Journal of Applied Pharmaceutical Science

Available online at www.japsonline.com

Facts on inhaled Insulin

Gowtham .T, Rafi khan .P, Gopi Chand .K and Nagasaraswathi .M

Gowtham .T, Rafi khan .P, Gopi Chand .K and Nagasaraswathi .M
Department of pharmacy,
Prist University, Thanjavur,
Tamil Nadu, India.

ABSTRACT

Until today, diabetic patients who need insulin to manage their disease had only one way to treat their condition but Exubera is an inhaled powder form of recombinant human insulin (rDNA) for the treatment of adult patients with type 1 and type 2 diabetes. American and European Drug Agencies (FDA and EMEA) approved the first pulmonary delivered version of insulin (Exubera®) for diabetic patients and hope that the availability of inhaled insulin will offer more options to patients for better control of their blood sugars. The safety and efficacy of Exubera has been studied in approximately 2500 adult patients with type 1 and type 2 diabetes. In clinical studies, Exubera reached peak insulin concentration more quickly than some insulins, called regular insulin, administered by an injection. Side effects associated with Exubera therapy seen in clinical trials included cough, shortness of breath, sore throat, and dry mouth. Exubera is not to be used for the patients who smoke or if you recently quit smoking (within the last 6 months). Exubera is not recommended in patients with asthma, bronchitis or emphysema. The main objective of this review is to elucidate the advantages and adverse events of inhaled insulin.

Keywords: Asthma, Bronchitis, Emphysema, Exubera, inhaled insulin.

INTRODUCTION

Diabetes mellitus refers to a group of metabolic derangements in glucose control caused by varying degrees of insulin production deficiency and peripheral utilization. Although lacking in the ability to produce insulin were observed in many patients with type 2 diabetes ultimately require insulin treatment. Generally two types of Diabetic patients are observed, Patients with Type 1 diabetes mellitus depend on external insulin for their survival because the insulin is no longer produced internally and Patients with Type 2 Diabetes mellitus are insulin resistance, have relatively low insulin production, or both. Newly Type 3 diabeties was investigated due to the lack of insulin in brain cells; generally brain cells also produce insulin similar to that of pancreas. Some of neuronal diseases are caused due to alternation of insulin production from brain cells. Targeted glycemic control in Type 1 and Type 2 diabetic patients is grossly inadequate, despite data demonstrating reduced microvascular and macrovascular diabetic complications with intensive treatment (Ghobrial., 2007; Nathan *et al.,* 2005; Stratton *et al.,* 2000). Inhaled insulin provides hopes to minimiz barriers for initiating insulin therapy, which will improve the overall glycemic control in both type 1 and type 2 diabetic patients (Rosenstock *et al.,* 2005). Years of failure followed scientists realized that they might be able to use new technologies to turn insulin into a concentrated powder with particles sized for inhalation. The main objective of this review is to elucidate the advantages and adverse events of inhaled insulin (EXUBERA) (Guntur and Dhand, 2007). Inhaled insulin is a powder form of recombinant human insulin (rDNA) formulation that has been approved for pulmonary route of administration in both type 1 and type 2 diabetic

For Correspondence
Gowtham .T
Department of pharmacy,
Prist University, Thanjavur,
Tamil Nadu, India.

patients. Over one in four of currently diagnosed patients use insulin for the treatment of diabetes (Ghobrial., 2007). However, an even higher proportion of diabetic patients actually require treatment with insulin. Since 1997, the prevalence of diagnosed diabetic patient increased from 10.4 million to 14.6 million, with an additional of 6.2 million undiagnosed cases accounting for associated morbidities and health care utilization. Diabetes mellitus is the sixth leading cause of death, claiming about 72,000 lives annually.

