Bioavailability challenges: new drug delivery methods

A special sp² Inter-Active report on the Catalent Applied Drug Delivery Institute inaugural UK training course held at the Royal Society of Chemistry premises in London.

Last October, the Catalent Applied Drug Delivery Institute hosted its inaugural training event in the UK focused on overcoming bioavailability challenges. The event was held at the Royal Society of Chemistry's premises in London.

Terry Robinson, executive director of the Institute welcomed attendees from a broad range of companies across the biotechnology and pharmaceutical sectors to the course which featured presentations on drug delivery technologies from hot melt extrusion to pulmonary delivery, bioavailability enhancement tools including nanotechnology and lipid-based solutions, and emerging technologies in drug delivery, including silica-based solutions and microneedles. The course included ample time for questions and discussions, with a concluding discussion session on trends in drug delivery.

Following her introduction, Robinson handed over to Richard Porte of the Royal Society of Chemistry who gave a resume of how the RSC was working with commercial companies and other organisations to disseminate knowledge and broaden the skill base of professionals working in the chemical and life sciences sectors. He also reviewed the in-house activities of the Society, describing its range of publications and services in the chemical area. In addition to its education and skills agenda, the Society is active in promoting 'Chemistry for Better Health' through the annual Chemical Sciences and Society Summit. The Society also has a number of initiatives in the drug discovery, diagnostics and education and public awareness fields.

Expanding the drug delivery toolbox

The drug delivery presentations sessions commenced with an introduction by Terry Robinson and Robert Smith of Catalent on how enhancing bioavailability is a well-known challenge, with tips on how to expand the drug delivery toolbox. Smith explained how enhancing bioavailability is multifactorial and how it is an important area as the outlook for new chemical entities (NCEs) includes more molecules with poor bioavailability. The Catalent Institute's mission is to improve outcomes for patients and innovators through expanded application of drug delivery technologies by connecting technology experts, pharmaceutical innovators and academia to improve clinical outcomes, medication delivery profiles, patient adherence and treatment efficacy. It achieves these aims through training, symposia and publications; collaborative technology incubation; and advocating drug delivery adoption to support improved patient outcomes.

The first of the technical presentations of the course was given by Dr Andreas Gryczke of BASF's Global Marketing Medical and Pharmaceutical Ingredients unit who described how hot melt extrusion technology works in the drug delivery area and how excipients can be used for successful formulation development. Gryczke described the principle of hot melt extrusion and the main parameters to consider when employing the technology in drug development. He went on to describe in depth the ingredients of solid dispersions (matrix polymer, solubiliser, plasticiser and disintegrant) and the various BASF excipient products available within these categories. He then outlined the principal activities involved in hot melt extrusion development, including glass solution screening and the miscibility of polymer and drug and solution and solubilising capacity, leading to long-term stability and good physico-chemical properties of the solid dispersion. Following a detailed description of how BASF's Kollidon matrix polymer has the properties that achieve the desired results, Gryczke explained how BASF explores the whole hot melt extrusion process to produce the final dosage form, including the desired release profile and the solubility of the API. This incuded a case study of the application of the company's Soluplus technology that compared the performance of a Soluplus-based formulation with a commercially available and therefore optimised drug product.

Dry powder inhaler technology

The second presentation in the bioavailability enhancement tools session was given by Professor Robert Price of the University of Bath with the title 'Fate of pharmaceutical aerosols: the material science perspective'. This presented the results of an evaluation of the effects of formulation and device design on in vitro comparability of dry powder inhalers as assessed by the Pharmaceutical Surface Science research Group of the Department of Pharmacy and Pharmacology at the University of Bath. Asthma treatments represent about half the value of the current market for inhaled drugs, the remainder being divided between a range of disease areas including COPD, antibiotics, antivirals, cystic fibrosis treatments, diabetes, hormone therapies, narcotic analgesics, influenza, anaphylaxis and multiple sclerosis drugs. The world market for asthma drugs is expected to exceed $25 billion by 2015 and the majority of compounds in this sector have or will soon lose patent protection. However, the erosion of branded inhaled drugs has been downgraded due to the difficulty in achieving generic entry in the USA. According to major generics supplier Teva the regulatory hurdles for winning approval for a sustainable inhaled drug such as Advair in the key US market are so high it will not be possible to deliver a generic copy.

Professor Price then went on to describe in detail the factors that control drug delivery to the lung, noting the correlation between the percentage lung deposition and the fine particle fraction of the dose. He then demonstrated how the mechanics of a DPI device can affect the performance (bioequivalence) of products and presented test versus reference data for a series of pharmacokinetic trials of an RPID and a modified Rotohaler device which showed that the devices were not bioequivalent based on pharmacokinetic parameters (PK). This posed

the question of how the same formulation could lead to significant differences in PK and described a number of in vitro and in vivo studies to establish the bioequivalence of test and reference dry powder inhalers (DPIs) containing fluticasone propionate and salmeterol xinafoate. The conclusions were that multiple mechanisms govern the device physics and deaggregation behaviour, for example, internal resistance of a device affects velocity and acceleration of airflow and there is a need to model fluidisation and aggregation within a DPI device and how it affects the microstructure of the dispersed particle and how the aerosol cloud structure in space and over time as it exits the device.

