

# A review of the BPC science abstracts

Joseph Chamberlain, science secretary for the British Pharmaceutical Conference from 1990 to 1999 and a former editor of *The Journal of Pharmacy and Pharmacology*, reviews a selection of the work reported in the science sessions at BPC 2006. The review supplements his taster of the science presentations already published in our conference week issue (*PJ*, 9 September, p316)

More than 250 science abstracts were presented during the 2006 British Pharmaceutical Conference. Most were presented as posters, with selected abstracts also presented orally in specialist sessions. There were also two podium sessions for which posters were not available — the Joint Pharmaceutical Analysis Group session for younger analysts and the “new scientists” session for scientists in industry or academia who are starting out on their research careers. These sessions are reported on separately at the end of this review.

## Analytical chemistry

**Shaw et al** (University of Queensland) claimed the first use of LC-MS-MS (liquid chromatography-mass spectrometry-mass spectrometry) for the quantitative analysis of paracetamol and its glucuronide and sulphate conjugates in mouse urine. Improved specificity and quantitation were especially important for the study of drug metabolism where only extremely small samples of biological material are available.

Aqueous nasal spray formulations need safe preservative systems and, with the current speculation around the long-term safety effects of benzalkonium chloride, new preservative systems are being developed. **Hall** (GlaxoSmithKline, Ware) described the development and validation of a generic, multi-component high performance liquid chromatography (HPLC) method able to separate and quantify three preservatives (EDTA [ethylenediaminetetraacetic acid], potassium sorbate and the antioxidant butylated hydroxyanisole) in new formulations, despite the variation in properties of the compounds and their difference in concentration. Isocratic reversed-phase HPLC separation could be adapted to all future aqueous nasal spray formulations containing different active ingredients.

**New et al** (GlaxoSmithKline, Ware) applied process analytical technology to aqueous nasal spray suspensions, using point conductivity measurements taken during small-scale manufacture. These conductance measurements reflect the underlying conditions prevailing within the manufacturing process allowing a continuous process signature to be derived.

## Biopharmaceutics

**Ord et al** (University of Sunderland) explored the hypothesis that the transdermal delivery of drugs can be enhanced by suppressing their melting points. The melting temperature ranges of solid dispersions of

ibuprofen in selected polymers were recorded using a hot stage microscope. The eutectic compositions were identified and binary mixtures of ibuprofen:polymer were prepared as solid physical mixtures and as solid dispersions. A significant increase in ibuprofen release was found for the compositions adjacent to the eutectic one.

**Zhang and Batchelor** (Aston University) described the development of buccal-adhesive tablets for prolonged release of the poorly water-soluble drug miconazole nitrate. Hydroxyethyl cellulose matrices showed greater drug release in dissolution tests than did methylcellulose matrices for all comparable formulations, probably due to its greater hydrophilicity. Drug is released from hydroxyethyl cellulose according to erosion controlled mechanisms, whereas methylcellulose is likely to control drug release via both erosion and swelling with diffusion through the swollen layer. Incorporation of carbopol, a water swellable polymer, greatly reduced drug release from both systems, whereas incorporation of lactose had little effect on the hydroxyethyl cellulose formulations, since both materials dissolve readily in water and the mechanism of release of the drug was unchanged.

**Ghimire et al** (University of Strathclyde) investigated the *in vitro* and *in vivo* performance of a press-coated tablet, consisting of a rapidly disintegrating theophylline core tablet, press-coated with barrier granules containing varying amounts of glyceryl behenate and low-substituted hydroxypropyl cellulose. *In vitro* studies consisted of dissolution experiments and *in vivo* studies consisted of gamma-scintigraphic studies carried out in four beagle dogs. All tablets except one (in the fasted state) disintegrated in the stomach and *in vivo* disintegration time

was very similar to that predicted by *in vitro* dissolution.

