

# The Buccal Delivery of Insulin

A system for the administration of medicines directly into the mouth for absorption by the buccal mucosa is showing promise in the oral delivery of insulin – as well as other large-molecule drugs.

## By Gerald Bernstein at Genex Biotechnology Corporation



Gerald Bernstein, MD, FACP, is currently Vice President for Medical Affairs at Genex Biotechnology and serves on its Board of Directors. He graduated from Dartmouth College and Tufts University School of Medicine, and is Board Certified in Internal Medicine (1966) and Endocrinology and Metabolism (1973). He entered practice in 1966 after completing a research fellowship. Dr Bernstein is an Associate Clinical Professor at the Albert Einstein College of Medicine in New York; he is also an Attending Physician at Beth Israel Medical Center, Lenox Hill Hospital (1974) and Montefiore Medical Center (1966). He serves on the National Board of Directors of the American Diabetes Association, its Research Foundation and many National Committees and was on the Editorial Board of the publication *Clinical Diabetes*. He has also been President of the New York Downstate affiliate of the American Diabetes Association. He is the author of many papers – both clinical and scientific – and the book *If it runs in your family: Diabetes mellitus, Reducing your risk*. Dr Bernstein is a past President of the American Diabetes Association and was Director of the Beth Israel Health Care Systems Diabetes Management Program.

**Insulin was discovered in Toronto in 1921 and arrived on the market in 1922. Since that time there have been episodic attempts to escape the inevitability of injection. In as much as insulin is a large peptide, and subject to the denaturing effect of stomach acid and the enzymatic maelstrom of the intestines, simple ingestion is not tenable. Initial attempts to deliver insulin through the rectum, lungs and buccal mucosa occurred as early as the mid 1920s. None of these pursuits were successful and the refinement of injectable insulin was undertaken. In recent years, the drive for a needle-free insulin delivery system has re-surfaced, and over the last decade a variety of portals have been studied including the lungs, nose, skin, intestines and buccal mucosa.**

The underlying forces energising this effort have to do with the explosive growth curves for the prevalence of diabetes mellitus – primarily Type 2 – along with obesity, cardiovascular disease and impaired glucose tolerance. Whatever the genetic intertwining that binds these conditions, the major underlying focus is on blood glucose. It is now unequivocal that a persistent elevation of blood glucose, as determined by A1c haemoglobin (HbA1c), increases the risk for microvascular complications such as retinopathy, neuropathy and nephropathy. (Glucose binds slowly to haemoglobin, forming the A1c subtype: the more glucose in the blood, the higher the level of HbA1c). On the other hand, years before these are manifest the risk for macrovascular disease begins in the Type 2 patient. The first clinical abnormality in Type 2 diabetes is a rise in post-prandial glucose. By definition, impaired glucose tolerance (IGT) is defined as

a post-prandial glucose between 140 and 199mg/dL. Current data implicate these glucose spikes – above the normal but below the definition of diabetes – as a source of oxidative stress to the endothelium. Thus, at least part of the knot between diabetes and cardiovascular disease becomes a little clearer.

With this preamble in mind, let's look at the current pharmacological approach to Type 2 diabetes. Up until now, primary treatment has consisted of life style changes and a variety of oral agents that either stimulate the beta cell or improve insulin sensitivity in the periphery. Insulin by injection was always an add-on when all else failed. It is outside the scope of this review to detail these treatments. For a number of reasons, the impact on post-prandial glucose has been minimal, even when achieving A1c goals; this still leaves cardiovascular risk in place, along with the untreated IGT population.

## THE BUCCAL MUCOSA

There are many advantages to the buccal mucosa as a delivery site. It is visible, resilient, protected by saliva, very vascular and has been used to deliver medications for hundreds (nitroglycerine) if not thousands of years (the yield from bark and leaves, or chewing tobacco – as the case may be). Transport across the buccal membrane is far more simple than the skin, alveoli or intestinal membranes (see Figure 1). Its structure consists of a layer of epithelium with more flattened cells at the surface, a lamina propria and submucosa with a rich vascular network draining into the superior vena cava. It is a tissue subject to daily trauma



from food ingested and chewed, especially coarse raw vegetable or hot spices. Healing is rapid – even from self-biting – because of the benefits of saliva.

Materials delivered to the buccal mucosa may pass through the cells or through the intercellular space (which widens as it gets closer to the basement membrane). These spaces do not contain peptidases or carbohydrases, which are located within the cells. It is felt that this is the pathway for large peptides such as insulin. Absorption and transport are affected by charge, conformation and lipophilicity.

