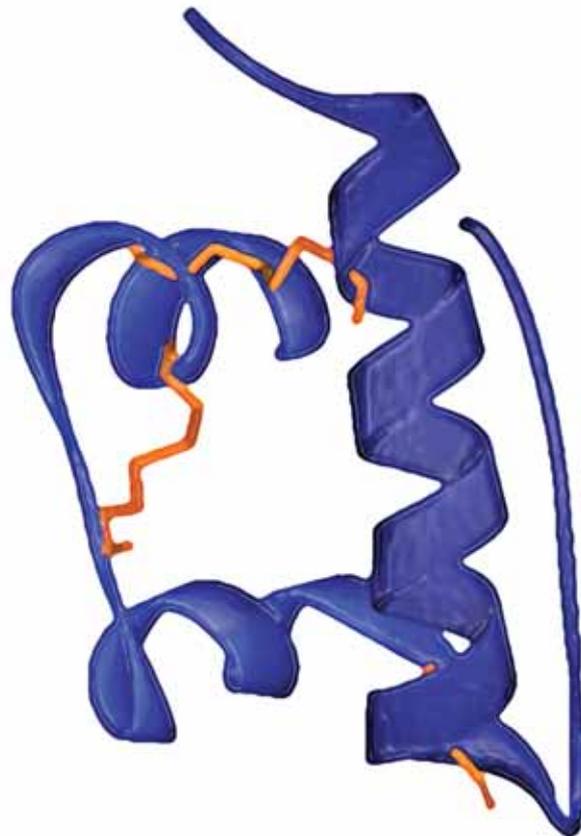


DRUG DELIVERY IN DIABETES

MAKING EFFECTIVE TREATMENT TOLERABLE



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“Drug delivery in diabetes: making effective treatment tolerable”

This edition is one in a series of sponsored themed publications from ONdrugDelivery Ltd. Each issue will focus on a specific topic within the field of drug delivery, and contain up to eight articles contributed by industry experts.

Full contact information appears alongside each article. Contributing companies would be delighted to hear from interested readers directly. ONdrugDelivery would also be very pleased to pass on to authors, or answer as appropriate, any queries you might have in relation to this publication or others in the series.

Forthcoming editions cover: needle-free injection; prefilled syringes; nasal drug delivery; oral modified release; solubilising technologies; delivering injectables; novel biomaterials for drug delivery; safer injections and transdermal delivery, among other topics. To find out more about receiving or participating with any of these issues, please contact ONdrugDelivery Ltd.

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“Drug delivery in diabetes: making effective treatment tolerable”

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Front cover design: based on an image of the tertiary structure of insulin, kindly supplied by Novo Nordisk

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INTRODUCTION



There is a difference between this publication and the others (previous and planned) in ONdrugDelivery's series. This issue's topic of focus, diabetes, is a therapeutic indication, whereas other editions cover a route of delivery or technology category.

The reason this topic fits is that the diabetes market, and particularly insulin development is, by its nature, a hotbed for new ideas in drug delivery. It is difficult to think of one other therapeutic area, let alone another single disease, where so many factors align to drive the development of novel delivery systems.

Let us take the active molecule as a starting point. For the treatment of diabetes, nothing better than insulin has been (or is even likely to be) discovered. With the best compound already available, enhancing its delivery becomes significant among the remaining opportunities to gain a therapeutic and commercial advantage.

Furthermore, insulin is difficult to deliver. When it was discovered in 1922 by Banting and Best, the initial expectation was that it would be readily available as an orally active form, like thyroid extract had been. It quickly became apparent that this was not to be, and it was then that parenteral delivery was adopted. At the same time, the quest began to develop technologies that would enable non-invasive forms.

Indeed, the first effective pulmonary formulation of insulin was described in a paper published in 1925. Eighty-one years on, the first pulmonary formulation has only just been approved (more on Exubera below), and oral formulations – such as that under development by Emisphere Technologies – have a fair distance to cover before they reach the stage of regulatory submission. The magnitude of the technical challenges at the heart of insulin delivery is revealed by the length of time it has taken (or is taking) to overcome them. The effect is to maintain a high entry level when it comes to new approaches for insulin delivery.

A technology push is important, but the market pull, demanding improved insulin delivery systems, is more powerful. Here are just a few of the factors at play:

- Insulin therapy requires regular self-administration over many years.

- People with diabetes therefore become highly involved in their treatment.
- Details of the specific roles insulin plays in the treatment of Type 1 and Type 2 diabetes can be found in the articles that follow, but to summarise, in both types there is strong evidence that tight control over dose accuracy and the timing of administration is key.
- Furthermore, there is evidence to suggest a relationship between therapeutic outcome and the degree to which the pharmacokinetic profile of insulin taken after food replicates that of endogenous insulin release in healthy individuals
- In Type 2 diabetes, while insulin therapy is not essential for good quality of life in the early stages, earlier adoption of insulin has been linked with improved outcomes. The principal reason that diabetics are resistant to beginning insulin treatment is the prospect of a lifetime of injections.
- There is a social stigma attached to self injecting, making it potentially difficult to administer insulin in front of others, perhaps even close friends

The definition I use for drug delivery is: *the science of delivering pharmaceutically active ingredients to the required site in the body, in the right quantities, at the correct time and in the most effective and convenient manner.*

The above examination of a selection of the characteristics of diabetes, and requirements for its successful treatment, although cursory, highlights the hand-in-glove nature of the relationship between insulin market and drug delivery industry.

... THE OTHER SIDE OF THE SAME COIN

The recent approval of Nektar Therapeutics' and Pfizer's inhalable insulin product, Exubera, has undoubtedly marked the end of a rather uncertain chapter in the relationship between non-invasive drug delivery and diabetes.

After an extended period of intense scrutiny, particularly in the area of safety, the regulatory authorities in the US and EU have given the first inhalable insulin product the all clear. Certainly it is extremely positive news for many, including the companies directly involved, other companies developing inhalable insulin products, the wider drug delivery industry, and, of course, diabetics.

However, we are at a watershed. During the years leading up to Exubera's approval thoughts were focused on the question of whether or not it would be approved. With that hurdle now successfully overcome, attention turns to how the end game will play out – market success.

The market awaits and, commercially speaking, this is of course the only true test of a product's success. Where could it go from here for Exubera? Moreover, what is in store for a) other non-invasive insulin delivery technologies that will be entering the market in the months and years ahead and b) the "invasive" insulin delivery methods that also remain available?

The contributions that appear on the following pages come from four companies involved at the leading edge of insulin delivery. Notice how completely different their products are from one another, especially considering they are all delivering the same compound for the same indication. MannKind Corporation is developing an inhalable product, Genex Biotechnology has a buccal formulation, Altea Therapeutics develops an insulin patch and Ypsomed produces self-injection solutions to enhance the safety and comfort of needle-based systems.

While each company naturally aims to succeed in the market by taking the largest possible market share, none of them would claim that their expectation is to take 100%, the entire global diabetes market.

This is because the diabetic population as well as being huge and growing, is diverse in the extreme – from age, level of health, cultural tastes, social background and degree of medical sophistication, to geographic location, economic status and the type of healthcare system patients' countries adopt. This means that for it to be served optimally, the diabetes market must be offered the widest possible choice.

The patient-centred characteristics outlined above have an important bearing on the way we must assess the potential commercial success of Exubera and other non-invasive and needle-based insulin products that will inhabit the diabetes market in the new era that we are about to enter.

Guy Furness
Managing Director, ONdrugDelivery Ltd

ALTEA THERAPEUTICS TRANSDERMAL PASSPORT™ SYSTEM: FREEDOM FROM INSULIN INJECTIONS FOR SUPERIOR DIABETES MANAGEMENT

While starting insulin therapy is often the best way for people with diabetes to ensure that they stay healthy, many factors including fear of needles, make many resistant to starting injected insulin. Factors associated with injecting insulin also lead to poor compliance. In this article, Yogi Patel, PharmD, Manager, Business Development, Altea Therapeutics, examines some of these problems and describes how transdermal insulin can overcome them.