Exubera is the brand name of first formulation of inhalable insulin to receive the US FDA approval. Insulin is traditionally prescribed in international units (IU), but Exubera is prescribed in milligrams (mg). 1 mg of Exubera is equivalent to 3 IU of INH insulin; however, the increment is not linear: 3 mg of Exubera is equivalent to 8 IU of insulin. Inhalable insulin was available from September 2006 to October 2007 in the market of United States for the treatment of diabetes as a new method of drug delivery system for insulin. Pfizer announced that it would be discontinuing the production and withdrawing the Exubera due to poor sales in October 2007. Several other companies are developing inhaled dosage forms to reduce the need for daily injections among diabetics (Siekmeier and Scheuch., 2008).

Role of Insulin

Insulin is a polypeptide hormone (MW: 6000 Da) secreted by the Islets of Langerhans and functioning in the regulation of the metabolism of carbohydrates and fats, especially the conversion of glucose to glycogen, which lowers the blood glucose level (Mantzoros and Serdy, 2006; Kahn, 1996; Enoksson, 1998; Farese, 1991) Insulin consisting of 2 chains (alpha and beta) linked by three disulfide bonds, has been isolated in 1921 by Banting and Best and was introduced into clinical treatment on January 11th 1922 (Hirsch, 2005). Heubner *et al (1924)* also performed study on inhalation of insulin in patients. Metabolism of glucose, fats, ketones and proteins all depend on adequate production and utilization of the insulin hormone. Insulin may also play a role in steroid synthesis vasodilation via activation of nitric oxide inhibition of fibrinolysis by stimulating production of plasminogen activator inhibitor and normal growth via anabolic effects on protein and lipid metabolism. Reduced insulin production in the pre-diabetic or early diabetic states leads to chronic hyperglycemia, the toxic effects of which may contribute pancreatic cell function impairment (Kaur and Dinesh, 2008).

Inhaled insulin is a powdered form of recombinant human insulin; inhaler is used to deliver the insulin into the lungs where it is absorbed. Insulin has also helpful for the patients with breast cancer. Diabetes still need to take a longer acting basal insulin by injection.

In lungs inhaled insulin produce a systemic drug delivery system where the dosage form transfer into the circulatory system which can be represented by fig 1(Maheux, 2006).

New Technology is developed for pulmonary route of insulin administration to achive effective biomedical parameters and patient comfort in case of type 1 and type 2 diabetes.
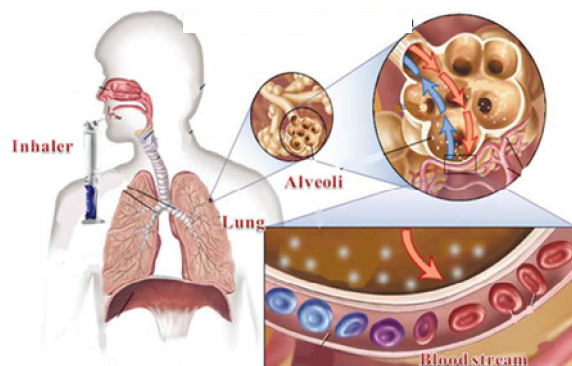

Fig. 1 Pulmonary delivery of inhaled insulin.

Efficacy

Several studies are conducted to determine the efficacy and safety of inhaled insulin (Exubera) is compared with subcutaneous injection in the patients with type 1 and type 2 diabetes. Black C *et al.,* (2007) study report suggested that the Inhaled insulin appears to be effective, well tolerated and well accepted in patients with type 1 and type 2 diabetes and provides glycemic control comparable to a conventional subcutaneous regimen. Comparative clinical trials between inhaled insulin used 3 times a day and 10 min before meals and subcutaneous longer acting insulin daily or twice daily indicate that inhaled insulin achieved glycaemic control similar to that of various subcutaneous insulin regimens, as measured by reductions in HbA 1c (Rosenstock *et al.,* 2005; Bellary and Barnett., 2006).

