Expert Opinion

Drug delivery global summit – evaluating emerging technologies

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Two day-long sessions at the Drug delivery global summit, organised by SMi Group Ltd, were devoted to discussion on critical aspects of drug delivery, including advances in drug delivery systems and their applications to new products, with a primary focus on oral systems, but also highlighting recent progress in inhalation, parenteral and transdermal delivery. The event included case studies from big pharma, biotech and drug delivery companies to illustrate emerging delivery technologies and how they can be applied to develop innovative products. The conference created a platform for discussion on a range of topics from scientific issues and challenges to ways of establishing mutually beneficial relationships between technology and pharma companies.

Expert Opin. Drug Deliv. (2005) 2(1):185-187

Novel drug delivery systems are becoming an increasingly important aspect of new product research and development in the pharmaceutical industry. This is mainly due to the fact that patient compliance is significantly improved when dosing regimens are more convenient. On the other hand, insoluble drugs, polar drugs and macromolecules continue to present challenges to pharmaceutical development, and thereby limit the potential usage of these therapeutic molecules to improve medicine. As a result, drug delivery companies are starting to position their technologies earlier in the drug development process.

Dr Paul Soltys (Schering-Plough Research Institute) began the day with an overview of the value of drug delivery systems, emphasising that we now have access to new molecular entities to which we can apply novel drug delivery technologies. Dr Soltys pointed out that in a strong competitive environment it is not enough to have a safe and effective product. Most of the drug delivery companies are now being pushed to create products, because often partners are looking for validation of the technology. Nevertheless, drug delivery companies are responding to the challenge and are increasingly providing solutions and creating value as large pharmaceutical companies continue to consolidate. A key success factor is to establish confidence in a new technology at an early stage to foster collaborative efforts between drug delivery and pharma companies in product development.

Dr Raj Khankari's presentation (CIMA Laboratories, Inc.) introduced the areas of orally disintegrating tablets (ODTs) and oral transmucosal (OTM) technologies. CIMA's principal activity is to develop and manufacture fast dissolving and enhanced-absorption intra-oral drug delivery systems through their fast dissolve technologies: OraSolv®, Sustained Release/Controlled Release and DuraSolv®. These products are oral forms that incorporate active drug ingredients into tablets, thus making them dissolve quickly in the mouth without chewing or the need for water. The oral transmucosal technology is OraVescent®, and the packaging technology is PakSolv®.

Dr Paul Clewlow, Business Development Director of Pharmaceutical Profiles, UK, presented the Enterion™ capsule developed by Phaeton Research (Nottingham, UK) for targeted delivery of a wide range of drug formulations to specific regions of the gut. This technology provides with an important new research tool and a revolutionary way to study the effect of the site of drug absorption in humans.

The capsule is activated by a radiofrequency signal that releases a spring-controlled piston; the movement of the piston down the barrel of the capsule initiates a rapid release of the contents into the specified area of the gastrointestinal (GI) tract. Suitable for a range of complex formulations, the Enterion capsule also has a feedback mechanism that will demonstrate to the operator that the external triggering has been successful. The location of the Enterion capsule within the GI tract can be identified using γ-scintigraphy. This information can be vital in establishing the extent to which a medication is absorbed from various different regions of the GI tract when given orally.

Dr Gabriela Mustata (Emisphere Technologies, Inc.) presented the uniqueness of Emisphere's *eligen*® technology for the oral delivery of polar therapeutic drugs. This technology is based on proprietary synthetic chemical compounds that facilitate the transport of therapeutic molecules across biological membranes. Studies have demonstrated that EMISPHERE® delivery agents (carriers) transport the drug transcellularly without compromising the integrity of the membranes. This technology is being applied to deliver a broad spectrum of drugs, including proteins, peptides, small charged molecules, and the charged polysaccharide heparin. So far, the application of this technology has been demonstrated with seven drugs in clinical trials under five US INDs.