It is a challenge for people with diabetes to keep track of their blood sugar levels and to take the right amount of insulin throughout the day. For a child these tasks can be extremely difficult or simply impossible without help. That is the case for eleven-year-old Taja. She has diabetes, which for most of her life has been under control – but not lately. “She woke up in the middle of the night and her glucose levels were a little

Taja was admitted to the hospital. “I talked to your parents yesterday,” says Dr Goo, “and they said that last weekend you had a sleep-over at your friend’s house and you may have forgotten to take your insulin. Is that what happened?” Taja nods yes.

Children like Taja who suffer from diabetes have to check their blood sugar and give themselves shots of insulin 3-6 times a day.

Furthermore, they have to calculate the correct dose of both basal and meal-time insulin for

PHARMACEUTICAL COMPANIES HAVE BECOME MORE INNOVATIVE IN ORDER TO RESPOND BETTER TO THE NEEDS OF PEOPLE WITH DIABETES

low – at about 67 mg/dL. When she got up the next morning, her blood glucose level was over 400 mg/dL,” her mother recalls.

Normal blood sugar is around 90 to 120 mg/dL, but that was not her only problem. “She was in what we call diabetic keto-acidosis,” explains Dr David Goo, Emergency Paediatrics, Children’s Healthcare of Atlanta. “That means that the acid in her blood was building up because she wasn’t getting enough insulin to convert sugar into nutrition, making her weak and nauseous.” If not caught and treated, unchecked keto-acidosis can be life threatening. But for Taja, what was the cause? “It’s kind of a puzzle,” says Dr Goo. “It could be triggered by an infection, emotional or physical stress, shifting hormone levels, or even by missing a dose of her medication.” To find out,

each injection. “For a young child that’s a lot of work, a lot of pain from the injections and finger-stick blood sampling and a lot of trouble. If they’re feeling good, playing and having fun, it is easy for a child to forget to do something they don’t really want to do to start with,” says Dr Goo. (Source: Diabetes Maintenance (ER). Newsfeed November 2, 2005. www.connectingwithkids.com/tipsheet/2005/253_nov2/diab.html (December 14, 2005)).

As reported by the World Health Organization (WHO), Taja was just one of the reported 200 million people around the world suffering from diabetes in 2005.¹ Diabetes is a serious condition and its rapidly increasing prevalence on the global scale is a significant cause for concern. By 2030, the WHO estimates that the number of people with diabetes will



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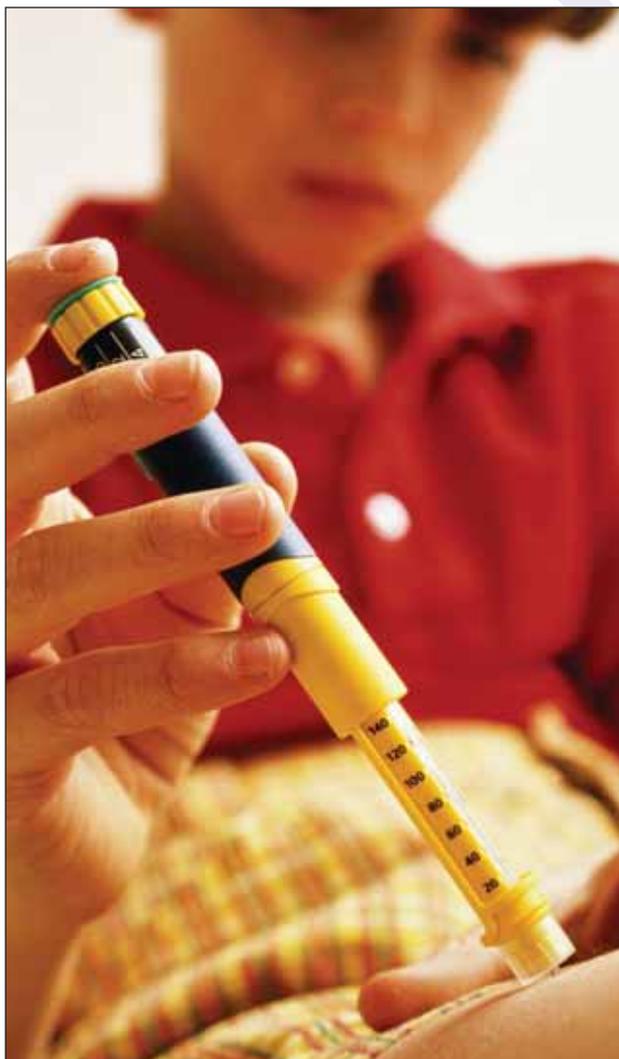


Figure 1: The new transdermal insulin patch, PassPort™ System, replaces injections thereby enhancing compliance in patients with diabetes

almost double to 366 million.²

About 40% of people with diabetes rely on insulin to maintain control of their blood glucose levels.³ Patients with Type 1 diabetes are completely dependent on insulin injections. For patients with Type 2 diabetes, which comprises 90% of the world's diagnosed cases of diabetes, about one-third of them rely on insulin as part of their regimen for controlling their blood glucose levels.

Patients with Type 1 diabetes require both basal and bolus (or mealtime) insulin to control their glucose levels effectively. Basal insulin provides the body with a steady, low level of insulin throughout the day and night. Bolus insulin is the faster-acting insulin that provides the boost of insulin needed to stop the rise in blood glucose level that occurs after meals. Bolus insulin is usually given as a before-meal injection.

For patients with Type 2 diabetes using insulin, the majority of them use only the long-acting basal insulin injections taken once or twice daily, frequently in combination with other medications. Most physicians agree that patients with

Type 2 diabetes are resistant to starting injected insulin therapy for a variety of reasons, especially the fear of needles. Medical facts, however, support that the sooner a person with Type 2 diabetes begins insulin therapy, the longer they will stay healthy and free of the long-term complications of the disease.

There are more than 20 types of insulin products available, each with a different time of onset and duration of action.⁴ The worldwide insulin market had sales of over \$5 billion in 2004 and yearly growth of almost 10%.¹ However, insulin is a fragile protein drug that requires refrigeration for storage, possesses a relatively short shelf life and can be potentially life threatening in case of an overdose. This requires patients with diabetes to inject themselves with carefully calculated insulin doses often several times per day (see figure 1), a procedure that is difficult, painful and impractical in many situations. These factors often lead to noncompliance in patients.

Lack of adherence to proper therapy in patients with diabetes can lead to life threatening conditions such as keto-acidosis (such as Taja's case) and various complications including blindness, kidney failure, heart disease, limb amputations and many more.³ These complications lead to a poor prognosis and significantly increase the cost of healthcare and the loss of productivity associated with diabetes.

Along with lack of compliance due to pain, needles and syringes present the risk for accidental injury. These injuries can occur at any time when people improperly use or dispose of needles. Infected needles can become concealed in linen or garbage and injure other workers or caregivers who encounter them. Most reported needle-stick injuries involve nursing staff, but laboratory staff, physicians, housekeepers, and other healthcare workers are also injured.

These injuries expose workers to bloodborne pathogens that may cause an infection. In the World Health Report 2002, the WHO reported that of the 35 million healthcare workers, 2 million experience percutaneous exposure to infectious diseases each year.⁵

The most important of these infectious, which are potentially life threatening, include HIV, Hepatitis B virus (HBV) and Hepatitis C virus (HCV).⁶

As a result of challenges associated with using injections for insulin, pharmaceutical companies have become more innovative in order to respond better to the needs of people with diabetes. In particular, companies are developing non-injection based insulin delivery alternatives for alleviating any pain and complication associated with injections and enhancing compliance in patients with diabetes – such as Taja.

