MEETING REPORT

Highlights from the Society for Medicines Research meeting Improving Medicines Through Drug Delivery, held in London on July 5, 2001.

Adaptations and Innovations in Drug Delivery

by David Cavalla

Summary

The most recent meeting organized by the Society for Medicines Research, entitled *Improving Medicines Through Drug Delivery*, was held at the National Heart and Lung Institute in London on July 5, 2001. Drug delivery is increasingly becoming a central technology in the research and development of better medicines. This is so for at least three reasons. First, new drugs are being derived from complex biological molecules that are not readily amenable to oral delivery. Second, improved medicine is recognized as requiring better dosing regimens for the patient. Both compliance and preference are improved by reduced dosing frequency, and it is rare for new products to require three-times-daily administration. Lastly, drug delivery technology has come a long way in the past 20 years, beyond controlled-release pharmaceuticals to polymer conjugates and dry powder-inhaled proteins.

A one-day conference on *Improving Medicines through Drug Delivery*, organized by the Society for Medicines Research (SMR), was held at the National Heart and Lung Institute in London on July 5, 2001, and dealt with a number of aspects of drug delivery, from inhaled methods for peptides and proteins to polymer conjugates for cancer and gene delivery. There are two reasons why drug delivery is becoming an increasingly important aspect in new product research and development in the pharmaceutical industry. First, patient acceptability and compliance are dramatically improved when dosing regimens are more convenient; second, new products are increasingly of biological origin and larger molecules pose a greater challenge to medicine regarding absorption and distribution. As a result of these factors, drug delivery is becoming more a core technology that often operates alongside earlier aspects of product development.

New technology, new hurdles

Harry Ferres started the day with an overview of the value of drug delivery systems, emphasizing that this technology, by virtue of its visibility to patients, was often one of the more obvious improvements in a medicine. While clearly there had been recent success—such as **dornase alfa** (*Pulmozyme*™; Genentech, Roche) for cystic fibrosis, **nifedipine** (*Procardia XL*®; Bayer) for hypertension and **liposomal amphotericin B** (*Abelcet*; The Liposome Co.) for fungal infections—there is also a lot to do in the future. Dr. Ferres posited the "smart tablet," which will in the future be able to produce tailored pharmacokinetics and pharmacodynamic effects in individual patients. This is an extension of controlled-release technology that has so far delivered chronopharmaceuticals (e.g., *Corvas*, a nighttime-release version of **verapamil** from Schering, expected to be on the market in 2002) and should also deliver cascade-release (i.e., natural rhythmic) capabilities.

  CCC: 0214–0934/2001

The commercial benefits of an improved pharmacokinetic profile should not be underestimated: *Cardizem DDS*, a simple once-daily form of **diltiazem**, has sold over USD 4 billion since the expiry of the native substance-of-matter patent.

The new technical hurdles that need to be overcome in order to realize this promise are substantial, but technology can be borrowed from other areas of high technology, such as freeze-drying techniques (compare instant coffee), electrospraying (from inkjet printer cartridges) and 3D printing technology (from the ceramics industry).

Inhaled delivery systems

Dry-powder inhalers

There followed two talks relating to inhaled delivery of proteins and other molecules. John Staniforth (Vectura, U.K.) introduced this area with a presentation on the challenges of deposition and distribution of drugs through the lung. The aim has always been to target the alveoli and conductive airways of the deep lung with a slow-moving cloud of particles containing the active drug. Prof. Staniforth's talk focused largely on the use of powders from **dry-powder inhalers** (DPIs). In this respect, size matters: the benefit of smaller particles is demonstrated with Inhale Therapeutic Systems' **inhaled insulin**, which is able to deliver up to 60% of the dose into the deep lung compared with around 10% available from the earlier metered-dose inhaler device for *Pulmicort*™. The technology is being driven by a more controlled regulatory requirement, particularly in terms of dose-content uniformity, that would have today posed substantial difficulties for the approval of the *Pulmicort* dry-powder inhaler.

The main factor that governs the delivery of powders is the particle aerodynamic diameter. Fine powders of 1–2 μm in size have high cohesiveness that causes agglomeration and makes them difficult to separate. This can be controlled by coating the active drug on to a lactose carrier, which improves flow and uniformity. The behavior of carrier particles is governed by their stickiness, which is heterogeneously distributed on the particle surface and governed by geometry and electrostatics.