## Drug delivery

**Notman et al** (King's College London) described how molecular simulations can lead to a greater understanding of the mechanism of action of skin penetration enhancers such as dimethylsulphoxide (DMSO). Atomistic molecular dynamics simulations of up to 40ns of bilayers consisting of 128 or 512 ceramides with a range of concentrations of DMSO were carried out. The results suggested that DMSO acts primarily through interactions at the bilayer/water interface. At low concentrations the DMSO accumulates at the headgroup region of the bilayer but has little effect on the properties of the bilayer. At high concentrations, DMSO induces a transition in the bilayer from the ordered, tightly packed gel phase, which is characteristic of the skin lipids, to the disordered, loosely packed liquid crystalline phase, suggesting that pore formation in ceramide bilayers becomes significantly easier in the presence of DMSO.

**Wong and Dodou** (University of Sunderland) examined the saturation solubility of ibuprofen in silicone and acrylic polymer adhesives and found that supersaturated layers with the silicone adhesives showed white ibuprofen crystals under the microscope, in contrast to the acrylic layers, which turned clear on storage. The absence of ibuprofen crystals even at high loadings in the acrylic adhesive, without the addition of crystallisation inhibitors, and the significantly higher ibuprofen release from the clear concentrated ibuprofen-acrylic formulations, rendered acrylic-based adhesives good candidates for further development of drug-in-adhesive formulations of ibuprofen.

**Jamil et al** (Queen's University Belfast) developed silicone intravaginal rings as a controlled release system for long-term administration of HIV microbicides to the vagina, as a prevention strategy for HIV transmission. Aciclovir was loaded into silicone rings and its release compared with three aciclovir esters. There was an average release of 0.54mg of aciclovir from the ring over the 14-day period, compared with 3.04mg for acetyl-aciclovir, 5.89mg for butyl-aciclovir and 46.75mg for the hexyl-aciclovir, illustrating that as hydrophobicity of the ester increased, the release from within the hydrophobic silicone matrix was enhanced.

**Hodges et al** (University of Strathclyde) described the enhancement of dissolution of the poorly soluble spironolactone by

## BPC science abstracts 2006

The BPC science proceedings abstracts are being published as a supplement to the October issue of *The Journal of Pharmacy and Pharmacology*. Copies of the supplement can be purchased for £14.95 from the Pharmaceutical Press, Turpin Distribution, Stratton Business Park, Pegasus Drive, Biggleswade, Bedfordshire SG18 8TQ (tel 01767 604971; fax 01767 601640; e-mail [custserv@turpin-distribution.com](mailto:custserv@turpin-distribution.com)). The abstracts are also available in the form of PDF files, which can be downloaded via the BPC section of the Royal Pharmaceutical Society's website ([www.rpsgb.org/events](http://www.rpsgb.org/events)).

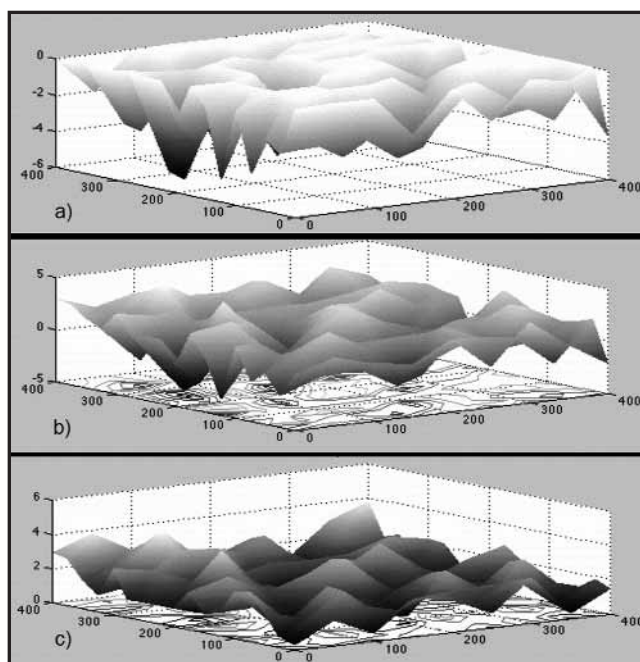
developing a novel method of producing amorphous spironolactone formulations in hard gelatin capsules. A co-solvent system of tert-butyl alcohol and water was used to achieve solutions of spironolactone which were filled into the bodies of size 000 hard gelatin capsules and freeze dried. It was confirmed by X-ray powder diffraction that all formulations were entirely amorphous. The basic formulation of the drug alone in the co-solvent system showed a linear release profile. Formulations containing sodium dodecyl sulphate or mannitol enhanced the dissolution of the drug with an immediate pulsed release.