Onset of action

Thirteen subjects with type 2 diabetes participated in this six-period crossover isoglycemic glucose clamp study (age 56 ± 7 years, body mass index 30.4 ± 3.0 kg·m-2, hemoglobin A1c $6.9 \pm 0.9\%$) and each subject received three single doses of Technosphere® Insulin (TI) and subcutaneous regular human insulin (sc RHI) on separate study days. The main objective of this study is to assess time action profile within and between the subject variability of TI compared with sc RHI (Rave *et al.,* 2008) Inhalation of TI resulted in a higher maximum serum insulin concentration and shorter intervals to maximum insulin concentration than sc RHI. Technosphere Insulin has a more rapid onset of action than sc RHI. About 60% of the glucose-lowering effect of TI occurs during the first 3 hours after application. In contrast, <30% of the glucose-lowering effect of sc RHI occurs in this period. (Skyler., 2006)

Safety

The experience of the last 80 years in millions of patients has shown that the treatment of diabetes mellitus with subcutaneously administered insulin is relatively safe. Most data regarding the long-term tolerability are published for the Exubera® system and the AERx iDMS® system for study periods of up to 2 years and more in patients with diabetes types 1 than 2 (Patton *et al., 2004*). The effect of insulin inhalation on lung function has been thoroughly investigated. In most studies inhalation of insulin

caused no changes of spirometric parameters of lung function (e.g., forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and parameters of diffusion capacity for carbon monoxide (DLCO) and blood gas analysis. In summary, the experience regarding the effect on lung function indicates that inhaled insulin is characterized by a low pulmonary toxicity, good tolerance, and good bioeffectivity. The total quantity of the inhaled substance is lower than the threshold value for dust inhalation of 30 mg/day recommended by the American Council of Government Industrial Hygienists. Since adipocytes are also located in the lung, inhaled insulin can also affect these cells after pulmonary deposition. However, at present it is not known if and how inhaled insulin affects pulmonary adipocytes. Cough is a typical symptom in clinical treatment with inhalation of dry powder aerosols which might affect patient convenience and compliance. Therefore, cough was addressed in a number of studies investigating inhaled insulin. Mild to moderate cough was reported to occur rapidly after inhalation (seconds to minutes) in up to 20-30% of patients. The data obtained in these studies are conflicting, demonstrating an increased frequency of severe hypoglycemic events in patients treated with inhaled insulin compared with patients treated with subcutaneous injections in some of these studies. However, there is no, or only little, difference regarding the risk for the occurrence of hypoglycemia between inhaled and subcutaneous insulin , whereas the risk is expectedly higher for patients treated with inhaled insulin when compared with treatment with oral antidiabetics (Skyler., 2006; Bellary and Barnett., 2006).

Patient Satisfaction

Cappelleri *et al.,* (2000) develop a self-administered method by alternative delivery routes of insulin and investigated the patient treatment satisfaction compared with both inhaled and injected insulin therapy. For this study 69 subjects were enrolled in a phase II clinical trial with type 1 diabetes who is previously taking injected insulin therapy. Exploratory factor analysis suggested two-factor, the first factor contained 10 reliable items relating to convenience to patient and ease of use, and the second contain relating to social comfort. This analysis highlighted and quantified two key factors observed in patients with type 1 diabetes which contributing to patient satisfaction: convenience/ease of use and social comfort.

Improve control

The pulmonary route of administration due to its rich vascularity, immunotolerant characteristics and large surface area may be an ideal target for drug delivery. Although the inhaled route has been used to deliver drugs for the treatment of respiratory disorders, success with peptide delivery has been limited by poor bioavailability. Recent advances in technology have overcome these barriers and developed new delivery devices (Exubera®) has now been approved for clinical use. In clinical trials Insulin is the first peptide to be delivered successfully by this pulmonary route and shown to be effective, apparently safe and a preferred alternative to subcutaneously injected meal-time insulin. This new

technology for insulin delivery offers great convenience to patients needing insulin treatment. While it will considerably reduce the number of injections needed for type 1 and type 2 diabetic patients. The potential benefits from improved adherence and better glycaemic control with this insulin are also significant (Rosenstock *et al.,* 2005; Skyler., 2006)**.**

