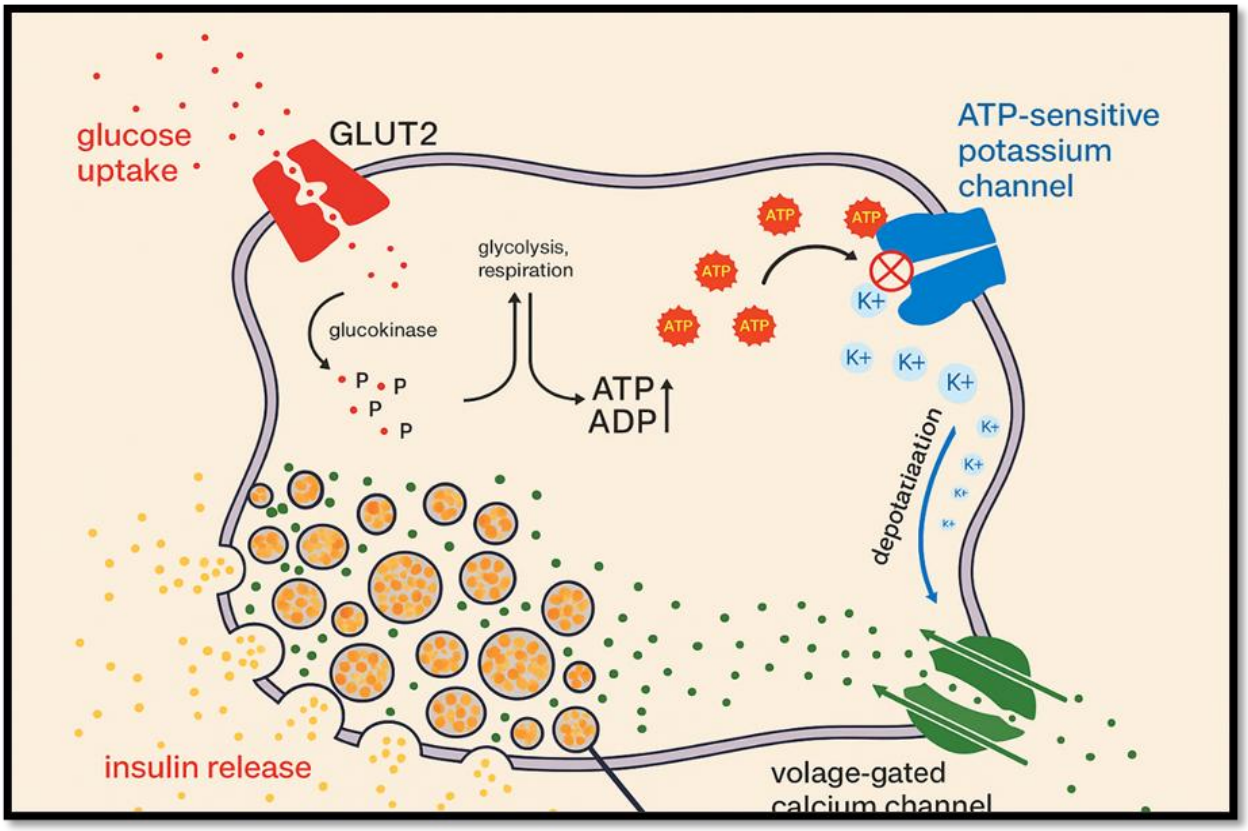

Figure 3 Mechanism of Action of insulin

Action of insulin producing hypoglycemia		
Liver	Muscle	Adipose Tissue
Increase glycogen production and glucose absorption [28]	Increase glucose uptake and utilization	Increases glucose uptake and storage as fat and glycogen
Inhibits glycogenolysis from glucose output	Inhibit proteolysis and release of amino acids, pyruvate, lactate into blood which form the substrate for gluconeogenesis in liver	Inhibit lipolysis and release of free fatty acid + glycerol which form substrate for gluconeogenesis in liver
Inhibits gluconeogenesis from protein, pyruvate, free fatty acid and glycerol		

Table 1Action of insulin producing hypoglycemia

Challenges for Insulin Administration:

The control and management of diabetes is complex process as there is general requirement of multiple risk-reduction programme alongwith glycemic control. [29] When the β-cells of pancreas fail to secrete insulin, it is administered externally.