**Briscoe and Dyas** (Liverpool John Moores University) described studies on the fate of methadone in therapeutic reefers and suggested that only 20 per cent of the dose of methadone in a 30mg reefer would be inhaled. LC-MS (liquid chromatography-mass spectrometry) of the extracts of the mainstream smoke revealed the presence of degradants which appear to be intramolecular ring-closure products. These included an N-desmethyl product which had previously been reported as a urinary metabolite in methadone patients.

### Materials science

**Dakić et al** (University of East Anglia) presented a novel method of mapping the three-dimensional distribution of tablet components using microthermal analysis. Tablets of paracetamol, hydroxypropyl methylcellulose (HPMC) and 50:50 mixes of the two were prepared and the materials characterised in scanning and localised modes. The study indicated that the microthermal analysis can image complex samples in two dimensions using thermal conductivity and in three dimensions using penetration profiling. The approach was seen as a useful novel method whereby tablets, film coats and other surface layers may be characterised.

**Hunter et al** (University of East Anglia) attempted to understand how simple carbohydrates may offer protection to some specialist species of plants, fungi and insects against the effects of dehydration by forming glasses. They described the use of solid state carbon-13 nuclear magnetic resonance (NMR) spectroscopy as a means of assessing the whole-molecule motions of a model glass-forming material, methyl rhamnoside, with a particular view to deriving novel information on mobility that may be related to recrystallisation phenomena. The methyl rhamnoside glass proved to be a useful model for the study and demonstrated the practicality of characterising motions in carbohydrate glasses but in practice its glass transition temperature is too close to room temperature to be suitable for stabilising pharmaceuticals.



Using microthermal analysis as a novel method for mapping the distribution of tablet components, **Dakić et al** produced these three-dimensional images of (a) surface topography, (b) depth of probe penetration through molten paracetamol and (c) paracetamol distribution through the top layer of the compact

In a novel approach to the problem of infectious endophthalmitis, **Parsons et al** (Queen's University Belfast) examined the potential of porphyrins, well established photosensitisers, attached to the surface of an intraocular lens biomaterial to prevent bacterial colonisation. Light activation caused the porphyrin to generate highly reactive singlet oxygen, a cytotoxic species leading to cell death due to peroxidative damage.

**Gibb et al** (AstraZeneca, Cheshire) reported on work aimed at achieving a better understanding of the consolidation behaviour of powder mixtures. The materials studied were microcrystalline cellulose, a plastically deforming material, and lactose monohydrate, which deforms by either plastic deformation or fragmentation depending on particle size. The results illustrated the complexity of the tablet-forming process. For mixtures of microcrystalline cellulose and lactose monohydrate, particle size was important for determining both the architecture of the system and the overall consolidation behaviour.

**Kan** (School of Pharmacy, London) reported on new methods to control the porosity of microspheres employed as tissue engineering scaffolds or as delivery systems for biotherapeutics. Hydroxypropyl- $\beta$ -cyclodextrin was found to be a candidate for application as a porogen and a protein stabiliser for fabrication of porous microspheres. By varying the ratio of hydroxypropyl- $\beta$ -cyclodextrin to bovine serum albumin, control over porosity, encapsulation efficiency, release kinetics and stability of the encapsulated protein was achieved.