Dr Andy Jones, CEO of Phoqus Pharmaceuticals, presented the company's new approach to drug delivery. Phoqus' systems are based on its platform technology of electrostatic dry power deposition. This technology allows very precise and controlled deposition of coating powder onto the surfaces of solid dosage forms. Phoqus' unique electrostatic deposition process coats each tablet with precise amounts of finely powdered drug compounds and coating polymers in a method similar to that used in office photocopiers and laser printers. The coating is then gently heated to fix and stabilise it. The major advantages offered by this technology are greater dosing range and accuracy of delivery, as well as capability of easy modification of drug-release properties.

Smart drug delivery systems are now being designed using nanoparticles to deliver medicine to specific parts of the body; for example, to tumours. Nanotechnology offers an opportunity to engineer unique solutions to drug delivery, which is significantly different from the molecule and macroparticle drug carriers, and enables the capability of delivering drugs to a well-defined cell population at a specified rate. Nanotechnology is also used to enable formulation and improve compound activity and final product characteristics. Almost 10% of currently marketed drugs are poorly soluble, and practically 40% of new chemical entities (NCEs) are dropped due to solubility issues. Poor water solubility leads to poor dissolution kinetics and suboptimal bioavailability. Two speakers focused on the use of nanotechnology in the field of drug delivery. Dr Gerrit Hauck (Aventis) introduced the area with a presentation on the application of Elan's proprietary NanoCrystal™ technology at Aventis. This technology, licensed to Aventis in 2003, is being used to enable formulation of poorly water-soluble compounds and improve compound activity and final product characteristics. The NanoCrystal technology can be incorporated into all dosage forms, both parenteral and oral, including solid, liquid, fast-melt, pulsed-release and controlled-release dosage forms. Dr Pramod Gupta (Baxter Healthcare) highlighted Baxter's development of NanoEdge® technology, which also involves decreasing the particle size of the actives to the nanometre size range; thus leading to an increase in the surface area and a subsequent increase in dissolution rate. These drug particles are stabilised against agglomeration by surface adsorption of selected proprietary GRAS excipients, such as ionic surfactants and block copolymers. The result is a colloidal dispersion, which can later be freeze dried or spray dried to yield nanoparticles in the 500 nm range. This is an attractive option for actives with high toxicity and low potency.

The next three lectures dealt with enabling technologies for protein delivery. Dr Leo de Leede (OctoPlus Technologies) discussed the challenges confronting the oral delivery of proteins, which are intrinsically fragile molecules that can easily undergo conformational changes. OctoPlus' technology consists of using novel polymeric systems for controlled-release parenteral protein delivery, such as PolyActive™ and OctoDEX™. OctoDEX is a delivery system for the controlled release of proteins (> 10 kDa), and is based on crosslinked dextran microspheres. PolyActive is a biodegradable multiblock polymeric drug delivery system based on two well-known polymers: polyethylene glycol and polybutylene terephthalate. Its biodegradability, extensive safety record and tunable release properties prove that this is an excellent choice for the controlled release of large proteins. Both PolyActive and OctoDEX have been extensively evaluated to demonstrate their safety. Furthermore, OctoPlus has demonstrated that these polymers can be made into durable films, coated onto medical devices and used to deliver a variety of large and small molecules.

Dr Charles Potter, Chief Technical Officer of Caretek Medical, UK, presented the company's needleless injector: ImplaJect™, a spring-powered device that looks very similar to a pen. In use, the device is pressed against the skin, which compresses a spring that when a critical loading is reached releases and pushes a pharmaceutical payload through the skin to a predetermined depth. The dosage form can be either a drug in solid form, or a solid 'pioneer tip' piercing the skin with the drug in a solid, semisolid or liquid form following immediately behind. The basic idea is protected by a number of patent applications. The key advantage of the device is that there is no needle and the drug is supplied in the form of a disposable cartridge so that the problems associated with needles (i.e., disposal, cross-contamination etc.) are eliminated. The device, ideally suited for self-injection, is small and inexpensive to manufacture, and allows variable spring settings for different skin types, drugs, and injection sites. Caretek is now in late-stage negotiations with a major global pharmaceutical

company to test the ImplaJect system with one of their proprietary drugs.