ADVERSE EVENTS

Cost

Cost planed for Exubera system can be classified into initial purchase costs, costs of replacement blisters, costs of replacement transjectors, and costs of annual lung-function tests. The cost of a blister replacement depends on the patient's insulin dose. For example, a patient who inhales insulin three times a day (at eight insulin units per inhalation) would require 1,095 (3x365) 3-mg blisters per year. The manufacturer recommends that patients should replace the transjector for every two weeks; therefore, 26 new transjectors should be purchased every year. Also, the Exubera inhaler itself is recommended for replacement every year. ECRI Institute estimated the annual cost of Exubera based on wholesale acquisition costs at \$1,578.00 for annual insulin. On average, patients with type 1 diabetes were willing to pay \$120 dollars per month (95% CI: \$53.4 to \$186.6) for inhaled insulin. Five Patients with type 2 diabetes were willing to pay \$18 dollars more than patients with type 1 diabetes.(Taghavi, 2002; Black *et al.,* 2007) The Average wholesale price of various insulin and insulin analogues (inhaled kit and 10 ml vial) are represented in Fig 2 (Ghobrial., 2007).
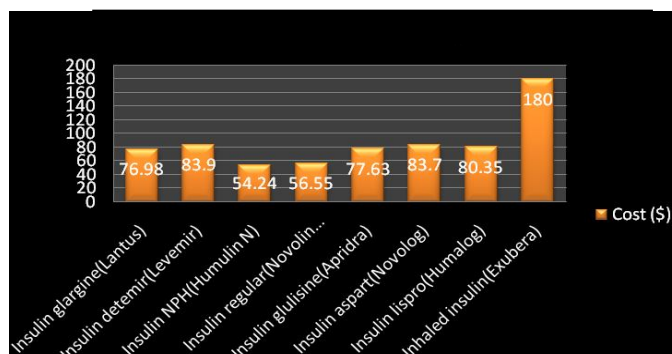

Fig 2 Insulin and Insulin Analogues Price.

Asthma and COPD

Dr. Jay Skyler presented two studies to determine the effect of inhaled insulin on lungs function and effect of inhaled insulin on diabetes with lung ailments. From the first study he concluded that Patients who used inhaled insulin had slight decreases in their pulmonary function that occurred early and Cough was reported by 38%. Bronchodilators and other inhaled products may alter the pharmacokinetic parameters of inhaled human insulin. In case of second study Inhaled insulin is less effective in diabetic patients with chronic lung conditions such as asthma and chronic obstructive pulmonary disease (COPD) because Inhalers that could deliver insulin via the lungs which will

alter the lung ventilation and morphology due to diseases like asthma and COPD having an influence on the alveolar deposition of inhaled particles. After deposition in alveolar the absorption of the biomolecules is affected by structure and function of the physiological pulmonary defense mechanisms (e.g., alveolar macrophages, physiological absorbance barriers, proteases/peptidases,) and specific properties of the biopharmaceuticals such as molecular weight, lipophilicity, solubility in water and lipids. An optimal pulmonary deposition of dosage form is achieved with a slow and deep inhalation procedure (Siekmeier and Scheuch., 2008).