Administration of insulin was major challenge for the formulator as insulin is distributed only extracellularly.

- It is peptide and undergoes degradation in the GIT when taken orally. [29]
- The liver is where insulin is processed most often, with smaller extent in kidneys and muscles. [29]
- Insulin entering portal vein from pancreas is inactivated in the first passage through liver.

The formulator discovered various approaches to fulfill the demand of insulin via supplying insulin through external routes:

The conventional and most reliable technique for method for the insulin administration is by the subcutaneous route (SC) i.e. via subcutaneous injections [30]. Subcutaneous route lack patient compliance as it is painful especially for those requiring multiple dose injections of four times day.

Along with the subcutaneous route various newer approaches where also discovered which include:

- Supersonic injector
- Infusion
- Pump
- Sharp needles
- Pens

Reasons for the Least Preferences of Subcutaneous Route: [31]

- Lack of patient compliances
- Painful administration especially for the patient requiring multiple dosing
- Incorrect injection technique
- Lipohypertrophy
- Skip of doses of injectable prandial insulin
- Inability to attain sufficient glucose control
- Weight gain
- Hypoglycemia

The above factor leads to the major challenge to control and decrease the rate of the diabetic patient in the world. This urge for the development of better and advanced route of administration of insulin which ensure better patient compliance with safety and efficacy. The recent development focus on the innovative method of administration of insulin in order to overcome the drawbacks associated with insulin administration [32]. After the year of research, the scientist put on the table the innovative method of administration of insulin that via inhalation route [33]. Development of inhalation route was discovered to be encouraging in terms of patient compliance and efficacy with improved quality of life if patient with diabetes by overcoming the psychological barrier associated with the subcutaneous insulin.

Advantages of inhalation route:

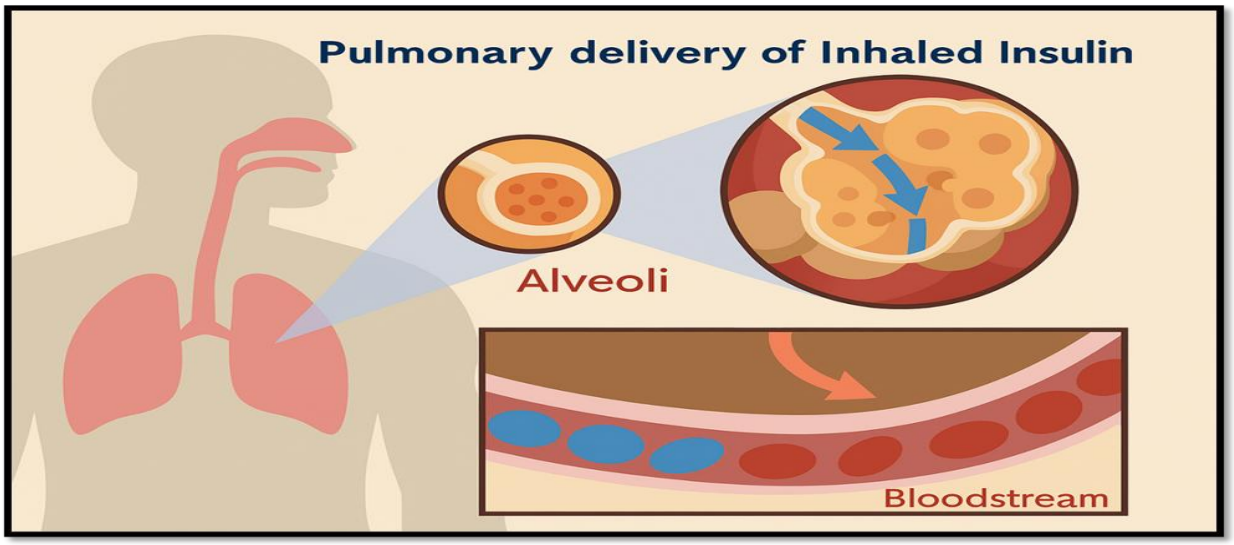

Figure 4Advantages of inhalation route.