### THE RAPIDMIST™ SYSTEM

At Generex we have developed a device, RapidMist™, for the administration of medications directly into the mouth as a metered-dose spray for absorption by the buccal mucosa. The benefits are compelling:

- ◆ Precise dosage control
- ◆ Rapid absorption
- ◆ A needle-free, pain-free, non-invasive technology
- ◆ Easy self-administration
- ◆ Improved compliance

The RapidMist™ technology has been specially designed for the delivery of large-molecule drugs, such as insulin. Oral-lyn™ is a unique oral formulation of insulin that is delivered via the RapidMist™ device directly to the mouth, where it is rapidly absorbed into the bloodstream through the buccal mucosa.

Crystalline human recombinant DNA regular insulin is put into liquid solution with a variety of GRAS-rated (Generally Recognised as Safe) additives; these are all commonly-used materials such as surfactants. Small micelles are created that are seven microns or greater, precluding entry into the deep lung. We believe that the usual hexamer is broken up into monomers, probably during the formulation. The formulation is placed into a slightly enlarged can commonly used in asthma sprays (see Figure 2). Used with the patented delivery device and standard propellant, a metered, reproducible dose is delivered into the oral cavity. It ‘umbrellas out’ and penetrates the epithelium of the mouth as described above (see Figure 3). Radionuclide studies show that any material not absorbed is swallowed. Of course the insulin, being an unprotected molecule, is denatured by the acid of the stomach and digested in the intestine by pancreatic enzymes.

Figure 1: Structure of the buccal mucosa

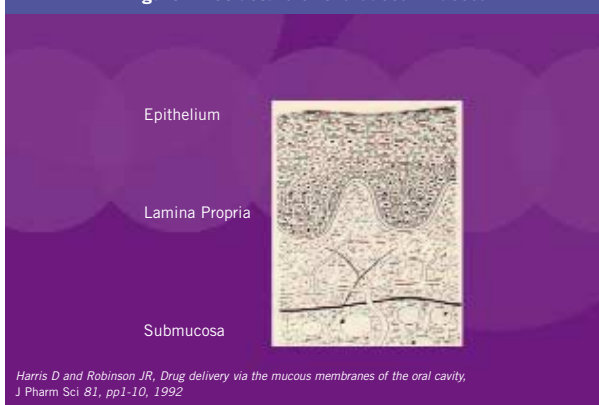


Figure 2: Overview of the RapidMist™ system

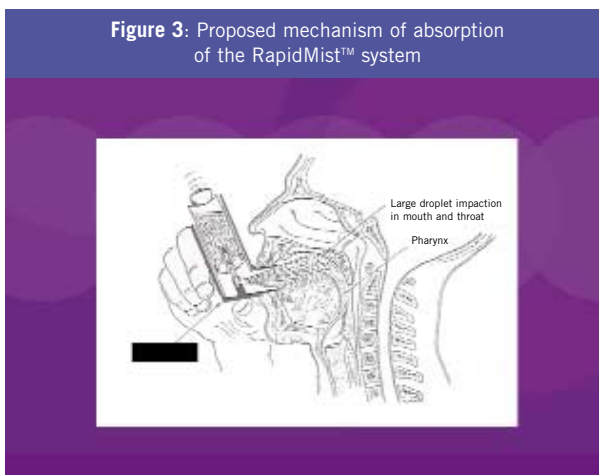
**Technology Overview**

- The Generex drug delivery system uniquely combines pharmaceutical agents in a proprietary aerosolised liquid formulation with a compact, easy to use device
- Compounds delivered through the buccal mucosa
- Substantial potential (applicable to most proteins and peptides)

**The RapidMist™ Device**

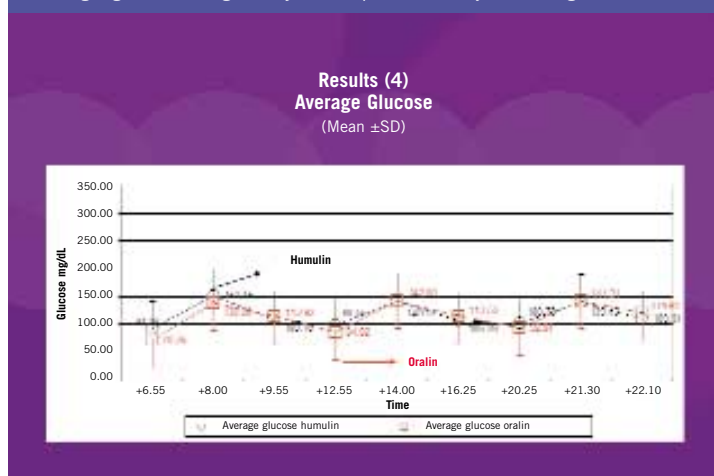
The image shows a yellow and purple metered-dose spray can. The can is cylindrical with a purple cap and a yellow body. It is shown in a three-quarter view, highlighting its compact and portable design.

