

KEY FACTS

- 171 million people are affected by diabetes.
- This number is expected to double by 2030.
- The greatest increases are in diabetes prevalence predicted to occur in India, China and US.

PERFECT DELIVERY

An accurate dose of insulin has to be taken daily by millions of people and yet fear of injections leads many to delay starting their medicine, with great detriment to their life expectancy. **Professor Stephen Bloom** and **Doctor Sagen Zac-Varghese**, Imperial College London, discuss the various delivery methods used to fulfil the demand for a safe, efficient and cost-effective needle-free method.

The World Health Organization estimates that 171 million people worldwide are affected by diabetes and predicts that this number will double by 2030. Insulin is the cornerstone of treatment for all types of diabetes. However, there is widespread reluctance to initiate insulin therapy, with injection phobia cited as a major cause of resistance.

There is a great need for a needle-free insulin delivery device that fulfils the criteria of being safe, efficient, user friendly, cost effective and that mimics the secretion of insulin from the healthy pancreas. Current guidelines for the management of type 2 diabetes advocate the initiation of oral hypoglycaemic agents, with insulin as a treatment of last resort. Earlier initiation of insulin may reduce morbidity and mortality from the complications of diabetes.

Insulin is a vulnerable two-chain peptide, too big to be easily absorbed through a biological surface and whose dose cannot vary without risking hypoglycaemia. There are a number of novel insulin delivery systems being investigated and the applicability of these devices may be extrapolated for delivery of other peptide drugs.

Author profiles



Professor Stephen R Bloom holds a dual role as chair of the academic Department of Investigative Medicine at Imperial College London, UK, and as clinical director for Pathology at Hammersmith Hospital, London. He is also a director of Thiakis and has been a member of the Main Scientific Board for AstraZeneca and advisory boards of Upjohn and Novartis.



Dr Sagen Zac-Varghese is an endocrinology and diabetes specialist registrar who is currently undertaking a PhD at the Department of Investigative Medicine at Imperial College London.

Subcutaneous insulin

Various injection regimes attempt to mimic actions of the pancreas. Traditional needle and syringes has been largely replaced by insulin pen injectors, which were introduced in 1985. Insulin pumps, continuous subcutaneous insulin infusion (CSII), were also introduced around this time. CSII mimics the actions of a normal pancreas and offers greater lifestyle flexibility, but it requires high user input and should only be considered for strongly motivated candidates.

Intraperitoneal insulin

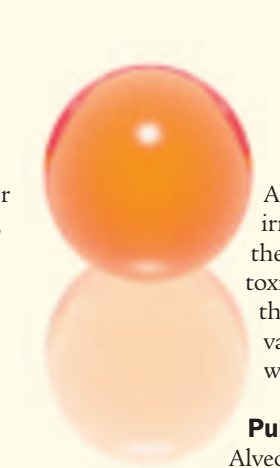
These devices are implanted under local anaesthetic, usually in the left, lower part of the abdomen. Insulin is absorbed rapidly by the portal system and so reduces peripheral hyperinsulinaemia. This is also the reason given for the lower rates of severe hypoglycaemia. The high initial failure rate of these pumps have been attributed to infection and pump blockage. These problems have now been largely resolved.

Jet injectors

Compressed air or a spring device creates a powerful, liquid insulin spray that is forced through the skin into the subcutaneous tissue. These needle-free devices were originally marketed as a painless alternative to needles and syringes. However, they can cause significant pain and bruising as well as damage to the skin's epithelial surface. Cost is also a prohibitive factor as the devices are not covered by many insurance plans.

Transdermal

Transdermal drug delivery is effective for many drugs. Skin has a large surface area, is easily accessible and allows for painless drug delivery. It avoids first pass hepatic metabolism, which increases bioavailability but leads to peripheral hyperinsulinaemia. Transdermal insulin delivery is not effective as the skin's outer layer forms a barrier to



large molecules. Attempts to weaken this barrier have used absorption enhancers, iontophoresis, sonophoresis and microneedles. These enhance transdermal transport by increasing drug solubility and diffusion, and by the provision of additional driving forces.

Microneedles

Microneedles painlessly disrupt the outer skin and facilitate transdermal drug delivery. Microneedle arrays can be silicon, metal or biodegradable polymers and can have solid or hollow needles with tapered or bevelled tips. The disadvantages of this delivery are the same as those for all forms of transdermal drug delivery.

Iontophoresis

Iontophoresis drives molecules down a potential gradient created by a small electric current. Insulin delivery by this route has proved a greater challenge: used alone it does not allow for sufficient insulin delivery. Efforts have focused on combinations of iontophoresis with other drug delivery systems, such as combining iontophoresis with chemical enhancers. Unfortunately, this increases the delivery of enhancer into the skin, which can cause skin irritation and other possible toxic effects.

More stringent toxicology studies are needed if iontophoresis is proposed for long-term treatment. The low bioavailability, cost of the device and potential damage to the skin make iontophoresis an unlikely candidate for insulin delivery.

Sonophoresis

Low frequency ultrasound waves increase the permeability of human skin enabling transdermal drug delivery. Skin permeability is increased with decreasing frequency, increased time of exposure and increased intensity.