Professor Price then considered how device differences may lead to variations in local dosimetry in the airways of the lung and examined the effects of modes of dissolution and absorption on drug performance.
He concluded that one of the reasons it is difficult to make a therapeutically equivalent inhaled product is that there is only limited knowledge of the scientific challenges associated with developing inhaled products and that generics need to quickly overcome these. The current release and acceptance criteria of marketed inhaled products are achieved post-processing using in vitro based QC testing and this provides only a limited insight into CMC, product and process understanding. As a result, it is only possible to make statements about correlation between attributes and functionality and thus knowledge of these systems remains relatively primitive. Industry is reliant on design of experiments (DoE) and multivariate data analysis (MVA) to support product development.

Advantages of oral disintegration

Catalent's global director R&D operations, Dr Karen McGregor then gave her presentation on how to advance the development pf oral disintegrating tablets. She described how bioavailability enhancement represents the biggest challenge in oral drug delivery and that many molecules in Phase 2 and 3 development are considered poorly soluble. She looked at how solid-state forms impact on clinical performance and the API modifications that are possible, and the importance of orally disintegrating tablets, describing in detail how Catalent's Zydis ODT technology provides fast dispersion rates and improved delivery, as well as how the latest development of the technology, Zydis Nano, offers the potential for improved oral bioavailability for poorly soluble APIs. She concluded that nanotechnology has great potential to impact medical research and drug discovery through the transformation of drugs and the production of otherwise unusable active ingredients as the 'nano toolbox' provides a template for manufactured particles, noting that there have already been a number of industry collaborations established in this area.

Dr Julien Meissonier, director of Catalent's R&D platform, looked at how to accelerate the development of compounds with bioavailability limitations, emphasising that time to market is critical. It is essential to expedite the early stages of drug development to verify a drug candidate's druggability as well as establish proof of concept for drug delivery technology. Catalent's Softgel technology, originally developed at RP Scherer, provides the means to formulate lipid-based systems to maximise bioavailability and is an established technology that enables drug development specialists to look beyond 'first-in-man' studies. In addition, the company's Softgel and OptiShell technologies have been developed to expand the range of fill formulations for enhancing the bioavailability of challenging drug compounds by pushing the drug concentration limit beyond 200 mg/g and enabling modified release of poorly soluble compounds. In addition, the application of analytical science accesses more accurate data earlier and faster: Meissner described how software-assisted UHPLC/UV-MS method development provides improved chromatography for the generation of key solubility or compatibility data, and how UHPLC/FT-MS allows the identification of potential API degradation pathways to establish optimal formulation strategies.

Emerging technologies: delivery of innovative drugs

Catalent's director of business development, technology licensing & product ventures, Akan Oton, then reviewed emerging technologies, noting that it has recently been an exciting time for innovative drugs and that nowadays drug delivery has evolved to the point where technologies are being utilised to achieve differentiated outcomes for NCEs. New technologies require collaborations to reach the market, covering the range from university research to technology development and large pharma activities. It is important to enable improved clinical outcomes and be cost-effective for global markets.

On this theme, the final two presentations of the course covered emerging technologies for improving drug performance. Dr Michel van Speybroeck of Formac Pharmaceuticals described how to overcome poor solubility using mesoporous silica materials. He outlined how the company's SilSol silica-based carriers worked and suppressed drug crystallisation, improving drug loading capacity and providing a contollable release rate. He described methods for tabletting SilSol carriers and presented assessments of the bioperformance of a number of drugs formulated using the technology. In conclusion, the SilSol technology provides the solubility benefits of the amorphous form of a drug without the issue of physical instability; the mechanism of physical stabilisation is applicable across a broad range of chemical classes; it provides a controllable release rate; and is amenable to tabletting.

Finally, Dr Kirsty Gapp of 3M Drug Delivery Systems described the company's Microneedle Platform, a novel delivery platform for small molecules and macromolecules. She reviewed changes in the pharmaceutical market, including how drug discovery is shifting towards biologics; how the patent cliff is 'crushing' big pharma; that generic drugs are becoming mainstream; and developing markets are offering growth opoortunities. She then looked at trends in transdermal delivery, with an overview of active transdermal systems and how microstructured transdermal systems are based on the industry's experience of drug product approvals and drug manufacturing. She described in detail the technical features of solid (coated) microneedles and presented a clinical study comparing drug delivery by microneedle with subcutaneous injection for an osteoporosis drug. The Phase 1 clinical studies for sMTS (solid microneedle) delivery of BA058 showed that the delivery system was well tolerated; that BA058 is rapidly released from sMTS and achieves a desirable PK profile; that it increases P1NP, a bone formation marker, consistent with ultimate bone anabolic efficiency; and that the short BA058-sMTS wear time of five minutes results in good delivery of the drug. She also described how 3M's hollow microneedle system (hMTS) works, and presented a number of studies of the delivery drug substances by hMTS compared with subcutaneous injection.

Further information

For further information on the companies and organisations featured in this report visit the following websites:

www.drugdeliveryinstitute.com
www.rsc.org
www.basf.com
www.catalent.com
www.formacpharma.com
www.3m.com