Inhalation route of administration gained importance over subcutaneous route due to following reason

- Patient compliance
- Large surface area for drug absorption due to the presences of blood vessel surrounding the alveoli and alveolus
- Accessibility and extensive alveolar capillary network for drug depositions
- Immense capacity for solute exchange
- Ultra thinness of alveolar epithelium leads to quick absorption [34] and distribution of insulin in systemic circulation.
- Facilitates the systemic administration of insulin [35]
- Faster absorption reduces drug latency which allows drug to become faster acting
- It has proven efficacious for passive drug delivery hence found its importance in neonatal intensive care, pediatrics and intensive care units.

Novel Route for Insulin Administration:

Exubera®:

Figure 5The first inhaled insulin Exubera®.

The first inhaled insulin was authorized by Food and Drug Association (FDA)[36] and European Medicines Agency (EMA) in 2006 was EXUBERA which was developed by collaboration of Nektar Therapeutics and Pfizer. In 2006 Exubera was approved for the management of both type-1 diabetes and type-2 diabetes [37]. Insulin administered in Exubera in the form of dry powder in pre-packaged blister packets which consist of 1 or 3 milligram doses of regular human insulin [38]. The reported bioavailability of Exubera was shown to be approximately 60% [39]. Administration and insulin delivery into the circulatory system takes places via mechanical inhaler [40] i.e. breathe actuated which efficiently delivered the insulin at the target site and shows the desired pharmacological action. This mechanical inhaler delivered the equivalent of three or eight units of insulin injected subcutaneously short–acting insulin [41].

Exubera is used as combination therapy with longer acting insulin for controlling and treating type 1 diabetes mellitus whereas monotherapy has been used for managing the type 2 diabetes mellitus [42] or else used in combination with longer acting insulin/ oral antidiabetic agent.

Contraindication:

Exubera is contraindicated for individuals [43] with smoking habit and are advised to stop using the product immediately if the patient is resumed smoking this is due to change in pulmonary lungs function which results in change effective absorption of insulin via inhalation route which leads to the increased risk of hyperglycemic/hypoglycemic affect depending upon the extent if absorption. It is also not recommended for patients with COPD, Asthma and other complication associated with nasopulmonary system [45].

Adverse effect:

Adverse effect reported with the Exubera includes

- Respiratory infection
- Cough
- Pharyngitis
- Rhinitis
- Sinusitis
- Nasopulmonary complication
- Lung's cancer

Exubera® manufactured by Pfizer had faced a dramatic failure and loss and are recalled from the market due poor sales volume and lack of marketing strategies twenty-one months after its approval. It also reduces the ability of lungs to exchange carbon dioxide and oxygen known as pulmonary diffusing capacity to larger extent. Other reason reported for the setback of Exubera[46] was high cost of inhaler, it does not sufficiently fulfill the need of customer that is because the delivery system of Exubera was large, awkward and dosed in milligram an also FDA warning regarding the potential for primary lung cancer.

After the ultimate market failure of Exubera another leading pharmaceutical manufacturing company MANKIND CO-OPERATIVE had endeavored and continue development of inhalation route for insulin administration. It was herculean task for the formulator and developer to come up with new idea and innovation after a huge commercial loss of Exubera. The investigation continued for development novel strategies for effective administration of insulin via inhalation insulin.

AFREZZA®:

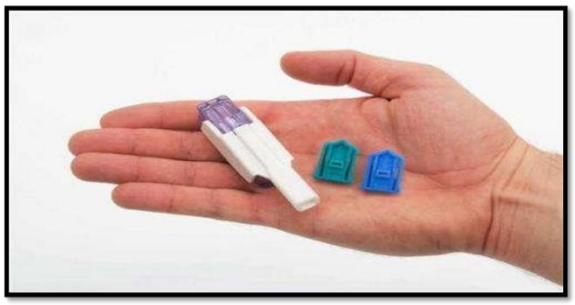

Figure 6 Afreeza®

Later after year of continuous investigation and development of new strategies for administration on 27 June 2014 the FDA (U.S. Food and Drug Administration) [47] approved insulin human inhalation powder AFREEZA developed by one of the most leading pharmaceutical industry MANKIND CO-OPERATIVES. It has found to be effective and promising compared to previously available Exubera. Afreeza employs the use of new Gen2 inhaler which is smaller and easier to use than the previously available Exubera device.

