# NOVEL TRANSDERMAL DELIVERY SYSTEMS FOR TREATMENT OF DIABETES

In the context of a diabetes epidemic, which he characterises in terms of incidence, prevalence and healthcare costs, Alan Smith, PhD, Vice-President, Clinical, Regulatory & Operations, 4P Therapeutics, outlines the stages of Type 2 diabetes treatment, progressing to extenatide and insulin injections, and makes the case, using clinical data, for the transdermal route as a viable alternative to injections.

## DIABETES EPIDEMIC

According to the International Diabetes Federation, as of 2013, 382 million people worldwide suffered from diabetes of which 46% are undiagnosed. In the US, there are 24 million people with diabetes and 27% are undiagnosed. The number living with diabetes worldwide is expected to grow to 592 million by the year 2035 (a 55% increase).

> "A safe and effective non-injectable method to treat diabetes has been pursued since insulin therapy was first developed more than 90 years ago"

The burden of diabetes is significant causing more than five million deaths every year (one death every six seconds) and treatment of diabetes and its complications costs a significant amount of all healthcare expenditures. In 2013, US$548 billion was spent on diabetes worldwide which is 11% of the total worldwide spending on healthcare. This is projected to exceed $627 billion by 2035.

Diabetes is a chronic disease that occurs when the body cannot produce enough insulin or cannot use insulin effectively. Insulin is a hormone produced in the pancreas that allows glucose from food to enter the body's cells where it is converted into energy needed by muscles and tissues to function. A person with diabetes does not absorb glucose properly, and glucose remains circulating in the blood in excess (hyperglycemia) damaging body tissues over time. This damage can lead to disabling and life-threatening health complications. Type 1 diabetes occurs due to insulin deficiency caused by destruction of the pancreatic beta cells and requires daily insulin administration. Type 2 diabetes occurs due to insulin resistance and deficiency. Worldwide, approximately 10% of people with diabetes have Type 1 diabetes and 90% have Type 2 diabetes.

As the majority of people with diabetes are Type 2, it is critical to get the disease under control early in its progression and prevent further deterioration in health. As patients move through treatments needed to achieve glycemic control, they typically start with diet and exercise and one oral antidiabetic (metformin), proceed to multiple oral therapeutics (including insulin sensitisers and dipeptidyl peptidase-4 (DPP-IV) inhibitors), and then eventually to injections after the orals fail to maintain control.

Injections include either basal insulin (insulin glargine, insulin detemir, insulin degludec), or glucagon-like peptide-1 (GLP-1) agonists (exenatide, liraglutide, lixisenatide), or combinations thereof. It is generally accepted that the majority of people with Type 2 diabetes will eventually need insulin [1] and that early initiation of injected therapy will slow down and potentially prevent further deterioration of pancreatic beta cell function (see Figure 1).

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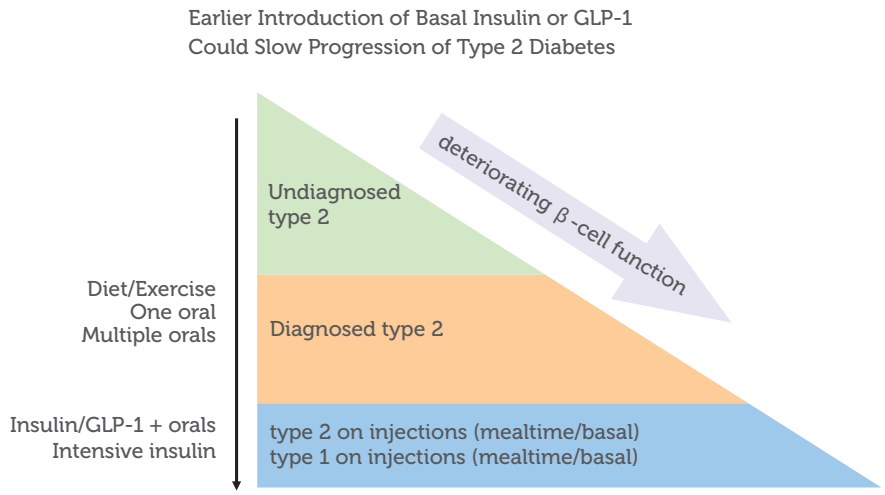


**Figure 1: Conventional Type 2 diabetes treatment sequence and relationship with pancreatic beta cell function: need for early initiation of injected therapy.**

## UNMET CLINICAL NEED

There is reluctance by patients and healthcare professionals to initiate insulin therapy for several reasons including the patients' fear of disease progression and needle anxiety; mutual concerns about hypoglycaemia and weight gain; and health professionals' use of insulin as a threat to encourage compliance with earlier therapies.[2] Despite advances in less painful insulin injections and pens, insulin injections are seen as a last resort by patients and providers. Finally, there is the real concern of insulin injections causing hypoglycaemia. Physicians, particularly general practitioners (GPs), may lack the support services required to train patients on how to determine the correct dosage and to perform injections properly.