Safety of long-term ultrasound use has yet to be established. Limitations include cost of the device, low bioavailability of delivered insulin and toxicity concerns.

Nasal

Nasal drug delivery was proposed early on, however, it was limited by the highly efficient nasal mucosal epithelial barrier and the mucociliary clearance system. In the 1980s, various research groups demonstrated that the combined use of insulin and absorption enhancers led to glucose lowering effects.

The pharmacological profile of intranasal insulin is similar to intravenous insulin with a rapid increase and decrease in serum insulin concentrations. This profile could be applied to treat post-prandial hyperglycaemia. Chitosan, microspheres, liposomes and gels have been used to enhance nasal insulin delivery. But nasal insulin delivery has many limitations.

Agents used to improve absorption can cause nasal irritation and mucociliary damage and weakening the mucosal barrier can lead to increased transport of toxic or infectious particles. Bioavailability is low and there is considerable intra/inter individual variability. High doses of insulin need to be used, which would increase costs.

Pulmonary

Alveoli are thin membrane and richly vascularised with a large surface area allowing for rapid drug absorption. Onset of action of inhaled insulin is faster than subcutaneous insulin. It can be used for post-prandial hyperglycaemia, but must be combined with long acting subcutaneous insulin.

There is wide variation in drug delivery due to changes in flow rate, inhaled volume and breath holding. Particle size and speed of delivery are also important parameters. Loss of drug in the pulmonary dead space leads to low efficiency with only 20-30% of the insulin reaching the alveoli. The overall bioavailability is low (<20%) so high doses are required to achieve glucose lowering effects.

Exubera is approved for use in type 1 and 2 diabetes. It is a rapid acting, recombinant human DNA, dry powder insulin, which is inhaled through the mouth into the lungs using a hand-held device. Randomised controlled trials showed that inhaled insulin was comparable over 24 weeks to subcutaneous insulin.

There is a wide variation in drug delivery due to changes in flow rate, inhaled volume and breath taking.

Studies showed that patient satisfaction for inhaled insulin was higher than conventional regimes and there was higher acceptance of insulin therapy. However, side effects include increased weight gain, episodes of hypoglycaemia and 25% had a mild to moderate cough. Insulin has growth-promoting properties and safety concerns have been raised regarding long-term lung damage.

Pfizer stopped marketing Exubera in January 2008 and it will no longer be available from September 2008. In January 2008, Novo Nordisk and, in March 2008, Eli Lilly halted trials of their inhaled insulin products. MannKind Corporation continues with phase 3 trials of their dry powder inhaled insulin Technosphere.

Buccal

Buccal drug administration has many advantages including its accessibility, large surface area, low protease enzyme activity and rapid recovery potential compared with other

mucosal surfaces. Disadvantages include the varying degrees of metabolism and the continuous flow of saliva into the mouth, which may wash away the delivery system.

Oral insulin

Oral insulin is absorbed through the gastrointestinal tract into the portal circulation, which would mimic the transport of endogenous insulin. An insulin concentration gradient exists between the portal and the systemic circulation, which may be important for glucose control.

Parenteral insulin leads to loss of this gradient, which may contribute to hypoglycaemia. Parenteral insulin also causes peripheral hyperinsulinaemia, which has been associated with atherosclerosis. The harsh gastrointestinal environment has made oral insulin delivery an elusive goal and various approaches have been attempted. Absorption enhancers such as bile salts, zonula occludens toxin, nanoparticles, liposomes and insulin conjugates have all been tried.

Future delivery systems

The importance of glycaemic control in reducing complications is undisputed. However, there is still widespread reluctance in initiating insulin therapy. The

greatest increase in diabetes prevalence is predicted in India, China and US. A needle-free, safe, efficient, accurate, cost effective and affordable delivery system is needed that would be accessible to developing countries.

All the proposed novel insulin delivery systems have large dose-to-dose variability. While this is not a major concern in people with mild to moderately severe type 2 diabetes, who still retain adequate endogenous beta cell function to maintain glucose homeostasis, this is a major cause for concern in people with type 1 or severe type 2 diabetes who lack this endogenous system of control. In such subjects, small increases in exogenous insulin administration could tip the balance and cause severe hypoglycaemic episodes.

Many advances in insulin delivery have come about over the past few years with the licensing of inhaled insulin and with buccal and oral insulin entering phase 3 trials. The withdrawal of inhaled insulin by many major drug companies has made the future uncertain, however, the advancement of nanotechnology will enable the development of delivery systems and there is hope for the future. **WPF**

References are available on request from the authors.

BD, BD Logo and all other trademarks are the property of Becton, Dickinson and Company. ©2008 BD. Link to Business.

BD Medical - Pharmaceutical Systems

Your confidence,
our commitment

BD Medical
Pharmaceutical Systems

11, rue Aristide Bergès
38800 Le Pont de Claix
France
Tel: +33 (0)4 76 68 36 36
Fax: +33 (0)4 76 68 35 05
www.bd.com

quality
compliance
safety
confidence