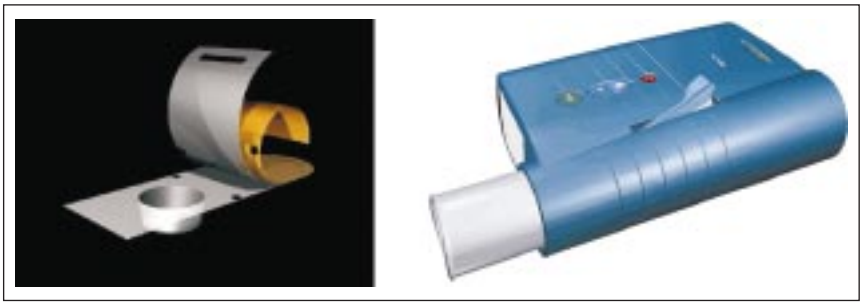

Fig. 1. Multilaminate dosage form holding liquid insulin formulation (left) in Aradigm's *AERx* inhaled insulin system (right).

Vectura's patented technology includes force control agents to mediate between the active drug and carrier particles to homogenize the interactions and improve uniformity. Using a modified mouthpiece, which through a static charge causes the release of drug particles from the carrier, the company has succeeded in delivering around 93% of the active drug into the deep lung.

Aerosol delivery

Despite the benefits of DPIs, the next speaker offered convincing arguments for the utility of aerosol delivery in some circumstances. Stephen Farr (Aradigm) talked about his company's development of **inhaled insulin** as a therapeutic treatment for diabetes. Although pressurized metered-dose inhalers (pMDIs) and DPIs are the major devices for lung delivery, patient compliance and education are poor. In particular, the way the patient inhales can influence substantially the distribution to the lung: fast inspiration tends to deliver more to the gut; slow inspiration delivers more to the lung. Delivery to the deep lung requires aerodynamic diameters of 1–3 μm. Such small particles have a propensity to aggregate, and Inhale Therapeutic's insulin DPI incorporates a power-assisted deaggregation mechanism.

As for **insulin**, there is still a need to improve the accuracy of subcutaneous needle injections, which are susceptible a patient margin of error of around 25% (this can be substantially improved with pen-injector systems). Insulin has an inherent bioavailability of only 20% by the inhaled route, a figure that is low compared with other proteins of similar molecular weight.

Breath-activated guidance

Aradigm's approach involves the control of the inspired flow rate through a **breath-activated guiding system** (*AERx*). Droplets of **insulin** are produced through a multilaminate strip precisely in the size (2 μm) required for deep lung penetration and capable of delivering free particle fractions in the 80% range (Fig. 1). The intersubject variability is similar to that found with the subcutaneous insulin pen injector; however, it has recently been found that smokers absorb substantially more than nonsmokers. This could become a problem for a molecule with as narrow a therapeutic range as insulin.

Through the colon

Moving from the top to the lower half of the body, Richard Palmer (Alizyme, U.K.) talked about the use of the colon as a delivery site, both for local therapeutic effects and for systemic delivery. There have been a great many approaches to colonic delivery over the years, including thick enteric coats, time-dependent release mechanisms, pH-dependent formulations and degradable prodrugs. All of these have produced very variable release pro-

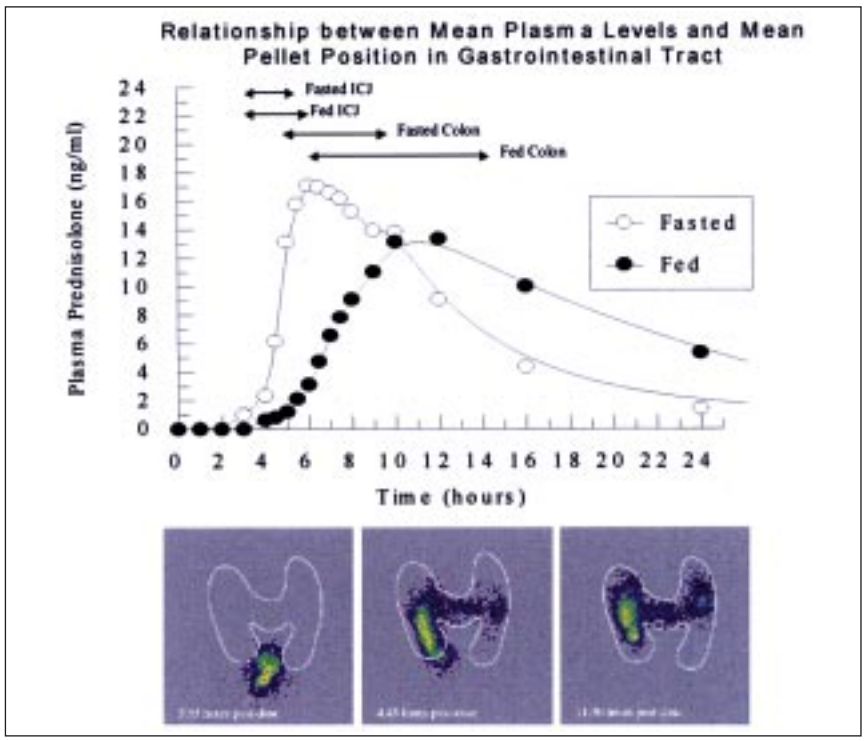

Fig. 2. Alizyme's *COLAL*™ colonic delivery system releases prednisolone into the colon in fasted and fed volunteers to a similar extent but at different times.

