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Alternative routes of insulin delivery

D. R. Owens, B. Zinman* and G. Bolli†

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Keywords

- ☐ routes of insulin delivery

Abstract

Attempts at replicating physiological insulin secretion, as a means of restoring the normal metabolic milieu and thereby minimizing the risk of diabetic complications, has become an essential feature of insulin treatment. However, despite advances in the production, purification, formulation and methods of delivery of insulin which have occurred in recent years, this has met with limited success. The current advocacy of intensive insulin therapy regimens involving multiple daily subcutaneous injection places a heavy burden of compliance on patients and has prompted interest in developing alternative, less invasive routes of delivery. To date, attempts to exploit the nasal, oral, gastrointestinal and transdermal routes have been mainly unsuccessful. The respiratory tree, with a large surface area, offers the greatest potential for the delivery of polypeptide drugs and there is renewed interest in administering insulin by the intrapulmonary route. Current pulmonary drug delivery systems include a variety of pressurized metered dose inhalers, dry powder inhalers, nebulizers and aqueous mist inhalers. Recent clinical studies suggest a possible role for inhaled insulin in fulfilling meal-related insulin requirements in persons with Type 1 and Type 2 diabetes. Most experience with inhaled insulin has been obtained using either dry powder formulation in the Nektar Pulmonary Inhaler/Exubera device (Nektar Therapeutics Inc., San Carlos, CA, Aventis, Bridgewater, NJ, Pfizer, NY) or a liquid aerosol formulation in the AERx® Insulin Diabetes Management System (Aradigm Corp., Hayward, CA, NovoNordisk A/S, Copenhagen, Denmark). If long-term safety and efficacy is confirmed, inhalation may become the first non-subcutaneous route of insulin administration for widespread clinical use. Despite overwhelming interest and investment in administering insulin via the oral route, success is not expected in the short term. Attempts at utilizing the buccal mucosa and skin are also continuing. Pancreatic transplantation will remain limited to those patients receiving a kidney transplant and immunotherapy. Islet cell transplantation is at an early though encouraging stage following the availability of new less toxic immunosuppressive agents. True insulin independence will require further advances in the combined fields of cell biology and genetics to ensure freedom from both the need for lifelong administration of insulin and the complications of diabetes.

Diabet. Med. 20, 886–898 (2003)

Introduction

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Since insulin was introduced into clinical practice in 1922, major developments have occurred in the production, purification, pharmaceutical formulation and methods of delivery. Despite these advances, replicating physiological patterns of insulin secretion has proved virtually impossible and the goal of restoring and maintaining blood glucose and other metabolic parameters at near normal levels in diabetic patients has proved elusive [1]. Vascular complications due to the long-term dysmetabolic milieu remain a major cause of morbidity and mortality among diabetic patients.

The administration of insulin in the form of a bolus subcutaneous (s.c.) injection has been the basis of insulin therapy since its introduction. However, this feature is central to the problem of glycaemic control since the pharmacokinetics of conventional insulin preparations given by this route make it virtually impossible to replicate the normal pattern of nutrient-related and basal insulin secretion [2–4]. Improvements in glycaemic control are expected with the combined use of rapid-acting and long-acting insulin analogues given by the s.c. route [5,6]. Hitherto, dependence on s.c. administration of insulin to improve glycaemic control has resulted in increasingly complex and intensive insulin regimens involving multiple daily injections, or continuous insulin infusion using a variety of pumps aided by increasingly sophisticated glucose monitoring devices.

Attempts to develop alternative routes of administering insulin began soon after the introduction of insulin therapy in the 1920s. Since then, almost every conceivable route has been tried but with only limited success [7,8]. Recently, however, attention has refocused on insulin delivered by the pulmonary route. This review examines some of the many attempts made to develop alternative, more convenient routes for insulin delivery to avoid existing long-term dependence on multiple s.c. injections, and improve insulin's pharmacodynamic properties. This article concentrates on the recent successes achieved in developing intrapulmonary administration and its future potential for providing meal-related insulin requirements. Developments in implantable pump devices, islet cell transplantation and the potential of utilizing stem cells will not be covered.

Peroral (enteric–gastrointestinal) route of delivery

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☐ oral

☐ buccal

☐ gastrointestinal

☐ nasal

☐ pulmonary

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Search

Accepted 7 June 2003

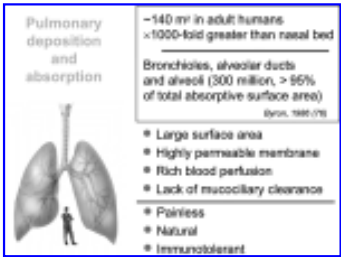
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Image Previews



[Full Size]

Figure 1 Rationale for the pulmonary route for insulin delivery.

Whilst oral administration of insulin is a potentially attractive option, attempts to develop this route have, so far, met with little or no success [9]. Polypeptide drugs, such as insulin, are degraded in the acidic environment of the stomach and by digestive enzymes, especially in the small intestine. The epithelial surfaces of the gastrointestinal tract itself present an effective barrier to the absorption of insulin.

Numerous individual and combined strategies have been devised to enhance insulin absorption. These include the co-administration of insulin with enzyme inhibitors and/or permeation enhancers, methods designed to improve insulin's chemical stability and the use of muco-bioadhesives, liposomes, emulsions and polymer-based delivery systems [10]. Despite the many different strategies tried, generally less than 1% of orally administered insulin is absorbed [11].

The use of liposome-based delivery systems has been extensively investigated in animal studies [10,12]. Variable reductions in blood glucose have been reported dependent on factors including the lipid composition, size, surface charge and the physical state of the phospholipid bilayer employed [13–15]. Conventional liposomes are susceptible to enzymatic degradation and bile salt dissolution, although they can be made resistant to the gastrointestinal environment by polymerization [16,17]. Coating insulin with a pH-dependent acrylic based biodegradable polymer [18] and its encapsulation in enteric coated microspheres [19] have also been tried. Microspheres in the nanosize range are absorbed intact across the intestinal epithelium and are taken up by the liver which degrades the polymer releasing the insulin. Oral administration of insulin encapsulated in biocompatible self-assembled 'nanocubicles' also appear to be effective in animal studies [20].

Other strategies employed to enhance absorption include modification of insulin by the covalent attachment of one or more low-molecular-weight amphiphilic oligomers (carriers). Absorption of encapsulated hexyl-insulin monoconjugate-2 (HMI2) across the gut wall has been demonstrated in healthy persons and those with diabetes [21–23]. The low-molecular-weight oligomer is covalently bound to lysine at position B29 of the recombinant human insulin. This covalent modification increases solubility and improves stability against gastrointestinal enzymes. Non-acylated amino acids can also increase the absorption of insulin. Non-covalent complexes formed between hydrophilic carrier molecules and insulin can induce partial and reversible unfolding of the insulin molecule, facilitating permeability by passive transcellular diffusion across cell membranes due to the increased flexibility and lipophilicity, before dissociation of the complex beyond the epithelial cell [24].

