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INVITED SPEAKER ABSTRACTS

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Life support systems for cell therapies

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The regenerative capacity of stem cells observed *in vitro* has led to the development of numerous clinical cell therapy trials (such as the trial described by Schächinger *et al.*[1]) where new cells were directly introduced into a tissue or organ, with the hope of treating degenerative diseases. However, little data exist as to whether the manipulations required to transfer the cells from cell culture conditions to the target tissue affect their cellular characteristics and ultimately their ability to engraft and form new functioning tissue.

In a recently published study,[2] we showed that processing primary murine mesenchymal stem cells into a concentrated cell suspension, drawing them up into a syringe with a 26s needle attached (114-μm internal diameter) and immediately ejecting them caused a significant decrease in viability (analysed using a metabolic MTS viability assay and using flow cytometry). Leaving the cells within the syringe chamber at room temperature for prolonged time periods caused to a further decrease in viability. These manipulations also led to an increase in cell debris. However, cells that were viable postejection were found to be functional with regard to their ability to spread on tissue culture plastic and their ability to proliferate.

These findings led to an assessment of whether an alteration of parameters relating to the cell manipulations could reduce this decrease in viability. Reducing the ejection rate (theoretically reducing the shear stress the cells experience during their passage through the needle) or using the antioxidant *n*-acetyl cysteine did not significantly improve viability, although using a wider bore needle (22 g, 394 μm) did improve viability.

For allogeneic (nonself) cell therapies to be routinely effective, not only would the parameters previously mentioned need to be taken into consideration but an effective means of transporting the cell suspension from a cell culture facility to the patient would be required. The set up and maintenance of a suitable culture facility would be expensive for many hospitals to manage, although transporting cell suspensions from a facility external to a clinic may affect the viability and characteristics of the cells delivered. Cells can be transported in a cryopreserved state, then thawed and administered at the bedside, but cryopreservation is expensive, and the cryoprotectants used often cause adverse reactions. Intercytex have developed a dermal fibroblast product that can be transported under refrigerated conditions,[3] but the ideal would be for a cell therapy product, enclosed within a life support system, to be transported under ambient room conditions and administered by the clinician with minimal processing.

Under new regulations set out by the Medicines and Healthcare products Regulatory Agency (MHRA), new products containing viable cells will require a medicinal product licence, and be assessed for safety and efficacy in a similar fashion to a new medicine. Cellular products are highly likely to have a paracrine effect on the recipient through the release of secretory factors, and these factors could potentially cause adverse reactions and interact with other medicines. For these reasons, it is likely that pharmaceutical expertise would be required in the future to bring effective cell therapy products to the market and to educate other health care professionals and patients regarding how these therapies would fit within a patient's overall medical care.

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Polymers for and against cell attachment

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Introduction

Synthetic polymers can be used in a variety of formats to interact with cells for specific capture or can be prepared to be antiadhesive, for prevention of cell binding at surfaces. Applications for these polymers range from delivery to, and of, cells, mammalian cell culture through to bacterial sequestration and prevention of surface fouling and biofilm growth. In all cases, knowledge of the mechanisms by which cells interact with polymer chains and surfaces/interfaces is important, and an ability to tailor the properties of polymers to exploit these mechanisms is needed if the interactions are to be controlled.

In this presentation, some highlights of our work in the area of polymers with switchable attachment to cells will be featured. Specifically, the lecture will cover patterned

surfaces for reversible capture of oral bacteria, glycopolymers for binding to specific bacterial strains and recent data on the interactions of switchable polymers for cell culture and cell delivery applications.

Conclusions

The new living polymerisation chemistries developed over recent years hold promise for materials that can deliver anti-infective agents to specific targets and can carry/support cells for treatment of diseased sites. Although many of these materials are still at the proof-of-concept stage, nevertheless their combinations of properties are appealing for further development.

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Microfluidic chips: testing for sexually transmitted diseases

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The trend of moving diagnostic tests out of centralised labs towards the point of care is placing tough new demands on diagnostic products, which are not addressed by existing technologies. The talk will explore the rational for point of care testing, the requirements that arise from new testing environments and how novel integrated microfluidic technologies are addressing these issues.

Point of care testing promises great benefit where patients can be tested and treated in a single appointment. Many central lab tests that are run today fail to deliver an effective clinical outcome because of the long turn-around time for the test, or because the patient cannot be contacted and never returns for the test result. This problem is particularly acute in clinics for sexually transmitted infections, where the number of patients returning for treatment following a positive test result can be as low as 50%. The impact of untreated infections is not only bad for the individuals but also for the spread of the disease. Point of care testing will remove this issue and, in addition, the increased portability will allow use in new environments, which could increase the volume of screening.

With point of care testing having clear benefits, why is it that it has not been widely adopted? The answer lies in the fact that point of care tests have a different set of performance requirements, which are not addressed by existing products. Point of care testing requires improvements in test simplicity, speed and cost and size of the instrument. All these must be addressed while at the same time maintaining the same level of clinical sensitivity as a lab test to be acceptable as a replacement technology.

A solution to these increased performance demands lies in the application of new technologies based on integrated microfluidic chips that can provide the level of sophistication required to run today's complicated molecular diagnostic tests while keeping the interface to the user simple. The change in scale enables size reductions, increases in speed and a greater degree of integration, which eliminates many user issues, including calibration, controls and interpretation errors. Combined with this, novel detection technologies based on low-cost electronic sensing methods result in lower cost, more robust instrumentation that can be used in a greater range of environments than existing technologies.

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Development of integrated predictive models for oral absorption

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After oral administration, a drug must go into solution in the medium present in the gastrointestinal lumen to create the driving force for absorption across the intestinal mucosa. Along with solubility, intestinal permeability is one of the key properties that determine intestinal absorption. As most pharmaceutical companies try to develop drugs that are effective after oral intake (economical reasons, improved patient compliance), the solubility and permeability of drug candidates will be estimated during early drug discovery to eliminate the drug candidates that are likely to fail in later development due to poor biopharmaceutical properties. However, test conditions during early discovery do not reflect the gastrointestinal environment. For instance, the use of media of limited biorelevance (e.g. plain aqueous buffer systems) may result in overestimation or underestimation of solubility and permeability, causing poor accuracy in prioritising new compounds at the discovery stage.

During the presentation, various systems that can be used to assess intestinal drug absorption will be discussed, along with the integration of biorelevant conditions into these procedures. Human intestinal media obtained from fasting and fed volunteers and aspirated from two different sites along the gastrointestinal tract have been used as reference media. More specifically, we will focus on (1) the integration of food effects into procedures to assess absorption, (2) the effect of compounds present in the intraluminal milieu on the functionality of carriers and (3) the potential impact of intraluminal supersaturation on intestinal drug absorption. In addition, the characterization of intraluminal drug and formulation behaviour as a tool for the optimisation of biorelevant conditions (e.g. drug concentrations) in in-vitro absorption assays will be discussed.

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Emerging treatment options for the management of type 2 diabetes

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Whilst insulin was first isolated in 1921 and produced commercially by 1923, it was not until the 1950s that the first sulphonylurea followed soon after by the first biguanide was marketed. We then waited another 30 years for the alpha-glucosidase inhibitors, followed by the meglitinides and then the first thiazolidinediones (glitazones) at the turn of the millennium.

There is now good evidence for the benefits of tight glycaemic control in reducing vascular risk, but type 2 diabetes is a progressive condition, and none of the traditional treatments have been shown to affect the natural history of the disease. This has led to the concept of step-wise management for type 2 diabetes using combination treatment. It is therefore gratifying that we now have a range of antidiabetes agents from which to choose – both traditional drugs and newer agents such as incretin mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins).

Metformin remains first-line pharmacotherapy for type 2 diabetes as it is weight neutral, does not increase the risk of hypoglycaemia and is vascular protective. The correct second-line agent is much more controversial, but there is still a wide usage of the sulphonylurea agents, although the price to pay is risk of hypoglycaemia and weight gain. The glitazones can also be usefully used in combination with other oral agents and by targeting a specific defect of type 2 diabetes, i.e. insulin resistance have beneficial effects on glycaemic control with evidence (at least with pioglitazone) for cardiac protection. However, possible increased risks of vascular events and death have been reported from a meta-analysis of rosiglitazone. Other issues with glitazones include weight gain, peripheral oedema and distal bone fractures in women.

The other basic pathophysiological defect in type 2 diabetes is pancreatic islet cell dysfunction involving both the beta cells secreting insulin and the alpha cells secreting glucagon. In normal people, the release of incretin hormones from the gut in response to food is a fundamental process in the maintenance of normal glucose regulation. The hormone which has gained most interest is glucagon-like peptide-1 (GLP-1), which enhances glucose-dependent insulin secretion from the pancreatic beta cells, reduces postmeal glucagon secretion resulting in reduced liver glucose output, slowing stomach emptying thereby reducing postprandial glucose and promotion of satiety/reduction of appetite. The so-called incretin effect defining enhanced insulin production when glucose is given orally, rather than intravenously, is significantly reduced in people with type 2 diabetes. Such patients respond normally to GLP-1, however, when it is given as a continuous intravenous infusion with significant improvement in the metabolic abnormalities associated with diabetes. This is impractical for long-term management. The reason for the very short half-life of GLP-1 is because it is rapidly broken down by the naturally produced enzyme DPP-4.

Therefore, industry has developed two new approaches to diabetes therapy based on incretin hormones. The first approach involves drugs that mimic the action of GLP-1 (incretin mimetics or GLP-1 agonists) but are not broken down by DPP-4. This has led to the development of exenatide (Eli Lilly) and more recently liraglutide (Novo Nordisk). These agents are given by subcutaneous injection, and initially there is a high frequency of nausea, which tends to disappear over time. These agents are licensed in Europe for combination treatment with oral agents and can be very effective, not just from the point of view of glycaemic control but also causing weight loss.

The other approach is to use drugs that inhibit the action of DPP-4 (DPP-4 inhibitors or gliptins) and these include sitagliptin (MSD) and vildagliptin (Novartis). They are administered orally with a license in Europe in combination with other oral agents and in the case of sitagliptin also as a triple therapy with metformin and sulphonylureas. These agents also improve glycaemic control, are weight neutral and do not increase the risks of hypoglycaemia. These are clear advantages over some of the more traditional agents in common use.

In this discussion, the mechanism of action and place in therapy of these new agents will be discussed in detail, including consideration of the new National Institute for Health and Clinical Excellence (NICE) guidelines for new drugs for type 2 diabetes.

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Emerging technologies on point-of-care diagnostic testing – pharmacogenetic testing and predictive medicine

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Pharmacogenetic (PGx) testing falls well within the domain of companion diagnostics. This testing not only objectively diagnoses disease status but also guides on the likely response an individual might experience to a (bio)pharmaceutical product. This response prediction may be an indication of the likely effectiveness of the medicine or the probable safety of the medicine, the latter particularly with respect to drug metabolism and thus pharmacokinetics and bioavailability. PGx testing has been performed for many years in the field of HIV therapy, with resistance genotyping being used to guide appropriate drug cocktails, but has also found more recent utility in the use of cancer medicines that operate through known molecular pathways. In addition, the release of cytochrome p450 (CYP450) laboratory tests have begun to move predictive pharmacokinetic safety testing into the mainstream.

In addition to scientific and medical considerations, PGx testing also has some impact on regulatory approval of new medicines, with testing even appearing on the label of approved new medicinal products. Such PGx testing is supported by a raft of regulator-issued guidance documents in all three major pharmaceutical markets, ranging from voluntary obligations through to mandatory obligations. Similarly, PGx testing now has an impact on reimbursement of the costs of medicines by showing that the most appropriate patients are receiving and benefiting from the prescribed medicines, and so payers should feel

comfortable while paying for such medicines and companion tests. Indeed, in some particular cases, a PGx testing may carry a higher reimbursement price tag than many medicines.

In this presentation, a variety of companion PGx tests will be discussed, including their utility and intrinsic value. The wider impact of PGx testing on the health care system will also be discussed given that it carries some considerable sociopolitical expectations that are often poorly articulated. Finally, some consideration will be given as to how PGx might aid the wider acceptance of predictive medicines and to the impact that such a philosophy towards health care might have on the management of well-being, particularly in the developed world.

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Combination of dissolution and clinical studies to understand product quality for a BCS class 4 compound

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The Quality by Design paradigm for pharmaceutical development, as outlined in International conference on Harmonization Q8, Q8R and Q9, focuses on producing a pharmaceutical product of the required quality through use of risk management and scientific understanding of critical quality attributes. Under this paradigm, the definition of product quality encompasses clinical safety and efficacy in addition to pharmaceutical quality in the traditional sense. An in-depth scientific understanding of aspects of the process and formulation which could impact on patient pharmacokinetics, and hence safety and efficacy, is therefore required. In-vitro tests such as dissolution are commonly used in development and routine manufacture as indicators of product quality. For these tests to also assure safety and efficacy, the relationship between the in-vitro test and performance in-vivo needs to be understood. For Biopharmaceutics Classification System (BCS) class 1 and 3 compounds, the link between dissolution in simple aqueous buffers and in-vivo performance is already well established. However, for BCS class 4 compounds, this relationship needs to be explored and understood on a compound-specific basis.