**Perkins et al** (Molecular Profiles Ltd, Nottingham) tackled the challenge of solid state characterisation of formulated products. The physicochemical characterisation of a controlled release formulation through the use of X-ray microtomography to provide structural characterisation and Raman microscopy to provide spatial and chemical identification of components was described. Employing these techniques in combination enabled cross-correlation of structural features with chemical identification and mapping. Using cross-sectional analysis and Raman microscopy it was possible to identify chemically and locate spatially the components within the formulation. Chemical analysis clearly discriminated the exterior coating from the active layer, as structurally observed by X-ray microtomography. Chemical mapping revealed that none of the active ingredient was incorporated into the coating. The use of Raman microscopy in solid dosage form also provided information regarding the form of the active ingredient and monitored whether any changes in the physical form had occurred during processing.

### Medicinal chemistry

**Dearden and Roberts** (Liverpool John Moores University) provocatively titled their contribution "Larger molecules penetrate membranes more readily". The contention arises from a critical study of quantitative structure-activity relationships on the penetration of membranes by drug molecules. Most such findings involve a positive hydrophobicity term and a negative molecular size term, thus suggesting that hydrophobicity aids penetration but that larger molecules penetrate less readily. The latter inference seems intuitively reasonable, since one would expect larger molecules to have to overcome greater resistance to penetration. However the authors suggest the negative size term in the latter correlations is simply a compensation for the large positive size requirement of log P itself. This requirement is probably related to dispersive interactions. However, in membrane penetration there is an additional factor, namely the diffusion of molecules through the membrane once they have partitioned into it. Since diffusion is inversely proportional to the square root of molecular mass, the overall size contribution to membrane penetration is less positive than is its contribution to partitioning. The suggestion that larger molecules penetrate living membranes more readily has significant implications for drug design.

**Soltan and Blagbrough** (University of Bath) investigated novel spermine-based cationic lipid formulations based on a rational molecular design scheme. The model for

designing novel diacyl lipospermine vectors consisted of a hydrophobic domain (long aliphatic chain or a saturated steroid), linkers (amides, esters, or carbamates), and a cationic head group (polyamine or guanidine). Increasing the distance between the carbonyl groups and the central secondary amines of spermine so that their basic character (pKa) will increase would be helpful in increasing the efficiency of DNA condensation and subsequent transfection. A series of heterocyclic cationic head groups enabled a favourable pKa of around 6.5 to assist in swelling via the proton sponge effect. Here the importance of protons accompanied by water molecules, and possibly by chloride counter ions, leads to swelling and eventually rupture of the sub-cellular organelle, the endosomal compartment, thus helping to avoid lysosomal degradation and leading to more effective transfection.

### Pharmaceutical microbiology

**Chapman et al** (The Robert Gordon University) reported on studies to ascertain the growth of staphylococci in occlusive and porous adhesive dressings containing benzalkonium chloride as an antiseptic, concluding that from a microbiological viewpoint the preferred adhesive dressing would be porous and contain an antiseptic.

Probiotics require high concentrations of beneficial bacteria to be effective. **Donthidi et al** (Glasgow Caledonian University) investigated the effect of lecithin on maintaining the viability and stability of such products. *Lactobacillus* and *Bifidobacterium* species were encapsulated using alginate/starch and different concentrations of lecithin to evaluate the effect of lecithin on viability of the probiotics. The inclusion of 1 per cent lecithin with alginate mix was found to be the optimum concentration for increasing the survival of probiotic bacteria during the freeze-drying process. The inclusion of lecithin with alginate and starch for encapsulation has shown significant improvement on the viability of probiotics from the point of encapsulation to storage.