Oral administration of subtherapeutic doses of insulin has also been suggested as a means of enhancing immune tolerance in individuals at high risk of developing Type 1 diabetes [25]. However, clinical trials evaluating this concept have so far failed to show any protective effect [26–28].

Oral-buccal and sublingual routes of delivery

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The oral mucosa offers a number of attractive features for administering polypeptide drugs. The oral cavity is easily accessible, has a large surface area for absorption (100–200 cm²) with little proteolytic activity and is highly vascularized. However, in practice the multilayered structure of the squamous epithelium of the buccal and sublingual mucosae (approximately 60% of oral mucosal surface area) combined with the continuous but highly variable flow of saliva in the mouth constitutes an effective barrier to absorption.

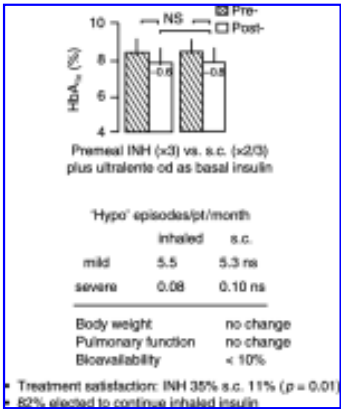
The use of absorption enhancers (surfactants, bile salts, chelators, alcohol and fatty acids), alone or combined with bioadhesive delivery systems (gels, films, patches), to enhance the mucosal permeability of insulin has been extensively tested in animal studies. Reductions in blood glucose of up to 30% relative to intramuscular insulin have been reported, but the studies have lacked reproducibility [29,30].

Many other options for improving absorption have been tried including the addition of enzyme inhibitors and/or molecular modifications to increase the lipophilicity of the insulin molecule (conjugation with various polymers, acylation, methylation) and the use of prodrugs [31–33]. Further efforts have been made to develop mucoadhesive delivery systems incorporating insulin, with or without enhancers, into liposomal formulations including highly



[Full Size]

Figure 2 The Nektar Pulmonary Inhaler and Exubera™; Nektar Therapeutics Inc, Pfizer Inc and Aventis Pha...



[Full Size]

Figure 3 Inhaled insulin: proof of concept study in patients with Type 1 diabetes (n = 72) over a 12-week...

deformable lipid vesicles (transfersomes) [34,35].

Few studies have evaluated the buccal and sublingual routes in humans. Reductions in blood glucose have been reported in a small number of patients with Type 1 diabetes using an aqueous human insulin spray, but only after multiple applications [36]. Another liquid insulin aerosol formulation comprising mixed micelles made from a combination of absorption enhancers has also been developed [37]. Limited data in patients with Type 1 and Type 2 diabetes suggest a more rapid and shorter lived hypoglycaemic response compared with s.c. soluble human insulin. Local tolerability appears acceptable, but bioavailability remains low, necessitating repeated administrations [37,38].

The multitude of techniques already tested illustrates the inherent difficulties associated with the oral-buccal route of insulin administration. Combined strategies seem to be the only likely route to possible future success.

Rectal Go to: ▲ ▼

The potential advantage of rectal delivery is avoidance of local enzymatic degradation with insulin entering the systemic circulation predominantly via the lymphatic system, circumventing the hepatic extraction of insulin that occurs by some other routes. However, absorption of insulin from the rectum is inconsistent and bioavailability in humans is very low (4–10%). Different absorption enhancers have been used, but it seems that this will not present an acceptable alternative route.

Ocular and intravaginal routes Go to: ▲ ▼

A small number of studies have also evaluated the potential of the ocular and intravaginal routes. Low and variable levels of absorption, even in the presence of absorption enhancers, and severe local adverse reactions mean that both these routes offer little or no real opportunities in the clinical management of patients with insulin-requiring diabetes.

Transdermal delivery Go to: ▲ ▼

Although the skin is easily accessible and has a large surface area (1–2 m²), it is relatively impermeable to large, hydrophilic polypeptides such as insulin. The impermeability of the skin is due predominately to the intercellular lipid layer of the stratum corneum [39,40]. Attempts to optimize transdermal drug delivery have involved breaking down or removing the lipid barrier by a variety of chemical, electrical or physical methods. Iontophoresis [41–44], low-frequency ultrasound (phonophoresis) [45,46] and/or the use of drug carrier agents [47] are the main methodologies being explored.

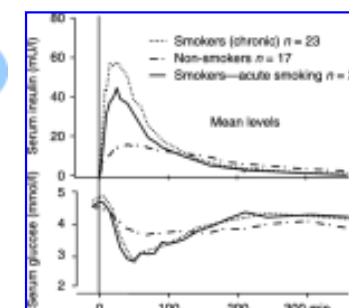
The use of cathodal iontophoresis to transfer hexameric soluble insulin across untreated skin is inefficient but can be improved by shaving the hairs, stripping off the stratum corneum, or by applying highly charged or monomeric insulin analogues following pretreatment of the skin with delipidating agents [44]. Even so, the amount of insulin transferred is barely enough to meet basal insulin requirements. Whilst some enhancement in absorption has been achieved with systems employing pulsed current, the transdermal transfer of insulin remains inadequate [48]. Apart from the issue of safety of the various chemical and physical pretreatments used, the long-term biophysical impact of iontophoresis [49] remains uncertain.

Several studies have demonstrated reductions in blood glucose using low-frequency (20–150 kHz) ultrasound (sonophoresis) to increase the transdermal transfer of insulin applied to the skin as an aqueous solution or mixed with an ultrasound coupler such as hydrogel [45–47,50]. The efficiency of the ultrasound technique depends upon the energy density and length of the ultrasound pulse [47]. It has been suggested that the



[Full Size]

Figure 4 AERx® insulin Diabetes Management System (AERx® iDMS); Aradigm Corp and Novo Nordisk A/S. Insul...



[Full Size]

Figure 5 The effect of smoking on the absorption of inhaled insulin in non-diabetic subjects. Smokers ...

combined use of iontophoresis and ultrasound may work synergistically [51].

The incorporation of insulin into highly deformable, liposome-like lipid vesicles known as transfersomes was reported to result in intercellular transdermal transfer rates of the order of 50%. However, more recent studies have been unable to reproduce these initial findings.

Despite the numerous strategies employed to enhance the transdermal delivery of insulin, success has been very limited. In order to provide a basal insulin supply by this route, new approaches, possibly involving combinations of physical and chemical methods, will need to be deployed [52,53].

Intranasal delivery

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The nasal cavity offers an epithelial surface of approximately 150 cm² but the main barriers to absorption include the very active mucociliary clearance mechanism and the presence of proteolytic enzymes.

An extensive range of enhancers has been used to increase the absorption of insulin across the nasal mucosa. These include bile salts and their derivatives, surfactants, fatty acids and their derivatives and cyclodextrins [53–57]. Histological studies in animals have revealed a variety of mucosal cell damage on exposure to absorption promoters, especially bile salt derivatives [54,58,59]. Other methods used to improve insulin absorption involve inhibiting nasal proteases and/or retarding the removal of insulin with bioadhesives [7,56,57].