A case study will describe the approach used to understand product quality for a BCS class 4 compound. The perceived wisdom is that these compounds carry a higher biopharmaceutics risk such that their in-vivo performance is highly sensitive to process and formulation changes, as changes in product dissolution due to these factors result in altered drug absorption and thus exposure, and therefore a potential impact on safety and efficacy. A combination of in-vitro dissolution data and pharmacokinetic data from clinical studies was used to explore the relationship between in-vitro dissolution and in-vivo performance, in relation to high-risk process and formulation variables. It was demonstrated that high-risk process and formulation changes had no significant impact on bioequivalence for this compound *in vivo*, despite giving different in-vitro dissolution profiles. This enabled a 'safe space' dissolution window to be defined, within which dissolution can be altered without impacting on bioequivalence. Based on this understanding, a dissolution test was defined which, in combination with a suitable specification, was suitable to assure quality, safety and efficacy for this product.

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Predictive technologies for drug behaviour

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Media to make in-vitro dissolution of oral-dosage forms of greater relevance to in-vivo conditions in the human small intestine by the inclusion of wetting and solubilisation agents such as bile salts and lecithin at levels that are similar to those present in the human small intestine were first widely reported in the literature about 10 years ago.

In the last decade, the field of so called 'biorelevant testing' has continued to develop, and to be of interest to oral formulation development. There have been some strong driving forces for the emergence and development of this area, including

(1) An increasing number of poorly soluble drugs and modified release formulations in the oral portfolio of many pharmaceutical companies, where understanding the influence of solubility and dissolution on in-vivo performance is key for successful, efficient product development.

(2) A recognition that if in-vitro formulation comparison can be performed reliably, then there is scope to reduce in-vivo (both in human and in preclinical species) formulation comparison studies.

(3) A growing desire from both industry and regulators to understand how changing specific product attributes influences actual in-vivo performance in the patient.

In addition to an understanding of fluid composition at specific locations within the human gastro-intestinal (GI) tract, a number of other factors need to be understood for in-vitro testing to be reliably related to in-vivo performance. These include the understanding of the dynamic nature of fluid movement and mixing, the fluid volumes available for dissolution, the significant differences between the fasted and fed states and the complex interaction between solubility, dissolution rate and permeability in the GI tract.

Today, various in-vitro and modelling tools are available to help the formulator understand likely in-vivo performance of oral-dosage forms. Some of the tools available from the perspective of a formulation development scientist will be discussed, with examples to demonstrate their optimal use provided.

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Polyunsaturated fatty acids, inflammation and inflammatory diseases

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Most interest in the influence of fatty acids on inflammatory processes has centered on the frequently opposing actions of n-6 and n-3 polyunsaturated fatty acids. The n-6 arachidonic acid gives rise to the eicosanoid family of inflammatory mediators (prostaglandins, leukotrienes and related metabolites), and through these mediators it regulates the activities of inflammatory cells and the production of damaging inflammatory cytokines, matrix metalloproteinases, etc. Arachidonic acid metabolism is a well-known target for pharmacologic control of inflammation. However, arachidonic acid metabolism is also subject to dietary control. Consumption of long-chain n-3 fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) found in oily fish and in fish oils decreases the amount of arachidonic acid in inflammatory cell membranes and so available for eicosanoid production. Thus, consumption of long-chain n-3 fatty acids results in decreased production of eicosanoids from arachidonic acid. EPA acts as an alternative substrate for eicosanoid synthesis giving rise to mediators that are often less potent than the analogues produced from arachidonic acid. EPA and DHA give rise to newly discovered families of mediators termed E- and D-resolvins, respectively, which have very potent anti-inflammatory and inflammation resolving actions in cell culture and animal model systems. In addition to this range of effects on lipid mediators, long-chain n-3 fatty acids also decrease the production of some peptide mediators of inflammation including the classic inflammatory cytokines. These effects appear to involve a reduction in gene expression through mechanisms currently being elucidated. These anti-inflammatory actions suggest that long-chain n-3 fatty acids could be useful to protect against and to treat inflammatory conditions. A number of clinical trials have been conducted using these fatty acids, usually in the form of fish oil. Trials in rheumatoid arthritis have been the most successful. Anti-inflammatory actions may also contribute to the widely recognised protective effect of long-chain n-3 fatty acids toward cardiovascular disease and may also contribute to a reduction in occurrence and severity of cardiovascular events.

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A small company's approach to developing innovative pharmaceuticals for treating peripheral conditions: from bench to registration

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The idea of transforming scientific findings into a useful, and a commercially viable, product is appealing. However, the path to such an idea realisation is steep and tortuous, especially in biotechnological and pharmaceutical industries. The main reasons are biological complexity, technological and financing challenges and the tight pharmaceutical industry regulation, which taken together explain the high rate of pharmaceutical products attrition.

Even with great skill and some luck one typically needs more than a decade and in excess of US$100 million to develop a therapeutic drug product; taking short-cuts normally prolongs the road to success, as do noncontrollable/planable partnering changes – time-wise as well as cost-wise. The history of IDEA AG, the first-wave, small, German biotechnology company and presently innovative products developer, exemplifies the situation.

Technological and economic bases of IDEA are 'smart' (self-optimising, self-driven and self-guided) carriers. In the form of ultra-adaptable mixed amphiphat vesicles, such Transfersome[1] carriers overcome the skin permeability barrier and can mediate the drugs targeting into peripheral tissues, and help avoid local drug clearance through cutaneous blood capillaries. The three key prerequisites for such carriers success are (1) high carrier surface hydrophilicity (and transcutaneous hydration gradient utilisation); (2) high adaptability of the vesicles bilayer (i.e. carrier ultradeformability); (3) appropriate stability of the carrier vesicles (i.e. negligible carrier fragmentation during narrow pores/skin passage). Under such proviso, the Transfersome carriers can also positively affect drug biodistribution and pharmacokinetics.

The first fully developed pharmaceutical product comprising the Transfersome technology is Diractin[1], a semisolid aqueous suspension of ultradeformable carriers loaded with ketoprofen, a broadly active nonsteroidal anti-inflammatory drug (NSAID). The product predictably and controllably deposits the drug bellow an epicutaneous application site and moreover ensures prolonged drug release into the deep target tissue. To date, Diractin passed a number of *in vitro* and *in vivo*, preclinical as well as clinical tests, and was partnered three times. The resulting product characteristics are attractive: use of smart carriers helps achieving relatively high (20–100×) and longer-lasting (2–3×) drug concentration on the target whilst minimising the systemic drug burden (Cmax <1% of oral Cmax). Results of the clinical studies confirm that epicutaneous applications of a formulation containing the Transfersome vesicles suppress the pain associated with osteoarthritis at least as well as either the selective (Celebrex, Pfizer) or nonselective oral NSAIDs (naproxen). The systemic adverse side effects of Diractin are no different than from that of placebo. Further pharmaceutical products targeting local, e.g. dermatological conditions are in clinical development.

[1]Diractin and Transfersome are trademarks of IDEA AG.

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Polymeric self-assemblies: the emerging nanocarriers for the oral delivery of proteins and drugs

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Amphiphilic polymers forming polymeric self-assemblies have been exploited in gene and drug delivery in the past two decades. The capability of these amphiphilic polymers forming different nano self-assemblies such as nanoparticles, vesicles and polymeric micelles indicates the versatility of these systems in delivering a range of therapeutic agents. To date, they have been widely explored in intravenous delivery. Here, we report on the emerging use of these polymeric self-assemblies in oral delivery of proteins and drugs.

A range of novel amphiphilic polymers based on water soluble polyallylamine (PAA) have been synthesised. For protein delivery, the influence of the polymer architecture (type and level of hydrophobic pendant groups and the presence of quaternary ammonium moieties) on the capability to complex with a model protein, insulin and protect against enzymatic degradation was determined. All amphiphilic polymers spontaneously formed nano-complexes with insulin (100–200 nm) in pH = 7 tris buffer after 2 h at room temperature.[1] The fabrication process did not involve the use of organic solvent and high temperature, which might degrade labile protein. This indicates the advantage of these nanocomplexes compared to conventional nanoparticles. It was shown that PAA modified with palmitoyl pendant groups had the highest complexation efficiency with insulin compared to PAA with cetyl or cholesteryl pendant groups. In-vitro enzymatic degradation studies showed all nanocomplexes were able to protect insulin from trypsin degradation although they offered a varying degree of protection against pepsin degradation depending on polymer architecture. Interestingly nonquaternised palmitoyl PAA significantly enhanced chymotrypsin degradation of insulin while cholesteryl and cetylated PAA offered protection against chymotrypsin degradation. Using CaCo2 cell as a model, nonquaternised palmitoyl PAA showed the capability to facilitate paracellular transport allowing the transport of insulin through tight junctions. In addition, these polymers were also able to increase cellular uptake through endocytosis pathway. However, the quaternised palmitoyl polymers exhibited a different uptake mechanism involving calcium-independent active transport.

For hydrophobic drug delivery, earlier work has shown that amphiphilic polymers based on polyethylenimine were able to promote in-vivo drug absorption of a hydrophobic drug via oral route demonstrating the potential of these self-assembled systems in oral drug delivery.[2] Our study indicates PAA modified with different hydrophobic pendant groups exhibit extremely high solubilising capacity for three hydrophobic drugs, and future work will investigate the use of these polymeric self-assemblies as oral drug delivery systems *in vivo*.

In conclusion, oral protein and hydrophobic drug delivery are two major challenges faced by pharmaceutical industry to date. These polymeric self-assemblies might offer an alternative strategy to conventional systems in the oral delivery of protein and hydrophobic drugs.

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An introduction to Raman chemical images and the understanding of pharmaceutical products

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Chemical images can be considered to be '...A photograph with chemical information...'. In reality, they are false colour images of solid samples (typically tablet cross-sections or compressed blends), which have good spatial resolution (1-10 μm) and spectral resolution (1-8 cm^{-1}). Raman microscopy is one of the nondestructive spectroscopic techniques that has the specificity to confirm material identity and form (e.g. polmorphs, salts/solvates) and can also be used to map or image solid dosage formulations. From the raw data, known as a hyperspectral data cube, chemical images can be produced, which show the size, distribution and adjacencies of each component. These images are used to better understand solid dosage formulations and their physical properties.

Raman mapping and imaging applications are as varied as understanding bead manufacturing processes to drug delivery from multidose inhalers. Other examples include identification of active pharmaceutical ingredient (API) forms with limits of detection of 0.01% and identification of API forms changing due to process-induced transformations (PIT). With increasingly more effort being placed in selecting the optimum form for the API, it is important to ensure that the API form is maintained in any manufacturing process or storage condition.

Care must be taken in determining particle sizes in chemical images due to inherent errors in the data acquisition and presentation. This is based on the fact that a 2D image can only approximate the size of a three-dimensional particle. As a result, the images tend to be used comparatively and not to provide absolute particle or domain sizes. However, the final size of components in drug products can still be estimated and

used to understand manufacturing processes and formulation performance. This is illustrated with an example of where API and dicalcium phosphate particle size and domain adjacency are essential for good formulation performance.

In conclusion, Raman mapping and imaging applications in the pharmaceutical industry offer the analyst unique, nondestructive methods to characterise formulations *in situ.* The techniques first used in dosage form troubleshooting are now being used more in product development as part of the quality-by-design initiative. This is to increase understanding and prediction of formulation behaviour, and ultimately ensure product performance and quality.

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The use of unlicensed and off-label medicines in children

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The drug licensing system was introduced with the Medicines Act in 1968 following a series of serious adverse events involving drugs in a number of patients including children. It aims to ensure that drugs are safe, effective and high quality. Unfortunately, babies and children still do not benefit from the reassurances the system should bring as everyday they are given unlicensed medicines, which have not been through the licensing process at all, and off-label medicines (licensed medicines used outside the terms of the license).

A research in the United Kingdom has shown that 70% of children in paediatric intensive care, 90% of babies in neonatal intensive care, 67% of children in general paediatric wards and 11% of children treated in the community by a general practitioner receive at least one unlicensed or off-label drug during the treatment episode. The issue is similar in hospitals and the communities across Europe and is not confined to the United Kingdom. The drugs involved are common drugs used everyday for common paediatric illnesses. Prescribing of these medicines is due to the lack of availability of suitable licensed drugs and formulations for children, not due to inappropriate prescribing in the majority of instances.

Until the EU regulation on medicines for children came into force in January 2007, the pharmaceutical industries were allowed to put statements into their product licenses/marketing authorisations for new drugs stating that 'there is insufficient evidence for use in children' and 'not recommended for use in children'. Consequently, for many years children have been 'therapeutic orphans' in terms of the lack of availability of suitable licensed products. This has led to a number of practical problems for health care professionals and families as well. These include a lack of suitable formulations to deliver the paediatric dose in a form that a child is able to take; problems in choice of dose due to a lack of prescribing information; medication errors due to the need to use adult-designed products in children; confusing patient information leaflets that reflect the product license; delays and mistakes at the primary or secondary care interface when children are discharged from hospital on an unlicensed or off-label medicine and a possibly higher risk of adverse drug reactions.

The new European paediatric regulation together with the UK Medicines for Children Research Network are now finally starting to address these issues, and although this will take time, children will hopefully not be therapeutic orphans for too much longer.

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Chlorhexidine skin antisepsis and penetration

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Microorganisms colonising the skin not only reside on the external surfaces but are also found to inhabit hair follicles and sites beneath the skin surface. Such resident commensal organisms can cause infection when the protective skin barrier is breached. Effective skin antisepsis is therefore required for preventing infections associated with invasive procedures, and an efficient and rapid permeation of the applied antiseptic agent into the deeper layers of the skin is essential in preventing infections associated with invasive procedure. Chlorhexidine is one of the most widely used antimicrobials within clinical practice for skin antisepsis, and a 2% w/w chlorhexidine solution is currently recommended by the evidence-based practice in infection control and Healthcare Infection Control Practices Advisory Committee guidelines.

