Due to the great progress in biotechnology, various therapeutic peptides and proteins can nowadays be produced in commercial quantities. With a few exceptions, all peptides and proteins are administered via injections. This administration route is often painful and patient compliance is low. Moreover, fear of needles can lead to patients failing to start treatment immediately. Therefore, academic and industrial research groups are working on the development of peptide/protein analogues with improved features for non-invasive drug delivery, as well as on novel drug delivery systems. Among the non-invasive delivery routes, including the buccal, nasal and pulmonary application, the oral route is the by far most favoured. Furthermore, it must be considered that oral drug delivery represents an estimated US$25 billion (€18.3 billion) market.

Besides the big pharmaceutical companies, which commonly have research departments focusing on novel drug delivery systems, there are various small, medium and big drug delivery companies, which usually have their own patented technologies. Products are often developed via collaborations between big pharmaceutical companies and drug delivery companies. The technologies of the drug delivery companies Emisphere, Merrion Pharmaceuticals, Nobex, Spherics and ThioMatrix have been discussed in the last issue of this series. Generally, once a delivery system for a certain peptide can be developed, the same technology might be suitable for the delivery of other therapeutic peptides. Having this in mind, the focus of this issue will be on recent (2006–2007) academic developments for oral insulin delivery as well as on current oral insulin delivery systems under investigation by pharmaceutical companies.

**Innovations in Academic Research**

In order to successfully deliver insulin via the oral route, some barriers must be overcome. These barriers are summarised in Table 1. Current strategies include the protection of insulin from degradation by gastrointestinal (GI) enzymes and the improvement of insulin permeation through the GI mucosa, as well as encapsulation of insulin in liposomes, micro- and nanoparticles or polymeric matrices. An overview of current approaches to delivering insulin via the oral route is provided in Table 2.

The great majority of articles focusing on novel oral delivery systems for insulin published within the last year are based on micro- and nanoparticles. Some of these particulate systems additionally exhibit muco-adhesive properties, facilitating a prolonged retention time of the dosage form on GI mucosa, which consequently leads to higher absorption rates. Such muco-adhesive nanoparticles have been prepared, for example by a French group using polyester (poly-ε-caprolactone) and a polycatonic non-biodegradable acrylic polymer. The nanoparticles displayed an insulin encapsulation rate of 96% and led to a decrease of the blood glucose level in diabetic rats. Another group investigated the potential of muco-adhesive nanoparticles based on a hydroxypropyl-β-cyclodextrin-insulin complex encapsulated...
polymethacrylic acid-chitosan-polyether (polyethylene glycol-polypropylene glycol copolymer) and concluded from in vitro data that these novel nanoparticles might be useful tools for oral insulin delivery.\textsuperscript{18} Other promising nanoparticles that have been evaluated in vivo regarding their potential for oral insulin delivery are based on chitosan and poly-γ-glutamic acid,\textsuperscript{6} polyactic-co-glycolic acid (PLGA) and PLGA-Hp55,\textsuperscript{6} lectin-modified solid lipid nanoparticles\textsuperscript{1} and soybean phosphatidylcholine and biodegradable polymers.\textsuperscript{19}

Besides nanoparticles, various microparticulate insulin delivery systems have been recently evaluated in vivo. Morishita et al. prepared muco-adhesive insulin-loaded polymer microcapsules composed of cross-linked polymethacrylic acid and polyethylene glycol and demonstrated their efficacy to lower blood glucose levels after oral administration to diabetic rats.\textsuperscript{20} The capability of other hydrogel microcapsules based on polyethylene glycol dimethacrylate and methacrylic acid to deliver pharmacologically active insulin via the oral route could be demonstrated in another study in non-obese diabetic rats.\textsuperscript{21}

Other strategies developed by academic research groups for which promising in vivo data are available include polymer-enzyme conjugates such as chitosan–aprotinin,\textsuperscript{15} polyactic acid-β-pluronic-poly-lactic acid vesicles,\textsuperscript{22} liposomal formulations based on cholesterol, dipalmitoyl phosphatidylcholine (DPPC)-cholesterol mixture and muco-adhesive agent (methyl cellulose)-added DPPC-cholesterol mixture\textsuperscript{17} and self-emulsifying formulations.\textsuperscript{24}

Industrial Approaches

Apart from academic research, various oral insulin formulations have already entered clinical trials. Companies to be highlighted in this context are Emisphere, Biocon, Apollo Life Science, Oramed and Diabetology.