The bioavailability of intranasal insulin varies according to the type, volume and concentration of both the enhancer and the insulin, in addition to the size, density, shape and hygroscopicity of the particles, the nasal airflow characteristics and the presence of any nasal pathology [7,56,59]. In humans, when compared with the s.c. route of administration, insulin absorption when delivered by the nasal route is much quicker, but the bioavailability is lower, at less than 20% [60–64], and the variability is higher [65].

Clinical studies in patients with Type 1 and Type 2 diabetes have revealed a rapid but relatively short-lived increase in plasma insulin following nasal administration with multiple doses required to control postprandial hyperglycaemia [66,67]. However, metabolic control was frequently inferior to s.c. insulin and many patients suffered local nasal irritation [67–69]. More recently, a lyophilized nasal insulin preparation containing sodium glycocholate given preprandially achieved glycaemic control equivalent to a regimen of twice daily NPH insulin in patients with Type 2 diabetes over a 4-month period [70]. A gel formulation developed subsequently was found to have equivalent efficacy to s.c. insulin and improved nasal tolerance in Type 1 diabetes patients treated over a 6-month period [71].

To date, the relatively limited clinical experience with intranasal insulin demonstrates a need for high and repeated doses to achieve glycaemic control. The occurrence of nasal irritation in up to 25% of patients and the potential for damage to the nasal mucosa and nasal-ciliary function [54,58,72] are a cause for concern, especially when viewed in the context of the need for long-term exposure. In order for intranasal insulin to become a clinical and commercially viable alternative to s.c. insulin, major obstacles still remain to be overcome.

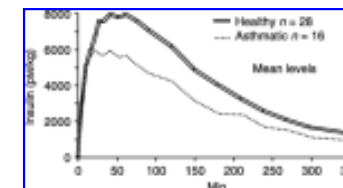
Pulmonary route

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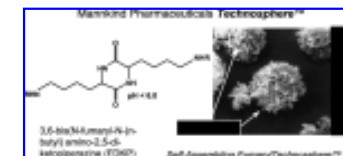
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The respiratory tree, with an estimated surface area of 140 m², offers the greatest potential for the delivery of polypeptide drugs such as insulin. (see Fig. 1) The alveolar surface, which accounts for > 95% of the absorptive area, is lined by a very thin (0.1–0.2 µm) vesiculated and richly perfused monolayer of epithelial cells. Transport of molecules across the alveolar wall (Type 1 cell) occurs by transcytosis for molecules in excess of 40 kDa and predominately by bi- or tri-junctional paracellular processes for smaller molecules such as insulin (5.7 kDa) [73]. Local cytosolic biodegradation



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Figure 6 The absorption of inhaled insulin in non-diabetic subjects with asthma.



[Full Size]

Figure 7 Insulin is trapped and encapsulated in the self-assembled microspheres. Crystalline dry powde...

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appears to be the most important determinant of bioavailability. The immunotolerant nature of the lung is also of potential advantage for drug delivery [74].

Short-term attempts to deliver insulin as an inhaled aerosol originally began in the 1920s [60,75]. There was renewed interest in the 1970s [61,62,76], but significant progress was not achieved until the 1990s when the importance of aerosol dynamics was recognized. Many factors are known to influence the site of deposition of inhaled particles, including size or 'aerodynamic diameter'[a function of the particles' geometric diameter and mass density referred to as the mass median aerodynamic diameter (MMAD)], surface morphology, charge, solubility and hygroscopicity [77]. Deposition in the lung periphery (alveolar or deep lung) is optimal for aerosol particles with a MMAD of 1.5–2.5 μm [63] with larger particles (5–10 μm or > 10 μm) deposited predominantly in the tracheobronchial or oropharyngeal regions, respectively, with the smallest particles (< 1 μm) mostly exhaled. The distribution of emitted particle sizes [geometric standard deviation (GSD)] and the fine particle ('respirable') fraction (FPF) are therefore critical determinants of the efficiency of delivery devices, along with the mass output (particle mass and number per volume).

The deposition of inhaled particles in the lung occurs by inertial impaction (at bifurcations), sedimentation and diffusion [78]. Breathing pattern is therefore a major influence on intrapulmonary absorption [64,79]. The presence of airflow obstruction and interstitial lung diseases [78,80], smoking [81–83], exercise [84,85] and patients' ability to operate inhaler devices [86] are all key factors that can influence the efficiency of inhaled insulin delivery.

Current pulmonary drug delivery systems include a variety of pressurized metered dose inhalers (pMDI), dry powder inhalers (DPI), nebulizers and aqueous mist inhalers (AMI). The pMDI and DPI systems are associated with large degrees of inter- and intrasubject variability due to a reliance on patient technique [87]. A further potential disadvantage of DPIs is powder hygroscopicity [88]. AMIs offer the advantages of nebulizers without the limited portability and excessive consumption of the active medication.

Dispensing an insulin aerosol at the beginning of a slow, deep inspiration optimizes alveolar deposition [64,79]. Therefore, controlling the breathing pattern, along with ensuring the delivery of a precise dose (based on mass output and particle dispersion), are critical to achieve a desired and reproducible response.

Most of the recent clinical experience with inhaled insulin has been obtained using a dry powder formulation in the Nektar/Exubera device (Nektar Therapeutics Inc., San Carlos, CA, Aventis, Bridgewater, NJ, Pfizer, NY), or liquid aerosols formulations in the AERx® Insulin Diabetes Management System (Aradigm Corp., Hayward, CA, NovoNordisk A/S, Copenhagen, Denmark) and in the Aerodose® Inhaler (Aerogen Inc., Sunnyvale, CA, USA). Other delivery technologies include the use of modified insulin particles in the AIR™ Pulmonary Drug Delivery System (Advanced Inhalation Research Alkermes, Cambridge, MA, Eli Lilly, Indianapolis) and in the form of Technosphere™ insulin (Mannkind Biopharmaceuticals, NY, USA).

Nektar/Exubera delivery device

The Nektar/Exubera device (see Fig. 2) is a DPI that uses compressed air to disperse an insulin powder formulation into a spacer reservoir prior to inhalation. The dry powder formulation consists of insulin (approximately 60%) and excipients, principally mannitol as a stabilizer. The insulin powder is packaged into single-dose blisters containing 1 or 3 mg (approximately 28 and 84 units) of insulin. For delivery, an individual blister is placed into a slot on the device and is dispersed by the inhaler into an aerosol cloud which is captured in a holding chamber. The patient then inhales the aerosol containing particles (MMAD of approximately 3 μm) at the beginning of a slow, deep breath during which air is drawn into the chamber extruding the aerosol into the pulmonary tree. Breath holding at the end of inspiration does not appear to enhance the bioavailability of the inhaled insulin. The overall system efficiency (a product of aerosolization losses and bioavailability) has been estimated at 10% relative to s.c. insulin during a glucose clamp procedure in healthy, non-smoking subjects observed over a 10-h post-administration period [89]. The inhaled insulin had a faster onset of action than s.c. human soluble insulin with a time to peak effect resembling fast-acting insulin analogues and a duration of action between 5 and 10 h. When used at doses that comparably reduce postprandial hyperglycaemia in patients with Type 2 diabetes, the reproducibility of the response to the pulmonary insulin is similar to s.c. insulin [90].