Pulmonary function

Teeter *et al.,* (2006) conducted 24-wk multicenter study on 226 patients with type 1diabetes were randomized to receive daily premeal inhaled insulin (INH) or subcutaneous (SC) insulin for 12 wk (comparative phase), followed by SC insulin for 12 wk (washout phase). Insulin antibody levels were measured and Spirometry tests were conducted throughout the study to estimate the changes in pulmonary function and increases in insulin antibodies with inhaled insulin compared with SC insulin. Acute insulin treatment changes in lung function were calculated as the difference between FEV1 before and after insulin therapy. There was a temporal dissociation was observed between insulin antibody generation and pulmonary function changes. Small treatment group differ with changes in FEV1 from baseline, favoring SC insulin, were fully manifest by 2 wk of INH therapy, did not increase during the remainder of the comparative phase, and resolved within 2 wk of INH discontinuation. Insulin antibody levels remained low for the first 2 wk with INH therapy follow by increased during Weeks 2 to 12, and gradually declined during washout. A small lung function changes observed with inhaled insulin therapy are not mediated by the humoral immune response, or associated with acute decrements in lung function immediately after insulin inhalation. Typical side effects such as coughing, shortness of breath, sore throat dry mouth and hypoglycaemia were observed with inhaled insulin therapy. Animal studies and investigations in diabetic patients demonstrated that diabetes and consecutive insulin treatment cause a morphological change of lung structure (e.g., thickening of the alveolar membrane and the capillary basal lamina, vascular hyalinosis, granulomas, intraseptal nodular fibrosis and emphysema-like septal obliteration) (Johnson., 2006).

Pregnancy and Lactation

Inhaled insulin absorption in pregnant patients with gestational or pre-gestational type 2 diabetes was compared with that of non-pregnant patients with type 2 diabetes. Inhaled insulin can cause fetal harm when administered to a pregnant woman. INH (Exubera®) is classified as a pregnancy-risk category C, defined as either animal studies have revealed adverse effects on the fetus or there are no controlled studies in pregnant women. However, SC insulin is classified as a pregnancy-risk category B and is the drug of choice for the control of diabetes mellitus in pregnancy. Human insulin is excreted in breast milk and caution should be taken when insulin is administered to a nursing woman. However, since the gastrointestinal tract destroys insulin, systemic absorption of the lactating infant is not expected. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both (Ghobrial., 2007).

Dose

Dose dependent problems were the inability to deliver precise insulin doses, because of its smallest blister pack available it containes 1 mg equivalents to 3 IU of regular insulin and this dose would make it difficult for most of the people who are using insulin to achieve accurate control, which is the real goal of any insulin therapy. For example, some patients with 60 IU of insulin per day would reduce the blood glucose levels about 90 mg/dl (5 mmol) per 3 U pack, while some patients with 30 IU a day would drop 180 mg/dl (10 mmol) per pack. Precise control was not possible, especially when compared with an insulin pump that can deliver one twentieth of a unit with precision (Ghobrial., 2007). The dose linearity of Exubera dose compared with that of SC Insulin was shown in table 1.

Exubera dose (mg)	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg	8 mg	9 mg	10 mg
SC Insulin dose (IU)	3 IU	6 IU	8 IU	11 IU	14 IU	16 IU	19 IU	22 IU	24 IU	27 IU

Most of the dose of inhaled insulin will never reaches the deep lung; around 15% of a total inhaled insulin dose reaches the blood (Maheshkumar and Misra., 2003). However, it is important to note the amount of absorbed insulin in relation to the amount of insulin inhaled which varies between 15% and 30% from dose to dose even in the same person and that this is approximately the same as with subcutaneously injected human insulin or rapid-acting insulin analogues. (Taghavi, 2002) Depending upon the particle diameter of a dosage form the drug deposit at different regions of the pulmonary system shown in Fig 3 (Maheux., 2006; Shyler *et al.,* 2002; Reinhard *et al.,* 2006).
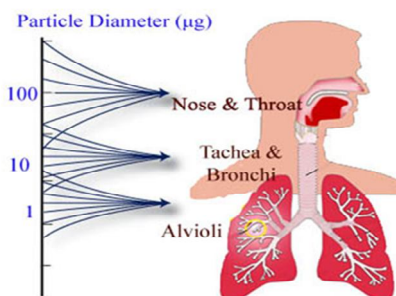

Fig. 3 Particle size influences site of deposition.