Figure 3: Proposed mechanism of absorption of the RapidMist™ system



The preparation has been given to dogs four times a day for 24 months without any detectable clinical effects; no changes in the epithelium were detected by visual examination and cytopathological analysis. Similarly, no changes have been noted in patients who have received this material for 90 days. Stability studies show that the preparation is stable for at least six months at room temperature in the northern hemisphere.

**Figure 4:** Blood glucose levels of 10 patients with Type 1 diabetes maintained on glargine receiving Oral-lyn™ compared with injectable regular insulin



## CLINICAL STUDIES

Although Oral-lyn™ and the RapidMist™ delivery system are safe and simple, the question from the beginning has been whether or not it would make a substantial difference in the treatment of diabetes. The goals of treatment are a better quality of life and the prevention of complications. Data from the Diabetes Complications and Control Trial showed that intensive treatment in Type 1 diabetes reduced the risk of microvascular complications. Risk reduction in Type 2 patients was looked at by the UK Preventive Diabetes Studies. The conclusions – plus what we know about IGT – suggest that the risk of macrovascular disease may also be reduced. Obstacles to achieving these goals include not taking insulin often enough in the Type 1 group, and hypoglycaemia and refusal to take insulin at all in many Type 2 patients – especially pre-prandially. The various studies referred to below will clarify the pharmacokinetics of Oral-lyn™, as well as its use in a variety of clinical situations. The studies will be discussed in logical order rather than the chronological sequence in which they were conducted.

Glucose clamp studies have repeatedly shown that, after a dose of Oral-lyn™, the insulin levels start to rise rapidly; first appearing in 5-10 minutes and peaking at 30 minutes, returning to baseline at 90-120 minutes. (A glucose clamp is the ‘gold standard’ test of the pharmacodynamic profile of any insulin analogue; the analogue is administered to a test subject by the same route as intended for clinical use and blood glucose concentration (BG) is subsequently clamped – that is maintained approximately constant.) The

glucose infusion rate (GIR) reflects the insulin curves, with the GIR returning to baseline in approximately 120-150 minutes.

In another clamp study, dose-response was examined. The patients were given 5, 10 and 20 puffs of Oral-lyn™ and insulin levels, and GIR were measured over 180 minutes. The insulin levels rose proportionately, as did the glucose infusion rate. A comparable study was done without the clamp, and similar results were obtained. In this study, the decline in blood glucose was in line with the amount of insulin delivered to the mouth. Similarly the insulin levels rose proportionally, and the C-peptide dropped as expected. (In the body, insulin is synthesised as a propeptide which is then split into C-peptide and insulin; C-peptide levels can be used to differentiate between insulin produced by the body and that administered by injection.)

A recent pilot study compared pre-prandial Humulin® regular insulin with Oral-lyn™ in 10 Type 1 diabetic patients receiving baseline glargine insulin therapy. The aim of the study was to determine the suitability of dose and formulation of Oral-lyn™ for its use in a larger multi-centre trial. Humulin® regular insulin and Oral-lyn™ were found to induce similar glucodynamic responses during the 12-day observation period (see Figure 4). The study showed that, for a period of nine days, 10 patients with Type 1 diabetes maintained on glargine showed comparable blood glucose levels with buccal administration of Oral-lyn™ (five to eight puffs given pre- and post-prandially) as compared with injectable regular insulin.

## LOOKING AHEAD

Our technology platform has the potential for development of a product pipeline that can support a large number of specific applications. Although this discussion has focused on the delivery of insulin, more than 150 compounds have been identified that may be used in the RapidMist™ system. Research has begun on four specific target compounds: morphine, fentanyl, low molecular weight heparin and flu vaccine. The approach has the potential to revolutionise the way many large-molecule drugs are delivered, by providing a convenient, reliable and non-invasive alternative to needle injections.

*The author can be contacted at  
gbernstein@generex.com*