In a 'proof-of-concept', open-label study, patients with Type 1 diabetes were given inhaled insulin immediately before meals with ultralente insulin at bedtime. The control group received two or three daily s.c. injections of human soluble insulin and NPH insulin at bedtime [91] (see Fig. 3). At the end of 3-months' treatment, HbA_{1c} levels in the inhaled and s.c. insulin groups were comparable (7.9% and 7.7%, respectively) and relatively unchanged from the baseline level at the start of treatment (8.5%). The estimated bioavailability of the inhaled insulin was 5–6% relative to s.c. insulin. The glucose profile during a test 'meal' (Sustacal) was similar in both treatment groups at the beginning and the end of the 3-month treatment period. The frequency and severity of hypoglycaemic episodes were also similar and no changes in body weight occurred. In this relatively short-term study, no significant changes in pulmonary function were observed with spirometry, diffusion capacity or resting oxygen saturation. Patient treatment satisfaction scores favoured inhaled insulin, with 82% of patients electing to continue treatment. Although the inhaled insulin therapy did not improve overall glycaemic control, the study demonstrated the feasibility of inhaled insulin for meal-related insulin requirements.

A further 6-month study was carried out in patients with Type 1 diabetes again comparing overall glycaemic control (HbA_{1c}) in patients receiving either inhaled insulin prior to meals and ultralente as basal insulin (prebed), or soluble human insulin preprandially with NPH insulin on a once or twice a day basis [92]. A similar proportion of patients receiving inhaled insulin achieved an HbA_{1c} of 8% and 7% compared with patients receiving s.c. insulin (64.2% vs. 60.4% and 23.3% vs. 22.0%, respectively). The overall rate of hypoglycaemia, measured as events/subject-month, was similar between the treatment groups. The inhaled insulin group developed increased insulin antibody serum binding. Coughing, although more frequent in the inhaled group, decreased over time. Whereas there was no change in forced expiratory volume (FEV_{1.0}) observed, a non-significant fall in diffusing capacity (DL_{co}) occurred in the inhaled insulin group. Further investigations are needed to explain this observation and assess its clinical significance.

In a study of similar design and duration, although the glycaemic control (HbA_{1c}) remained essentially the same, the 2-h postprandial glucose and interestingly the reduction in fasting plasma glucose concentration was lower in the inhaled insulin patient group [93]. The overall risk of hypoglycaemia was slightly less with inhaled insulin, with no difference in the frequency of severe events, but with improved treatment satisfaction. There was, however, increased insulin-binding antibodies with inhaled insulin which may or may not have contributed in the lower fasting glucose described. The forced expiratory volume (FEV_{1.0}) remained unchanged but there was a slight fall in diffusing capacity (DL_{co}).

In a 3-month controlled study involving patients with Type 2 diabetes who required insulin treatment, subjects were randomly assigned to inhaled insulin before each meal and ultralente insulin at bedtime or patients remained on their pre-existing insulin regimen of two to three daily s.c. injections [94,95]. A test meal (Sustacal) carried out preconversion (baseline) and after 12 weeks showed no difference in postprandial glycaemia between the two treatment groups. A similar improvement in HbA_{1c} (approximately 0.7%) was observed at the end of the study period in both groups and there was no difference in the frequency of hypoglycaemic events during the study. Pulmonary function tests remained essentially unchanged in response to inhaled insulin. In a more recent study of patients with Type 2 diabetes failing to achieve adequate glycaemic control on combination oral therapy, the introduction of inhaled insulin either alone or in combination with existing oral agents over a 3-month treatment period improved glycaemic control (HbA_{1c}) [96]. The introduction of the inhaled insulin, however, increased the overall rate of hypoglycaemia, produced a slight increase in body weight with the occurrence of insulin-binding antibodies more frequent than in those patients who remained on combined oral treatment. There were no treatment differences in either the forced expiratory volume (FEV_{1.0}) or diffusing capacity (DL_{co}). Those patients receiving insulin via the pulmonary route had greatest overall treatment satisfaction. Comparing twice a day mixtures of soluble and NPH insulin with inhaled insulin prior to meals and ultralente insulin at bedtime for an extended period of 6 months in patients with Type 2 diabetes did not demonstrate any difference in overall glycaemic control [97]. There was neither any real difference in the rate of any or severe hypoglycaemic events between the two treatment groups. Patients on inhaled insulin were again seen to develop increased insulin antibody binding but with no obvious clinical consequences. Whereas there was no impact on the forced expiratory volume (FEV_{1.0}), a reduction in the lung's diffusing capacity (DL_{co}) was observed with the inhaled insulin. In this patient group treatment satisfaction was clearly enhanced by inhaled insulin. The clinical impression from surveillance of Type 1 and Type 2 patients continued on inhaled insulin suggests that glycaemic control and lung function tests (spirometry) remain reasonably stable during the second year of treatment [98].

These studies, designed predominantly for regulatory purposes, demonstrate the feasibility of using inhaled insulin to cover mealtime insulin requirements in patients with Type 1 and Type 2 diabetes. However, information from longer-term controlled clinical trials will be essential to further ensure the continued efficacy and clarify the mainly local safety issues relating to the dry powder formulation of inhaled insulin.

AER_x® insulin diabetes management system (IDMS)

The AER_x IDMS system (see Fig. 4) is an aqueous mist inhaler in which single-use insulin strips are combined with a hand-held, breath-activated, microprocessor-controlled device. The device delivers a low-velocity, fine particle aerosol spray early during inhalation, but only when appropriate breathing conditions are satisfied. Scintigraphic studies have established the ability of the device to minimize patient-related variability in inhaled lung dose [79,99,100]. Breath holding has been shown not to be necessary to enhance the absorption of insulin [101].

A comparison of an early prototype of the AER_x delivery system with a conventional pMDI, where both employed microprocessor-controlled actuation, revealed a more homogeneous distribution pattern with the AER_x delivery system [99]. In contrast to conventional nebulizers and inhalers, where the estimated delivery of drugs to the lung is 10–20% of the loaded dose, the AER_x system achieved deposition of 50% of the extruded dose [99,102]. The uniform deposition throughout the deep lung was attributed to the emitted particles having a MMAD of 2 µm.

Studies in healthy subjects show that insulin delivered with the AER_x device is more rapidly absorbed and has a shorter time to maximum plasma concentration compared with s.c. soluble insulin injection (7–20 min vs. 100–120 min, respectively) [79]. The rapid bioavailability of insulin when delivered by the AER_x device resembles that of rapid-acting insulin analogues administered subcutaneously [103]. In a glucose clamp study carried out over a 10-h period, a dose–response relationship was seen for both bioavailability and hypoglycaemic effect in normal subjects with the inhaled insulin [104].