Afreeza is manmade ultra-rapid acting inhaled Insulin comparable to the rapid-acting injectable insulin like (Apidra, Humalog or Novolog) [48]. It is mealtime insulin and should be used alongwith basal insulin.

Jean- Marc Guettier, MD, director of the FDA, Department of metabolism and endocrinology products said that, Afreeza is treatment option for the patient with diabetes mellitus requiring mealtime insulin.

Technosphere Technology:

Afreeza is a represents a drug-device combination consists of dry powder formulation filled inside handheld, pocket-sized, breath-powder inhaler device that accept single use Cartridge. Principle behind the development of the Afreeza is based on techno sphere technology. It is a monomeric human insulin developed via recombinant DNA technology [49] utilizing a nonpathogenic, lab strain Escherichia coli (K12) adsorbed onto Technosphere particle.

Technosphere technology is a generally drug carrier technology based on the adsorption phenomenon where the microencapsulated peptide, protein or drug with larger molecular weight is adsorbed onto the microparticle composed of novel small molecule excipient named Fumaryl diketopiperazine (FDKP). This (FDKP) self-assemble them via hydrogen

bonding in mild acidic environmental condition to form microsphere. Which is then freeze dried (lyophilized) to form a dry powder suitable for the inhalation purpose. This microparticle provides effective absorption and distribution of the drug deep into the pulmonary system i.e. Into alveoli which is highly vascularized and rapid absorption of drug delivered into the bloodstream take place due to its smaller diameter of this microparticle ranging between (~2-5µm) [50]. This FDKP is excreted intact primarily through the kidney. About 90% of the insulin formulation, consisting of excipients, is expelled as ammonium salts in the urine within hours' post-administration [51].

How the drug (Insulin) gets released from this Technosphere Microparticle?

Technosphere particle acts as carrier which carries insulin into the nasopulmonary system (target site for where the insulin adsorbed into the bloodstream). Technosphere particle have ability to readily dissolve in the lungs neutral pH environment [52], once the technosphere particle are aerosolized and deliver to the lungs, at the PH of lungs the carrier particle i.e. technosphere particle readily start dissolving thus the absorbed microencapsulated are released from the surface of the carrier particle thus allowing rapid, fast, and efficient absorption microencapsulated particle into the bloodstream [54].

AFREEZA® inhaler:

It is a second inhaled approved product by FDA. Afreeza got approval by the FDA in year 2014.Afreeza has found to be promising as compared to previously discovered Exubera. It Consists of a dry powder formulation of recombinant monomeric human insulin adsorbed onto the technosphere microparticle [55]. It is ultra-rapid acting insulin. It shows faster onset i.e. within 12-15 minutes. Due to faster onset it has brief duration of effect ≤3 hours [56]. Hence is used alongwith basal rapid acting insulin as is used as mealtime insulin therapy used for the treatment and improves glycemic control in adults with diabetes mellitus by fulfilling the prandial insulin need in patient with diabetes it also proven its efficacy in postprandial and overall glycemic control. Afreeza the inhaler is activated by the patient's breath [56]. Drug is aerosolized into the lungs through the devices depending upon the pumping efficiency. The amount of Afreeza delivered depends on individual patient factor.

Afreeza shows a key advantage over Exubera in the following terms [57]

- Its delivery system is compact, sleek.
- It is Dosed in units, providing simple dosing charts
- It provides more discreet administration process and dosing regimen that is easier for both prescribers and patients to comprehend

Advantage of Afreeza in terms of traditionally used method (subcutaneous insulin)

- Patient compliance
- Large surface area for drug absorption due to the presences of blood vessel surrounding the alveoli and alveolus
- Accessibility and extensive alveolar capillary network for drug depositions
- Immense capacity for solute exchange
- Ultra thinness of alveolar epithelium results in fast absorption and distribution of insulin in systemic circulation [58]
- Facilitates the Insulin delivery into the bloodstream
- Faster absorption reduces drug latency which allows drug to become faster acting
- It has proven efficacious for passive drug delivery hence found its importance in neonatal intensive care, pediatrics and intensive care units
- Inhaled insulin overcome psychological barrier associated with subcutaneous insulin
- Gives flexibility to eat when you want while providing prevent blood sugar control
- Control blood sugar level within 12-15 minutes
- Provides dose flexibility to take additional dose if needed based on the level of glucose in the blood after meals as it has shorter action time [59].

