intolerant of regimes involving needle-sticking for insulin injections and finger-pricking for glucose monitoring. This population offers an important market opportunity for more user-friendly insulin administration technology and non-invasive blood glucose monitoring. The latter need is already being answered by the device industry.

2.3 Opportunities for drug delivery technology

2.3.1 Insulin

During the years when there seemed no alternative to insulin injections, the best that the industry could do was to make those injections as non-threatening as possible. The skin still had to be penetrated by a needle, but the needle and syringe were disguised as a colourful pen-like object. Insulin pens have been a feature of the market for a decade and have been widely adopted, especially in Europe. This is perhaps due to the European hegemony of Novo Nordisk.

For more than ten years, companies have been attempting to develop non-invasive ways of delivering insulin, but it is only within the past five years that success came within reach. This may well be a sign that the drug delivery sector has finally developed technologies to overcome the problems of getting large-molecule drugs reliably and fairly efficiently into the human system without injecting them.

There are, essentially, three alternatives to insulin injections: inhalation into the lung, mucosal absorption from the mouth or nose, and transdermal absorption. The size of the insulin molecule is a problem with all routes, but products currently in development indicate that it can be overcome.

Inhalation: The first insulin product for delivery by inhalation into the lung, in a similar manner to giving a bronchodilator by metered-dose aerosol, is already marketed. This is Pfizer's Exubera, confidently predicted at the time of launch to have a peak sales potential of $1-2 billion but still struggling to pass £300 million. It is probably facing the same problem as so many pioneering ventures: good in theory and principle, but needing some problems tackled in the practical area. The companies developing follow-on inhaled products (Lilly in collaboration with Alkermes and Novo Nordisk in collaboration with Aradigm) are doubtless hoping to overcome these problems before going to market.

Mucosal absorption: Absorption of insulin through the buccal or nasal mucosa is also at an advanced stage of development; companies include Aegis, Nastech, Bentley, Nanoderma and Generex. The feasibility of the mucosal route for systemic drug delivery has long been recognised; glyceryl trinitrate, for example, is often given by sublingual spray and a formulation of fentanyl for buccal administration is in advanced development. More uncertain is the prospect of efficiently delivering a measured dose of a large-molecule compound like insulin in a highly reproducible way. This will be essential for Type 1 diabetes and important, though not so crucial, in Type 2 disease.

Transdermal delivery: There are several companies investigating this route, indicating that it is a realistic target for development. They include Altea, Alza, Transpharma and Phosphagenics. To drive a large molecule across the dermis requires some means of active transport, and these companies are exploring technologies such as electroporation which opens temporary channels through which the drug molecules can pass. Transdermal delivery is well documented for a range of drugs and its prospects for insulin appear good; one advantage over pulmonary, nasal and buccal approaches is that it is not likely to be affected by respiratory tract infections.

Improvements in injection technology: Delivering insulin by injection will always have the attraction that it is reliable and reproducible.. Thus we expect that for some years to come many doctors, and even a majority of diabetic patients – especially those with Type 1 – will continue to rely on insulin by injection.

There is now a new generation of devices on the market and in development to make insulin injection not only less intrusive but also more flexible and efficient. Insulin pumps, which deliver the hormone through a small cannula permanently inserted into the skin of the abdomen, are now smaller than a personal pager and highly sophisticated in design. It is only a matter of time before such a pump is twinned with a sensitive, robust blood

7 Delivery platform: other insulin delivery routes

Alternative routes for administering insulin aim to get it into the bloodstream via a mucosal surface (nose or mouth); by active transport across the skin or by the oral route using a formulation to protect the hormone from degradation. Formulations designed to deliver the drug through the lining of the mouth are termed “buccal” in this report, to distinguish them from oral forms which are swallowed.

7.1 Delivery technology: buccal insulin delivery

7.1.1 Case Study: Oral-lyn buccal spray (Generex)

Generex Biotechnology Corporation (Toronto, Ontario, Canada) is engaged in research and development of drug delivery systems and technologies. Generex has developed a proprietary platform technology for the delivery of drugs into the human body through the oral cavity with no deposit in the lungs. The company's proprietary liquid formulations allow drugs typically administered by injection to be absorbed into the body by the lining of the inner mouth using its proprietary RapidMist device.

The device is a small, lightweight, hand-held, easy-to-use aerosol applicator comprised of a container for the formulation, a metered dose valve, an actuator and dust cap. Using the device, the patient self-administers the formulation by spraying it into the mouth. The flagship product, Oral-lyn (oral insulin) is in late stage clinical trials around the world. In fact Oral-lyn is already on sale in Ecuador for the treatment of Type-I and Type-II diabetes.

Figure 7.1: Oral-lyn aerosol applicator

Source: ”Drug Delivery in Diabetes”, publication OnDrug Delivery Ltd

In 2006 Generex registered a new patent in the US that covers broad claims for the delivery of macromolecules via the buccal cavity of the mouth, further safeguarding its RapidMist drug delivery technology. The new patent pertains to the making of the oral formulation that allows absorption of a drug by the buccal cavity of the mouth.