Skin permeation studies to determine the penetration of chlorhexidine were carried out using full-thickness human skin in a Franz diffusion cell model. The skin was exposed to chlorhexidine solutions for different durations, starting at 2 min to mimic current guidelines and increasing to longer exposure times. Although chlorhexidine in alcoholic solution has been shown to have superior antimicrobial activity compared with aqueous solutions, its efficacy in reducing catheter colonisation and infection is comparable, and we have demonstrated the limited permeation of chlorhexidine gluconate following application of either alcoholic or aqueous solutions.[1,2] Moreover, the negligible concentrations of chlorhexidine detected at skin depths of >300 μm may indeed allow for microorganisms residing in the deeper layers, e.g. around hair follicles, to survive the skin antisepsis procedures recommended in the current guidelines.

The antimicrobial efficacy of essential oils has been known for several years, and many studies have demonstrated activity against bacteria, fungi and viruses. More recently, in the light of increased antimicrobial resistance within the clinical setting, the potential of essential oils for the prevention and treatment of infection has been researched in several studies. We have demonstrated a synergistic antimicrobial activity of chlorhexidine and essential oils including eucalyptus oil against *Staphylococcus epidermidis.*[3] Using the same human

skin model, we have shown that the combination of eucalyptus oil and chlorhexidine applied at the skin surface increases both the rate and extent of delivery of chlorhexidine within the deeper skin layers. Such a combination may aid in preventing infection and microbial recolonisation of the skin in clinical practice following invasive procedures.

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Targeting the delivery of proteins, DNA and vaccines to the skin

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The delivery of macromolecular therapeutics, such as vaccines and other biological therapies, to patients relies primarily on traditional injection practices. These are invasive, require skill and usually restrict treatment to the primary/secondary care setting. Delivery into/across the skin is an accessible, patient-friendly alternative, but it is significantly constrained by the inherent barrier properties of the outer skin layer, the stratum corneum. Consequently a number of technologies have emerged, which temporarily physically disrupt the skin barrier to facilitate localised delivery. Devices use a range of approaches including particle/liquid jet acceleration, laser ablation, radiofrequency ablation, microscission, abrasion and microinjection amongst others. One such technology is the microneedle array device (MD), an arrangement of micron-sized needle-like projections that penetrate the skin barrier without impinging on underlying nerves or blood vessels.

Investigations within our laboratory have used silicon, metal and polymer MDs with variant microneedle geometries and arrangements for the intra-epidermal/dermal delivery of a range of molecules. Studies principally use ex-vivo human skin obtained from surgical procedures. Importantly, the tissue is obtained immediately after excision and maintained in a validated organ culture model that preserves tissue viability for up to 72 h. This provides a laboratory model that is analogous to the in-vivo setting. Studies to date have confirmed the clinical potential of the MD as a means to deliver plasmid DNA,[1] proteins and nanoparticles[2] to the skin, and a pilot clinical study has confirmed significantly reduced pain and bleeding upon its application.[3]

Investigations are currently focussed on optimising MD delivery of a sufficient and reproducible dose of candidate therapeutics to its target regions of human skin. Therapeutic candidates include vaccines, which are targeted to the viable epidermis (residence of immune-competent antigen presenting cells), and botulinum toxin A, a potent therapeutic protein that acts on eccrine sweat glands in the dermis to prevent hyperhidrosis. Targeted MD delivery for such applications relies upon effective and predictable penetration of skin tissue by the device; however, the mechanics of microneedle penetration into human skin is poorly understood. Mechanical indentation tests using a hydraulic testing machine are being used, in conjunction with computational models, to determine the properties of the skin layers and the mechanics of microneedle insertion. This will inform MD design and application methods. Parallel studies are investigating formulations that are designed to facilitate (1) coating of proteins on to the microneedle surface and (2) deposition of proteins in the skin following MD application.

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Materials Science aspects of Dermal Delivery Systems

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Introduction and Objectives

The objectives of this study were to investigate the utility of silicon, polymeric and carbohydrate materials in the production of microneedle arrays and to use optimised microneedle arrays in transdermal and intradermal drug delivery.

Methods

Silicon microneedle arrays were made by wet etch processing, whereas polymeric and carbohydrate microneedles were prepared by a micromoulding process using poly (dimethylsiloxane) moulds made either by using silicon microneedles as master templates or by a 2.5D laser-microengineering process. Microneedles were characterised in terms of their tensile strength and the force required to pierce the stratum corneum of excised porcine skin. Microneedles were then used in enhanced delivery of insulin, bovine serum albumin, theophylline and photosensitising drugs.

Results and Discussion

Microneedles prepared from carboxyrnethyl cellulose, amylopectin and hydroxyethyl cellulose had poor physical properties. Galactose microneedles were extremely hygroscopic.[1] Microneedles prepared from poly(methylvinylether maleic acid) (PMVE/MA) possessed superior physical properties. Silicon microneedles required a two-step application process when used for transdermal and intradermal drug delivery.[2,3] As this was undesirable, we used PMVE/MA microneedles to deliver the drug substances of interest. Greatly, enhanced delivery was observed in all cases, with the reduction in blood glucose in diabetic rats, which was comparable to a subcutaneous injection of insulin, the most notable finding.

Conclusion

We are now pursuing development of PMVE/MA microneedle arrays for use in transdermal and intradermal drug delivery systems.[4]

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Polymer therapeutics as anticancer nanomedicines

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A growing number of 'polymer therapeutics',[1,2] including polymer-drug conjugates (and their combinations), polymer-protein conjugates and related polymeric micelles to which the drug is either covalently bound or is simply entrapped, have been transferred into clinical development. PEGylated proteins have also been transferred to market as novel anticancer agents. These systems can be considered first-generation nanomedicines. Drug conjugates arose from rational design attempting to capitalise on passive tumour targeting enhanced permeability and retention effect and, at the cellular level, lysosomotropic drug delivery to improve therapeutic index. For many conjugates, early clinical results have been promising confirming activity in chemotherapy refractory patients. The polyglutamic acid-paclitaxel conjugate OPAXIO has been submitted to European Medicines Agency (EMEA) for regulatory authority review. Our early research led to a series of 2-hydroxypropyl methacrylate (HPMA) copolymer conjugates, most recently the polymer platinate ProLindac, that have progressed into clinical trial. Subsequently, HPMA copolymer conjugates containing a combination of endocrine and chemotherapy were developed.[3] This approach and our recent studies involving bioresponsive dextrin-phospholipase A2 conjugates[4] and PEGylated coiled-coil motifs designed as molecular switches[5] indicate many interesting future possibilities for this family of compounds. The preclinical and clinical observations made and lessons learnt during transfer from laboratory to clinic will help shape the development of next generation anticancer polymer therapeutics.

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Characterisation and control of structured liquids and semisolids for dermatological use

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Dermatological preparations, which range in consistency from structured liquids (lotions, sprays) to soft semisolids (creams, ointments and gels) and stiff semisolids (pastes) are often complex multicomponent blends of interacting surfactants, clays, polymers and other excipients. Batch variations of the individual components as well as differences in manufacturing techniques such as the heating or cooling rate or the extent and order of mixing of the excipients can cause variations in structure and stability. An understanding of the microstructure of such products and the various methods of stabilisation and breakdown is essential to optimise manufacture, provide cosmetic elegance and to understand drug delivery to the skin.

The challenges of formulating and controlling the various types of liquid and semisolid formulation will be discussed. It will be shown how an understanding of the relationship between microstructure (at all stages of manufacture and storage) and various physical properties is essential to develop meaningful tests to characterise the formulation and control quality. Particular emphasis will be given to rheological testing. Semisolids are often liquid during their manufacture so that the in-process test is on a liquid, whereas the end-process test is on a semisolid. The relationship between microstructure and rheology will be discussed with a view to avoid the development of rheological tests that are invalid.

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Development of a new engineered peptide compound platform creating new anticancer derivatives with increased brain penetration for the treatment of brain cancers

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The blood–brain barrier (BBB) is mainly formed by brain capillary endothelial cells, which are closely sealed by tight junctions and express high levels of active efflux transport proteins, including P-glycoprotein (Pgp). As a result, the overwhelming majority of small molecules, proteins and peptides do not cross the BBB. Angiochem's engineered peptide compound (EPiC) technology platform provides a noninvasive and flexible platform for small and large molecules creating new drugs able to cross the BBB to treat brain diseases. The lead carrier peptide (Angiopep-2) was evaluated in an in-vitro model of the BBB and *in vivo* by in-situ brain perfusion and a noninvasive optical imaging in mice. Fluorescence associated to Cy5.5-angiopep-2 was detected very rapidly in the brain parenchyma after in-situ brain perfusion in mice. On the basis of these properties, we have created a portfolio of new drug entities composed of chemotherapeutics, siRNA, peptides and mAbs, the most advanced of which is ANG1005 formed by chemical conjugation of our peptide to three molecules of paclitaxel. ANG1005 has shown efficacy in animal models with brain tumours and is currently under evaluation in two phase ½ clinical trials for the treatment of primary and secondary brain tumours in humans. Human data have now confirmed the preclinical results validating the technology.

We are now presenting data on the brain uptake of new chemical entities synthesised with Angiopep2 conjugated to anticancer agents such as etoposide and doxorubicin, to neuroactive peptides, to larger proteins e.g. mAbs and to agents based on nucleic acid such as siRNA. The new chemical entities have been synthesised using different approaches and characterised after purification by chromatography and mass spectrometry. The activity of the modified compounds was measured and was mostly none affected by the incorporation of peptides. Furthermore, we show by mice in-situ brain perfusion that these new EPiC compounds demonstrate higher brain distribution than the unmodified molecules. In addition, brain perfusion studies performed with Pgp knockout mice showed that the chemotherapeutics (Etop-An2 and Doxo-An2) conjugate bypass the drug efflux pump Pgp at the BBB. Approximately 5- to 10-fold higher brain distribution is measured for the anticancer agents, peptides, mAbs and siRNA when modified with our peptide technology. Finally, in-vivo studies using mice models demonstrate that these EPiCs can reach therapeutic amount in the brain.

In conclusion, these data confirm that conjugation of a drug to the peptide Angiopep-2 significantly enhances their entry into the brain and further validate the use of Angiochem's technology for improving drug access to the brain.

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The regulatory landscape: implications for design and development of nanomedicines

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The first nanomedicines 'nanopharmaceuticals' already came onto the market more than 18 years ago and since a steady stream of products have followed. These first generation products were able to meet the evolving general regulatory standards.[1] However, with increasing complexity in nanomedicine structure, use of new materials, new characterization methods and manufacturing processes, and not least, the convergence of science that is bringing together nanopharmaceuticals and nanodevices, there will be pressure to define a new regulatory environment able to bridge the gap in biomedical nanotechnology between medicines and medical devices regulation.[1,2]

Appropriate risk assessment and risk/benefit analysis are major issues for Regulatory Agencies in respect of all new medicinal products.[3] Some of the most important issues currently discussed in nanomedicine include the question of whether the currently required toxicological studies will be adequate for new nanomaterials, and whether the major differences in biofate and increased complexity of clinical use (integrating different technology subsets from therapeutics to imaging as well as integrated non-invasive diagnosis) are adequately covered. Increasing application of nanotechnology in biomedicine brings highly complex problems and a globally integrated regulatory structure would promote better (fast and safe) access to these new technologies. Europe is playing an important role in the global arena through the participation of the EU member states experts and their networking through the European Medicines Agency (EMEA). The International Conference for Harmonisation (ICH) also provides

opportunities for global scientific advice already being implemented in close collaboration with the FDA.

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Evidence-based therapy in health inequalities

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Background

The south Asian population in the United Kingdom are up to six times more likely to get diabetes and are at a higher risk of cardiovascular disease, which accounts for higher morbidity and premature mortality.[1] South Asians have been described as a 'hard to reach' group.[2] Cultural factors can determine lifestyle behaviours, which are detrimental to their diabetes, and there is a higher level of deprivation among this group.[3,4] South Asian patients with diabetes are less likely to be prescribed key drugs.[5] There is evidence of self-regulation of diabetic drugs among this group with cultural beliefs having a role in this.[6]

Changing the model of care

In Glasgow, a general practice-based pharmacist medication review service was established in 1997. It became apparent that it was not meeting the needs of south Asian individuals: attendance at these clinics was less than 50% compared with greater than 80% for the indigenous population.

1. Changing the *National Health Service* (NHS) invitation process: as a result of low attendance to pharmacy-led clinics, the following service was adapted: we targeted high south Asian-populated general practices and invited them to attend using an Urdu-speaking administrator to ensure the first point of contact being in Urdu; a language that most south Asians understand. This lead to an increase of greater than 80% attendance to pharmacy-led clinics.

2. Enabling access through community venues: access to health services is an inequality that exists in the south Asian population. To tackle this, clinics were set up in community venues. Examples of venues targeted were a mosque, elderly and voluntary centres.

3. Using community pharmacies: community pharmacies can be easily accessed by 99% of the population, even in the most deprived areas.[7] Regular and opportunistic customers were targeted to attend a diabetic medication review clinic, which was set up in a community pharmacy that was located in an area with a high population of south Asians.

4. Setup of a new access point: increased demand for the service has resulted in formation of minority ethnic long-term medicines service (MELTS). MELTS is an open referral service for any minority ethnic patient who wishes a medication review. Referral to the service can be made *via* self referral, a family member or any health care professional. Agreement has been gained from the local consultant diabetologists group who have agreed to refer individuals in from secondary care.