The adherence of bacteria to biomaterials is the first step in the process leading to device-related infection. **Hamill et al** (Queen's University Belfast) focused on the effect of the conditioning film on a range of performance characteristics of a range of potential urinary biomaterials including 2-hydroxyethyl methacrylate hydrogels alone or containing 20 per cent methacrylic acid, diethylaminoethyl methacrylate and trifluoroethyl methacrylate. They demonstrated the need to mimic *in vivo* conditions when testing potential urinary biomaterials to ensure that all conclusions are based on actual potential performance rather than being skewed by experimental parameters.

### Pharmaceutical technology

**Kattige and Rowley** (University of Bath) described studies to improve the utility of solid dispersions by investigating the effect of

ageing of poloxamer solid dispersions on storage at 25°C using isoniazid as a model drug with low polymer solubility. They conclude that solid dispersions formed a stable system with unchanged drug dissolution rate for up to six months, confirming the suitability of poloxamers as thermosoftened carriers for liquid-fill hard gelatin capsules. Furthermore, the results indicate that the structure of the polymer/particulate dispersion can play a significant role in controlling the release of drug from the semi-solid matrix and is a function of the poloxamer molecular weight.

**Blackshields et al** (University College Cork) described experiments to establish the influence of processing parameters on bead size and shape, using assessment by both optical microscopy and mathematical modelling. The products resulting from each of the experiments fell into one of four categories described as spherical beads, irregular shaped beads, gel clumps, and stringy gel. The sizes of the beads produced varied from 640µm to 1,668µm. Both experimental design and polynomial modelling assisted in the determination of the processing parameters that influenced bead formation, shape and size. The data used in polynomial model development was limited due to the inability to quantify the non-spherical bead formations.

### Pharmacognosy

**Annan et al** (King's College, London) reported on studies to isolate the components of *Paullinia pinnata* (Sapindaceae) responsible for its antibacterial and wound-healing activity according to traditional Ghanaian medicine. Bioassay-guided fractionation and isolation of a methanol extract led to the isolation of five compounds with significant antibacterial effects. These findings strongly support the folkloric use of the plant as a natural health product in wound healing.

A number of laboratories continue to uncover previously unacknowledged activities in natural products, including cytotoxic stilbenes from *Cajanus cajan* (L) Millsp leaves (**Ashidi et al**, King's College London), hypoglycaemic and antidiabetic activity of seeds of *Myristica fragrans* (**Somani et al**, Sinhgad College of Pharmacy, India), antibacterial and resistance-modifying activities from *Mezoneuron benthamianum* (**Dickson et al**, King's College London), and antihepatotoxic activity of *Tinospora cordifolia* Miers (**Sagar et al**, Lloyd Institute of Management and Technology, Greater Noida, India).

**Lu et al** (Hong Kong Baptist University) reported on the comparative assessment of the processing methods for radix angelicae sinensis (danggui) [*Angelica sinensis* root] as part of the drive in China to develop a standard method for processing danggui based on good agricultural practice guidelines. The overall results indicate that the processing method of fumigation from burning wheat stems can be considered as the most suitable for processing danggui, as reflected by the analytical data obtained for some of the active ingredients, which

included polysaccharides, ligustilide, and free and total ferulic acid.

**Wilson and Heinrich** (School of Pharmacy, University of London) used near infrared spectroscopy for identification and quality control of plant material, without a separation step and obtained spectra which are representative of the sample as a whole. The procedure was applied to characterisation of cannabis samples, which were assigned as either "high THC" or "low THC" in the spectral library; the use of spectral correlation methods allowed for the correct identification of all samples tested. This demonstrated the robustness of the analytical models used to discriminate between the THC-rich and hemp forms of cannabis.

