The oral delivery of macromolecules: 75 years of need

A new carrier technology should enable the oral delivery of macromolecules such as insulin and heparin

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On January 11th 1922 a young boy, Leonard Thompson, was given an experimental daily drug therapy. Active pancreatic extracts were administered by injection to attempt to reduce the boy’s blood glucose levels, which were measured at 500mg/dl. The child had been excreting nearly five litres of urine per day, and despite a strict and controlled diet, it was expected that he would die within a few months. The effect of the new therapy was dramatic: there was an immediate improvement - the child looked better, felt stronger and had more energy. One is hard-pressed to find medical history as significant a case of the prevention of a fatal illness. The disease was diabetes mellitus; the drug was insulin.

In that same year, a researcher named Howell discovered a mucopolysaccharide abundant in the liver. This compound had shown activity in vitro in preventing the clotting of shed blood. It was soon used in vivo to treat venous thrombosis. The drug was heparin.

In the 75 years since the use of these compounds first came into being, tens of millions of patients have been treated with insulin and heparin. The value of these drugs in terms of the number of lives saved is immeasurable. If there is a downside, it is that the patient must submit multiple injections per day with each compound. Injections are painful, inconvenient and often difficult, but given the alternative, the patient is prepared to endure the process.

Oral delivery of macromolecules

Insulin and heparin must be delivered by syringe because they are macromolecules, compounds with molecular weights of several thousand daltons. Today, macromolecules are administered only by injection, but drug delivery companies such as Emisphere and others are working to change this.

The main barriers to effective oral drug delivery of macromolecules are degradation of the active drug and poor absorption. The high acid content and enzyme activity of the digestive tract can degrade some drugs well before they reach the site of absorption into the bloodstream. All natural and recombinant peptides, as well as certain compounds with carbohydrate and lipid components, are susceptible to this degradation. In addition, the size of these compounds generally means that they

Figure 1. The proposed mechanism of action for Emisphere's oral drug delivery technology.
cannot effectively traverse the cells of gastrointestinal tract to reach the bloodstream. Thus, drugs with beneficial medicinal properties such as insulin and heparin are limited to injectable formulations. This absorption problem may even render important therapeutic compounds impractical for the treatment of chronic disease, even if they are effective, as patients would no be willing to submit to routine daily injections. An effective, new delivery system would make the development and commercialisation of many macromolecules and other poorly absorbed compounds much more practical.

The need for improved delivery systems

There are pressures in many countries to reduce overall healthcare costs. One way of lowering costs is by moving patients more quickly from in-hospital to outpatient care. At the same time as there are cost pressures, the biotechnology industry has produced vast array of new therapeutic macromolecules (proteins and peptides); these compounds require an injection or intravenous infusion, which is often best rendered by a healthcare provider in a hospital or clinic. Unfortunately, patients' lack of tolerance for needles often result in an inadequate compliance when a prescribed injectable dosing regimen is done in an outpatient setting. An oral delivery system for macromolecules would be of major benefit in helping reduce overall health costs, as greater outpatients care could be instituted.

Oral products would increase compliance by creating a more user-friendly dosage form. This would have the advantage of increasing the use of prescribed medications, thereby reducing the incidence of disease. Since oral dosage forms can be taken on an outpatient basis, the burden on clinics and hospitals to administer such drugs would be reduced.

Emisphere's oral delivery technologies

Emisphere has synthesised a library of well-defined, proprietary compounds (Carriers) that are single molecular entities, which can form supramolecular complexes with a diverse array of injectable therapeutics. These Carrier molecules vary widely in their chemical structure, solubility, hydrophobicity, electrostatic and other physical/chemical properties. In most cases, an individual therapeutic agent will require a unique Carrier for optimal oral delivery. Based upon the chem-
ical and physical properties of an individual therapeutic, Emisphere seeks to identify the optimal Carrier by in vitro and in vivo screening of the company’s expanding library of Carrier compounds. Technologies being developed by Emisphere would allow high throughput synthesis and screening of Carrier compounds thereby reducing the time required for identifying a Carrier for a given injectable therapeutic. (A schematic showing the proposed mechanism of action for Emisphere’s oral drug delivery technology is given in Figure 1.)

On the basis of preclinical testing and clinical trials, Emisphere’s technologies have demonstrated the key properties essential for an effective oral drug delivery system for macromolecules. These properties include: 1) significant absorption of a macromolecule in humans, 2) an acceptable, palatable oral dosing formulation, 3) a lack of system toxicity, and 4) maintenance of the biological effects of the drug.

The supramolecular complex formed by the Carriers and certain therapeutic compounds has applications in the delivery of drugs through other biological membranes, including intestinal, nasal, buccal, sublingual, subcutaneous and intra-ocular membranes. Emisphere has shown that the Carrier technology can increase absorption through these and other biological membranes.