Ingredients of AFREEZA®:

Active ingredient: Regular human insulin

Excipient: Fumaryl diketopiperazine (FDKP) and Polysorbate 80. [60]

Mechanism of Action:

Afreeza control then blood glucose level by lowering glycosylated hemoglobin HbA_{1c} level by stimulating uptake of peripheral glucose via fat and Skeletal

muscle and adipose [61] and by inhibiting hepatic glucose production. It also inhibits lipolysis in adipocytes, inhibits proteolysis and hence enhanced protein synthesis.

Pharmacokinetic:

Technosphere particle have ability to readily dissolve in the neutral pH state within the lungs [62], once the technosphere particle are aerosolized and deliver to the lungs, at the PH of lungs the carrier particle i.e. technosphere particle readily start dissolving thus the absorbed microencapsulated are released from the surface of the carrier particle thus allowing rapid, fast, and efficient absorption microencapsulated particle into the bloodstream.

It shows faster onset i.e. within 12-15 minutes

- It has shorter duration of action ≤3 hours.
- Cmax was 45% higher in case inhaled insulin compared to the conventional subcutaneous insulin [63]
- Relative bioavailability of technosphere insulin was reported 21-25% compared to subcutaneous route
- $T_{1/2}$(Elimination half-life) is around 45 minutes.
- FDKP levels in lungs decline over time with values being 12%, 1.6%, and 0.3% of maximum at 4, 8 and 12 hours post dose, respectively.

Dosing AFREEZA®:

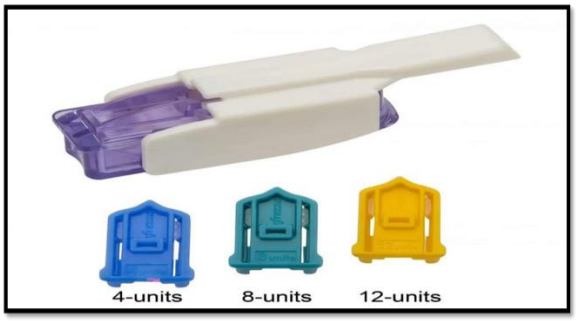

Figure 7 Plastic Cartridges Dosing Afreeza.

Technosphere insulin is administered as single use plastic cartridges of available in colour coded cartridge of 4(blue), 8(green), and 12(yellow) units.

Units of cartridge	Colour code	Dose of insulin (mg)
4	Blue	0.35
8	Green	0.7
12	Yellow	1

Dosing Criteria for Starting Mealtime Insulin:

Patient with insulin naïve start on with 4 units of Afreeza.

Patient using subcutaneous mealtime (prandial) insulin should determine the appropriate dose of each meal by transforming the injected dose to inhaled dose [64].

Mealtime Dose Conversion:

Units of Subcutaneous Insulin	Units of Inhaled Insulin
Up to 4 unit subcutaneous	= 4 units of inhaled
4-8 units subcutaneous	= 8 units of inhaled
9-12 units subcutaneous	=12 units of inhaled
13-16 units subcutaneous	= 16 units of inhaled
17-20 units subcutaneous	= 20 units of inhaled
21-24 units subcutaneous	= 24 units of inhaled

Dosing of the Mealtime Insulin can be adjusted based on following factor:

- Change in the physical activity of an individual
- Change in meal pattern of an individual
- Based on metabolic need of an individual
- Blood glucose monitoring results
- Glycemic control goals.

General Consideration Prior to Administration of Afreeza:

- Detailed medical history of patient
- Physical examination of patient
- Spirometry report to assess pulmonary function

Side Effect Associated with Afreeza®:

Patient comes across with following side effect: [65]

Irritated or painful throat (4.5-5.5%	Severe hypoglycemia (5.1%)	Headache (3.1-4.7%)	Pulmonary function test decreased (2.8%)
Bronchitis (2.5%)	Fatigue (2%)	Difficulty in breathing	Swelling of face, lips tongue or throat
Diarrhea (2.7%)	Nausea (2%)	Unusual muscle pain	Dizziness
Urinary tract infection (2.3%)	Nonsevere hypoglycemia (67%)	Lightheadness	Slow regular heart rate
Productive cough (2.2%)	Cough (25.6-29.4%)	Diabetic ketoacidosis	Hypersensitivity reaction