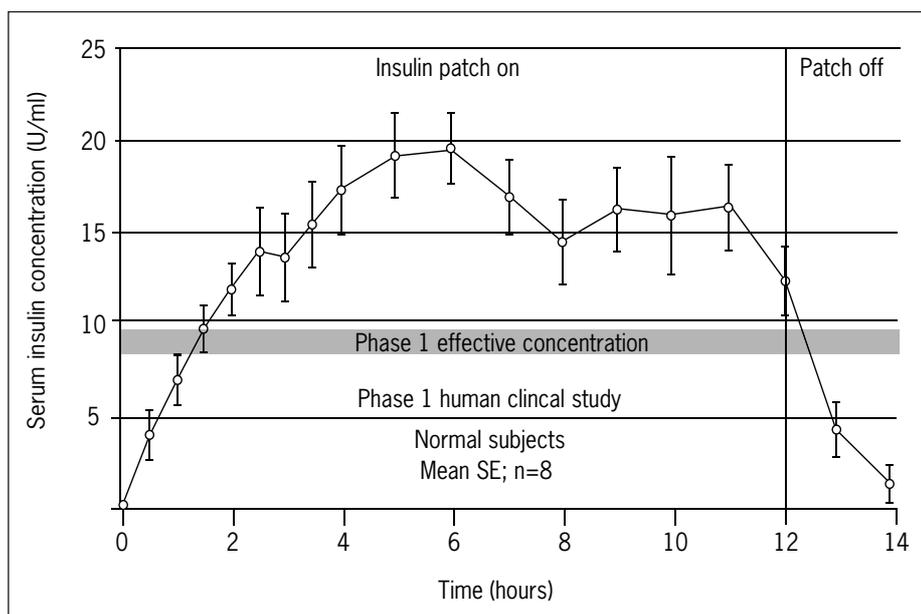


Figure 2: Results of Phase I insulin trials in humans using the PassPort™ System show sustained delivery of therapeutic levels of insulin over a 12-hour application period



Figure 3: The PassPort™ System is comprised of an applicator (on the left) and a reservoir patch; the latter is placed on the skin and provides for painless delivery of insulin

Altea Therapeutics has developed an innovative technology that provides convenient and painless delivery of basal insulin for people with diabetes.

A NEW TRANSDERMAL PATCH

The Altea Therapeutics PassPort™ System was the first product in development shown in US FDA clinical trials to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the skin. The PassPort™ System enables fast, controlled drug delivery without the pain of an injection or the possible complications associated with inhaled medications. It also avoids the first-pass gastro-intestinal and liver metabolism that occurs often after oral administration. It creates an effective, economical and patient-friendly delivery of insulin as well as the delivery of drugs for a wide variety of conditions.

Using the PassPort™ System, Altea Therapeutics has demonstrated effective delivery of insulin via the skin in Phase I clinical trials (see figure 2). The basal insulin skin patch, the first non-injectable daily insulin product, is

AQUEOUS MICROPORES PERMIT THE RAPID AND SUSTAINED FLOW OF PROTEINS, PEPTIDES, CARBOHYDRATES, AND SMALL MOLECULES INTO THE BODY WITHOUT THE USE OF NEEDLES OR PUMPS

designed to achieve normal basal levels of insulin to enable patients with diabetes to maintain better control of their blood glucose levels.

The insulin transdermal patch maintains constant basal levels while avoiding skin depots of insulin common with subcutaneous injections. As a safety feature, if a patient begins to

experience the hypoglycaemia associated with an inadvertent overdose of insulin, they may simply remove the insulin transdermal patch, thus immediately ending the influx of insulin. In contrast, if a patient experiences an overdose of injected insulin, there is no practical way to stop the build-up of serum insulin levels.

The patient-friendly insulin patch is designed to encourage early adoption of insulin therapy by people with Type 2 diabetes and thus increase compliance with insulin therapy in all patients, particularly those with needle phobia. Early adoption and increased compliance will help delay disease progression and reduce the complications associated with poorly controlled diabetes.

In addition to improved compliance and safety profile, the insulin transdermal patch presents several significant advantages over injected long-acting insulin formulations. Some of the important advantages include the elimination of complex training to administer subcutaneous injections and improved safety through steady basal levels. Moreover, there is no risk of nee-

dle-stick injuries with a patch, eliminating the potential of transmitting blood-borne infections and the general difficulty associated with the correct disposal of needles.

HOW IT WORKS

Conventional transdermal systems are normally limited to very potent, lipid-soluble drugs with a molecular weight of less than 500 Daltons. The PassPort™ System can be used for small water-soluble drugs as well as water-soluble macromolecular drugs and vaccines at doses ranging up to tens of milligrams that cannot be delivered via the skin using conventional passive transdermal patch systems.

The PassPort™ System uses extremely short bursts of focused thermal energy to create hundreds of tiny channels, or micropores, in the surface of the skin. The process is painless, as the short yet rapid delivery of these measured amounts of thermal energy ensures that none penetrates deep enough into the skin to reach the heat-sensing nerve endings in the dermis. These aqueous micropores permit the rapid and sustained flow of proteins, peptides, carbohydrates, and small-molecules into the body without the use of needles or pumps.

The delivery method can be configured to achieve systemic or local action of a therapeutic agent.

The PassPort™ System is comprised of an applicator and a PassPort™ Patch (see figure 3). The PassPort™ Patch contains a reservoir of drug and a tiny screen made of wafer-thin metallic filaments, known as the porator.

Using the PassPort™ System is easy:

1. Clip a PassPort™ Patch onto the Applicator and place against the skin
2. Press the activation button of the Applicator
3. Remove the Applicator, thereby leaving the transdermal patch on the skin
4. Fold over the transdermal drug patch to initiate drug delivery.

When the patient places the PassPort™ Patch against the skin using the Applicator and

Human clinical studies (US):

- Insulin
- Interferon-alpha
- Parathyroid hormone
- Hepatitis B surface protein antigen
- Hydromorphone hydrochloride
- Morphine salts

Preclinical studies:

- Influenza HA protein antigen
- Avian Influenza antigen
- Tetanus protein antigen
- DNA vaccines
- Erythropoietin
- Apomorphine hydrochloride
- Fentanyl citrate

Figure 4: Altea Therapeutics has shown the delivery of therapeutic levels of many compounds in human clinical trials and in animal studies

presses the activation button, a single pulse of electrical energy is released to the porator, where it is converted to thermal energy. The rapid conduction of this thermal energy into the surface of the skin painlessly ablates the stratum corneum under each filament to create micropores. Once the Applicator is removed, the transdermal drug patch remains behind on the skin, and a simple fold-over design aligns the transdermal patch with the newly formed micropores.

PRODUCT PORTFOLIO

Along with developing insulin in Phase I clinical trials, Altea Therapeutics is developing the first non-injectable product to deliver rapid onset and sustained therapeutic levels of hydromorphone hydrochloride for the management of moderate-to-severe acute and chronic pain. The company has concluded a Phase II study and is preparing for Phase III clinical trials of this product.

Altea Therapeutics is also developing a fentanyl citrate transdermal patch for moderate-to-severe acute and chronic pain. In several pre-clinical studies, the company has demonstrated delivery of sustained therapeutic levels with drug utilisation of 90%.

In addition Altea Therapeutics is developing a daily apomorphine patch for managing Parkinson's disease, with plans for initiating clinical development in 2006.

Several pilot studies in human subjects have demonstrated the use of the PassPort™ System to deliver protein drugs, vaccines and highly water-soluble small-molecule drugs. This research includes the delivery of interferon-alpha, parathyroid hormone 1-84 and 1-34, hepatitis B protein antigen vaccine, and morphine (see figure 4).