Other studies have demonstrated a much faster and greater degree of absorption in habitual smokers resulting in a three-fold higher peak serum insulin concentration [105] (see Fig. 5). Intrasubject variability in insulin absorption associated with the AER_x system appears slightly lower (approximately 20%) in both smokers and non-smokers compared with s.c. soluble insulin [106]. Whereas asthmatic patients absorb less insulin compared with non-asthmatics [107], inhalation of a relatively high dose of aerosolized insulin (equivalent to approximately 18 units s.c.) did not exacerbate the baseline airway hyper-reactivity state of asthmatic patients (see Fig. 6). During mild upper respiratory tract infection in non-diabetic subjects, a shorter time to peak insulin concentration with the inhaled insulin has been observed, although the difference was not reflected in the glucose response [108]. There was no difference in the overall bioavailability of inhaled insulin during and after resolution of the infection. The pharmacokinetics of inhaled insulin delivered by the AER_x delivery device is similar in young and elderly patients with Type 2 diabetes, although the hypoglycaemic effect was somewhat less in the elderly [109].

In patients with Type 1 diabetes, a near linear dose–response relationship was seen for both pharmacokinetic (insulin profile) and pharmacodynamic (glucose infusion rate) parameters during a 10-h glucose clamp study carried out following inhalation of insulin (0.3–1.8 U/kg) using the AER_x device [110]. For the inhaled insulin, the time to maximum plasma insulin concentration was approximately half that of s.c. soluble insulin. The overall efficiency of the AER_x pulmonary delivery system estimated over an initial 6-h period was 13%, based on the loaded dose. The intrasubject variability in the pharmacokinetic and pharmacodynamic parameters measured was essentially the same as for s.c. soluble insulin administration [111–113].

In a 'proof of concept' trial, patients (non-smokers) with Type 2 diabetes received inhaled insulin delivered by the AER_x device or s.c. insulin at meal times with NPH insulin at bedtime for a period of 3 months [114]. During the study there was no difference found between the two treatment groups in overall glycaemic control (HbA_{1c}), although the fasting glucose was lower with the inhaled insulin. Based on the bioavailability of inhaled insulin relative to s.c. soluble insulin, bioeffectiveness was estimated at 16%. Although the total number of hypoglycaemic events was lower with inhaled insulin, the difference was not significant. No changes in lung function tests or chest X-rays were observed in either group. The study did not report

data on the occurrence of insulin-binding antibodies or treatment satisfaction.

Despite the technical differences between the Inhale/Exubera and AERx delivery devices, their mean bioeffectiveness, estimated in glucose clamp studies, is similar (10% and 13%, respectively) [115]. In meal challenge type studies, the respective mean bioavailability is 11% and 16% with mean bioeffectiveness of 13% and 17%, respectively.

Advantages of the dry powder insulin formulation may include better stability at room temperature, higher possible insulin content per puff and reduced potential for microbial growth. The use of a liquid insulin formulation may also avoid problems related to the production of dry insulin powder formulations and the influence of external humidity on the dispersion of the preparation. The extrusion mechanism of the AERx iDMS device can uniquely control the amount delivered, allowing smaller dose adjustments. The potential of the different pulmonary insulin formulations to induce the production of insulin antibodies and the clinical implications of such antibodies on the metabolic control and the immune system remain unknown at present [116].

Aerodose™ inhaler

The Aerodose Inhaler is a breath-activated delivery device developed by Aerogen Inc. The device uses a liquid insulin formulation (Humalin I™ 500 units) to produce an aerosol with a mean dispersed particle size of 3.3 µm and a fine-particle (1–6 µm) ('respirable') fraction of 87%[117]. In non-diabetic subjects, the time to peak plasma insulin concentration was shorter with the inhaler device compared with s.c. soluble insulin (50 min compared with 85 min, respectively). The relative bioavailability and biopotency of the inhaled insulin, estimated during a glucose clamp study, were 9.3% and 10.3%, respectively. The inhaled insulin preparation was well tolerated and no acute changes in pulmonary function tests were seen. A study in Type 2 diabetes patients confirmed the shorter time to peak insulin concentration and the earlier metabolic effect on inhaled insulin compared with subcutaneous administration [118]. Reproducibility of the inhaled and s.c. soluble insulin were similar at about 20% for both absorption and action.

Modification of inhaled particles

Advanced Inhalation Research (Alkermes/Eli Lilly)

Large, porous, insulin-containing particles (10–20 µm) of low-mass density (< 0.03 g/cm³) have been developed by Advanced Inhalation Research (AIR) using a biodegradable polymer matrix composed of phospholipids [119–121]. The formulation is easily aerosolized using a simple, breath-activated DPI. Although the particles are physically large, their MMAD is within the aerodynamic window of 1–3 µm [120]. The large porous particles appear to have a reduced tendency to aggregate, facilitating dispersion, and may be less susceptible to phagocytosis [120]. Potentially sustained release insulin formulations can also be incorporated into the polymer matrix [120–122]. Results from human studies are awaited.

Technosphere™ insulin

Mannkind Pharmaceuticals (Elmsford, NY, USA) have developed a drug delivery system known as Technosphere™ which captures insulin or other polypeptides utilizing a diketopiperazine derivative [123]. The formulation self-assembles into an ordered lattice array at low pH which dissolves at the neutral pH of the alveolar surface rapidly releasing the insulin (see Fig. 7). The formulation is designed for use with the Medtone® DPI, a capsule-based high-impedance inhaler using a passive powder deagglomeration mechanism.

Evaluation of the Technosphere™/insulin formulation in healthy and diabetic subjects shows that its performance is intermediate between that of i.v. and s.c. soluble insulin with respect to time to peak insulin concentration (13 min), and time to maximum activity (39 min) [124]. Values for bioavailability and biopotency relative to s.c. insulin of 26% and relative biopotency of 19% have been recorded [124].

Clinical perspective on inhaled insulin

The onset of action of inhaled insulin is comparable to the rapid-acting insulin analogues but with a slightly more prolonged effect, theoretically making it suitable for meal-related insulin supplementation. The frequency and severity of hypoglycaemic events appear equivalent to those of s.c. human soluble insulin in patients with Type 1 and Type 2 diabetes [90,92,94,125].

Ease of use and patient acceptance may greatly influence the choice of delivery system for inhaled insulin. This is especially important when considering the requirements of different patient groups such as children, adolescents and the elderly. For persons with significant airway obstruction and interstitial lung disease, intrapulmonary delivery of insulin is less appropriate given the lack of information about the influence of lung pathology on inhaled insulin absorption. In this respect, it is of interest that up to two-thirds of patients with long-standing diabetes are reported to have some abnormality of lung function [126,127]. Special caution also needs to be exercised when inhaled insulin is used in patients who are habitual smokers, due to the very rapid absorption observed, and smoking cessation will require adjustment to the insulin dose also [83,105,128–130]. Exercise may also be expected to enhance the pulmonary absorption of inhaled insulin.