Once patients start on injections, they struggle with compliance. Most patients will only inject at home and one-third will skip injections once per week. Noncompliance affects glycaemic control and treatment outcomes. Clearly, injections are a barrier to initiating therapy and maintaining compliance, but what alternative delivery options are there? A safe and effective non-injectable method to treat diabetes has been pursued since insulin therapy was first developed more than 90 years ago. In spite of this long history, however, no satisfactory non-injectable insulin delivery system has emerged.

Certainly, inhaled insulin has made significant progress towards providing a non-invasive alternative to mealtime insulin injections and possibly even once-daily basal injections. The Pfizer/Inhale (now Nektar Therapeutics) inhaled insulin product, Exubera®, was taken off the market in 2007 as a result of low sales and poor market uptake mainly due to issues of device size, ease of use and high cost. Mannkind Corporation is awaiting a decision on approval in the summer 2014 for its Technosphere® inhaled insulin, Afrezza®, which offers a more rapid absorption profile than subcutaneous injection, and Dance Biopharm/Aerogen are making headway with their aerosol insulin product, OnQ™, towards Phase III trials planned for 2015. However, there is a risk that there will always be the safety concern of delivering a growth factor such as insulin to the lungs which will potentially limit uptake of the product in the marketplace.

Other options in development include oral pills or sprays and varying degrees of success have been achieved by several groups including Generex (Oralyn™ mouth spray), and the recent initiative undertaken to develop an oral insulin tablet by Novo Nordisk.

## TRANSDERMAL INSULIN DELIVERY

Insulin is a 5,808 Da peptide that that is produced and stored in the pancreas as a hexamer (35 kDa) but active as a monomer. It is typically administered as a subcutaneous injection either as a bolus before meals or as a once or twice daily long-acting injection to achieve a basal profile.

Transdermal delivery of insulin offers several potential benefits. Delivery through the skin bypasses metabolism in the gastrointestinal tract which typically contributes to the very low bioavailability of oral formulations of proteins and peptides. In addition, transdermal delivery is well suited for steady infusion throughout the day as a way to meet the basal insulin needs of patients. Basal insulin typically accounts for 50% of the daily insulin needs of patients with diabetes. Transdermal patches are conventionally used to achieve steady serum levels of drug and avoid the "peak-valley" effect; however they are limited for use with small-molecule lipophilic drugs. This is mainly due to the barrier function of the *stratum corneum*, which is rate-limiting for transdermal transport.

There is a plethora of methods used to deliver insulin through the skin, including iontophoresis, permeation enhancers, solid and hollow microneedles, microporation by thermal ablation, radiofrequency ablation, erbium:YAG laser used directly on the skin, ultrasound, electroporation, pressure waves, nanoparticulate and microparticulate systems and use of carrier molecules. However, each of these methods has limitations in terms of success, typically limited to academic settings in preclinical models. Two approaches though – microneedles and microporation – have been utilised to deliver insulin in human subjects at therapeutic levels.

Microneedles can be used to deliver peptides and proteins through the skin but the dose per needle may be limited when using microneedles with a shallow depth of penetration and maintaining a reasonable patch sizes. In addition microneedle systems are more suited for bolus pharmacokinetic pro-