CONCLUSION

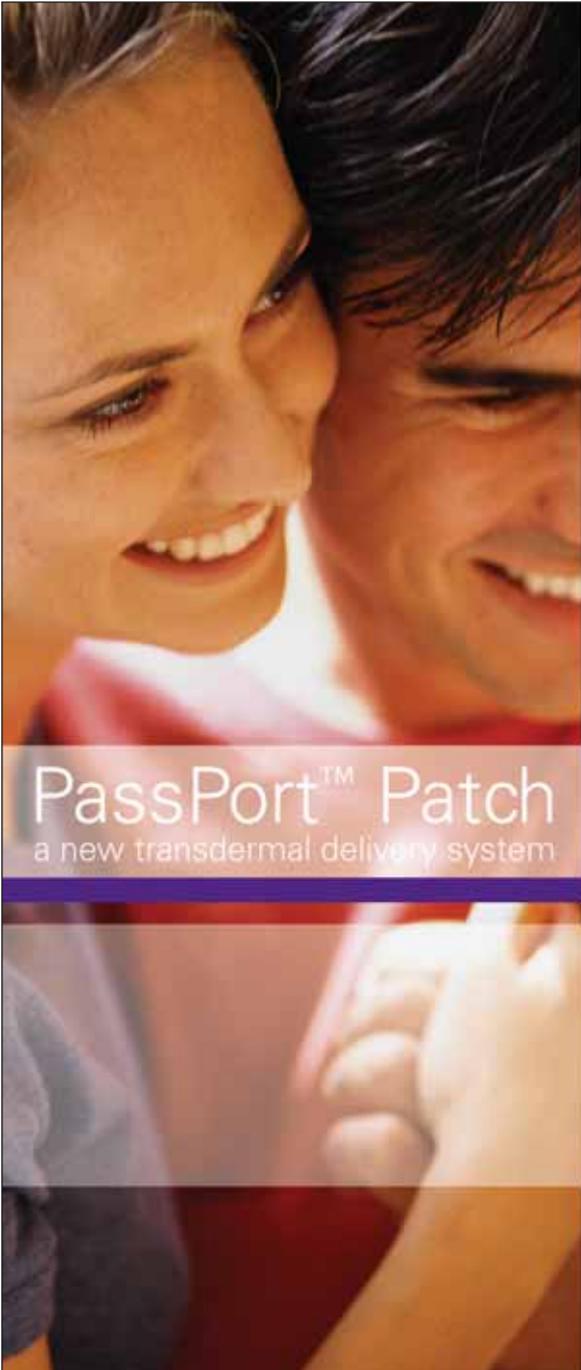
Altea Therapeutics has made a key scientific and commercial breakthrough in the delivery of drugs and vaccines via the skin with its proprietary technology, the PassPort™ System. The PassPort™ System enables the affordable, non-invasive, and controllable delivery of a wide range of drugs via the skin that cannot be delivered using conventional patches.

This breakthrough technology is about freedom from needles and pumps and costly, complicated devices.

Imagine one day children like Taja will be able sleep over at their friend's home without having to worry about taking their painful insulin injections. A simple glance at their patch will tell them that all is well, sleep tight!

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THE NEXT GENERATION INSULIN THERAPY

In this article, David Brandt PhD, Director of Research and Development and Anders Boss, MD, MFPM, Senior Vice-President, Clinical, Medical and Scientific Affairs, both of MannKind Corporation, discuss the development of a novel pulmonary insulin formulation, currently in Phase III clinical trials, which aims to achieve strict glycaemic control through its unique characteristics, one of which is that it closely mimics early post-prandial insulin release.

Diabetes affects nearly 20.8 million people in the US, with more than 90% suffering from Type 2 diabetes, a syndrome of relative insulin deficiency characterised by defects in insulin sensitivity and secretion. Insulin resistance is a phenomenon of muscle, adipocytes, and the liver that manifests early in the disease and requires increased insulin production. To compensate for insulin resistance, a state of hyperinsulinaemia initially occurs and degrades as the disease progresses.¹

Patients in the early stages of disease are encouraged to change their lifestyle, improve nutrition, increase exercise and reduce weight. When adhered to, this approach is highly effective in controlling blood glucose levels early in the disease. However, with disease progression the failure to maintain glucose control with lifestyle results in a need to shift to antihyperglycemic therapy, followed by a progression to full dependence on insulin therapy.

In the next few years, the treatment of diabetes may change dramatically. If the recently approved products and those in Phase III trials fulfil their current promise, we will see the following developments:

- For patients requiring insulin, the insulin can be delivered in various non-injectable forms such as inhaled, oral, buccal, etc.
- Therapies will provide glucose lowering ability without increasing adverse events, such as weight and hypoglycaemic.
- Treatment with incretin hormones will preserve beta cell function, arresting or slowing the natural progression of diabetes.
- Treatments for glucose lowering may also reduce cardiovascular events.

Currently, insulin treatment is introduced when glucose control can no longer be maintained with oral medications. Once the decision to start insulin treatment is made, the patient must participate in the treatment process. The Cross-National Diabetes Attitudes, Wishes, and Needs (DAWN) Study concluded that both patient and provider

are reluctant to commence insulin therapy. The fears associated with injections need to be overcome and the benefits of insulin therapy stressed. Even though insulin is the most effective therapy in diabetes, resistance to self-injection and concerns related to weight gain and in particular hypoglycaemia, limit the use of insulin therapy.²

For years, patients with diabetes and the clinicians who treat them have agreed that the biggest drawback to starting insulin therapy was the accompanying needle. The ability of the patient to gain strict glycaemic control remains the greatest challenge to the long-term treatment of diabetes. The Diabetes Control and Complications Trial provided conclusive evidence that strict glycaemic control reduces the incidence and progression of neuropathy, nephropathy, and retinopathy in patients with Type 1 diabetes.³ Data from the Wisconsin Epidemiologic Study, the UK Prospective Diabetes Study (UKPDS)⁴, and several other trials demonstrated a strong correlation between glycaemic control and complications in patients with Type 2 diabetes.

PROBLEMS WITH CONVENTIONAL INSULIN THERAPY

One of the unresolved problems with subcutaneously injected conventional insulin therapeutics is their inability to mimic the normal insulin secretory response. Normal endogenous insulin secretion can be classified as basal or post-prandial.

Basal insulin secretion is responsible for the maintenance of basal glucose homeostasis. Secretion occurs continuously between meals and throughout the night. Insulin regimens that used intermediate-acting or long-acting insulin in an attempt to mimic this basal secretory pattern have been superseded by the basal insulin analogue Glargine.

Post-prandial insulin secretion (see figure 1) occurs in response to a meal and normal insulin response ranges from 430 to 574 pmol/L prior



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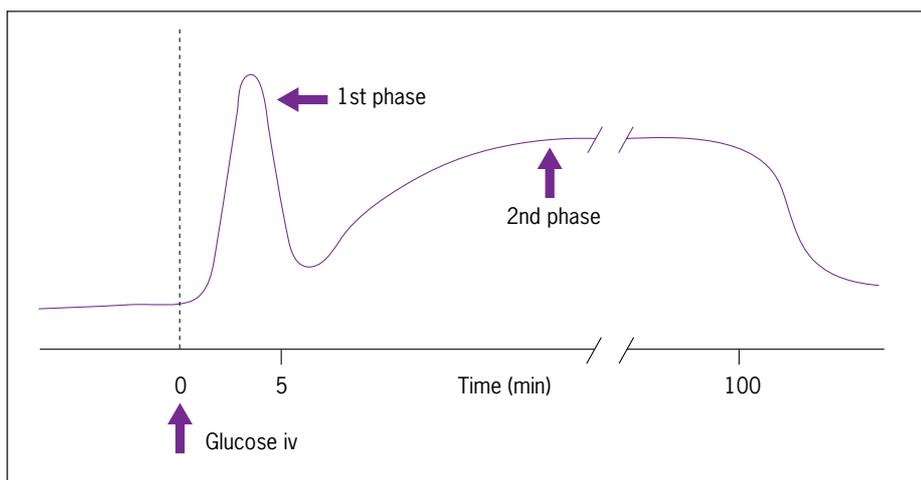


Figure 1: Post-prandial insulin release. This cartoon describes the endogenous kinetics of insulin release after a bolus intravenous injection of glucose. Early post-prandial insulin release is characterized by a large rapid release of insulin that declines within ten minutes followed by a second phase where insulin is released gradually over a 120 minute time-frame.

to a meal and up to 30 minutes post-meal, returning to basal levels within two to four hours.⁵ In the diabetic state, post-prandial insulin levels are typically higher, reaching concentrations of 120 units or more.⁶ While currently available treatments have made improvements, *no commercial insulin therapy closely mimics the post-prandial insulin release.*

The goal of exogenous insulin regimens in patients with diabetes is to provide physiological correct insulin profiles. However, subcutaneously injected conventional insulin formulations have pharmacokinetic profiles that do not closely follow physiologic insulin secretion (see figure 2).