Dr Stephen Farr, Senior Vice President and Chief Scientific Officer of Aradigm, presented two technology platforms: AERx® for pulmonary delivery, and Intraject® for dermal delivery. AERx delivers a liquid aerosol drug formulation to the lung. Clinical trials with pulmonary delivery of insulin are ongoing using this technology. The needle-free strategy for drug delivery, Intraject, uses a gas actuator to create a short-lived pressure peak in the skin to deliver the drug through to the subcutaneous layer. Following administration, the drug is absorbed by the local tissues and blood capillary networks, and subsequently gains access to the systemic circulation. In clinical studies, Intraject was well tolerated and patients preferred it over the traditional needle and syringe.

The second day of the conference focused on the latest advances in pulmonary drug delivery, and other innovative methods. The development of the first pressurised metered dose inhaler in the mid-1950s was a major advance in the administration of drugs locally to the lung, especially for the treatment of asthmatics. More recently, research has focused on using the lung as a conduit to deliver biomolecules such as peptides and proteins to the systemic circulation. Describing research in inhalation drug delivery, Dr Robert Clayborough (3M Healthcare) highlighted the fact that drugs inhaled into the lungs have many advantages over other delivery methods such as capsules and injections. Inhalation delivers chemicals into the body quickly and effectively. For medications designed to work on the lungs, direct delivery through inhalation means smaller doses, and, therefore, fewer side effects, than with oral therapy. Dr Khurshid Iqbal (West Pharmaceutical Services, Inc.) discussed the use of ChiSys™ delivery system (based on the use of chitosan): a cationic polysaccharide obtained from partial deacetylation of chitin. ChiSys exploits the bioadhesive properties of chitosan to enhance transmucosal absorption, especially for nasal delivery of polar drugs, including peptides and proteins. West Pharmaceuticals successfully demonstrated that chitosan is highly biocompatible, bioadhesive and nontoxic when administered to mucosal membranes.

Dr Sarvajna Dwivedi (Nektar Therapeutics) mentioned that even if traditional nebulisers can deliver large doses, they have significant compliance issues. Dr Dwivedi presented Nektar's Pulmonary Particle Technology, which is based on the development of fine, aerodynamic drug particles; thus enabling efficient dispersibility and reproducible delivery to the lung in a single inhalation. Nektar's Pulmonary Delivery System combines innovations in drug powder formulation and processing with state-of-the-art inhalation devices and packaging technologies to efficiently and reproducibly deliver both large and small molecules to the deep lung for both systemic and local lung drug administration.

Dr Alessandro Martini discussed the area of anticancer agents and drug delivery technologies. He pointed out that oncology drugs have unique features in terms of high potency, cytotoxicity and limited safety margins which require special formulation techniques. In this case, the term 'enabling technology' encompasses not only formulation technologies that allow delivery, but also methods for internalising drugs into target cells, for triggering the drug release in specific organs of the body and for tailoring the appropriate release profile. Dr Jörg Breitenbach gave an update on Soliqs' technology (Soliqs is the drug delivery business of ABBOTT GmbH & Co. KG), which is designed to enhance oral bioavailability, especially for compounds with low aqueous solubility combined with defined release profiles. Dr Thomas CK Chan, Vice President of R&D and Chief Technology Officer of MacroChem Corp., listed various physical methods of delivering drugs through the skin: MacroChem's core technology is in modulation of skin absorption. Its current pipeline utilises SEPA™ (soft enhancement of percutaneous absorption): a patented compound that enhances absorption of drugs that penetrate poorly through skin.

Dr Stephen Perrett (Eurand) and Ian Jobling (Perlos) concluded this two-day conference by focusing on the commercial issues related to drug delivery. They emphasised that the importance of drug delivery technologies lies in developing actual products that can bring value not only to the companies developing their products, but also to the benefit of society to improve the quality of healthcare.

In conclusion, this meeting offered an opportunity to review some of the latest advances in drug delivery technologies, their potential applications, how new approaches are coming to market, and how they might change clinical practice. It is clear that drug delivery technology holds great promise for the future and is increasingly finding application in modern medicines.

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