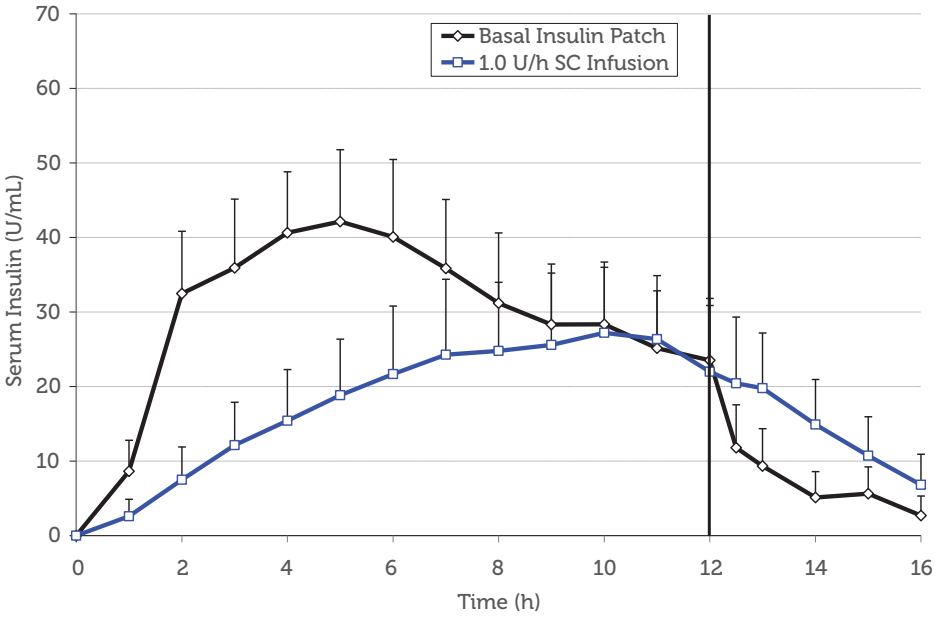


Figure 2: Basal insulin microporation patch versus continuous subcutaneous infusion pump (CSII) set at 1.0 U/hr. At 12 hr, patch removed and insulin pump turned off/infusion set removed. (Mean +SE, N=7).

files. However, relatively long microneedles have been used to achieve a therapeutically relevant intradermal injection of insulin as an alternative to SC injection.[3] The microporation approach (thermal ablation) is well suited for relatively large doses and for a sustained basal delivery pharmacokinetic profile, although it depends on the specific technology being utilised.

Microporation technologies have been developed that overcome the *stratum corneum* barrier by creating micropores by thermal ablation that extend into the viable epidermis. Micropores are created by the rapid localised application of thermal energy to the skin surface that results in the vaporisation of the *stratum corneum* cells in a microscopic area. One microporation approach that has had some success utilises an array of resistive filaments applied to the skin surface which are briefly heated by applying a short pulse of electric current to create micropores approximately 100 µm wide and 50 µm deep, which extend through the *stratum corneum* into the viable epidermis. This technique has been investigated in clinical studies for the rapid extraction of skin interstitial fluid for glucose monitoring[4] and for the delivery of insulin[5-8] for the development of a basal insulin microporation patch intended for daily administration in patients with Type 1 or Type 2 diabetes.

An open-label randomised crossover pharmacokinetic / pharmacodynamic (glucose clamp) and safety study in C-peptide negative patients with Type 1 diabetes evaluated transdermal insulin *versus* continuous subcutaneous insulin infusion (CSII insulin pump).[8] The study was conducted to demonstrate unambiguous therapeutic insulin levels in comparison with CSII as all subjects were required to be C-peptide negative (no endogenous insulin secretion). Subjects stopped use of long-acting insulin injection (48 hours prior) or discontinued insulin pump use prior to dosing (eight hours prior). Subjects were randomly assigned to one of two treatment arms: insulin patch applied for 12 hours followed by CSII treatment at 1.0 U/hr for 12 hours or CSII treatment at 1.0 U/hr followed by an insulin patch. In clinical use, insulin infusion basal rates are typically 0.5 U/hr to 2.0 U/hr.

The basal insulin microporation patch had an active area of 12 $cm^2$ with 80 micropores/$cm^2$ and contained a dry-polymer film formulation of 15 mg recombinant human insulin. The CSII treatment consisted of a Medtronic Paradigm 722 insulin pump with Humulin® R 100 U/mL (Eli Lilly). Glucose levels were clamped at 100 mg/dL which was initially reached by IV infusion of insulin lispro and maintained after insulin treatment by IV glucose infusion (D-20). Serum samples were analysed for insulin using an insulin-specific ELISA (no cross-reactivity to lispro).

The basal insulin patch mean serum insulin concentration curve reached a $C_{max}$ of 42 µU/mL at five hours. The insulin pump (1.0 U/hr CSII) reached a steady state level of 27 µU/mL at seven hours until the pump was discontinued at 12 hours (see Figure 2).

Although the patch did not achieve a pharmacokinetic profile suitable to maintain a steady state level after repeated daily dosing, transdermal insulin therapeutic levels were achieved within two hours and the pharmacokinetic profile indicated a faster transdermal infusion rate in the first six hours than the second six hours. This may be desirable from a pharmacodynamic perspective (tailored profile to match morning or evening needs as a daytime or nighttime patch). The relative bioavailability of the patch compared with the CSII was approximately 4% using a non-optimised system. The transdermal insulin patch was well tolerated and the skin response was limited to mild transient erythema at the application site.

The study demonstrated that the basal insulin microporation patch achieved a therapeutic basal infusion rate comparable with that achieved by a continuous subcutaneous insulin infusion pump in patients with Type 1 diabetes.

## TRANSDERMAL EXENATIDE DELIVERY

Exenatide (exendin-4) is a GLP-1 receptor agonist with a molecular weight of 4,186.6 Da (39 amino acid peptide amide). It is a synthetic version of a salivary protein found in the Gila monster lizard. It exhibits similar glucoregulatory effects to the naturally occurring incretin hormone glucagon-like peptide-1 (GLP-1) but has a longer half-life.