Rapid-acting insulin analogues have an onset of activity from 30 to 60 minutes after injection, typically reaching a peak at four hours, with a duration of eight hours.^{7,8} The poor pharmacokinetic characteristics of human insulin have been attributed in part to insulin's unusual self-association characteristics. Thus, a hexameric form of six associated insulin molecules is the most prevalent form in solution. To be absorbed, this complex must dissociate via a dimeric inter-

mediate.⁹ The monomeric form can then be readily absorbed into the circulation. The rate-limiting step in the absorption of insulin is dissociation to the monomeric form.¹⁰ Rapid-acting insulin analogues have incorporated amino acid substitutions to block the formation of the hexameric form thereby improving the speed of absorption. *Still none of these analogues mimic the early post-prandial insulin release.*

The pharmacokinetic and pharmacodynamic profiles of current insulin therapies present several problems for the patient. First, regular human insulin is inconvenient to use because the patient must carefully time the insulin injection to 15 minutes or more before a carefully planned meal. Second, between-meal hypoglycaemia can be a problem with regular human insulin since the dose required to reduce blood glucose to baseline within 2-3 hours will have a residual effect after three hours that can increase the risk of hypoglycaemia. The patient is left with the choice either to reduce the insulin dose and prolong the hyperglycaemic period, or to counter the effect of the prolonged insulin action by snacking. The issue is not

solved by using intermediate-acting human insulins, NPH or lente, that deliver peak concentrations 4-10 hours after injection with an effective duration of action of 10 to 20 hours.

TECHNOSPHERE®/INSULIN MIMICS EARLY POST-PRANDIAL INSULIN RELEASE

A major advantage of Technosphere®/Insulin (TI), an inhalable formulation under development by MannKind Corporation, is the speed with which the insulin is delivered to the patient's bloodstream. Pharmacokinetic studies in man have shown that Technosphere®/Insulin produces peak insulin levels in 12 to 14 minutes after inhalation. This would allow patients to administer their insulin immediately before a meal. The pharmacokinetic profile approximates the onset and rise of the natural early insulin release spike. The clinical data described below and summarised in figure 3 provide an example of the Technosphere®/Insulin first-phase insulin release spike in more detail.

Technosphere®/Insulin is well absorbed, with a relative bioavailability of approximately 28%. Bioavailability is typically expressed as a relative measure, compared with the amount of insulin that enters the bloodstream over the same period of time following the subcutaneous (sc) administration of regular human insulin. *Based on the results of clinical trials and on published reports of the performance of other pulmonary insulin systems in development, we believe that the relative bioavailability associated with Technosphere®/Insulin is up to three times greater than that reported for the other inhaled insulin platforms.*

TECHNOSPHERE®/INSULIN CLINICAL RESULTS

Phase I and Phase II clinical trials have been conducted and Phase III trials initiated in both Europe and the US. Studies to date have demonstrated that the speed of absorption of Technosphere®/Insulin exceeds the response time of the body. Thus, insulin with even faster pharmacokinetics will not be able to increase response time.

The C_{max} for a 50 U dose reaches about 120 mU, comparable with that seen in individuals with increased insulin resistance (for example, in obesity or pre-diabetes). About 74% of the effect of a Technosphere®/Insulin dose is exerted within 180 minutes after dosing. The variability of both absorption and effect is less with Technosphere®/Insulin than with sc insulin. The glucose lowering effect following a standard meal is better with Technosphere®/Insulin than with an equivalent sc dose of regular insulin

Insulin therapy	Onset (min)	Peak (min)	Duration (hr)
Endogenous post-prandial insulin	1-2	3-4	2
Technosphere®/Insulin	5	15	2-3
Novolog Humalog	30	60	3-4
Standard	30-60	120-360	3-8
NPH	240-480	240-600	10-20
Lente	180-240	240-720	10-20
Glargine	120-180	none	24
Ultralente	360-600	dose dependent	16-20

Figure 2: Kinetics of different insulin therapies (data extracted from refs 5,8,10)

(proof that the absorption profile, not only the dose, matters for post-prandial glucose control) (see figure 4).

In a three-month, placebo-controlled study of Technosphere[®]/Insulin in patients treated with 1-2 oral hypoglycaemic agents and diet and exercise, Technosphere[®]/Insulin reduced HbA1c by 1.34% in patients with baseline HbA1c between eight and 11.5%. This study demonstrated a significant decrease in post-prandial excursions (about 50%) and a lowering of fasting blood glucose (FBG). There was no demonstrable effect on pulmonary function and no increase in frequency of hypoglycaemia. In some patients, mild coughing was reported, usually limited to the period when learning to use the inhalation device. Other adverse events reported in clinical trials, including back-ache, common cold, pneumonia, anaemia and diarrhoea, were found to be either unrelated to the administration of Technosphere[®]/Insulin or could not be conclusively linked to its usage.

No significant safety issues have been observed to date. Pulmonary function was assessed in a patient group that received Technosphere[®]/Insulin over a 12-week period. No clinically or statistically significant difference between the baseline values and the final test results were observed for this group. Furthermore, no treatment-induced insulin antibodies occurring in patients treated with Technosphere[®]/Insulin were evident.

Studies are currently under way in both Type 1 and Type 2 diabetics, including a two-year study to evaluate pulmonary safety. In addition, the use of Technosphere[®]/Insulin will be studied in a number of different populations, including patients with specific pulmonary conditions.

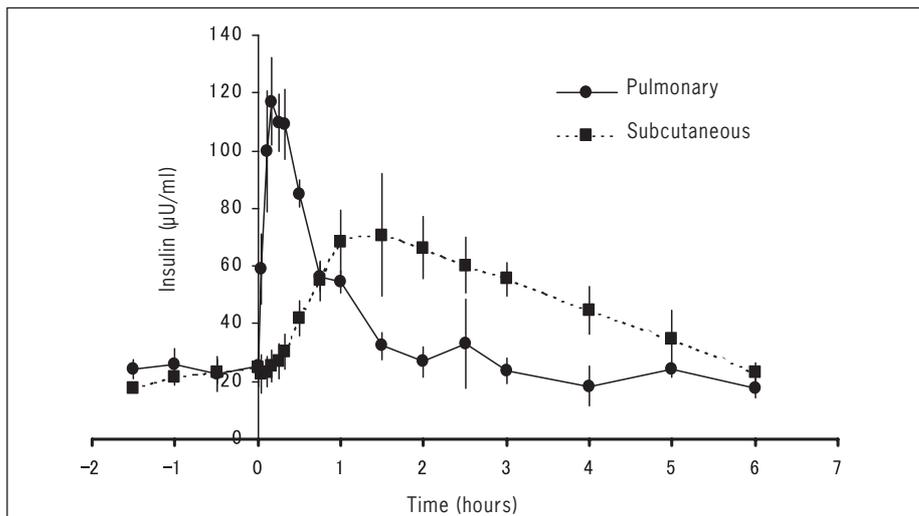


Figure 3: Technosphere[®] Insulin displays rapid pharmacokinetics. The pharmacokinetic profiles from inhaled Technosphere[®] Insulin (48 units) were compared with subcutaneous injected insulin (24 units) in diabetic patients. Technosphere Insulin displays kinetics similar to a endogenous early-phase insulin release.

THE MEDTONE™ INHALER

To facilitate the delivery of Technosphere[®]/Insulin to the deep lung, an inhaler utilising single-use, disposable, plastic cartridges was developed. The MedTone™ inhaler is light, easy to use and fits in the palm of the patient's hand (see figure 5).

The device incorporates an airflow regulator that is designed to ensure a consistent airflow from patient to patient and from use to use, even in patients with restricted airflow capacity. In addition, the inhaler is breath actuated, which means that the patient does not need to co-ordinate a breath with any manipulation of the device, such as priming or pumping. In multiple Phase I and Phase II clinical trials of

Technosphere[®]/Insulin, patients reported a high level of satisfaction with the MedTone™ inhaler.

The ease of use of the MedTone™ inhaler complements the time-action profile of Technosphere[®]/Insulin to produce a highly effective and convenient system. Due to the rapid pharmacokinetics associated with Technosphere[®]/Insulin, the optimal and the most convenient time for patients to take a dose is right at the start of a meal or shortly thereafter. This is in sharp contrast to sc injection and other pulmonary delivery technologies where it is recommended that the user try to time a dose 15 to 45 minutes before the expected mealtime, raising issues such as miscalculation of time or unanticipated change in meal availability.