Discussion

The processes described in steps 1–4 have enabled vulnerable individuals, including asylum seekers with long-term conditions, living in areas of socioeconomic deprivation to access an outreach pharmacist service. This has resulted in an increase in the prescribing of medicines, which will impact favourably on morbidity and mortality. There is onward referral to the wider primary health and social care team and an increase in the detection of conditions. This service has shown that pharmacy-led clinics in a variety of settings can tackle access issues and health inequalities among a vulnerable population.

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Making the future Pharmacist

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Two major developments have focussed attention on the future direction of the profession: the white paper 'building strengths and delivering the future' and the 'splitting of the regulatory and professional functions of the Royal Pharmaceutical Society'. It can be argued that the future described in the white paper points to developments in current working

practices demanding strong leadership and direction from a new professional body.

The white paper recognises the progress in hospital pharmacy practice regarding clinical activities and medicines management and describes ways in which these can be integrated into community care. It does, however, describe a far greater clinical remit for community pharmacists in a wide range of activities, including, for instance, management of long-term conditions, meeting public health agendas through lifestyle and screening and the treatment of minor ailments. The implication is that pharmacists will be effectively running a form of community clinic from local pharmacies. If this agenda is to be met, it certainly involves a change in working practice focussed outside the dispensary environment, which the recent 'Responsible Person' legislation has been intended to facilitate. Other important legislation is already in place and being increasingly taken up by pharmacists in both the community and hospital sectors, including the use of patient group directions and independent/supplementary prescribing. Combined with deregulation from Prescription Only of various medicines, these changes give pharmacists the potential for clinical activities unthought-of in the previous decade. There are a number of challenges to meeting the vision of the white paper: motivation for pharmacists to change working practices, methods of remuneration, access to an effective on-line common patient record and ensuring competence.

There are obviously implications for Continuing Professional Development (CPD) and training of pharmacists, but one of the most important keys to the long-term success of this vision for pharmacy lies in the restructuring of the MPharm programme. This is currently being debated and the first reports are expected in the summer of 2009. There is little doubt that a great emphasis will be placed on clinical components in the 4-year programme and that this will be achieved through greater placement opportunity in both the hospital and community sectors. Together with a major curriculum change is the proposal that the preregistration year be merged into one 5-year programme. A number of models have been identified, ranging from an integration of placements throughout the year to a 'four plus one model' similar to the present arrangement. The key principle though is that for the first time the preregistration training will fall under the remit of the Schools of Pharmacy. It is generally accepted that the science component be maintained, but will there be a shift from the material to the biological sciences and what implication does this have for those entering pharmaceutical industry?

There is huge potential for the future pharmacist but this will need two important and integrated components: education and motivation.

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Your future in pharmacy: the world is your oyster

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The skills that are learned during the MPharm course and preregistration year can be put to good use in a number of different pharmacy sectors. A thorough grounding in all aspects of the development and use of medicines, 'from bench to bedside', enables the pharmacist to apply natural science and social science principles to real-life challenges at a patient and/or population level.

The Royal Pharmaceutical Society has recognised and promoted the role of the community pharmacist as 'the scientist in the high street' for a number of years. When the latest media 'scare' strikes, many customers head off to the local pharmacy to get reassurance and guidance. The recent swine flu situation has demonstrated this yet again. Another excellent example of proactive pharmacy advice was during the 'pill scare' of the 1990s, when some pharmacists used patient medication record (PMR) information to send official advice to all women on their list taking the medicines concerned. Such positive action by pharmacists, using the valuable information within their PMR, probably avoided some unplanned conceptions.

Since 2005, the community pharmacy contract has moved away from a fee-for-dispensing approach to recognise the wider role of pharmacists, and their support staff, in promoting and maintaining health. The scientific knowledge of pharmacists can be applied to screening for long-term conditions, such as diabetes, and monitoring medicines with a narrow therapeutic window, such as warfarin. This enables people to access high-quality services, close to home. The natural and social science skills of pharmacists can be harnessed in synergy to help people to overcome problems with adherence: be it unintentional problems such as chewing prolonged release formulations in error or intentional problems relating to their beliefs about specific medicines (such as fear of weight gain when taking oral steroids). Spending time in practices to advise on other professionals' prescribing, or indeed to do specialist sessions as prescribers themselves, is becoming a more commonplace for community pharmacists.

The practice of pharmacy in hospitals has, for some years now, pushed boundaries as pharmacists have moved out of the dispensary and on to the wards. Directorates within the hospital now directly employ pharmacists as part of their multidisciplinary team, and supplementary and independent prescribing has been a logical progression for many specialist pharmacists in areas such as HIV/AIDS and intensive therapy unit. As part of the hospital pharmacy team, pharmacists can also specialise into teaching roles. Some hospital pharmacists are extending the scope of their practice into roles outside the hospital, into patients' homes and other community settings.

There are also many opportunities for strategic and administrative roles for pharmacists in all sectors. Primary care organisations have medicines management teams and pharmacy development teams. Pharmacists have been seconded and moved into executive teams. These roles might entail liaison with community and hospital pharmacy and other professionals in any sector. A pharmacy qualification is a gateway to any number of career options.

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Repairing tissues: taking cues from biology

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Significant advances in the medical sciences mean that our average lifespan has increased significantly over the past 50 years. Although we are now living longer, the associated increase in the average age of the population means that we spend most of our lives living in relatively poor health. As a consequence, there has been a drive toward developing new medical technologies that are able to replace diseased or damaged tissues. Our approach to developing such technologies has evolved in the past years. For example, materials used for the replacement of hard tissues were initially selected based on their 'inertness' when placed in the body. A second generation of materials was subsequently developed that mimicked the composition and structure of the tissues that they replaced and could bond with both hard and soft tissues. Although this approach has had some success and a number of hard tissue replacements are now available (hydroxyapatite granules or blocks), the structural and chemical similarity to bone means that the materials can remain *in vivo* for a significant period of time following implantation and therefore present a prolonged risk of implant failure. A vast array of materials exist that can be formed from the anionic and cationic components of serum and hence can be cleared from the body following dissolution, and the majority of these remain relatively unevaluated for use in medical applications. In this presentation, the formulation and characterisation of such materials and how they can be designed so that they may be modified or degrade in response to local tissue specific stimuli are discussed. This approach has been used to develop controlled degradation bioceramic materials and complex hard/soft tissue interfaces.

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Physical–chemical characterisation of polymers and actives to model and understand the chances of successful extrusion

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Melt extrusion is becoming an accepted technology in the pharmaceutical industry. An understanding of what can happen during the melt extrusion process is very important.

The pharmaceutical melt extrusion (PhME) can be seen from two sides.

One is to see it as a process only. The extruder can act as a melt supplier, where the melt gets shaped into granules (e.g. Strand Pelletizer), microspheres (e.g. micropelletizer), powder, sheets, films, foils and all other imaginable forms. The PhME can be used for degassing if necessary, e.g. to dry the products. PhME is mainly used for compounding of two or more components, in addition to supplying melt for down streaming. A single-screw extruder is used for melt supply, and a co-rotating twin-screw extruder is often used for compounding.

Second, PhME can be used as a 'formulation aid,' which provides a solid dispersion. For example, all melt extrudates with EUDRAGIT polymers should form a solid dispersion.

Although solid dispersion can be obtained by other processes such as spray drying, freeze drying and solvent/nonsolvent precipitation methods, PhME can do this faster as it is a continuous process and does not need any solvent or water. Using solid dispersion, we can get solubility enhancement of poorly soluble drug molecules, sustained release, controlled release, and taste masking. In general, all extrudates are matrix systems and means to use solid dispersion (which did not go wrong completely till date). Solid dispersion is obtained by compounding, of course.

We can obtain dosage forms not only in various shapes but also with specific pharmacokinetic functionality. This means that we can obtain microspheres that provide an enhanced release for poorly soluble drugs or microspheres that provide sustained release.

For enhancing drug solubility, the formation of a solid glassy solution might be advantageous. Solubility parameters can be used in an experiment to estimate the miscibility between a drug molecule and a polymer. Solubility parameters can be calculated using several methods such as the group contribution method of van Krevelen and Fedors method. This article gives an overview on existing methods, their advantages and disadvantages and also an example study for the enhancement of solubility of Felodipin.

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The challenges of developing inhalation products in the era of Quality by Design

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Since the concept of Quality by Design (QbD) was first introduced at the beginning of this century, QbD has evolved into a structured, risk-based approach for the development of pharmaceutical products. QbD recognises that an effective development programme must be focussed on those aspects of product performance that impact on the safe and efficacious treatment of patients. To achieve this there is a need to fully understand products, manufacturing processes and analytical methods. This thorough understanding also supports the establishment of a cost-effective manufacturing

environment and, more importantly, a reliable supply chain that ensures patients have access to their medicines wherever and whenever they need them.

Inhalation products are a complex amalgam of drug substances, excipients, devices, manufacturing processes and test methodologies that present both opportunities and challenges to the effective implementation of QbD. The quest for understanding begins with the development of a Target Product Profile (TPP) that embodies clinical, safety and quality requirements. This is the starting point for the development programme and is where pharmaceutical opportunities and risks are often first evaluated in a structured manner. The selection of a device appropriate to the disease and patient population is a necessary early decision although a number of device options may be evaluated in parallel adding another level of complexity to the development process.

Understanding of the drug substance is vital. Selection of the appropriate salt and polymorphic form are important development decisions and may be substantially influenced by the choice of device or devices. Particle morphology has always been an area of intense scrutiny and this continues to be the case. Different therapies may need to be targeted to different areas of the lung, whereas the co-location of receptors may require the delivery of two active moieties to the same location for another product. Emerging technologies offer the opportunity to modify particle morphology and these may become increasingly important in ensuring effective and reproducible drug delivery to specific locations within the lungs.

Many formulation options are available and a structured approach to the selection and optimisation of inhalation product formulations is required. Of course, this cannot be done in isolation of the drug substance and device leading to extensive programmes of experimental design. Defining the appropriate design space and control strategy is, therefore, complicated and must be linked to appropriate clinical and safety data.

The development of high-quality inhalation products in the QbD era is challenging but provides a great opportunity to deliver safe, efficacious and cost-effective products.

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The effects of crystal properties on formulation success

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Crystal properties may have an influence in powder processing, particle handling and particle performance related to pharmaceutics, drug delivery and/or the pharmaceutical technologies. Here, the effects of crystallisation and processing on particle interfacial surface properties are investigated and related to their performance. We reported that crystalline solids have highly variable (anisotropic) surface energetics, confirmed by sessile drop contact angles on individual crystalline facets and XPS. A new methodology based on inverse gas chromatography (IGC) for determination of surface energy distributions will be presented. Vapour adsorption measurements over a wide range of alkane vapour concentrations and surface coverage are undertaken, resulting in a distribution of γ as a function of the solute surface coverage being determined. This technique was applied to study variations of surface properties due to crystallisation conditions, milling and their impact on dissolution rates and granulation. Our results show that IGC heterogeneity mapping is able to map differences in surface properties of particles. The differences were related to changes in crystal properties such as shape/habit and exposure of internal cleavage planes. Changes in solid surface roughness and topography due to processing and storage conditions were also measured using white-light interferometry. Surface properties variation was directly related to the spreadability of binder solutions on crystalline pharmaceutical solids and resulting granule characteristics, dissolution rates and phase transformation. In this talk, I will also attempt to demonstrate that interfacial properties could have a major impact on pharmaceutical manufacturing practices: improved control over crystallisation processes for optimal crystal properties; new methodology for discovery of polymorphs; capability to engineer crystal shape (habits) and improved downstream separations for (bio)pharmaceuticals.

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The hypoxia inducible factor-1α and p300 interaction as a therapeutic target of the epidithiodiketopiperazine class of natural products

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As tumours grow, the ability of the native vasculature to supply them with nutrients diminishes and the level of oxygen in cells reduces to the point whereby they can become hypoxic. Under these conditions, tumour cells activate pathways that regulate proliferation and angiogenesis to facilitate their rapid growth and survival and it is this process that is associated with therapeutic resistance, increased risk of invasion, metastasis and ultimately poor patient prognosis. Hypoxia inducible factor-1 (HIF-1) is a transcription factor that regulates the expression of a large number of genes, including those responsible for cell proliferation, angiogenesis and cell survival. Under normoxic conditions, levels of one of the subunits, HIF-1α are tightly regulated, but in the hypoxic environment found in many tumours, HIF-1α accumulates leading to activation of transcription and hence tumour growth and metastasis. Chetomin, a structurally complex dimeric member of the disulfide bridged epidithiodiketopiperazine (ETP) class of

natural products, has recently been demonstrated to target this response *via* inhibition of the interaction of HIF-1α and the transcriptional coactivator p300. In xenograft studies, levels of vascular endothelial growth factor (VEGF) were attenuated in a dose-dependent manner and more significantly, tumour growth was inhibited. However, chetomin itself is unlikely to be used clinically due to the fact that local toxicity effects were observed at the site of injection. Therefore, a small suitably designed molecule based on chetomin that selectively abrogated the hypoxic response in cells would be an attractive target for cancer chemotherapy. All members of the ETP class of compound display potent and varying biological activity but medicinally useful synthetic analogues are yet to be studied in detail due to their structural complexity. We have recently described new methodology for the synthesis of molecules based on the ETP core, and our recent synthetic developments towards this class of compound and our approach towards dimeric derivatives and the natural products will be described. In preliminary studies, we have demonstrated that monomeric ETPs display potent in-vitro inhibition of the HIF-1α and p300 interaction and have demonstrated that the disulfide bridge is essential for the observed biological activity. Insights into the mechanism of action of this unusual and promising class of compound will also be described.