files, often because the transit time through the colon can vary substantially, from as low as 6 to as high as 30 hours. In the case of pH-dependent release, gastrointestinal pH is different from person to person and also depends greatly on food intake. These elements can cause the drug to be released very quickly or not at all. The prodrug approach—which has variously been based on glucuronidases, glycosidases, azo-reductases, dextranases and others—involves the creation of a new chemical entity that must undergo all of the toxicological examination required of such a species.

Alizyme's approach (*COLAL*™) is based on technology that originated at the Institute of Food Research in Norwich, U.K., and involves the incorporation of the drug behind a glassy amylose coat that is broken down by colonic bacterial amylases. The system can use conventional film-coating equipment; it can be used with most solid oral-dose forms, can provide a pulse or controlled release, and can also be applied for local or systemic delivery. The amylose is not broken down by pancreatic amylases and is mixed with ethyl cellulose to provide robustness. In proof-of-concept studies, the system was used to dose volunteers with **ranitidine**, **salbutamol**, **glucose** or **prednisolone sodium metasulfobenzoate** (ATL-2502; a prodrug of prednisolone). There was no substantial intersubject variability, and although food delayed the onset time, this was because of delayed stomach emptying, with no effect on AUC of the drug (Fig. 2). For the prednisolone delivery system, there is a marked reduction in systemic absorption of prednisolone; phase II results are expected to be available in the second half of 2001.

Polymer conjugates

The next two lectures dealt with the technology of polymer conjugation, both for small-molecule anticancer agents and for large proteinaceous therapeutics. Ruth Duncan (Welsh School of Pharmacy) has been working since the 1980s on the polymer-conjugated doxorubicin code-named **PK1**. Polymer-conjugated successes have greatly stimulated interest in this area, which was until recently treated with some skepticism by the mainstream pharmaceutical industry. One of the first examples in the cancer field was N. Maeda's **polymer conjugation of neocarzinostatin to polystyrene maleic acid**, which showed efficacy in liver cancer. Developments on this theme have highlighted the importance of the polymer itself, which should be nontoxic, nonimmunogenic and around 40 kDa in molecular weight to avoid renal elimination. ***N*-Hydroxypropyl methacrylate** (HPMA) is a preferred polymer that has been used as the basis for a number of anticancer therapeutics. Since PK1, which was discovered by Farmitalia and is now in phase II investigation under development by Pharmacia, other conjugates have been investigated for **platinate** (Access Pharmaceuticals, in phase I), **paclitaxel** (Cell Therapeutics, in phase I) and **camptothecin** (Enzon, in phase I).

Polymers offer the ability to target extracellular regions of tumors because of the greater leakiness of the vasculature around such areas. As a result, the doses of polymer conjugate anticancer agents can be increased. In phase I examination of **PK1**, the maximum tolerated dose reached 320 mg/m^2 compared with the normal maximum tolerated dose of 60 mg/m^2 of doxorubicin itself. Chemical targeting is another means of producing additional selectivity. In **PK2**, an additional galactose moiety is attached to the doxorubicin–HPMA conjugate in order to enhance liver targeting. Another development in polymer targeting is to coadminister the polymer conjugate with a monoclonal antibody conjugate of an enzyme that is capable of cleaving the covalent bond linking the polymer to the active drug. Polymers also offer the ability to deliver oligonucleotides. Certain amphoteric polyamide amines are taken into cells by endocytosis, and this offers the possibility of a nonviral gene vector able to deliver genes into the cytoplasm of a cell.