There are several important key advantages to Emisphere’s technology. The Carriers are able to deliver a diverse group of molecules (proteins, carbohydrates, peptides and other poorly absorbed compounds). Oral drug delivery using the Emisphere Carriers does not rely upon the addition of other agents that can have adverse effects on the intestinal membranes or digestive process. Various types of oral formulations, including suspensions, tablets and capsules, can be created using the technology. In addition, the manufacturing processes required to produce the Carrier material or the final drug formulation in commercial quantities are readily available.

**Oral delivery of proteins**

In the early part of 1997, Eli Lilly & Company, the world’s leading protein research and development company, entered into a strategic alliance with Emisphere to develop oral products for two protein products. Lilly became interested in forming the partnership after testing the Emisphere technology in its own laboratories.

Emisphere has several programmes in progress to explore the use of the company’s technology in the field of oral protein delivery. One programme is to create an oral form of the drug first taken in 1922 by Leonard Thompson - insulin. Hundreds of Emisphere Carriers have been screened over the years to determine their activity in delivering insulin (porcine) orally. Emisphere has conducted both pharmacodynamic (pD) and pharmacokinetic (pK) testing. The pK analysis involved the direct measure of porcine insulin in rat serum. A radioimmunoassay with an antibody having only a 7 per cent cross-reactivity to rat insulin was used confirming that the insulin delivered was not endogenous. Three dosing regimens were used in the testing: oral gavage (oral), intraduodenal injection (ID) and subcutaneous injection (SC). The dosing solutions were prepared by dissolving the Carriers in water and simply mixing the Carrier solution with the drug solution. These solutions were then dosed to the rodents as clear liquids. The insulin activity and pD effect were confirmed by measuring the change in serum glucose. Demonstration of oral
delivery of insulin in a rat model is shown in Figure 2 (pK effect) and Figure 3 (pD effect).

As part of Emisphere’s continued studies in the area of oral drug delivery, the company discovered a novel Carrier compound, sodium N-8-[2-(hydroxybenzoyl) amino] caprylate (SNAC), that promoted the gastrointestinal absorption of heparin following oral administration to rats, dogs, primates and healthy human subjects. The company decided to initiate a clinical development programme with the SNAC Carrier to create an oral formulation of heparin.

SNAC was screened for potential unwanted pharmacological activities in a battery of 75 functional and receptor-mediated assays. The Carrier was found to have no significant pharmacological activity. Acute toxicology studies were then carried out in two species to assess the safety of the Carrier/heparin oral dosing solution. Mice and monkeys were subjected to multiple (28 consecutive days) oral dosing of the Carrier (up to 1800mg/kg). No damage was observed in any of the organs or tissues examined (1). SNAC was negative in a Salmonella typhimurium/Escherichia coli Reverse Mutation Assay, did not induce gene mutation at the XPRT locus in AS52 cells, and was negative in a mouse micronucleus assay. The Carrier is neither a clastogen nor a spindle fibre toxin at the doses tested.

The combination of Carrier and heparin is not comparable with anything previously studied. Unlike prodrugs, Emisphere Carriers and heparin are not covalently linked in a fixed stoichiometry. Preclinical studies have demonstrated that, over the range tested, heparin absorption increase with increasing Carrier dose. Conversely, for a fixed oral

doC of Carri, heparin absorption increase with increasing heparin dose.

Efforts in formulating the SNAC Carrier with heparin resulted in the development of several palatable taste-masked solution formulations. Under an IND, Phase I dose studies in healthy volunteers were designed and conducted to establish the safety, tolerance and pharmacokinetic profiles of orally administered single and multiple-doses of Carrier, alone and in combination with heparin at various heparin, SNAC and vehicle concentrations. Figure 4 shows the results of oral dosing of Heparin UF using Emisphere’s oral drug delivery technology in normal healthy volunteers.

Phase II and Phase III studies will be carried out in joint replacement patients to assess the clinical outcome following a two-week course of oral heparin therapy using the SNAC carrier.

The future of drug delivery

Emisphere’s clinical results portend a future trend in drug delivery - increasing patient comfort. Clearly the animal and human results generated by the company indicate that the oral delivery of macromolecules is possible, and that commercial products are indeed likely. Emisphere believes that its first products will be commercialised in the next few years. The company has entered into strategic alliances with a number of major pharmaceutical companies (including Eli Lilly and Elan) to develop productions using the novel Carrier technology. If Emisphere and its partners are successful, the next century will not only see a significant improvement in the convenience of drug administration, but also an improvement in overall healthcare at a lower cost.

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References