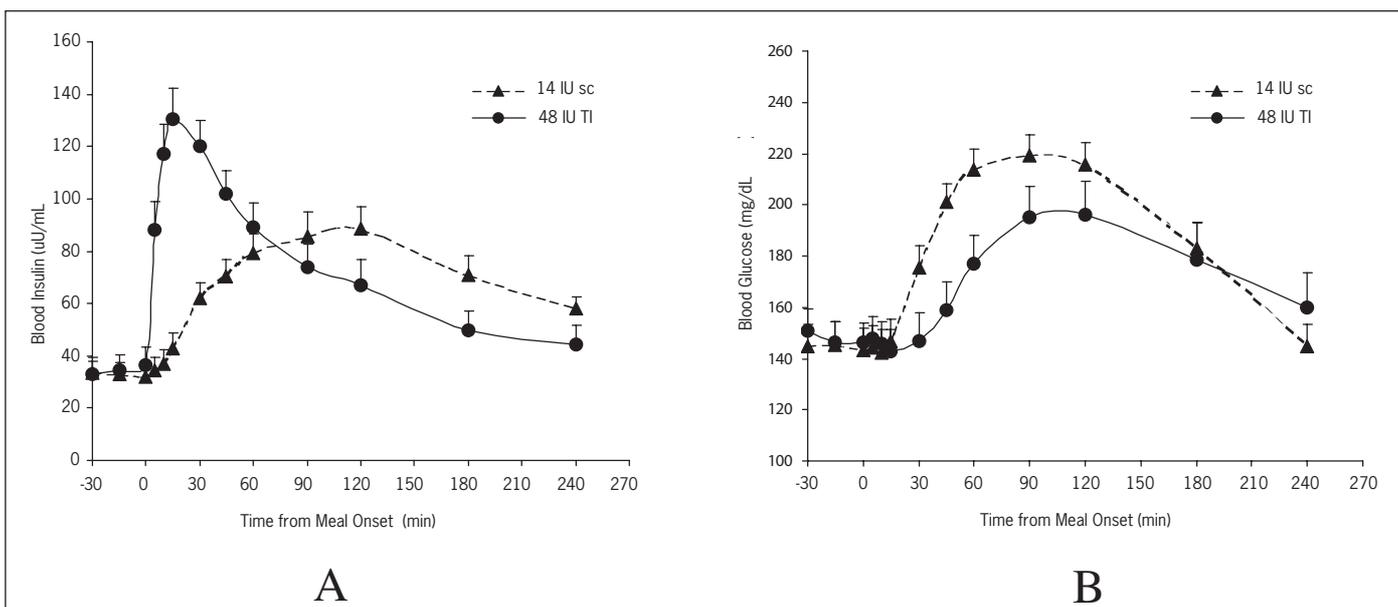


Figure 4: Blood insulin concentration (A) and blood glucose concentration (B) following Technosphere[®]/Insulin (TI) and SC insulin administration as individual doses following a meal. TI insulin 48 IU resulted in higher blood insulin and greater reduction in blood glucose, compared with SC insulin 14 IU.



Figure 5: The MedTone™ Inhaler has been designed specifically to optimise the delivery of Technosphere® formulated products

SUMMARY

Insulin substitution is a requirement in Type 1 diabetes, and may have unrecognised clinical benefits even in the early stages of Type 2 diabetes, where the initial insulin spike becomes absent. However, current insulin products are not able to provide pharmacokinetics that resemble those of the first-phase insulin release. Also, there is considerable resistance amongst both patients and clinicians to the introduction of insulin therapy. Both the fear of hypoglycaemia associated with post-prandial exogenous hyperinsulinaemia, and the reluctance towards injections, contribute to this.

Technosphere®/insulin is a pulmonary delivered insulin with a very rapid absorption and may overcome these concerns. The product is delivered via a small, proprietary inhaler and in clinical trials has demonstrated very fast absorption and superior post-prandial control in comparison with regular injected insulin. No negative effect on pulmonary function has been demonstrated in initial studies.

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ORAL-LYN NEEDLE-FREE BUCCAL DELIVERY OF INSULIN:

A PRODUCT WHOSE TIME IS NOW

When insulin was first discovered more than eighty years ago, the value of a needle-free method for delivering it was recognised. Since then, the incidence of diabetes has spiralled upwards and efforts to optimise its treatment have meant that every possible route into the body has been explored, with each facing its own limitation. Here, Gerald Bernstein, MD, FACP, Vice-President, Medical Affairs, Generex Biotechnology, and Associate Clinical Professor of Medicine, Albert Einstein College of Medicine, NY, US, argues that the buccal mucosa meets all of the requirements for successful insulin delivery.

Diabetes mellitus looms as the greatest public health threat the world has ever seen short of the plague in the 14th century. This is a disease that is genetically present from birth and is ultimately expressed when certain conditions are met. Simply stated, these conditions are weight (body-mass index), physical activity and the inevitability of age.

Type 1 diabetes, an autoimmune disease, represents only 5% or so of the total and is a somewhat different story. Type 2 diabetes con-

The product of these pathways results in alteration of the basement membrane of the capillaries as well as causing malfunction of other cells. This is the basis for the classic complications of retinopathy, neuropathy, nephropathy and certainly a role in limb loss. Although suspected we now know that there is a more extensive issue, the cardiovascular complications of diabetes.

For more than a decade there has been a succession of studies correlating coronary artery disease and deaths with the level of glucose control (A1c haemoglobin).

In September 2004 a meta-analysis confirmed this correlation and recommended A1c as a risk factor for cardiovascular disease. In a follow up to the Diabetes Complications and Control Trial, origi-

nally published in 1993, it was found that an intensively treated patient with Type 1 diabetes had less cardiovascular complications ten years later than did casually treated patients. Finally on a physiological level, data from a number of investigators show that glucose spikes, as seen post-prandially, create oxidative stress on the endothelium.

With this background in mind it is important to review how diabetes mellitus is treated today. Type 1 diabetes is treated with a basal bolus regimen. This may be supplied by a basal insulin

AN ACCEPTABLE ALTERNATIVE DELIVERY SYSTEM MUST MEET THE FOLLOWING CHARACTERISTICS: SAFE, SIMPLE, FAST, FLEXIBLE AND...FAMILIAR TO PATIENT AND PHYSICIAN ALIKE

stitutes the great threat. What we know in 2006 is that Type 2 diabetes and cardiovascular disease are inexorably linked. The common denominator is the endothelium, the lining of the vascular system. Like the skin it is an extensive organ in surface area, if only a few cells thick.

We ordinarily think of the complications of diabetes mellitus as being related to the microvascular pathway through mechanisms of nonenzymatic glycosylation or the polyol pathway and abnormal function of aldose reductase.



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Figure 1: The RapidMist™ device

injection and pre-prandial boluses of short-acting insulin plus incidental injections as needed at other times (a relatively small number use an insulin pump).

Many might accept this, but the majority of patients prefer 2-3 injections per day. Type 2 patients may receive basal or NPH insulin with a variety of oral medications but uncommonly receive preprandial injections as both doctor (primary care) and patient prefer avoiding the complexity of multiple injection. Finally a major deterrent to people

attempted by many but the encumbrances and technology have often made it impractical. Further attempts at delivery with a patch are still in the works. Nasal delivery was rejected because of the fragility of the nasal mucous membrane and possibly the venous drainage. Insulin has been put in a pill in an altered form that allows it to pass through the acid environment of the stomach and be absorbed by the small intestinal epithelium. The yield is very low and it lacks sufficient flexibility. Delivery through the lungs has been studied by 5-6 different companies.

Most prominent is pulmonary insulin, developed by Nektar, and produced and studied by Pfizer. Insulin is altered and put into a powdered form and inhaled into the lungs. About 80% of the inhaled insulin is trapped in the bronchial system with the rest entering the alveoli. Insulin progressively crosses the alveolar membrane into the capillaries. This affords a rapid appearance in the blood stream but a tail of activity that exposes the patient to possible hypoglycaemia, similar to injection. Concerns about antibodies, pulmonary function and unknown long-term effects have been of concern to many healthcare professionals. Nevertheless it has been approved in Europe and as of February 2006 has been approved in the US with some restrictions.

The remaining route of absorption turns out to be the only one that satisfies the previously set down criteria of safe, simple, fast, flexible and familiar. This is the buccal mucosa. The latter has been used for thousands of years to absorb, for good or bad reasons, a variety of drugs and natural materials. It is a highly vascular and resilient tissue protected by the salutary effects of saliva. As each of us knows injuries from biting ourselves or eating abrasive, spicy food stuff heals very rapidly.