The practical demonstration of the use of polymer conjugates for proteins was expounded in the next talk from

Stephen Charles (Shearwater Polymers, now part of Inhale Therapeutics). Shearwater offers a one-stop-shop drug-enhancement capability for pegylation of proteins, small molecules, peptides and oligonucleotides. **Polyethylene glycol** (**PEG**), a highly water-soluble molecule, can enhance the bioavailability of water-insoluble and poorly soluble drugs. Shearwater has successfully developed two compounds through U.S. FDA approval, three more are in preregistration, and more than a dozen are in other stages of development. In addition to pegylated interferon gamma (**peginterferon gamma**) for hepatitis C virus, other major projects have included **polymer conjugates of interferon alfa** (with Roche), PEG-hGHra (**pegvisomant**, *Somavert*®; Pharmacia) and **PEG-filgrastim** (*Neupogen*; Amgen). As a polymer, PEG presents a large hydration volume and is a highly flexible structure. It is present in ointments, shampoos and some foods, and is entirely nonimmunogenic. Lastly, it is FDA-approved for intravenous, topical and oral use and is readily cleared from the body. PEG conjugates have improved solubility, stability (from months to years), reduced immunogenicity, proteolysis and increased bioavailability from the injection site.

Despite the advantages, in early chemistry of PEG conjugates, problems were found in stability and low selectivity of conjugation. Shearwater's approach involves the conjugation of one molecule of active principle per molecule of PEG, the use of a narrow range of molecular weights of PEG (around 30 kDa) and a low proportion of the diol impurity, which has the potential for producing a crosslinked conjugate. The chemical link can incorporate an amide, a carbamate or a Michael adduct of sulfur on to an α,β-unsaturated carbonyl system. The PEG polymer wraps around the protein to stabilize it with respect to proteolysis and immunogenicity.

Shearwater's collaboration with Roche resulted in *Pegasys*™, a **pegylated version of interferon alfa-2a** for hepatitis C virus with improved clinical efficacy. The percentage of patients with a sustained reduction in viral levels was increased to 40% compared with the 10% achieved with conventional interferon therapy. At the same time there was reduced immunogenicity. *Pegasys* was launched in September 2001 in Switzerland, where it is marketed as a prefilled syringe. FDA approval is expected in the second half of 2001.

Oral delivery of proteins and peptides

Perhaps the philosopher's stone of the drug delivery scientist is the oral delivery of proteins and peptides, which in the absence of an enhancer can only expect bioavailabilities of the order of a few percent. There have been numerous attempts in this area, but obtaining efficacy without compromising safety has proved a substantial challenge. Emisphere Technologies has in recent years seemed to succeed where others have failed, and it fell to Tim Corless to tell the symposium how this had been achieved. Emisphere's technology is organized around a number of carrier molecules, which, in combination with the native protein itself, seem to promote oral absorption through the stabilization of alternative conformations that are more amenable to passive transportation through the transmembrane route. There is no evidence from the work carried out so far that the system has produced any damage to cells of cellular junctions. The carriers themselves are new chemical entities that have molecular weights in the region of 300. The particular carrier that is good for one molecule may not be particularly good for another, although there are some physical chemical characteristics that seem to be associated with good carrier properties based on logP and some other (undefined) measures, and some carriers work well for more than one protein.

Emisphere is working with a number of major pharmaceutical companies, including Lilly (HGF, **humatrope**), Novartis (**salmon calcitonin**), Regeneron (**ciliary neurotrophic factor** for obesity) and Cubist (**cyclic antibiotic peptide**). In addition the company has applied its technology to **oral heparin** by itself (although nearly licensed to DuPont before DuPont's acquisition by Bristol-Myers Squib), and this is in phase III evaluation. Preclinical success has also been determined for **low-molecular-weight heparin**, **rhGH** and **EPO**, among other substances. The projects are typically started by administration of a number of candidate carrier molecules in association with the protein of interest by oral gavage in the rat. Blood levels are determined and bioanalysis used to identify the most successful candidate. In collaboration with a partner, the company aims to identify the optimal carrier within six months of starting the collaboration, and then enter into toxicological trials and human trials within 15 months. The optimal carrier can reduce the dose of the biomolecule, as well as increase the efficiency of absorption. For instance, in the case of heparin, the carrier is **sodium *N*-[8-(2-hydroxybenzoyl)-amino]caprylate** (**SNAC**) (Fig. 3), and the resulting complex has a bioavailability of 17%.

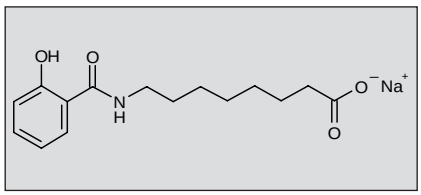

Fig. 3. Emisphere Technologies' carrier molecule for oral delivery of heparin, SNAC.

Emisphere is predicting a substantial opportunity with this product, since the market for heparin is currently USD 2 billion and is growing at a rate of 15% annually. Emisphere is developing both a liquid oral form and a solid-dose form (about 18 months behind). In addition to the anticoagulant use, heparin also has some antiinflammatory properties, and Emisphere is investigating its formulation in these indications.