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Manufacture and delivery of a investigational medicinal product for a stem-cell clinical trial

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Stable culturing of stem cells in sufficient quantities for widespread therapeutic applications presents technical challenges. Chief among these is retention of phenotypic and genotypic stability of the cell line through enough generations (population doublings) to allow early characterisation and screening of lines, proof-of-concept assays in disease models, then development into a manufactured product. By adopting a conditional cell immortalisation strategy (c-mycERTAM), ReNeuron has delivered all these requirements without affecting the intrinsic characteristics of the stem cells. Hence, the use of c-mycERTAM has allowed a standard biotechnology banking process (MCB, WCB, DS and EOPCB), readily adapted from the R&D laboratory culture practice.

For stem-cell drug substance investigational medicinal product (IMP) lots for phase I/II clinical trials, the key consideration for successful outsourced manufacture is a thorough and continuous technical transfer of process that has been carefully defined, suitable for the scale necessary to provide material for the trial and good manufacturing practice compliant. For subsequent trials and for pipeline projects, any hard-learned inadequacies of the manufacturing process should be addressed. Embracing a quality-by-design approach to process optimisation leads to advances in efficiency and scale, driving down costs of goods, and reducing the risks of failure.

A particular challenge for stem-cell therapies is the provision of sufficient shelf-life for the IMP to take it to the clinic. The shelf-life must extend beyond the necessary pharmacopoeial testing and QP-release time, the delivery to the pharmacist, the handling in the operating theatre and administration to the patient. Stem-cell manufacturers will react to shelf-life shortcomings as they are identified, leading to process and product improvements. These changes have to be justified by the use of comparability assays, showing that the active pharmaceutical ingredient (i.e. the cells) is not affected. In the absence of a true potency assay, as will often be the case in early stem-cell clinical trials, comparability of manufactured lots may be addressed by appropriate characterisation with respect to cell phenotype and function. Next-generation products will pay closer attention to this issue, with the advent of novel preservation approaches extending shelf-life of cell therapy drug products from hours or days to months or even years.

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New in-vitro gastric model for the biorelevant dissolution assessment of orally administered pharmaceutical drug products

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Predictive dissolution testing to preempt oral absorption for pharmaceuticals remains one of the key areas of unmet industrial and regulatory needs. Currently available Pharmacopeia tests are confined to quality control whilst more advanced methodologies still do not provide adequate replication of gastric processing. The Dynamic Gastric Model (DGM) provides a key advancement in the in-vitro simulation of gastric conditions. Its design has been underpinned by extensive studies in humans to validate the physical and biochemical parameters using echo-planar magnetic resonance imaging, ileostomy, nasal gastric/duodenal aspiration and plasma analysis of nutritional delivery. The DGM processes real food input and can fully replicate the dynamic biochemical environment of the human gut as well as reproducing the array of complex mixing modalities necessary for accurate in-vivo simulation. In addition, the DGM allows for adjustment of gastric residence time, acid and enzyme additions and physical processing (depending on the food matrix), to provide close representation of the human gut. These advancements make possible the ability to undertake dissolution studies (under gastric conditions) in an in-vitro model that is predictive of in-vivo performance. Furthermore, the specificity of gastric shear simulation also makes possible the assessment of gastric processing on dosage form integrity

and potential for dose-dumping, especially pertinent in the development of modified release dosage forms.

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Crystallisation control and formulation-friendly pharmaceuticals

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Introduction and Objectives

The aim of this study was to show that controlled crystallisation processes can produce particles with controlled particle size reproducibly, and to assess the subsequent effects on material properties.

Methods

Crystallisation methods based on seeded cooling crystallisations of a model active pharmaceutical ingredient were developed. Crystallisations were carried out in temperature-controlled, jacketed vessels, fitted with a Lasentec FBRM (Mettler-Toledo Ltd, Leicester, UK) to give in line measurement relating to particle size (chord length distribution (CLD)). Control of particle size was addressed by investigating the effects of seed loading and cooling profile.

Initial characterisation of the product crystals was based on microscopy, XRPD and particle size measurement. Material properties of selected batches were further characterised by various methods, including specific surface area, flow (shear cell) and compaction profiling, both before and after particle size reduction.

Results and Discussion

We found that it was possible to control the particle size by using appropriate seeding conditions and keeping supersaturation low to avoid secondary nucleation. We were able to produce material with median sizes between 10 and 40 μm, avoiding the bimodal particle size distributions seen in standard crystallisations, and to do so reproducibly. Material characterisations showed these batches had favourable compression properties compared to the control, even after particle size reduction. Electron micrographs of the 'size-controlled' batches are compared to a standard crystallisation in Figure 1.

Conclusion

Control of particle size during crystallisation has been shown for a model API, and this resulted in tangible benefits for formulators, including the possibility that particle size reduction might be avoided in some cases. These benefits were achieved by using seeded crystallisations in which secondary nucleation was avoided. Online control of solution concentration was not necessary, but monitoring particle CLD *via* an inline probe was essential.

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Delivery of proteins to the lung

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Protein pharmaceuticals have offered new opportunities for addressing unmet clinical need by the supplementation of endogenous physiology, or by the highly specific pharmacology achievable by antibodies. Invariably, protein pharmaceuticals have limited extravasation, a short half-life and require high mass doses compared to small-molecule drugs. Therefore, the inhaled delivery of protein pharmaceuticals presents an attractive option for respiratory indications for efficiency and convenience reasons. Also, given that proteins are not orally bioavailable, inhaled delivery offers a potential alternative to injection as a means of systemic administration. Both of these concepts have been achieved with Pulmozyme and Exubera, respectively, although for Exubera bioavailability was only ~10%.

Current small-molecule respiratory drugs are typically highly potent, are cheap and have a large therapeutic window

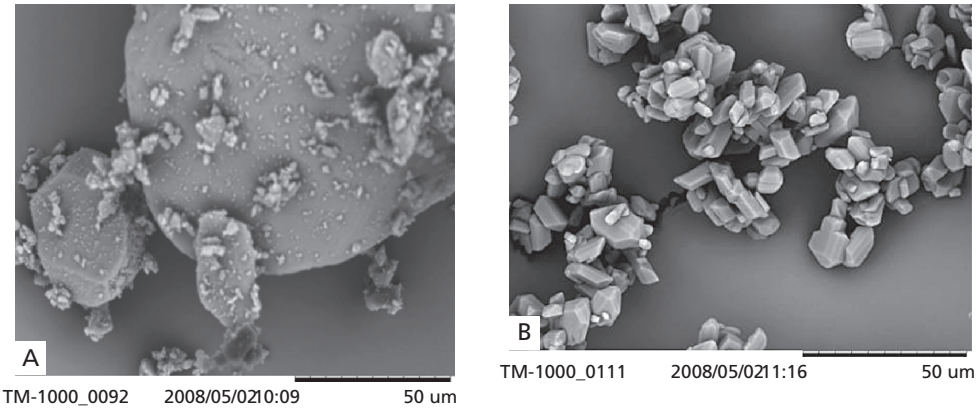

Figure 1 Comparison of particles from A: unseeded crystallisation; B: controlled, seeded crystallisation.

and act in the central airways. Therefore, current inhaled formulations and devices provide satisfactory dosing, despite typically only having 10–20% lung deposition efficiency, limited drug capacity per dose and variable, user-dependent performance. For protein pharmaceuticals, it is unlikely such luxuries can be afforded since proteins are typically less potent by mass, and more expensive, therefore requiring much more efficient delivery systems to be efficacious and cost-effective treatments. Depending on the pharmacological target site, there may also be a requirement to deposit a higher proportion of the dose in the distal airways.

Delivery options for inhaled medicines include solutions for nebulisation, pressurised-metered dose inhalers and dry-powder inhalers. Each of these approaches has special considerations when applied to protein pharmaceuticals and may require innovation in terms of both the formulation and the device. In particular, a dry powder, inhaled delivery system would rely on being able to isolate the protein in the solid state. This invariably requires excipients for stability and a manufacturing process capable of producing respirable particles. In terms of the device, an active dispersion mechanism may be required to enhance delivery efficiency and to ensure consistent dosing.

For certain applications, a modified-release formulation may be required. A recently published paper by Kaye *et al.*,[1] conducted at the School of Pharmacy, University of London, detailed the concept of SIMANIM particles. This technology demonstrated the potential to achieve a modified-release formulation of a protein that is suitable for dry-powder pulmonary delivery with high aerosolisation efficiency.

The presentation will end by summarising some of the physicochemical properties of proteins as a means of addressing some of the safety concerns that may be experienced by formulation and analytical scientists new to working with biopharmaceuticals.

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Predicting drug response and toxicity from molecular profiles: the potential of metabonomics

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Metabolic biomarkers have much potential in biomedical and toxicological research. They can be measured noninvasively via imaging or body fluid profiling, which is better for the welfare of both patients and animals and facilitates longitudinal studies and translation of results between models and man. Metabolites are also defined chemical entities without genetic variation or posttranslational modifications, which also help to translate analytical methodologies directly between the bench and the bedside. A substantial body of research has shown that metabolic profiles can report sensitively and specifically on a number of pathological states, both in terms of clinical disease processes and laboratory studies of genetic manipulation or chemical exposure. Certain conditions, such as type II diabetes or cancer, have defined metabolic phenotypes that are already exploited in diagnosis and therapy. Importantly, metabolic biomarkers have been shown to be predictive of the way that individual people or animals metabolise and respond to drugs. I review some of this evidence and present data from our own laboratory to show that metabolic profiling (metabonomics/metabolomics) is a crucial element of systems biology, enhancing the information ('pathway') recovery from other 'omics' data sets.

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Oral insulin: from bench to humans

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Oramed Pharmaceutics has developed a novel drug delivery technology platform enabling oral administration of polypeptides and proteins typically administered by injection. Clinical trials conducted with healthy human volunteers and type I and type II diabetes patients have shown that application of drug delivery technology of Oramed in oral insulin formulations can effectively reduce plasma glucose and c-peptide levels and potentially foster glycemic control.

By mimicking the physiological route of insulin secretion and absorption, Oramed's oral insulin may offer distinct advantages over systemically administered insulins. Such insulin formulations are expected to facilitate commencement of insulin therapy at significantly earlier stages than currently practiced and will likely foster long-term adherence and compliance among patients. Both patients and clinicians await alternative drug delivery routes to replace the subcutaneously injected insulin. Overall, oral insulin formulation of Oramed is expected to lead to improved glycemic control in the diabetic community.

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The UK response to the problem of counterfeit medicines

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Sampling and analysis of suspected counterfeit medicines present a unique challenge to the regulator, due to the lack of

any knowledge about the history of the manufacture, supply and distribution.

Counterfeit medicines present a risk to the health of the public for the following reasons:

- They may contain no active ingredient.
- They may contain the wrong active ingredient.
- They may contain an unapproved active ingredient.
- They may contain undetected impurities or adulterants.
- The content of the active ingredient may be significantly different from the declared amount.
- The product is badly manufactured, that is, the product quality is poor.

For these same reasons, application of the standard quality control tests to counterfeit the products may not provide the analytical information that is needed when assessing the risks to public health they present.

Since 2004 there have been a number of incidences of penetration of the legal regulated supply chain in the United Kingdom by counterfeit medicines; Cialis, Reductil, Zyprexa, Lipitor, Plavix and Casodex are examples of this. The Medicines and Healthcare Product Regulatory Agency (MHRA) responded quickly and effectively to these incidents, rapidly removing the products from the market, but should have taken a reactive approach when doing so. Clearly, proactive sampling to prevent counterfeit medicines reaching the legal market is preferred; as part of its overall anticounterfeiting strategy, the MHRA is developing new screening protocols for counterfeit medicines. Analytical data that can indicate common sites of manufacture are also valuable information for the enforcement investigation. New techniques that can provide such data are being evaluated.

This paper will discuss the MHRA approach to screening the UK medicines supply chain for counterfeit medicines and use case studies to describe some of the challenges the detection and analysis of counterfeit medicines present.

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Radiopharmaceutical imaging of molecular targets in cancer

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The specialised medical field of nuclear medicine is concerned with the use of unsealed sources of radioactivity either to diagnose or to treat a range of diseases. The range of diseases in which nuclear medicine plays a role is wide and includes, among others, the fields of microbiology, endocrinology, neurology, oncology and cardiovascular medicine. However, cancer probably represents the most important and growing area of application for this modality. Nuclear medicine uses radiopharmaceuticals. These are radiolabelled ligands that have the capability to interact with molecular targets that are relevant in the aetiology or treatment of cancer, and in many respects, nuclear medicine can be considered the archetype for the application of 'molecular medicine'.

Any biological target that is present at increased (preferably) or decreased levels in cancer cells can be usefully pursued. Because there are hundreds of pathways that are implicated in malignancy, a more discriminating selection can be made as follows: ideally the target should be as specific as possible for the disease, i.e. not present in normal tissues or those involved in other diseases such as inflammation and should be present as abundantly as possible on cancer cells. In selecting a target, consideration should also be given as to the type of information that would be gained from a diagnostic or therapeutic procedure that interacts with this pathway. Thus, the requirements for developing an imaging procedure that provides a sensitive and specific means for staging cancer on first presentation will be different to those required for a well-validated marker for assessing response in clinical trials of a new therapeutic agent.