As early as 1925, attempts were made to utilize the buccal mucosa for insulin absorption but, in 2006, we have come a long way. Generex

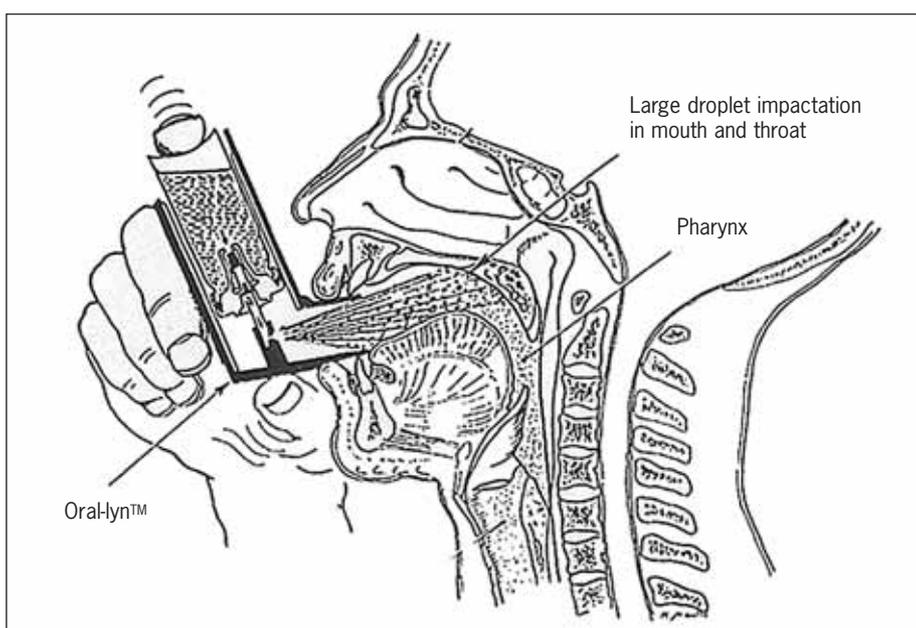


Figure 2: The formulation is delivered to the oral cavity for absorption via the oral mucosa



Figure 3: Structure of the buccal mucosa

attempting tight control is frequent and bothersome low blood sugars.

It was recognisable even at the time of the discovery of insulin that a possible needle-free route would be of value. Every imaginable body membrane has been tried and one way or another, insulin has been delivered to the blood stream from all of them but each has its limitations. I have stipulated that an acceptable alternative delivery system must meet the following characteristics: safe, simple, fast, flexible and, most importantly familiar, to patient and physician alike.

The vagina and rectum have been studied as absorptive sites for insulin but even with a degree of success they obviously present limitations as socially acceptable and convenient sites. Similarly the colon is not a practical solution. Transport through the skin has been

ORAL-LYN®, DELIVERED BY THE RAPIDMIST™ DEVICE, PENETRATES THE BUCCAL EPITHELIUM AND ENTERS THE RICH VASCULAR SUPPLY

Biotechnology has developed a platform delivery system, Rapidmist™ (see figure 1), a device similar to that used by people with asthma.

Human regular insulin is put into a liquid formulation with minimal amounts of GRAS excipients resulting in small micelles greater than 7 μm – too large for entry into the lungs. The formulation, called Oral-lyn™, is delivered to the oral cavity for absorption through the buccal mucosa (see figure 2).

The structure of the latter consists of an epithelial layer and a lamina propria filled with a large network of blood vessels (figure 3). Oral-lyn™, delivered by the Rapidmist™ device, penetrates the buccal epithelium and enters the rich vascular supply. Like sublingual nitroglycerine, insulin appears quickly into the blood stream. Radionuclide studies (summarised in figure 4) show that no labelled insulin entered the respiratory tract and therefore none is swallowed and destroyed by the gastric and intestinal juices.

Glucose clamp studies show that insulin appears in the blood stream at five minutes, peaks at 30 minutes and is back to baseline at two hours with no apparent tail. The insulin is released from the device as a metered dose, identical from first puff to last.

Oral-lyn™ was administered to 40 dogs for 24 months along with another ten receiving the solution without insulin. No abnormalities were seen either by observation or cytopathology. Similarly, in close to 1,000 patients, no visible abnormalities have been observed in the oral cavity.

Clinical studies to be presented below all resulted in either non-inferiority to injected insulin or significant improvement in A1c haemoglobin. Utilising the glucose clamp technique a dose response was observed (figure 5). Doses of 75, 150 and 225 units were delivered to the buccal cavity of Type 1 diabetics. Insulin levels and glucose utilisation rose in a linear relationship to the administered insulin. Similar results without the clamp were observed in normal patients.

A group of Type 1 patients were given Oral-lyn™ or an equal amount of injected insulin followed by a test meal. Insulin and glucose levels were measured for four hours. The Oral-lyn™ phase was repeated two more times separated by 4-7 days. The results for buccal insulin were virtually super imposable showing reproducibility at 85-90% (see figure 6).

A group of Type 1 patients using an insulin pump were studied. Patients were maintained on basal insulin from the pump and received either placebo, Lispro or Oral-lyn™, followed by a test meal. Insulin and glucose levels were measured for four hours. Insulin levels rose as in the clamp studies, appearing in five minutes and peaking at 30 minutes. Blood glucose levels rose more slowly after Oral-lyn™ confirming the more rapid onset of action. Comparable studies were performed in Type 2 patients with similar results.

The next series of data looked at Oral-lyn™ in Type 2 patients who were failing conventional treatments. These were 90-day studies with A1c haemoglobin as the end point. In the first a

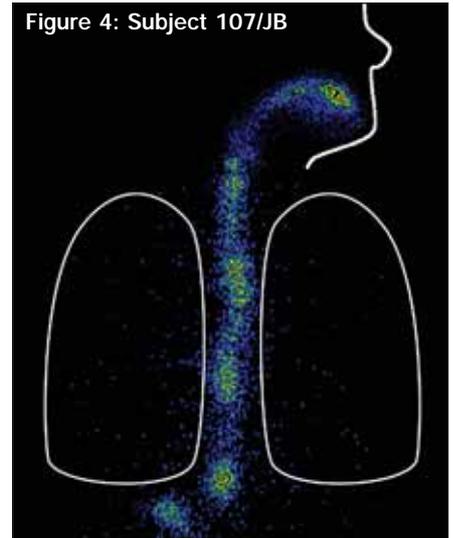
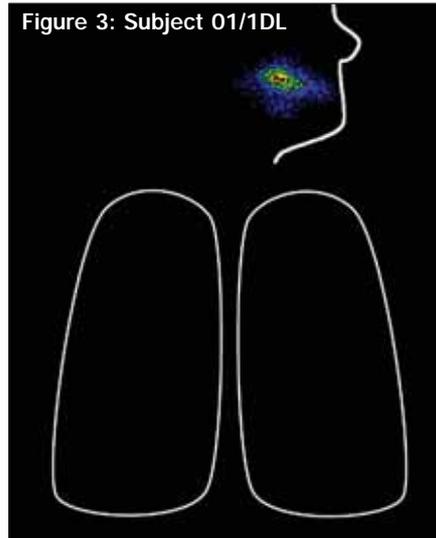


Figure 4: In vivo radiolabelled Oral-lyn™ study

group of patients treated but failing on diet and exercise were either continued with their regimen or had Oral-lyn™ added to their treatment. After 90 days the A1c haemoglobin in the latter decreased close to 1%.

A second study looked at patients failing on pioglitazone (figure 7). One group continued on the pioglitazone and the other had Oral-lyn™ added. Again, A1c haemoglobin levels

decreased by 1% more in the latter group. In the final study of this group, patients failing on metformin and sulphonylureas had Oral-lyn™ added to half the group. Over the next 90 days the A1c haemoglobin decreased to levels below those observed in the placebo group.