Current clinical experience with inhaled insulin is limited to 3, 6 or 12-month treatment periods with data from longer exposure studies eagerly awaited. To date, there is little evidence of local adverse reactions other than a throat clearing-type cough associated with the act of inhalation in approximately 10% of patients [90]. Lung function tests seem to indicate in most studies little or no change in FEV_{1.0}, there appears to be a consistent fall in DL_{CO} in both Type 1 [92,93] and Type 2 diabetes patients [96,97]. Careful re-appraisal of the data will be necessary before cause and effect can be established, accepting the need for standardization and quality control in assessing lung function. Data from longer-term controlled studies supported by limited but more specialized studies, such as lung (alveolar) lavage, are needed to establish the safety of the different formulations of inhaled insulin. Other concerns expressed include the possibility of inducing pulmonary hypotension and pulmonary oedema due to supraphysiological acute insulin concentrations achieved in the pulmonary vascular bed, especially in patients with cardiac dysfunction [131] or patients with lung disease (pneumonia, asthma, and chronic obstructive pulmonary disease) [132]. Insulin's proinflammatory effects may also potentially unmask airway obstruction such as asthma, again emphasizing the need for detailed acute and long-term surveillance [131].

The immunogenicity of inhaled insulin is another important consideration, especially as relatively high insulin-binding antibody concentrations are in evidence in patients with Type 1 and Type 2 diabetes treated with a dry powder insulin formulation (Inhale; Pfizer, Aventis). The potential role of excipients such as mannitol in this process needs to be elucidated and the impact of circulating insulin antibodies on the pharmacokinetics of the absorbed insulin requires clarification. The observation of a fall in fasting plasma glucose concentration with inhaled insulin may well relate to the presence of insulin-binding antibodies functioning as a repository and slowly releasing insulin. Studies are needed to examine this possibility.

Patients with diabetes given insulin by inhalation (Inhale-Exubera) report improved satisfaction [91–93,96,97,131,133]. However, the introduction of intrapulmonary insulin into clinical practice will depend upon demonstrating a satisfactory long-term efficacy, acceptability, and more especially safety profile. Cost will also feature predominantly in relationship to this less intrusive route of insulin administration, especially in view of the relatively low bioavailability with the current delivery devices and insulin formulations [134].

Having satisfied the necessary regulatory requirements for the introduction of inhaled insulin, adequate patient education will be mandatory. Currently, as certain delivery devices remain fairly bulky, significant social stigma may result from administering insulin by the pulmonary route. However, translating the differences between various delivery devices into clinical benefits will become evident with more extensive clinical use and this experience will also guide the design of future delivery devices. Insulin formulation changes are also to be expected, including the use of bioacceptable absorption enhancers, protease inhibitors, micronano spheres and/or mucoadhesive nanoparticulate systems, amongst others. Assessment of the long-term efficacy and safety of intrapulmonary insulin itself, the use of excipients, absorption enhancers, delivery devices, cost and patient preference will all remain essential elements in the continuing debate relating to the place of inhaled insulin.

Conclusions

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Until relatively recently, the search for alternative routes to s.c. insulin administration has been relatively unsuccessful. Although the efficiency of absorption across epithelial surfaces of the mouth, gastrointestinal tract, skin and nose has increased somewhat using a wide variety of absorption-enhancing techniques, bioavailability remains too low and erratic to be of any real clinical value. After being dormant for almost half a century, interest in the intrapulmonary route has been regenerated with the advent of new delivery devices and an increasing choice of dry powder or liquid aerosol formulations. Improving the delivery of insulin to the 'deep lung' has benefited from a greater understanding of the relevance of aerosol particle size, inspiratory flow rate and inhaled volume. However, methods of estimating bioavailability need to be standardized to allow meaningful comparisons between delivery devices. Precision of dosing, dose adjustments and reproducibility will remain key issues in exploring the viability of this approach.

Clinical studies to date suggest a possible role for inhaled insulin in the control of postprandial glucose excursions in patients with Type 1 or Type 2 diabetes. An important benefit may be derived by those with Type 2 diabetes in whom insulin therapy would otherwise be delayed. However, the need for supplementary s.c. basal insulin in patients with Type 1 and possibly Type 2 diabetes means that complete avoidance of s.c. injections cannot be achieved at present. The availability of intrapulmonary, long-acting insulin is much further down the road in development. Only following confirmation of its long-term safety will inhaled insulin possibly become the first widespread non-subcutaneous route of administration. The cost of this less intrusive and perceived more convenient route of insulin administration will also determine its availability to the ever-increasing insulin-requiring diabetic population.

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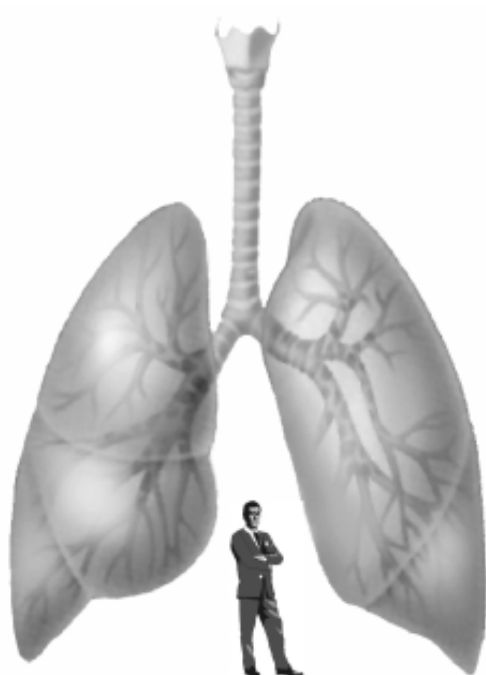
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Figure 1 Rationale for the pulmonary route for insulin delivery.

Pulmonary deposition and absorption



~140 m² in adult humans
×1000-fold greater than nasal bed

Bronchioles, alveolar ducts
and alveoli (300 million, > 95%
of total absorptive surface area)

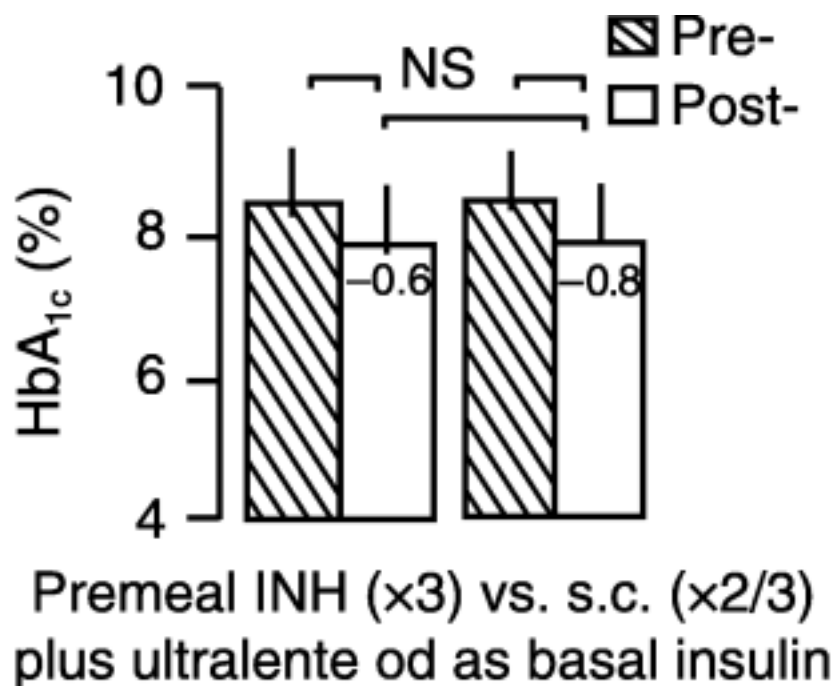
Byron, 1986 (76)