Gene delivery

The final talk of the day, delivered by Kari Airenne (Ai Virtanen Institute and Ark Therapeutics, Finland), concerned gene delivery, a subject that remains controversial despite the approval in 1999 of the first antisense therapeutic (**fomivirsen sodium**, for treatment of cytomegalovirus retinitis; Isis Pharmaceuticals). Gene therapy in the widest sense involves the transfer of genetic material into somatic cells of a host to treat or prevent an inherited or acquired disease. The main targets are to eliminate, repair or replace a mutated gene; to regulate gene expression and signal transduction to achieve a useful therapeutic effect; to regulate the immune system; or to target malignant and other cells for destruction.

Although nonviral or naked DNA or plasmid liposomes or cationic polymers have been contemplated, most approaches to gene therapy involve delivery via a viral vector, of which there are multiple types. Adenoviral vectors have been advocated because of their high efficiency in terms of incorporation of the inserted gene into the target cell or organ; however, they also have high immunogenicity. By contrast, the retroviral vectors have reduced immunogenicity but also reduced efficiency. Dr. Airenne advocated the use of the baculovirus vector because it is not known to infect invertebrate hosts (and is therefore safer). Baculovirus vectors are currently used as biopesticides (and therefore have a known toxicity profile). By including a mammalian promoter in the BCV gene, a large amount of foreign DNA can be incorporated. The system's ability to transfer a gene successfully into a mammalian system was demonstrated by the transfer of galactosidase into a rabbit carotid artery. The transfection efficiency was similar to that of adenoviral transfer, but the presence of galactosidase enzyme was not observed beyond two weeks after the experiment. While the system also has applicability for skeletal muscle, choroid plexus of brain and endothelial cells, the long-term expression of the transferred gene remains a problem to be solved.

In conclusion, this represented a timely review of the advances in drug delivery that will increasingly become part of future medicines. The existing technology is wide ranging, from controlled-release formulations to permit reduced dosing frequency through to polymer conjugates to target anticancer drugs to their site of action. The future technology is even more exciting, with the realization of orally delivered proteins from biotechnological processes and the improved use of the lung as a route for large molecules to enter the body.

Dr. David Cavalla is Chief Executive Officer, Arachnova Ltd., St. John's Innovation Centre, Cambridge CB4 0WS, U.K., and chairman of the Society for Medicines Research (SMR) committee. The SMR Committee organizes conferences on behalf of the Society four times a year. These one-day conferences are of a multidisciplinary nature, therapeutically focused and normally staged in or around London. Details about forthcoming meetings can be obtained from: SMR Secretariat, Triangle House, Broomhill Road, London, SW18 4HX, U.K.. Tel: +44 (0)20 8875-2431; Fax: +44 (0)20 8875-2424; E-mail: secretariat@socmr.org; URL: http://www.socmr.org.

POSITIVE RESULTS SHOWN IN PRELIMINARY ANALYSIS OF PHASE II PTI-555 TRIAL

Pain Therapeutics, Inc. announced October 4, 2001, positive results from preliminary analysis of a large phase II clinical trial with **PTI-555**, the company's investigational pain killer. This phase II trial was a multicenter, randomized, double-blind, placebo- and active-controlled study comparing PTI-555 with morphine sulfate and placebo. The trial enrolled 210 patients with moderate to severe pain following major oral surgery significant enough to warrant opioid analgesia. Immediately after surgery, patients were randomly assigned to receive a single oral nominal dose of PTI-555, morphine sulfate or placebo. PTI-555 is the company's proprietary combination of morphine sulfate and low-dose naltrexone.

The primary efficacy end point in this trial was pain relief within eight hours of dosing and was achieved with a high degree of statistical significance, even though this trial was not powered to generate statistically meaningful efficacy data. Patients given a single oral dose of PTI-555 of 90 mg achieved significantly more total pain relief over four hours (TOTPAR4) compared with patients given a single 90-mg dose of oral morphine sulfate, with no significant change in the incidence of side effects. Patients given a single oral dose of PTI-555 of 90 mg also achieved significantly more total pain relief over four hours (TOTPAR4) than patients given placebo. Twenty-five percent of patients given a single oral dose of PTI-555 of 90 mg achieved complete pain relief within eight hours of dosing, compared with just 3% of patients given a single 90-mg dose of morphine sulfate. PTI-555 was well tolerated and was not associated with any serious adverse events during the trial or the subsequent follow-up period. The percentage of patients reporting any drug-related adverse events during the 24 hours following dosing was approximately the same in both active drug groups. Certain nervous system conditions, such as somnolence, fatigue and euphoria, occurred less frequently in the PTI-555-treated group.