Smoking

Conducted randomized two-period crossover efficacy and safety trial in 27 nondiabetic smokers and 16 nonsmokers (mean age of 28 years, mean BMI 23.0 kg/m2) to determine the effect of inhaled insulin in smokers, subjects received single doses of

inhaled insulin following overnight fasting on consecutive dosing days. On one dosing day, insulin administered ("acute smoking") in subjects immediately after smokers smoked three cigarettes and smokers had not smoked since midnight ("nonacute smoking") on the other dosing day. After inhalation of insulin, serum insulin and serum glucose profiles were determined to observe the pharmacokinetic results. From this study he concluded that the Absorption of inhaled insulin via the AERx iDMS was significantly greater in smokers, with a higher AUC(0–6 h) and *C*max and a shorter *t*max (Siekmeier and Scheuch., 2008; Ghobrial., 2007; Himmelmann *et al.,* 2003; Reinhard *et al.,* 2006).

Age

Lung morphology and functional changes occur depending upon age. Elder individuals show a decrease of the alveolar surface, a variation of lung elasticity, a decrease of the alveolar capillary volume combined with a decline of the ventilation/perfusion ratio, a decrease of the pulmonary diffusion capacity for carbon monoxide (DLCO), and an increase of the pulmonary residual volume (RV). Therefore, the age is another important parameter influencing the pharmacokinetics of inhaled insulin. Henry *et al.,* (2003) reported similar values of Cmax and AUC in patients with diabetes type 2 aged >65 years and young individuals of the age between 18 and 45 years. The variability in these parameters was not different between both study groups either. However, the observed decrease of plasma glucose concentrations was more pronounced in younger individuals than in elder patients indicating a requirement of higher doses in aged patients (Ghobrial., 2007).

CONCLUSION

The inhaled insulin (Exubera) appears to be effective, safe and quick on set of action when compared to SC insulin but the cost is so much more that it is unlikely to be cost-effective. New technology of pulmonary drug delivery system is developed for avoiding or minimising injections to treat type 1 and type 2 diabetes. Data on adverse events lead to Exubera being contraindicated for smokers and pregnancy which altered the pharmacokinetics of inhaled insulin. As rapid changes in systemic insulin exposure increase hypoglycemia risk, inhaled insulin should not be used in people with diabetes who choose to continue smoking and not recommended for people with underlying lung diseases, such as asthma or COPD.

REFERENCES

Anders Himmelmann., Johan Jendle., Anders Mell., Astrid H. Petersen., Ulf L. Dahl and Perwollmer. "The Impact of Smoking on Inhaled Insulin". *Diabetes Care.* 2003; 26:677–682.

C Black, E Cummins, P Royle, S Philip and N Waugh. The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation. *Health Technology Assessment.* 2007;11: 33.

Enoksson S, Degerman E, Hagstrom-Toft E, Large V, Arner P. Various phosphodiesterase subtypes mediate the in vivo antilipolytic effect of insulin on adipose tissue and skeletal muscle in man. Diabetologia. 1998; 41(5): 560–568.

Farese RV , Yost TJ, Eckel RH. Tissue-specific regulation of lipoprotein lipase activity by insulin/glucose in normal-weight humans. Metabolism. 1991; 40(2): 214–216.

Heubner W., de Jongh SE and Laquer E. Uber Inhalation von Insulin. Klin Wochenschr. 1924; 3: 2342-2343.

Hirsch IB. Insulin analogues. *N Engl J Med.* 2005; 352 : 174-83.

Inhaled insulin (Exubera). National Prescribing Centre. Available at www.npc.co.uk.

Inhaled Insulin for the Treatment of Type 2 Diabetes. ECRI Institute Health Technology Assessment Information Service. June 2007. Issue No. 146.