Drawbacks:

- With Afreeza it is a challenge to achieve narrow glucose goals
- Afreeza Significantly decrease the diffusing capacity of lungs for carbon monoxide (DLCO) [66] relative to SC insulin

Contraindications:

Drug that affect the glucose metabolism are contraindicated with Afreeza as it lowers effect of Afreeza. Afreeza are contraindicated with antiadrenergic drug e.g. beta-blocker, clonidine, reserpine guanethidine as these drugs reduced the symptoms and signs of hypoglycemia if administered with Afreeza.

It is also not recommended during the episodes of hypoglycemia, chronic lungs disease (Asthma and COPD) [66] due to the risk of acute bronchospasm. It is contraindicated patient having smoking habit

Warnings and Precautions:

The prescribing information of Afreeza contain black box warning which state that patients have experienced acute bronchospasm with chronic lungs disease like asthma and COPD [67]

Black warning also states that before initiating the use of the Afreeza one should perform detailed medical history, physical examination alongwith Spirometry (FEV1) to identify and potential lungs disease in an individual.

Precaution Must Be Taken in Following Mention Condition:

1) Change in insulin regimen: It may affect the glycemic control and may leads to predispose hypoglycemia. So any change in insulin regimen should be taken under the close supervision of medical supervisor or registered medical practioner (RMP)
2) Acute bronchospasm in patient with chronic lungs disease: IN patient with asthma reported bronchoconstriction associated due to Afreeza was around 29%. Mean decline in in FEV1 in patient with asthma was around 400mL after 15 minutes if single dose administered whereas in patient with COPD it was reported around 200mL after 18 minutes of single administered dose.
3) Lungs cancer: In the study two cases of lungs cancer was reported in patient exposed to Afreeza in both the cases there was prior history of high consumption of tobacco was reported. Two additional cases of lungs cancer were reported in non-smoker patient exposed to Afreeza.
4) Diabetic ketoacidosis was more common in patient exposed with Afreeza dosage administration
5) Hypersensitivity reaction is monitored in patient with inhalation therapy and therapy is immediately stopped is any hypersensitivity reactions are monitored
6) Hypokalemia is most common adverse effect seen in patient with insulin therapy as it causes a shift in potassium from the extracellular space to intracellular space leading to Hypokalemia [68]. The can severe damage such as respiratory paralysis, ventricular arrhythmia and sometimes death.
7) Heart failure: heart failure is observed in patient undergoing treatment with Afreeza and PPAR-gamma agonist as this may lead to fluid retention and ultimately heart failure.

Drug Interaction:

1. Drugs that increase the risk of hypoglycemia: Risk of hypoglycemia has been associated by use of Afreeza with following drugs

• Antidiabetic agent • ACE inhibitors • Angiotensin II receptor blocker • Disopyramide • Fibrates • Fluoxetine	• Monoamine oxidase inhibitors • Pentoxifylline • Pramlinitide • Propoxyphene • Salicylates • Somatostatin analogs • Sulphonamide antibiotics

2. Drugs that decrease the blood glucose lowering effect of Afreeza: When the Afreeza is co-administered with the following the efficacy of Afreeza to lower the blood glucose level decreases,

- Atypical antipsychotic drug
- Corticosteroid
- Danazol
- Progesterone
- Protease inhibitors
- Somatropin
- Sympathomimetic agents
- Thyroid hormones

Special Indication: [69]

1. Pregnancy category C: pregnancy and teratogenic effect: Afreeza should not been used during pregnancy as Afreeza has not been researched in pregnant women.
2. Nursing mothers: Afreeza has not been studied in lactating women. It should been given to nursing mother. As we know most of the drugs are excreted in human milk. A study in rats was carried which shows results that the carrier is excreted in milk with approximately 10% of maternal exposure levels. Hence in is highly likely that the carrier and Insulin may be excreted in human milk
3. Afreeza efficacy and safety studies has not been yet carried out in patient below 18 years of age.
4. Efficacy and safety of Afreeza has not been investigated in patient with hepatic impairment and renal impairment. But routine glucose monitoring and dose modification is suggested and necessary in such patient.

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