Targets of current interest in radiopharmaceutical development can be divided into two main (overlapping) categories: (1) cell surface markers or receptors that show significantly increased level of expression on malignant cells and (2) intracellular metabolic pathways that are either upregulated in cancer or implicated in the response to various types of treatment. This study discusses the ways in which radiopharmaceuticals can be used to image these targets *in vivo* and describes their potential applications in drug development and in clinical management of patients with cancer.

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Nanosensors for superbugs and superdrugs

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The widespread and often indiscriminate use of antibiotics has fuelled the alarming growth of antibiotic resistant superbugs, including methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococci* (VRE). To remain one step ahead of the superbugs, it is vital to develop new antibiotics, and yet the drug pipeline is severely limited. We recently reported the nanomechanical detection of vancomycin-cell wall peptide interactions on cantilever arrays and discriminated between vancomycin-sensitive and vancomycin-resistant phenotypes.[1] In this discussion, I will present our new work that exploits this technology to search for new superdrugs active against VRE. We have investigated a series of vancomycin derivatives and detected a dramatic enhancement in surface binding affinities compared to homogeneous solution measurements. We identified a glycopeptide that binds 11 000 more strongly to resistant VRE phenotype analogues. Our findings revealed a fundamental new nanomechanical framework to understand the *surface* mechanism of glycopeptides binding to model bacterial cell wall peptides, which not only has important

implications on the design of nansensors with significantly improved drug detection sensitivity but will also impact on our understanding of antibiotics on real bacteria.[2–4]

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Colonic vaccination

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Although the targeting of drugs to the colon is a well-established scientific field, targeting of vaccines to the colon is much less researched, and antigen presentation and processing in the colon is virtually unknown. The long colonic residence time and low enzyme activity (hence, reduced possibility of antigenic degradation) are possible advantages of colonic vaccination over conventional oral vaccine delivery where the vaccine is expected to be largely taken up in the small intestine. The presence of large numbers of lymphoid follicles in the colon indicates that targeting vaccines to the colon may be a feasible alternative to conventional oral vaccination, whereas the significant differences between the small and large intestines' immune environments[1] suggest that colonic vaccination could yield different immune responses. Colonic intraepithelial lymphocytes are predominantly $CD4^+$ and $\alpha\beta TCR^+$, in contrast to $CD8^+$ and $\gamma\delta TCR^+$ in the small intestine. A preponderance of IgA2 cells over IgA1 cells is also seen in the colon (as in the rectum and vagina), in contrast to a predominance of IgA1 cells in the small intestine. In addition, the induction of immune responses to bacterial antigens is thought to preferentially occur in the colon. Thus, the colon might prove to be a more appropriate site of vaccination against enteric bacteria, sexually and vertically transmitted diseases and colorectal tumours, where antibody responses in the colon and/or rectum and genital tracts are desired.

To test the hypothesis of different immune responses when vaccines are taken up in the small or large intestines, we investigated the antibody levels (serum IgG and mucosal IgA) generated in response to antigen administered colonically or orally in the mouse model. As anticipated, colonic antigen administration (via the rectum) generated significantly higher levels of antigen-specific serum IgG and IgA in faecal and colonic extracts and in the vaginal wash compared with oral antigen administration (by gavage). Smaller differences were seen in the small intestinal IgA levels. This reflects the compartmentalisation within the common mucosal immune system and suggests that the colon may be an appropriate vaccination target for diseases of the colon and for sexually and vertically transmitted diseases. Proof of the working hypothesis paves the way for further work in colonic vaccination.

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Antitumor marine natural products that inhibit HIF-1 activation

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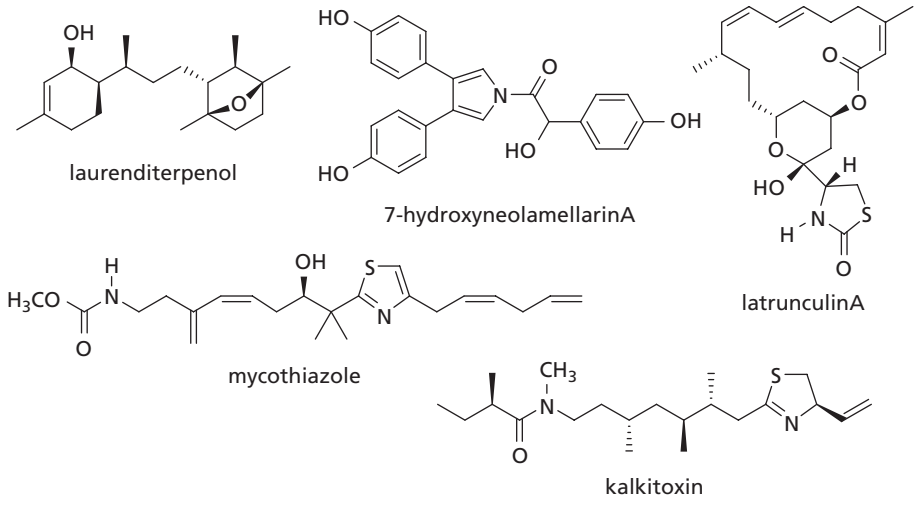
Rapid solid tumour proliferation outstrips the oxygen-supplying capacity of the existing vasculature. As a result, hypoxic regions develop within the tumour mass. The extent of tumour hypoxia correlates with the advanced stages of cancer and treatment resistance. The transcription factor hypoxia-inducible factor-1 (HIF-1) promotes tumour cell adaptation and survival under hypoxic conditions. HIF-1 has emerged as an important molecular target for anticancer drug discovery. A T47D breast tumour cell-based reporter assay was developed and used to evaluate samples for HIF-1 inhibitory activity. Extracts from our repository and the National Cancer Institute's Open Repository of marine invertebrates and algae were evaluated for the ability to inhibit HIF-1 activation.

The first marine natural product found to inhibit hypoxia-induced HIF-1 activation was the diterpene laurenditerpenol, isolated from the red alga *Laurencia intricata*. Sponges, cyanobacteria, and other marine organisms have since been found to produce an array of HIF-1 inhibitory compounds. Recently, the antitumour sponge natural product mycothiazole and the marine cyanobacterial (*Lyngbya majuscula*) metabolite kalkitoxin have been found to be among the most potent marine natural product inhibitors of hypoxia-induced HIF-1 activation (IC50 values 1 and 5.6 nM, respectively). These natural products inhibit the hypoxic induction of HIF-1 target genes and the pathophysiological processes associated with HIF-1 activation (e.g. expression of the angiogenic factor VEGF and induction of tumour angiogenesis). Marine natural product-based HIF-1 inhibitors vary widely in potency and selectivity. These compounds function through distinctly different mechanisms that include suppression of mitochondria-associated HIF-1 signalling and disruption of nuclear HIF-1α protein induction.



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Top-down nanofabrication techniques applied to the design of engineered drug therapies

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A novel method for the fabrication of organic particles on the order of tens of nanometers to several microns will be described. Our imprint lithographic technique called Particle Replication in Non-wetting Templates (PRINT®) takes advantage of the unique properties of elastomeric moulds comprised a low surface energy perfluoropolyether network, allowing for the production of monodisperse, shape-specific particles from an extensive array of organic precursors. The engineered nature of particle production has a number of advantages over the fabrication of traditional nanoparticles such as liposomes, dendrimers and colloidal precipitates. The nature of PRINT technology takes drug delivery for the first time into the uncharted realm of engineered drug therapies given its *á la carte* approach and versatility. PRINT allows for the precise control over particle size, shape, composition, cargo, modulus and surface properties with the ability to independently design these attributes to create truly engineered drug therapies.

For the first time, key therapeutic parameters such as bioavailability, biodistribution and target-specific cell penetration can be simultaneously designed into a therapy or an imaging agent. Preliminary in-vitro and in-vivo studies are being conducted to show the promise of PRINT particles as delivery vectors and novel imaging agents for the treatment and diagnosis of the disease. Cellular uptake of PRINT particles is strongly influenced by the size, shape, charge and targeting ligand. The HeLa cell line (human epithelial) was used to investigate the uptake of cubic particles and cylindrical particles, with sizes varying from several microns to several hundred nanometers, with a cationic or an anionic surface charge and fluoroscein isothiocyanate incorporated as a tracking agent. These findings suggest that cellular internalisation of particles exhibited a strong dependence on size and shape.

Understanding the parameters for cellular uptake will aid us in designing particles that will perform and function as required by the application. PRINT particles have been decorated with a variety of targeting ligands for targeted delivery of therapeutics or imaging agents *in vivo*. The targeting ligands have included monoclonal antibodies to the transferrin (mouse antihuman IgG1, clone OKT-9); folate α receptors, Herceptin and Her2/neu and their binding and internalisation were studied on a variety of cancer and control cell lines. Biodistribution of nanoparticles of varying size and surface functionalities in both healthy and tumour-bearing mice models are also being examined. Two modalities are used to track the PRINT particles *in vivo*; a static profile using a fluorescent label and a dynamic MR profile obtained using metal-oxide contrast agents incorporated within the particle. Knowing where the PRINT particles travel *in vivo* forms the foundation for development of effective drug delivery vectors. The knowledge garnered from these studies will be used in the development of novel particle–based chemotherapeutic and imaging agents.

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Cardiovascular risk reduction: using a pharmacist-prescriber to treat to target in people with diabetes

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The early evidence from UK Prospective Diabetes Study[1] put intensive management of blood pressure in people with diabetes to the forefront of their care. The study showed that tight blood pressure control in patients with hypertension and type 2 diabetes achieves a clinically important reduction in the risk of death related to diabetes, complications related to diabetes, progression of diabetic nephropathy and deterioration in visual

acuity. The management of hypertension in this group of people often demands a number of drugs. The complexity is reflected in the general practitioner contract, which awards the highest number of points in the diabetes subgroups for the management of diabetic hypertension.[2]

Some years ago it was recognised by the consultant diabetologist that pharmacists working in a multidisciplinary diabetes team could offer intensive management of cardiovascular risk. A pharmacist-led diabetes cardiovascular clinic was set up in a secondary care setting in Harrogate District Hospital in 2002.

The clinic sought to provide help to the patients to self-manage as promoted in the National Service Framework for Diabetes.[3] A patient education booklet from the Blood Pressure Association[4] and a simple hand-held record are used. Patients are referred from any member of the diabetes team. Patients are seen every 4 weeks to ensure optimal maximisation of their drug therapy and are discharged at target blood pressure and lipid levels where possible.

Early research of this clinic was published in *Pharmacy World Science*.[5] This demonstrated that the use of an intensive pharmacist-led clinic produces clinically significant reductions in the risk of cerebrovascular accidents and coronary heart disease in patients with type 2 diabetes mellitus, and the clinic received a national award in 2003 (Royal Pharmaceutical Society of Great Britain, Pharmaceutical Care Award for pharmacist-led diabetic hypertension/cardiac risk management clinic 2002/2003).

More recent research will be presented to review the success in achieving target levels of blood pressure and lipids and also to obtain the views of the multidisciplinary team.

The support of the team is a major requirement for pharmacist prescribers, as it provides support for the management of patients who are therapeutically challenging and examples of these will be presented. The plan for the clinic is to move into intermediate care, and the prescribing role of the pharmacist will be a key to this.

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Medicines for children: national, European and global initiatives

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Recognition that children have not had access to the authorised drugs or age-appropriate dosage forms that they require led to many initiatives that are beginning to make a difference. The USA and EU now have legislation in place that encourages and/or requires companies to research and authorise appropriate medicines for children.

In the United Kingdom, the British National Formulary for Children is now well established but may not satisfy the needs of specialists. The NIHR Medicines for Children Research Network has successfully completed its first 3 years and has a portfolio of 30+ industry-sponsored trials and 75+ publicly funded. Clinical studies groups (CSGs) are setting the research agenda with a publication on excipients in medicines for neonates exposing a significant knowledge gap. The Pharmacy and Pharmacology CSG has encouraged collaboration between the UK scientists.

The EU regulation required specific funding for research on older, off-patent medicines to be made available. The UK scientists are collaborating with other European partners to develop these framework 7 initiatives. EMEA is facilitating a 'network of networks', and there are now well-established networks in United Kingdom, Holland, France and Germany.

Developing age-appropriate formulations remains a challenge, and academics, practitioners and industry-based formulation scientists have begun an initiative to share information on excipients, taste and taste-masking, extemporaneous dispensing and administration devices. A similar initiative has been sponsored by NIH in USA, and a programme of work sharing has begun.

In 2007, an international alliance for better medicines for children was developed between pharmacists and pharmacologists following a meeting in Shanghai. The World Health Organisation followed with an initiative called 'Make Medicines Child Size' and has now published two editions of the paediatric essential medicines list. With support from the Bill and Melinda Gates Foundation, this work is being extended to maximise delivery of the millennium goals relating to HIV, TB, malaria, pneumonia and neonatal diseases.

This talk will explore the contribution made by these initiatives to improve access to age-appropriate medicines for children.

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Twenty-first-century toothpaste: formulation, characterisation and control

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Toothpaste is used to maintain good oral health; it can aid in the removal of plaque and debris from teeth, prevent caries,

protect against acid erosion, aid in the elimination of halitosis and deliver therapeutic ingredients. Toothpaste, as such, did not come into general use until the nineteenth century, and it was not until the second half of the twentieth century that modern toothpastes were developed to help prevent or treat specific diseases and conditions, for example, dentine hypersensitivity or enamel erosion.