GLP-1 is a naturally-occurring peptide that is released within minutes of eating a meal. It is known to suppress glucagon secretion from pancreatic alpha cells and stimulate insulin secretion by pancreatic beta cells. The half-life of GLP-1 is approximately two minutes due to dipeptidyl peptidase-4 (DPP-IV) inactivation. Exenatide is 53% identical to native human GLP-1. It binds to known human GLP-1 receptors on pancreatic beta cells *in vitro* and is resistant to dipeptidyl peptidase-4 (DPP-IV) inactivation. As a result, the half-life of exenatide is 2.4 hours which is 10 times longer than GLP-1.

Exenatide was developed by Amylin and

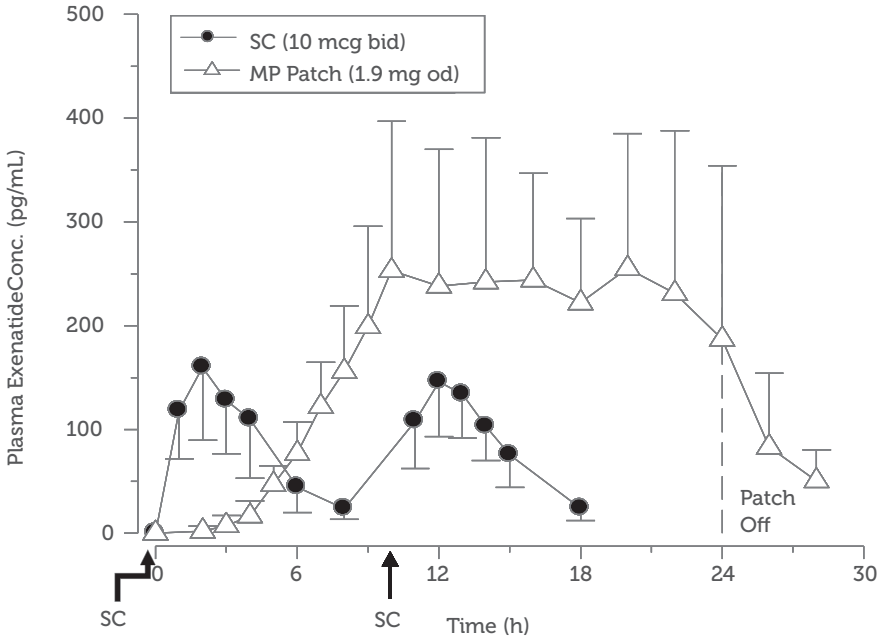


Figure 3: Plasma exenatide concentration comparing SC injection to transdermal microporation patch (TDP) (patch mean+SD, SC mean-SD; N=8).

Lilly and is currently marketed by Bristol-Myers Squibb and AstraZeneca (co-marketing arrangement). It is administered as a twice-daily subcutaneous injection given one hour before the breakfast and dinner meals (Byetta® 5 µg or 10 µg) or as a once-weekly subcutaneous injection (Bydureon® 2 mg exenatide extended-release microsphere suspension).

A Phase I clinical study was conducted using a transdermal exenatide microporation patch.[9] The study design was a double-blind, placebo controlled, three-period, three-treatment study evaluating the pharmacokinetics/ pharmacodynamics (PK-PD) and safety of the exenatide transdermal patch (TDP) in nine Type 2 diabetics. On separate days, subjects received a single dose of exenatide TDP (1.9 mg exenatide, 3 $cm^2$, 120 microchannels/$cm^2$) or exenatide SC (10 µg bid Byetta®). The investigator and subject were blinded to exenatide/placebo patch content for assessment of skin responses. Standardised breakfast, lunch and dinner meals were provided. The skin response to the patch was evaluated by visual scoring (modified Draize scale) and transepidermal water loss (TEWL) measurements. Exenatide concentrations were determined by ELISA.

After a single exenatide patch application, plasma exenatide concentrations increased gradually for 10 hours reaching a $C_{max}$ of 301 pg/mL. On average, plasma concentrations were sustained after 10 hours at approximately 250 pg/mL until the patch was removed at 24 hours (see Figure 3). Plasma exenatide concentrations were maintained above 50 pg/mL for 21 hours (median) with a range of 14-25 hours. The minimum effective plasma exenatide concentration required for a glucose lowering effect is 50 pg/mL.[10] The relative bioavailability of the exenatide patch compared with the 10 mcg SC injection treatment was approximately 3% using a patch formulation that was not optimised for bioavailability. There were no skin reactions and the exenatide patch was well tolerated in terms of skin response. As the exenatide microporation patch is a drug delivery system, with several key variables that can be optimised, the film formulation can be adjusted to decrease the delay and increase bioavailability while maintaining sustained plasma exenatide concentrations for 24 hours.

The studies reported here showed that insulin and exenatide can be administered by the transdermal route resulting in sustained therapeutic blood concentrations suitable for treatment of diabetes.

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