The technology of Emisphere is based on patented delivery agents. These small molecular delivery agents, of which more than 4,000 are available, enhance the uptake of hydrophilic macromolecules such as insulin via the trans-cellular way. They act as a kind of carrier and dissociate from insulin after they have transported the drug into the bloodstream. In October 2006, Emisphere announced the results of their phase II clinical trial for an oral insulin tablet based on the Eligen\textsuperscript{TM} technology. Although the evaluated delivery agents displayed a good safety profile, mixed results regarding the efficacy of the formulation were obtained. To move their oral insulin programme forward, Emisphere has recently recruited a scientific advisory board of highly qualified persons in the field of diabetes.

Biocon, an Indian company, has also already conducted clinical trials. Their delivery system is based on Nobex technology. In brief, a low-molecular-weight polymer is attached to insulin at specific sites. Such a modification can reduce enzymatic degradation of insulin during GI passage and furthermore improve insulin permeation through GI membranes. Biocon’s oral insulin programme has successfully completed phase I human clinical trials and is expected to enter phase II human clinical trials soon.

Other promising nanoparticles that have been evaluated in vivo include

<table>
<thead>
<tr>
<th>Technology</th>
<th>Comments</th>
<th>Information</th>
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<tr>
<td>Capsulin\textsuperscript{TM}</td>
<td>The Capsulin delivery technologies are based on a mixture of permeation enhancers and solubilisers that can be generally regarded as safe.</td>
<td><a href="http://www.diabetology.co.uk">www.diabetology.co.uk</a></td>
</tr>
<tr>
<td>Eligen\textsuperscript{TM}</td>
<td>For this technology, a multitude of data demonstrating the efficacy for oral peptide delivery is available. Eligen technology can be regarded as safe.</td>
<td><a href="http://www.emisphere.com">www.emisphere.com</a></td>
</tr>
<tr>
<td>Nobex\textsuperscript{TM}</td>
<td>Conjugated drug-polymer molecules are created by attaching low-molecular-weight polymers at specific sites. Biocon uses Nobex technology in its oral insulin programme.</td>
<td><a href="http://www.biocon.com">www.biocon.com</a></td>
</tr>
<tr>
<td>Oramed Technology</td>
<td>Oramed announced the start of its phase I clinical trial for oral insulin in 2007.</td>
<td><a href="http://www.oramedpharma.com">www.oramedpharma.com</a></td>
</tr>
<tr>
<td>Thiomers\textsuperscript{TM}</td>
<td>Thiomers are polymers that display thiol groups. Such modifications lead to an improvement of the muco-adhesive, cohesive and permeation-enhancing properties.</td>
<td><a href="http://www.thiomatrix.com">www.thiomatrix.com</a></td>
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</table>

Diabetology, a UK-based company, has developed an oral insulin capsule named Capsulin\textsuperscript{TM}. Besides unmodified insulin, the capsule contains a mixture of absorption enhancers and solubilisers. A major advantage of this technology is that all utilised excipients are generally recognised as safe. Therefore, one major aspect of regulatory risks, the toxicity of novel delivery agents, can be obviated. Capsulin for the treatment of type 2 diabetes mellitus has already entered phase II clinical trials. Another company that has developed a capsule for oral insulin is Oramed in Israel. In May 2007, Oramed announced the official commencement of phase I clinical trials in Jerusalem.

Apollo Life Sciences in Australia recently announced promising pre-clinical results for oral insulin. OraCad\textsuperscript{TM} is a delivery system based on small-molecule transporters that protect insulin from degradation in the stomach, and improves insulin permeation through mucosal membranes. Apollo plans to start phase I clinical trials this year.

Conclusion

In Table 3, various technologies for oral insulin delivery are summarised. According to the ongoing clinical trials, it is believed to be only a matter of time before the first oral insulin formulation enters the market. Academic researchers are already working on optimised novel oral insulin delivery systems, mainly based on micro- and nanoparticles. The delivery technologies discussed in this article might furthermore be used for the oral delivery of other therapeutic peptides and proteins, including calcitonin and parathyroid hormone.