The aim of the modern toothpaste formulation is to develop the simplest, most stable composition that meets the target product profile. For standard toothpaste, the target profile is typically cleaning; however more recently specific products have been formulated to deliver a therapeutic benefit in addition to those benefits associated with a standard toothpaste. Recent examples include Pronamel and IsoActive developed by GlaxoSmithKline.

In developing a toothpaste formulation, consideration must be given to (1) optimising the efficacy of any therapeutic ingredients within the toothpaste vehicle, which may include developing in-vitro methods and assessing their in-vivo relevance, (2) minimising the interaction between the therapeutic ingredients and the excipients and exploring what impact, if any, they have on performance, stability and irritancy, (3) ensuring acceptable organoleptic/aesthetic properties are achieved and perhaps most importantly (4) delivering a product and proposition that is acceptable to the consumer. For instance, in the development of an efficacious therapeutic toothpaste consideration needs to be given to the effective delivery of the therapeutic ingredients to the tooth surface. One way of achieving this may be to increase the residence time of the toothpaste on the tooth surface since the longer such additives remain in contact with the tooth the more likely they are to contribute their benefit. Thus, it could be reasoned that a toothpaste that does not readily disintegrate at the tooth surface (good film former) may provide a higher residence time and as such may be expected to contribute more of the benefits to the tooth. However, such a formulation is likely to have poor organoleptic/aesthetic properties, i.e. the formulation may be too 'runny' to be applied to the brush or so 'stringy' that it ends up in places that the consumer would wish it did not. Ultimately, compliance of the product would be compromised, which would impact the realised efficacy.

This study presents an overview of modern toothpaste development, formulation, characterisation and control in the context of delivering a consumer preferred therapeutic product.

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Understanding your formulations: characterisation of phase separation and drug distribution across hot melt extruded solid dispersions containing poorly water-soluble drugs

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Introduction and Objectives

To investigate the phase-separation behaviour and drug distribution in hot melt extruded (HME) solid-dispersion formulations containing a poorly water-soluble drug at a micron to submicron scale of resolution.

Method

Felodipine was incorporated into EUDRAGIT E (Röhm Pharma, Darmstadt, Germany) matrices, using hot melt extrusion. The drug/polymer ratios of the HME formulations were between 10/90 and 70/30. The differential scanning calorimetry (DSC) results of the physical mixtures of the two were used to estimate the miscibility and solubility of the active pharmaceutical ingredient (API) in the polymer. Heat-capacity measurements using modulated temperature DSC (MTDSC), pulsed-force mode atomic force microscopy (PFM-AFM), local thermal analysis (LTA) and solid-state nuclear magnetic resonance (SS-NMR) were performed to identify phase separation in the formulations. A Q-1000 MDSC (TA Instruments, Newcastle, USA) was used to generate all DSC experiments. Photothermal microspectroscopic (PT-MS) measurements were carried out by interfacing a Fourier transform infrared (FT-IR) spectrometer (Bruker Optics Limited, Conventary, UK) with an AFM equipped with a Wollaston probe (Veeco, California, USA); these experiments were performed at different locations across the surface and the cross-section of the HME strands. The photoacoustic (PAS) spectra were taken using a Bruker IFS 66/S spectrometer (Bruker Optics Limited) fitted with a PAS cell. The PAS spectral depth profiling of the HME samples were obtained using step scans at different frequencies.

Results and Discussion

The enthalpy values of the endothermic peak of the physical mixtures were plotted against the drug concentration. From the plot, the solubility of the drug in the polymer was estimated as around or below 10% wt/wt. The heat capacity (Cp) measurements revealed the phase-separation behaviour, despite no clear melting or separation of Tg being found in the formulations. The PFM-AFM imaging revealed phase separation in the solid dispersion of low-miscible felodipine and EUDRAIGT E after hot melt extrusion. Particles can be seen in the HME formulations with drug/polymer ratios at and above 30/70. The LTA measurements performed on the particles and the surrounding areas indicated the presence of different phases in the HME formulations. The presence of phase separation was further confirmed by multiple relaxation times detected using SS-NMR. ATR-FTIR spectroscopy results indicated differences in drug concentration and distribution on the surface and cross-section of the HME strands with drug/polymer ratios at and above 30/70. PT-MS allowed localised analysis of the drug distribution on a micron scale. PAS step-scan measurements provided depth profiles of drug distribution in the HME formulations.

Conclusion

In this study, the miscibility and solubility of the felodipine in EUDRAGIT E were estimated by examining the melting behaviour of the physical mixtures. It was established that the two components have low miscibility and the solubility of the drug in the polymer is below 10% wt/wt. Phase separation was not observed in the HME formulations after aging, using conventional DSC and IR. However, the combined application of macro- and micron characterisation using thermal, microscopic and spectroscopic techniques confirmed the presence of phase separation in the HME formulations with all drug loadings. The analyses also provide insights into the drug-distribution profile across the hot melt extrudates. This approach should allow elucidation of the impact of phase separation and drug distribution within the HME strands on drug-release behaviour.

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Application of noninvasive characterisation during pharmaceutical development: an example for the optimisation of lyophilised products

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In understanding the mechanism of action of a pharmaceutical formulation, and to assist in the design, optimisation and development of a product, a range of imaging techniques, such as Raman microscopy, XPS, ToF-SIMS, SEM, optical microscopy and AFM are available. All are essentially surface-sensitive techniques, and a combination of these techniques can provide detailed physicochemical characterisation; to elucidate the internal structure of a formulation, invasive sectioning methods are required. However, X-ray micro computed tomography (CT) is a noninvasive technique that provides a series of 2-D images that can be reconstructed to form a 3-D representation of the internal microstructure of a formulation. In essence, it is a medical CAT scanner but on a micron scale of resolution. The technique till date has largely been used for biological specimens and in the field of material sciences, and its applicability to the pharmaceutical industry has not been exploited to the same extent. The CT can be applied to a whole host of formulations; from granule formulations as a tool to understand how specific binders affect granule structure; to solid dosage forms with the view to mapping the spatial distribution of excipients and active pharmaceutical ingredient in the final product; to lyophilised dosage forms to assist in formulation design and optimising processing parameters. The technique creates an image based on the different X-ray absorbencies of the material components that comprise a formulation. How well a material absorbs the X-ray depends on its atomic composition, material density and the energy of the X-rays.

In a case study, CT has been used to better understand the relationships between lyophilisation process parameters of a biopharmaceutical dosage form, protein concentration and the resultant microscale structural attributes of the freeze-dried cakes. It is known that primary drying parameters can have a significant impact on the product microstructure, solid state properties and long-term stability. Analytical approaches, such as mercury porosimetry and specific surface area measurements using Brunauer, Emmett and Teller (BET) method, are commonly used to elucidate morphological attributes such as pore shape and connectivity, which can have a significant impact on the structural stability of the lyophilised product. One drawback of these techniques is that they assume excellent pore connectivity between the surface and the interior to generate representative data. The CT overcomes the shortcomings of these empirical approaches, providing information on pore size, residual porosity, matrix connectivity, and resolves structural attributes in 3-D on the micron scale.

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Adoptive cellular immunotherapy for the treatment of infectious disease in immunosuppressed patients

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Clinical research has established that adoptive cellular immunotherapy (ACT) provides a safe and efficacious treatment strategy for infectious disease in immunosuppressed patients. This approach is used to accelerate immune reconstitution against specific pathogens, notably latent viruses such as cytomegalovirus, in patients who are at high risk of infection following allogeneic haematopoietic stem cell transplantation (allo-HSCT). Cell Medica is now commercialising this innovative application of cell therapy technology and is able to offer the treatment for routine clinical use in the UK. Cell Medica has recently launched a confirmatory randomised study involving 11 transplant centres across the UK to provide the clinical and pharmacoeconomic data required to establish ACT as a routine treatment alternative for infections in patients following allo-HSCT.

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Delivering on a promise? Synthetic vectors for the genetic therapy of cancer

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Genetic therapies hold the promise of more specific and efficacious anticancer medicines, but their further clinical

development is currently hampered by the lack of safe, efficient and cost-efficient vector systems, which allow the systemic delivery to remote and inaccessible tumours and metastases. We have developed synthetic (nonviral) vector systems based on DNA nanoparticles formed with the lower generation polypropylenimine dendrimers. These dendrimers are nonstochastic star-shaped polymers 10–20 times smaller than many polymers commonly used non-viral vector systems. They bind DNA in a generation-dependent fashion (G1–G5), with the lower generations striking a good balance of compact complexation and low toxicity. Nanoparticles formed with the most efficient of these molecules, the generation 3 dendrimer DAB-Am 16, efficiently transfect solid tumours after intravenous injection.

When this system is used in conjunction with plasmids expressing the gene for the pleiotropic cytokine tumour necrosis factor (TNF)-α, a highly potent but well-tolerated anticancer gene medicine is created, which leads to regression of 100% of tumours and long-term cure of up to 80% of animals after a week of treatment. Therapeutic gene expression with tumour growth delay/shrinkage has been seen in a broad range of xenograft and syngeneic models, including various carcinomas. In fact, we have been able to demonstrate that this vector system is able to effectively deliver a range of reporter and therapeutic genes as well as shRNA to tumours. In contrast to other systems, the nanoparticle vector does not accumulate at off-target sites such as the liver or the lungs but in fact specifically and selectively targets the tumour. Using molecular imaging to visualise expression of the sodium iodide symporter gene driven by cytomegalovirus *in vivo*, we were able to demonstrate essentially exclusive expression in the tumour. Our data thus suggest that synthetic (nonviral) vector systems could potentially overcome many of the current bottlenecks in delivery of cancer gene medicines and thus hopefully help to finally deliver on the promise of this type of therapy.

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Top-down and bottom-up approaches to hydrogel-based glucose sensor/insulin delivery system

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Over the past several decades, there has been great progress in materials engineering and integration at the microscale and nanoscale. These advances are applicable to the development of biomedical devices. Microscale engineering typically involves processes that are considered 'top-down', since they involve lithographic and moulding techniques. At the nanoscale, it is more convenient to use chemical self-assembly, which is considered 'bottom-up'. Microscale and nanoscale processes have been developed for 'hard' materials such as metals, silicon, and glass and for 'soft' materials such as polymers. One class of soft materials is hydrogels, which swell and shrink depending on local conditions such as temperature, pH or glucose concentration. Confined hydrogels exert pressure on the confining structures. In this discussion, we discuss novel devices for glucose sensing and closed-loop insulin delivery that use microengineering and nanoengineering with hard and soft materials.

In one device, a small glucose-sensitive hydrogel containing phenylboronic acid (PBA) sidechains are introduced between a micromachined, rigid membrane and a flexible glass diaphragm. The diaphragm is coated with a thin metallic layer, which serves as the top plate of a microcapacitor, which in turn is integrated with a microinductor to form a microresonator circuit. When the PBA hydrogel swells and shrinks in response to changes in glucose level, it distorts the glass diaphragm, alters the capacitance and hence the resonant frequency of the microcircuit. The whole device is integrated into a small chip that can be implanted, and the resonant frequency is monitored using a wireless, radio-frequency emitter-receiver. After implantation, no skin breach is needed, and batteries are not required to operate the chip. This implantable sensor may be preferable to glucose electrodes that puncture the skin.

In the second device, swelling and shrinking of the PBA hydrogel drive opening and closing of a microvalve, which is connected to an insulin line. This configuration may provide automatic control of insulin delivery in response to changes in glucose concentration. In the third device, the PBA hydrogel is placed under a microcantilever beam. Swelling or shrinking of the hydrogel distorts the beam, which can be detected by a number of optical and electronic techniques.

The response time and biocompatibility of these devices depend on their size and their materials interface with the biological host. With these considerations in mind, we have engineered a thin asymmetric membrane, with a size-selective nanoporous membrane coating a microporous, silicon support structure. Conventional plasma and chemical etching techniques were used to produce the microporous array. The nanoporous top layer was produced from a triblock polymer of polystyrene-polyisoprene-poly(lactic acid) (PS/PI/PLA), with block lengths selected such that the polymer self-assembled into a hexagonal lattice of cylindrical PLA domains rimmed by PI, within a continuous PS sheet. PLA cylinders were removed by etching with NaOH, leaving behind nanopores bounded by PI. The PI rim can later be functionalised to enhance biocompatibility and/or molecular transport selectivity.

We believe that glucose sensing and insulin delivery systems will make use of diverse techniques and processes at the microscale and nanoscale in the future.

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Are unit-dose dry powder vaccines intrinsically safer than liquid vaccines?

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The use of needles to inject liquid suspensions for immunization or treatment of infectious diseases has saved many lives. Injections carry significant risks that can be avoided using dry microparticulate powders in single unit-dose packaging that can be inhaled and rapidly dissolved, are stable, and are less susceptible to contamination than traditional liquid vaccines. For example, when live-attenuated Edmonston–Zagreb measles vaccine is formulated with sugar stabilizers, such as myo-inositol, and other excipients such as amino acids, and a buffer, and dried by CO_2-assisted nebulization by a bubble dryer (CAN-BD), the air-dispersible microparticles with mass median aerodynamic diameters of 2–3 μm can be maintained almost unchanged for more than 1 year when stored at 2–8°C. Yet within a few seconds they can be inhaled, deposited and dissolved in the aqueous films coating the mucosa of respiratory tracts of animals. Within several weeks, immune responses are induced that are as robust as those stimulated by traditional subcutaneous injection of lyophilized measles vaccine reconstituted with water for injection. A group of rhesus macaques was immunized by inhalation of the aerosolized dry-powder measles vaccine in April 2008, and plaque neutralization reduction assays showed development of a strong virus-neutralizing immune response. Powder vaccine was inhaled by at-liberty breathing through masks or nasal prongs from aerosol plumes generated using two novel dry-powder inhalers. All of the macaques have so far enjoyed normal health, and testing the persistence of their protection by challenge with wild-type Bilthoven measles virus is scheduled in June 2009.