- Large surface area
 - Highly permeable membrane
 - Rich blood perfusion
 - Lack of mucociliary clearance
-
- Painless
 - Natural
 - Immunotolerant

Figure 2 The Nektar Pulmonary Inhaler and Exubera™; Nektar Therapeutics Inc, Pfizer Inc and Aventis Pharma. The insulin is a fine dry powder formulation [mix of insulin (60%), mannitol, glycine, and sodium citrate]. Single-dose blisters (1 and 3 mg, equivalent to 3 and 9 units) are utilized. The air-assisted mechanism disperses the powder into a respirable cloud captured in a holding chamber 'spacer'.



Figure 3 Inhaled insulin: proof of concept study in patients with Type 1 diabetes ($n = 72$) over a 12-week study period to compare premeal inhaled insulin (three times daily) vs. subcutaneous insulin twice or three times a day, with ultralente insulin as the basal supplement [91].



'Hypo' episodes/pt/month

	inhaled	s.c.
mild	5.5	5.3 ns
severe	0.08	0.10 ns

Body weight	no change
Pulmonary function	no change
Bioavailability	< 10%

- Treatment satisfaction: INH 35% s.c. 11% ($p = 0.01$)
- 82% elected to continue inhaled insulin

Figure 4 AERx® insulin Diabetes Management System (AERx® iDMS); Aradigm Corp and Novo Nordisk A/S. Insulin in liquid formulation is contained in single-use strips equivalent to 1 unit subcutaneous insulin. The delivery system is a breath-activated microprocessor-controlled battery-operated device. The data (dose, date, time and breathing technique) are captured electronically, allowing tracking of compliance.

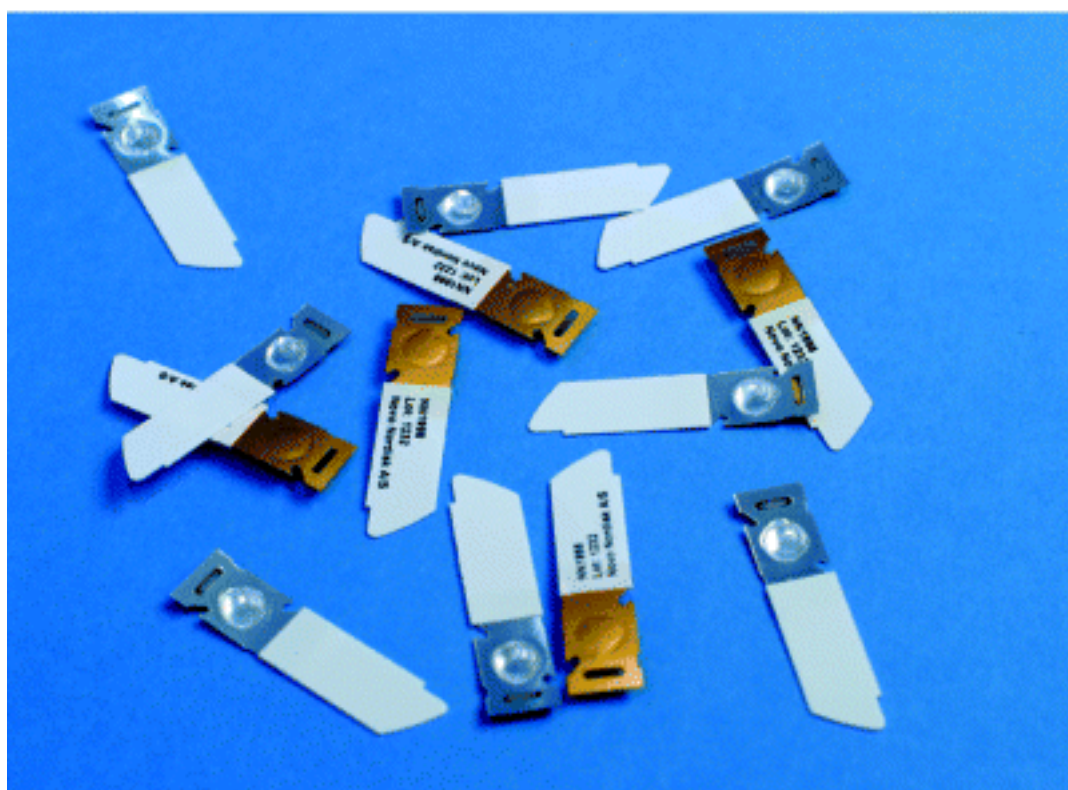


Figure 5 The effect of smoking on the absorption of inhaled insulin in non-diabetic subjects. Smokers experience an earlier and three-fold increase in the peak insulin concentration compared with non-smokers [105].