Jasleen Kaur and Dinesh K. Badyal. Newer Insulins. 2008; 10 (3): 107-111.

Jay Skyler. *Pulmonary insulin: current status.* 2006; 51 (1), 23-25.

John G. Teeter and Richard J. Riese. Dissociation of Lung Function Changes with Humoral Immunity during Inhaled Human Insulin Therapy. Am J Respir Crit Care Med. 2006;173:1194–1200.

Joseph C. Cappelleri, Robert A. gerber, Ione A. kourides and Robert A. Gelfand. " Development and Factor Analysis of a Questionnaire to Measure Patient Satisfaction With Injected and Inhaled Insulin for Type 1 Diabetes". Diabetes Care. 2000;23(12): 1799-1803.

Kahn BB. Lilly lecture 1995. Glucose transport: pivotal step in insulin action. Diabetes 1996;45(11):1644–1654.

Kate Johnson. "Inhaled Insulin Had Little Effect on Lung Function". Metabolic Disorders. Family practice news. Oct 15, 2006.

Klaus Rave., Tim Heise., Lutz Heinemann and Anders H. Boss. "Inhaled Technosphere® Insulin in Comparison to Subcutaneous Regular Human Insulin: Time Action Profile and Variability in Subjects with Type 2 Diabetes". Journal of Diabetes Science and Technology. 2008; 2(2): 205.

Linda Ghobrial. Use of Inhaled Human Insulin in Patients with Diabetes Mellitus. Pharmacotherapy update. 2007; X,(I) available at http://www.clevelandclinicmeded.com/medicalpubs/pharmacy/pdf/Pharmaco_X-I.pdf.

Mantzoros C, Serdy S. Insulin action. UpToDate February 27, 2006.

Nathan DN, Cleary PA, Backlund JY *et al*. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-2653.

Patton JS, Bukar JG, Eldon MA. Clinical pharmacokinetics and pharmacodynamics of inhaled insulin. Clin Pharmacokinet. 2004; 43: 781-801.

R. Siekmeier and G. Scheuch. INHALED INSULIN – DOES IT BECOME REALITY?. Journal of Physiology and Pharmacology. 2008; 59(6), 81-113.

Reinhard H.A. Becker, Sue Sha, Annke D. Frick and Robert J. Fountaine. The Effect of Smoking Cessation and Subsequent Resumption on Absorption of Inhaled Insulin. DIABETES CARE. 2006; 29 (2): 277-282.

Robert R. Henry, Sunder R.D. Mudaliar, William C. Howland , Neelima Chu, Dennis Kim, Bob An and Rickey R. Reinhardt. Inhaled Insulin Using the AERx Insulin Diabetes Management System in Healthy and Asthmatic Subjects. Diabetes Care. 2003; 26(3): 764-769.

Rosenstock J, Zinman B, Murphy LJ, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. Ann Intern Med 2005;143:549–558.

Shyler JS, Cefalu IA, Landschulz WH, Balagtas CC, Cheng S-L, Gelfand RA. Efficacy of inhaled insulin in Type 1 diabetes. Lancet. 2002:357:331-335.

Srikanth Bellary and Anthony H Barnett.Inhaled insulin (Exubera®): combining efficacy and convenience. *Diabetes and Vascular Disease Research* 2006; 3: 179.

Stratton IM, Adler AI, Neil HAW *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000; 321:405-12.

T. Mahesh Kumar and Ambikanandan Misra. Influence of Absorption Promoters on Pulmonary Insulin Bioactivity. AAPS PharmSciTech. 2003; 4 (2), 1-12.

Taghavi M. Inhaled Insulin as a Novel Administration Form for Insulin. Shiraz E Medical Journal. 2002; 3(4): 109-111.

UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352: 837–853.

Vamsi P Guntur and Rajiv Dhand. Inhaled Insulin: Extending the Horizons of Inhalation Therapy. Respiratory Care. 2007; 52 (7): 911-922.