To evaluate the question of whether dry-powder vaccines are generally more stable and safer than their liquid forms, one might consider the experiences in mass-immunization campaigns with measles vaccines after reconstituting lyophilized solids. Product use directions specify that the liquid vaccine be used or destroyed on the same day that water is added. In spite of this requirement, in 2008, there were several reports of 'clusters of deaths' following subcutaneous injection of liquid measles vaccine from multidose vaccine vials into which reconstitution fluid had been added. Amdekar and Singhal concluded that one likely cause was contamination of the vaccine with bacteria followed by rapid growth: 'These vaccine vials act as culture media for bacteria chiefly exotoxin producing S. aureus'.[1]

When dry powders are inhaled, liquid for reconstitution is provided instantaneously by the subject's respiratory tract, so there is no chance for contamination arising from reconstitution fluids or mix-ups in fluid identifications, thus reducing the risk. Upon rapid dissolution of microparticles, the resulting solutions or suspensions become the virtual equivalent of wet-mist vaccines that have been used successfully in immunizing ca. four million subjects during a measles outbreak in Mexico and are being studied now in Phase-II clinical trials by another group in India. The safety and efficacy of using dry powders continue to be evaluated, and, if warranted, Phase-I clinical trials will be scheduled to begin in 2010.

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Reference

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Development of crystallisation methods from gram to tonne scale

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The development of a pharmaceutical process from the laboratory scale to manufacturing scale has many challenges. In the new quality-by-design (QbD) environment, there is a requirement for more robust processes and understanding around these processes. In the final active pharmaceutical ingredient (crystallisation) step, this is even more crucial because there is inevitably a need for control of the material physical attributes such as particle size distribution, bulk density, specific surface area and so forth, which can be very sensitive to scale effects. Often (particularly in historical processes) there is a lack of understanding around the effects of mixing, heat/mass transfer, vessel geometry etc and as such these processes can often be nonrobust. Consequently, in the modern pharmaceutical environment, the development of a process is a multifunctional task that consists of particle scientists, engineers, physical properties analysts, amongst others. This allows all aspects of scale-up effects to be

addressed and potential effects mitigated against. In this discussion, we discuss the challenges involved in taking a crystallisation process from the laboratory to the production scale whilst maintaining control of the physical properties of the material. The challenges are illustrated through real case studies.

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Automated basal–boost insulin delivery

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Insulin-treated diabetes needs a better treatment for safer outcomes. Presently, the dose of insulin that has to be administered must be a combination of the basal contribution that keeps the background blood-glucose level within normality, and the additional boosts that provide cover for mealtime peaks in glucose.

The normal pancreas would automatically deal with both kinetic requirements but for the patient with diabetes using the insulin therapy, although the basal level can mainly be fixed, the postprandial blood-glucose level is a moving target for which a boost dose should ideally be calculated on each occasion.

However, even the most compliant patient will find success in glucose control to be elusive because of the variables involved. For example, the predicted assimilated carbohydrate value of meals and the utilisation of calories must be balanced by an estimated dose that would have to be absorbed optimally from the injection site every time.

The inevitable deviations from normal glucose-tolerance zones produce cumulative tissue damage by well-known mechanisms that eventually produce the secondary illness. The amelioration and delay in the onset of complications of diabetes depend on the individual's history of accuracy in controlling glucose, including the postprandial peaks.

Making this insulin titration simpler or automatic would represent a leap forward in the approach to diabetes. Currently, the NHS spends about £9 billion p.a. (£1 million per hour!) on treating diabetic complications. Consequently, a successful intervention using an autofeedback or 'closed loop' system might not only increase the length and quality of life but also be cost-effective.

Potentially, methods for achieving this could comprise implanted or externally sited insulin-administration sources. Biological and electronic systems have been explored for implantation, while external administration devices have lately been coupled with some electronic sensor capability. In the current absence of a commercially available closed-loop product, however, it would seem that an opportunity to explore other strategies still exists. This could include those methods depending on insulin-permeable biomaterials that are glucose-sensitive, allowing differential delivery that responds to ambient glucose.

In the context of the closed-loop concept, here, our own proposals for a system that has been developed using a responsive material have been discussed. We will present the in-vivo data and describe the plans for extending the concept to a refillable but implantable closed-loop insulin-delivery device.

This proposed system circumvents some of the difficulties that have thus far prevented greater success in the more traditional closed-loop designs. The proposed system has no need for battery power, no moving parts and could be cheaply made, thus offering a feasible route to a closed-loop insulin-delivery option.

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New paradigms for the treatment of bacterial infections

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Over the last two decades, there has been a steady decline in the number of new antibacterial agents launched into the market; this period has coincided with a substantial rise in the frequency of isolation of multi-drug-resistant pathogens from nosocomial and, increasingly, community-acquired infections. Currently, useful antibiotics impose enormous selective pressure on bacterial populations, and the emergence of resistance to these drugs is all but inevitable. The majority of recent introductions of new antibacterial agents are molecular variations of established chemical structures, with only two belonging to novel classes and therefore displaying little or no capacity for cross-resistance with established antibiotics. There is a growing realisation that we have come to the end of the road with respect to the advantageous modification of tried and tested classes such as the β-lactams, and new antibacterial drugs with novel modes of action are urgently required to continue the fight against infection. The hope that the exploitation of genomics and target-based high-throughput screening would yield a new generation of novel drugs addressing new molecular targets, which has not been realised in spite of massive investment; furthermore, a recent molecular analysis of protein expression in experimental infection raises the possibility that we may have already exploited most of the broad-spectrum targets essential for bacterial survival *in vivo*. To a limited extent, smaller biotechnology companies are filling the gap left by the withdrawal of their larger counterparts; as they are lacking the financial resources of the major companies, they are either in the process of licensing the partly developed antibiotics or searching for niche products. This new development paradigm may fortuitously present prescribers with what they want – drugs with a narrow spectrum of activity against specific pathogens and the potential for consequent reduction of resistance. As academia and government agencies are being urged to become more involved in the process of antibiotic development, the time may be right to begin to exploit more unconventional approaches to the eradication of infection. This contribution will focus on alternatives to conventional antibiotic

chemotherapy for the resolution of troublesome infections, particularly those due to multi-drug-resistant pathogens such as MRSA, XDR-TB and the like. Thus, bacteriophage therapy, phage components such as lysins, constructs that interact with previously unexploited bacterial targets, compounds that stimulate cellular immune functions and agents that advantageously modify the antibiotic resistance and virulence of bacterial pathogens will be evaluated.

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Regenerative medicine: where are we at?

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Regenerative medicine (RM) is a nascent therapeutic area with a large and diverse product pipeline. It offers the exciting potential to cure many serious chronic conditions associated with failing or damaged tissue function. However, the promise of RM to deliver complex new tissue on demand has not yet been realised. The industry suffered a collapse in the early part of this decade, and the success of some early products in reaching the market has been tempered by low adoption and the failure of more advanced products. The major issues for the industry stem from the fact that many RM therapies incorporate living cells. This generates new challenges in development, manufacture, quality control, distribution, clinical application and regulation. The field requires highly interdisciplinary input to address these challenges with a science base covering stem cells, cell biology, biomaterials and engineering amongst others.

Recently there have been significant scientific, engineering and clinical advances in RM. The field has been revolutionised by the derivation of induced pluripotent stem cells and the associated potential for patient-specific tissue growth. Advances have been made in the in-vitro environments for the expansion and differentiation of stem cells as well as the manufacturing bioprocess and the development of manufacturing platforms for these cells. Landmark phase I clinical trials have been approved in the USA (Geron) and the UK (ReNeuron) for spinal cord injury and stroke. This study introduces the RM area, the current state of the science, the challenges for translating the science into clinical products and question how RM therapies may affect pharmacists in the future.

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Identifying and developing novel therapies for cancer treatment: right drug, right patient

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The study of cancer progression has led to the identification of many putative targets against which novel therapeutics are being developed. The drug discovery phase alone contains many challenges, which, for small-molecule inhibitors of targets, includes reaching the desired potency, selectivity and pharmacokinetic and safety profiles. This must also be accompanied by the development of appropriate robust biomarkers of pharmacodynamic activity, which can be applied to tumour biopsies or surrogate normal tissues to demonstrate target modulation in patients and assist early clinical dose ranging studies. In addition, prospective studies are increasingly required to identify those patients who are most likely to benefit from a given treatment, particularly in the major solid malignancies with a heterogeneous molecular pathology. Finally, while these molecular targeted drugs may provide benefit as monotherapy, their use in combination with established therapeutic modalities also warrants examination in an attempt to augment treatment outcomes.

To illustrate some of the concepts pertinent to biomarker development and patient selection strategies, this presentation will examine approaches that were designed to predominantly target the tumour cell, such as inhibitors of epidermal growth factor receptor tyrosine kinase, mitogen-activated protein kinase kinase (MEK) 1/2 or poly(ADP)-ribose polymerise. Inhibitors of vascular endothelial growth factor signalling, designed to inhibit the host angiogenic response, will also be discussed.

Collectively, the insights gained from these current research efforts should help to deliver optimal therapy to patients and further advance our understanding of cancer biology.

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Strategies for designing multipharmacology drugs

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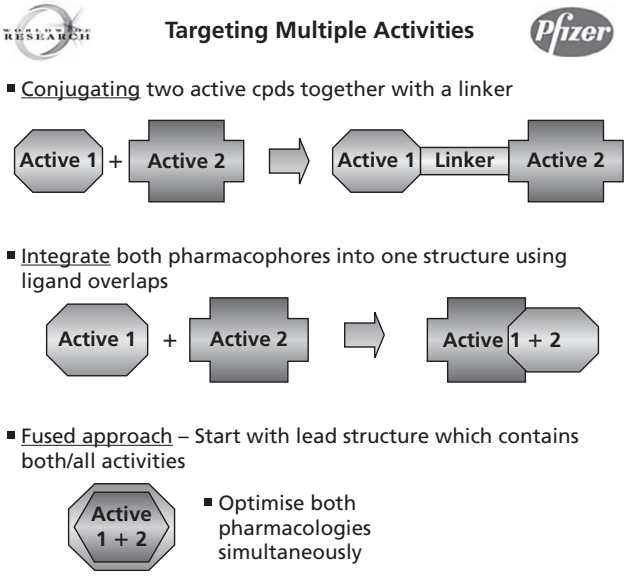
Modern drug design strategies are currently focussed heavily on identifying molecules that selectively modulate a single biological target. However, this approach may not deliver the required clinical efficacy because of inherent redundancy in complex biological pathways. Another drug discovery approach involves the rational design of molecules that interact with multiple biological targets, and this strategy has the potential to deliver increased efficacy against complex diseases.

This presentation will discuss the different strategies that have been employed when targeting multiple pharmacologies (Figure 1). In particular, the challenges associated with balancing multiple activities while retaining good drug-like properties will be highlighted, and exemplified with case-histories from the literature and Pfizer medicinal chemistry programs.



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European regulatory requirements for early clinical studies: experiences from a pharmaceutical industry perspective

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In early clinical research and development, the main goal is to assess the safety, toleration and pharmacokinetic profile of an investigational medicinal product (IMP) and to seek an indication of its potential efficacy. Due to the high attrition of drug candidates during this phase of development, the pharmaceutical industry typically aims to make a minimal investment in the clinical formulation(s). Often very simple (but appropriate quality) 'enabling' formulations are used, such as solutions, suspensions, drug powder in capsules, prototype tablet formulations and investment in commercialisable dosage forms is deferred until a candidate has successfully progressed into later development.

From a regulatory perspective, the requirements and expectations for the 'quality data' on the IMP which will be submitted in the clinical trial application differ for different phases of clinical development. It is recognised that the data available at the time of first-in-human, Phase 1 and early Phase 2a studies will be more limited than during later clinical development (Phase 2b and Phase 3). Despite this general understanding, one of the challenges often experienced by industry is that regulatory agencies may express different expectations and preferences for the extent of quality/chemistry, manufacturing and control (CMC) data which is submitted. These differences can result in additional work in providing country-specific clinical trial applications and can hinder the rapid start of global, multicentre clinical studies.

In the EU, the Clinical Trial Directive (Directive 2001/20/EC) and the Committee for Human Medicinal Products (CHMP) guideline on the 'Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials', also commonly known as the IMPD-Q guideline has sought and to a large extent, has helped to harmonise the regulatory expectations across EU member states. There remain some areas where member states show a divergence in their expectations, e.g. in their acceptance of proposed shelf-life assignments, classification of CMC changes as substantial amendments versus nonsubstantial changes, application of limits of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) for impurities even during early clinical development, requirement for additional documentation (to name a few recurring themes). At best, these divergent demands can require additional resources to satisfy country-specific needs. At worst, higher regulatory expectations than the industry sponsor considered appropriate or achievable at early stages of development may result in clinical trial applications being withdrawn from that country with an adverse impact on the recruitment for clinical studies.

Continued discussion between regulators and industry is highly welcome and will help to continue to build a common understanding of realistic expectations for quality data during early development. This dialogue is important in the joint goal to improve the attractiveness of the EU as a region for conduct of early clinical studies.