In the last group of trials, both Type 1 and Type 2 diabetics were studied. A group of 26 Type 2 patients treated with metformin and

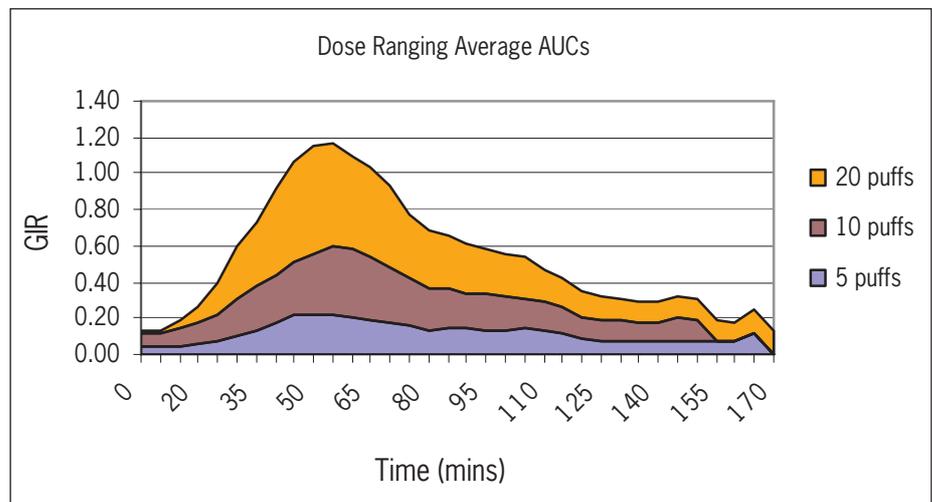


Figure 5: Dose ranging clamps study

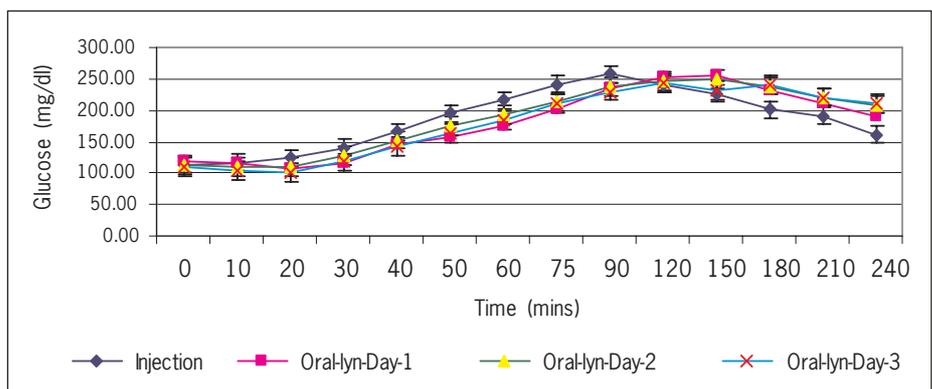


Figure 6: Reproducibility of Oral-lyn™ absorption in Type 1 diabetics on three occasions

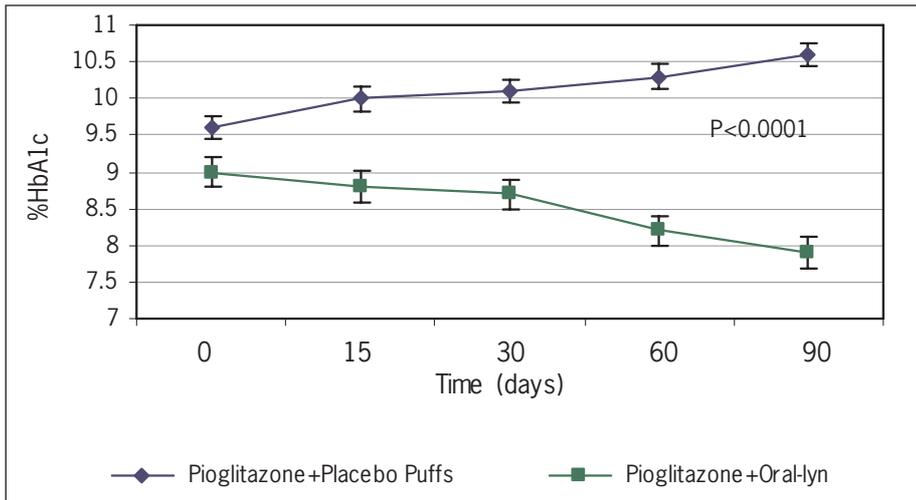


Figure 7: Long-term safety and efficacy study in Type 2 diabetics taking pioglitazone + Oral-lyn™

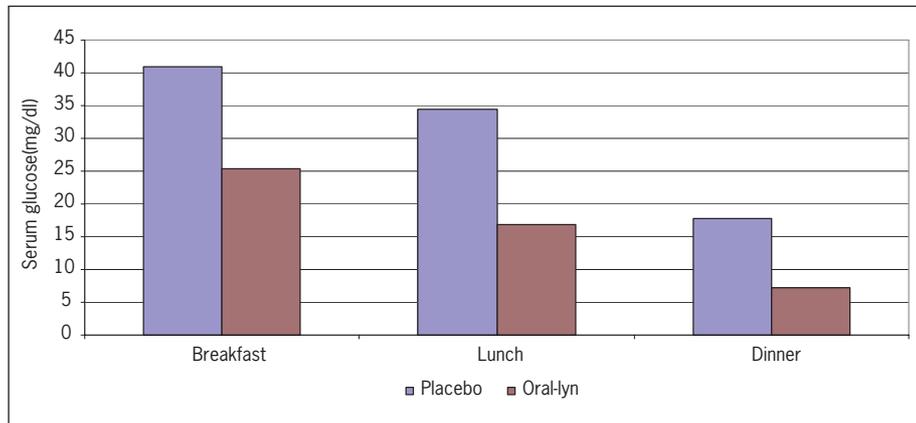


Figure 8: Weeks 8-12 differences in pre- to post-prandial serum glucose by treatment assignment

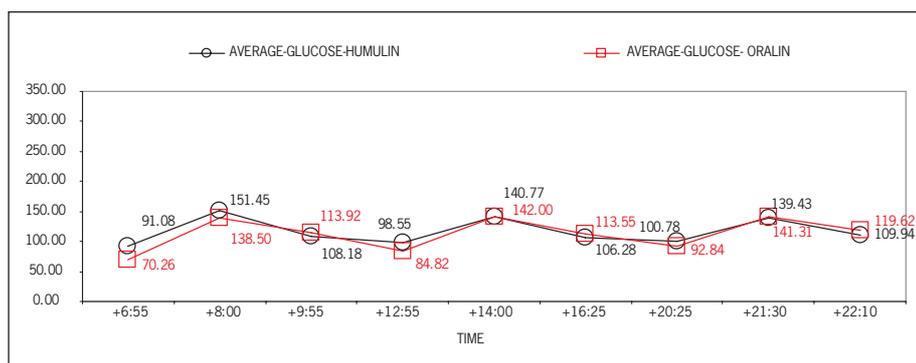


Figure 9: Superimposable glucose concentration curves from Humalin and Oral-lyn™ in Type 1 diabetics

glargine was divided in half. One group received preprandial placebo spray and the other Oral-lyn™. The goal was to measure impact on post-prandial glucose.

Over a period of 12 weeks there was a persistent fall in post-prandial glucose so that average values fell after all meals (see figure 8). The study in Type 1 diabetes, a prototype for Phase III protocols, looked at nine Type 1 patients. During a break in period they were managed on glargine and human regular insulin AC twice daily, and as required if the blood glucose was elevated. Once stabilised, they tested their glucose levels ten times daily for three days, before and after meals and before sleep. They were then continued on glargine but Oral-lyn™ was substituted for the human regular insulin injections at the same times. The difference was that the buccal insulin was given in split doses just before and just after each meal and as needed. For nine more days the patients tested ten times daily as before. The resultant curves were superimposable on the injection phase, indicating non-inferiority (see figure 9).

CONCLUSION

At the present time the prevalence of diabetes ranges from 8-16% of populations around the world and growing. As quality of life improves, even slightly, a better diet and technology will lead to increased weight and less physical labour. For many this will be a great benefit but along with it will be the greater expression of the genes for diabetes.

In the US, at the current growth rate of 9%, we are likely to see 100 million people with diabetes over the next quarter century with another 100 million with prediabetes or impaired glucose tolerance. The US Centers for Disease Control has stated that of all the people born after 2000 one out of three will develop diabetes in their lifetime. As mentioned earlier the accompanying cardiovascular disease will muddy the waters further.

Simple, acceptable interventions like Oral-lyn™ can serve to reduce the risk for microvascular and macrovascular complications by changing the paradigm for treatment and neutralising this burgeoning epidemic.



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