In April 2007 Generex entered into an exclusive master product licensing and distribution agreement with Leosons General Trading Company, a leading distributor of North American products in the Middle East, for the commercialisation of Oral-lyn in 15 Middle Eastern countries, including Saudi Arabia and the United Arab Emirates (UAE). The Agreement requires Leosons to file all requisite applications for approvals by the Autumn of 2007. (According to the International Diabetes Federation, the UAE has the second highest rate of diabetes in the world, affecting 70 per cent of residents. Other Gulf States also have significant diabetes problems, with Saudi Arabia ranked third, Bahrain fourth, Kuwait fifth, and Oman sixth.)

3 Key drug delivery companies in diabetes research

Table 3.1 provides brief details on companies involved in drug delivery research and development in relation to the treatment of diabetes. The majority of the companies included are small-to-medium sized outfits specializing in focused technologies and/or specific routes of administration. The pharmaceutical companies leading the diabetes market in terms of drug sales do not, in general, have the expertise to develop specialized delivery solutions, when these are required, thus they enter into strategic collaborations with drug delivery specialists many of which are included in Table 3.1: .

Table 3.1: Leading drug delivery specialists in diabetes research

Company	Technology Platform	Route of Administration	Diabetes Product Pipeline
Access Pharmaceuticals	Colabamin-mediated transport	Oral	Development of oral insulin
Aegis Therapeutics LLC, San Diego, CA	ProTek technology, applied to intranasal absorption of insulin	Intranasal	Development stage
Alkermes, Inc	AIR Insullin System – solid insulin dosage	Inhalable	Phase III development with Eli Lilly
Altea Therapeutics	PassPort transdermal system using electroporation	Transdermal	Phase I trial completed
Alza Corp., Mountain View, CA	e-Trans electrotransport technology (iontophoresis)	Transdermal	Development stage
Amylin Pharmaceuticals Inc., San Diego, CA	Various	Subcutaneous	Long-acting s.c. injection of Byetta (exenatide) in Phase III; intranasal exenatide in Phase I.
Apollo Life Sciences	Oradel delivery platform	Oral	Oral insulin
Aradigm	AERx delivery system	Inhalable	Phase III development with Novo Nordisk
AVI BioPharma	Neugene antisense (Exon skipping technology)	Systemic	Preclinical development
Band & Olufsen Medicom, Denmark	Insulair pressurized metered-dose inhaler for insulin	Pulmonary	Development stage
Baxter	Promaxx protein microspheres	Pulmonary	Promaxx formulation of insulin: Phase I study completed
Bentley Pharmaceuticals Inc, Exeter, NH	Nasulin recombinant insulin formulation	Intranasal	Phase II studies of Nasulin completed
BioDel Inc., Danbury, CT	Recombinant human insulin	Injectable and sublingual	ViaJect injectable in Phase III trials; ViaTab sublingual in early development
ConjuChem	Drug affinity constructs	Subcutaneous	GLP-1 receptor agonists in development
Depomed Inc., Menlo Park, CA	AcuForm extended release technolc	Oral	Glumetza, metformin ER tablets, commercialized
Eiffel Technologies	SCF technology	Transdermal	Insulin

8.3 Our opinion on delivery of non-insulin drugs

Where the technology is now, its evolution, achievements and pitfalls

Most of the candidate products described in this chapter are incretin mimetics (GLP-1 analogues). Closest to market would appear to be the once-weekly injection Byetta LAR from Lilly/Amylin/Alkermes, and the once-daily injectable liraglutide from Novo Nordisk. At first glance, a once-weekly injection has a major advantage over a once-daily injection, but some observers have expressed uncertainties about the pharmacokinetics of the once-weekly product. Another factor is the size of the needle used for injection; Byetta LAR requires a coarser needle than liraglutide.

No oral formulation of an incretin mimetic has yet reached the clinical trials stage.

Competition

The incretin mimetics are a new class of anti-diabetic agents, unique in that they act selectively to reduce postprandial blood glucose levels; their competition might be expected to come from bolus-dose insulin formulations. However initial licenses for incretin mimetics specify their use in Type 2 diabetes as add-on to other oral hypoglycemics when the response to these is unsatisfactory. In this context the incretin mimetics occupy a niche in the market which they share with the glitazones (aka thiazolidinediones) Avandia and Actos. These latter products currently face significant negative publicity because of safety concerns (particularly in the case of Avandia) and this might operate in favor of incretin mimetics.

Potential future applications

As the incretin mimetics build a reputation for efficacy and safety, they will probably come to be used, in time, as part of first-choice therapy in Type 2 diabetes, rather than for refractory cases as at present. The availability of products with more convenient dosage regimes than the present twice-daily injections will be important in encouraging the widespread acceptance of incretin mimetics.

Activity in the market

With the glitazones under a cloud because of safety concerns, interest in alternative drug classes, including incretin mimetics, has heightened. There are a number of candidates in the pipeline and if they all present similar dosage problems to the original Byetta, they will present an opportunity for drug delivery development work.

Major players

Contenders in this field now include three of the "big guns" in the diabetes market – Eli Lilly, Novo Nordisk and Roche. A fourth, sanofi-aventis, has in development AVE0010, an injectable GLP-1 agonist, licensed from Zealand Pharma and now completing Phase IIb trials in patients with type 2 diabetes, which will probably require formulation development in order to compete with other GLP-1 agonists in dosage convenience. The field also includes a smaller company with a strong foothold in the diabetes arena – Amylin – and at least one recent entrant, ConjuChem. Thus, it is a diversely populated arena.