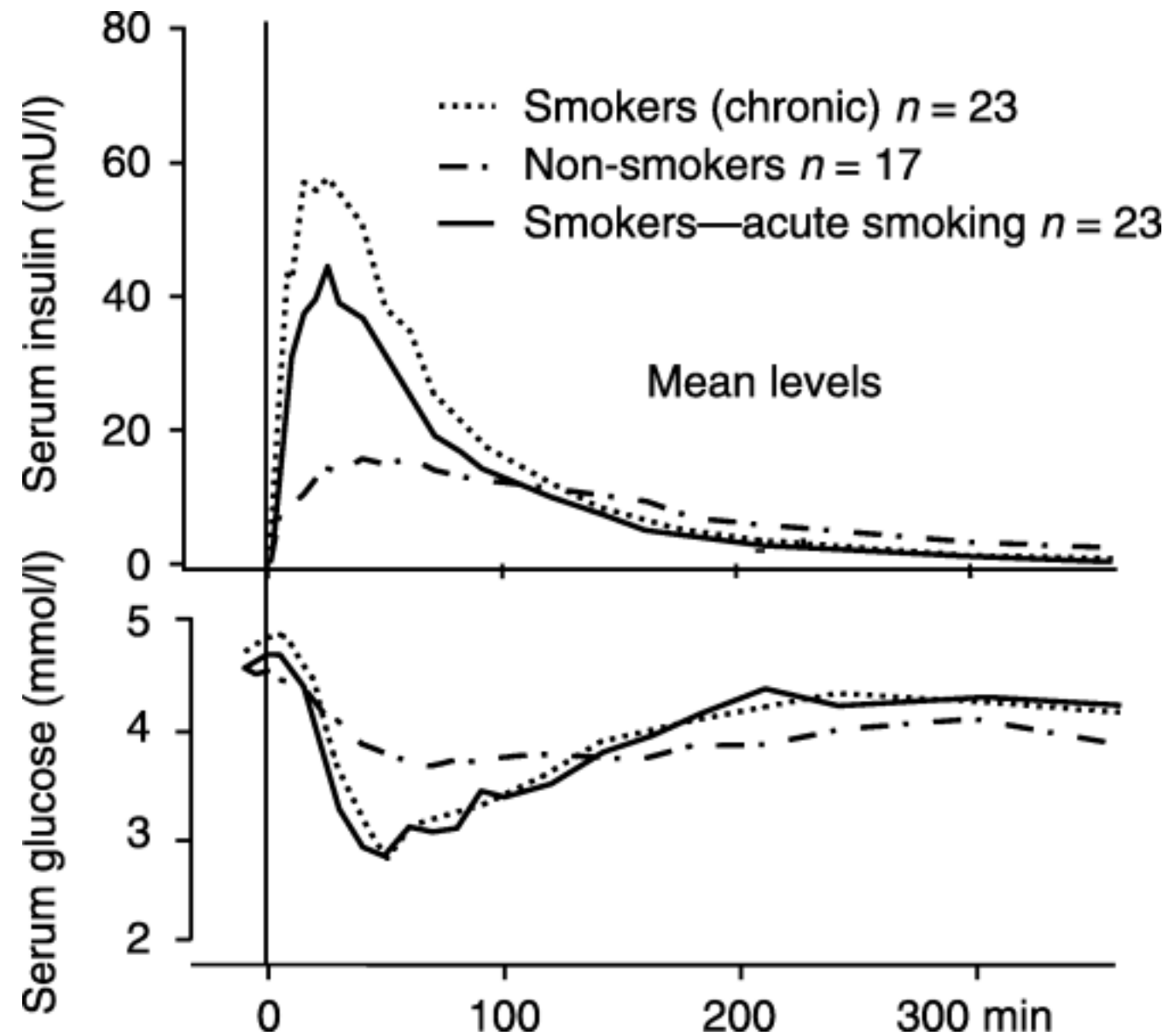


Figure 6 The absorption of inhaled insulin in non-diabetic subjects with asthma.

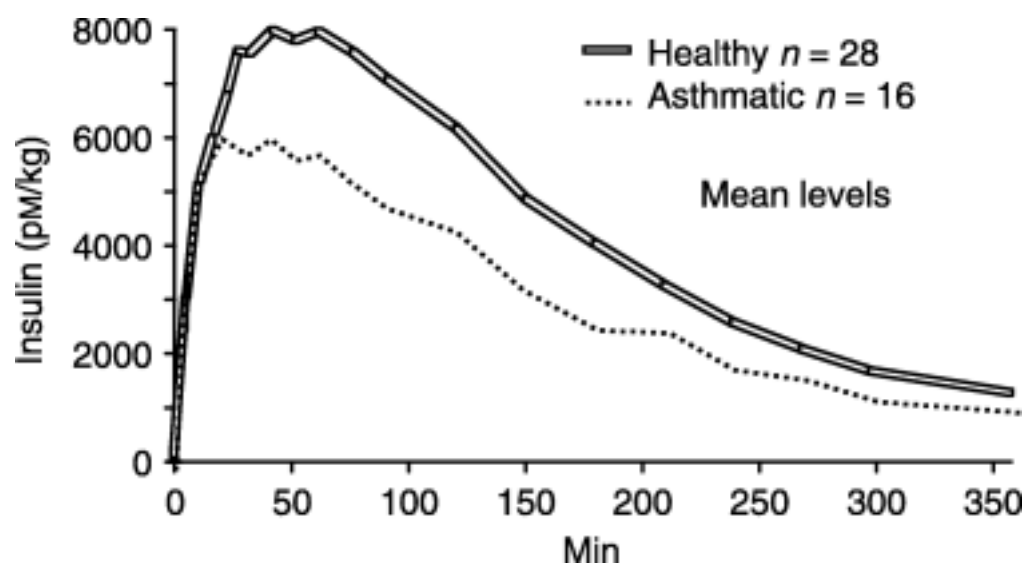
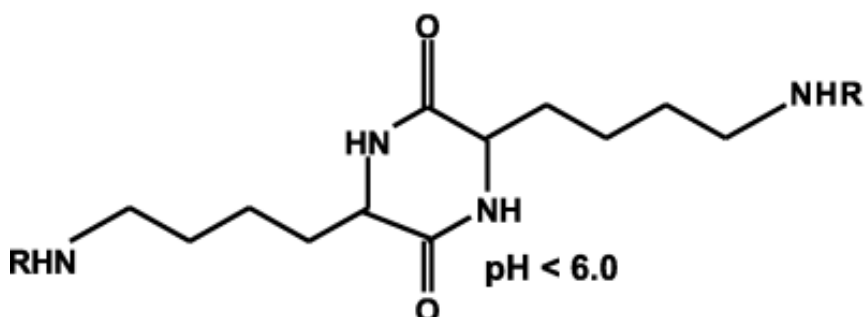
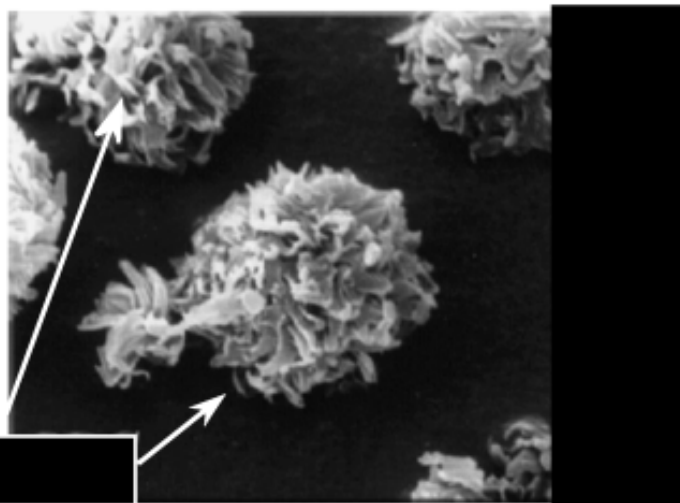


Figure 7 Insulin is trapped and encapsulated in the self-assembled microspheres. Crystalline dry powder insulin in gelatine capsules (50 IU of insulin). Mass median aerodynamic diameter 3.3 μm ; FPF ($> 0.4 < 5.8 \mu\text{m}$) 65%. Passive powder deagglomeration. Delivery device: Medtone, a high impedance inhaler. Dosage forms, 6, 12 and 24 IU equivalent to 2, 4 and 8 IU of s.c. soluble insulin.

Mannkind Pharmaceuticals **Technosphere**TM



3,6-bis(N-fumaryl-N-(n-butyl) amino-2,5-di-ketopiperazine (FDKP)



*Self-Assembling FumarylTechnosphere*TM