### Pharmacology

**Ingram et al** (University of Brighton) reported on the synthesis and ACE-inhibitory activity of captopril nitroxyethylamide, a novel hybrid prodrug of captopril and itramine. This putative nitric oxide amide derivative should be more resistant to degradation. Itramine was used as a suitable nitrovasodilator due to its established pharmacological profile. The putative derivative captopril nitroxyethylamide was synthesised via the direct reaction of captopril and ethanolamine in the presence of *N,N'*-dicyclohexylcarbodiimide to form captopril ethanolamide, followed by halogenation using thionyl chloride and final nitroxylation using silver nitrate. Captopril and the two derivatives were examined quantitatively for their ability to inhibit angiotensin I-induced contractions of rat aortae *in vitro*. Angiotensin II produced dose-related contraction which were unaffected by prior administration of captopril. Angiotensin-I induced contractions are, however, diminished in the presence of captopril, indicating the necessity of the conversion of angiotensin I to angiotensin II by endothelial angiotensin-converting enzyme. Captopril ethanolamide and captopril nitroxyethylamide were unable to achieve total inhibition at 10<sup>-6</sup>M, achieving 40 per cent of the inhibition associated with captopril, suggesting they retain some of the ACE-inhibitory properties of captopril despite the masking of the carbonyl functionality, while *in vivo* metabolism to captopril will result in full ACE inhibitory activity of the parent molecule.

**McCurrie and Murphy** (University of Bradford) continued their work on the smooth muscle relaxant activities of tamoxifen. They suggested that since the natural product, resveratrol, which is found in red wine and grapes, possesses oestrogenic activity and also acts as a selective oestrogen receptor modulator its presence may attenuate the beneficial dilator actions of tamoxifen. However their studies with rat smooth muscle demonstrated that the relaxant effects of tamoxifen *in vitro* were not attenuated by the presence of resveratrol; addition of resveratrol slightly increased the extent of relaxation observed.

## First JPAG Conference Analytical Science Award presented

Bronwyn Grout (Pfizer UK Ltd and the School of Pharmacy, University of London) is the first recipient of the Joint Pharmaceutical Analysis Group's Conference Analytical Science Award, presented at the British Pharmaceutical Conference this year.

The award was made on the basis of the scientific quality, originality and potential impact of the work presented at JPAG's "Short papers in pharmaceutical analysis" session at the BPC. Mrs Grout's presentation was on "Use of near-infrared conformance methods for tablet in-process monitoring and quality assurance".

The award consists of a certificate and a bursary of up to £2,000 to allow the recipient to attend a



Professor Moffat presents the award to Mrs Grout

scientific meeting of his or her choice. The award was presented to Mrs Grout by JPAG chairman Tony Moffat.

### Joint Pharmaceutical Analysis Group

The Joint Pharmaceutical Analysis Group organised its traditional podium session for presentations by young analysts and offered a Conference Analytical Science Award, in the form of a bursary of up to £2,000 for attendance at a relevant conference in 2007. The award was presented to **Bronwyn Grout** (Pfizer Global Manufacturing, Sandwich) for her work on near-infrared conformance methods for tablet in-process monitoring and quality assurance. The conformance method was comparable with traditional methods, and enabled rapid analysis of large numbers of tablets during manufacture providing a simple system for process monitoring and quality assurance.

**Gaisford et al** (School of Pharmacy, University of London) also tackled the problem of *in situ* process monitoring. They demonstrated that calorimetry could be used to monitor swelling and that there are demonstrable differences between polymer and formulation types. More generally it was shown that calorimetric methods offer an alternative suite of analytical tools for direct assays.

Traditional analysis was represented by **Hawwa et al** (Queen's University Belfast) who described an improved HPLC procedure for the determination of mercaptopurine and its metabolites in plasma and red blood cells, and by **Vadnerkar et al** (Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal, India) who described and evaluated some simple HPLC methods for the analysis of etoricoxib in plasma.

A major limitation of the technique of near-infrared (NIR) spectroscopy is the difficulty in transferring a spectral library created on one instrument for use on another instrument. Setting up a robust spectral library is time consuming and costly and in an attempt to reduce this cost, **Palmer et al** (School of Pharmacy,

London) investigated the effects of differences in the wavenumber scales of the instruments on library transfer. **Shek et al** (School of Pharmacy, London) applied the techniques of near-infrared spectroscopy to detect standard generic medicines, demonstrating the feasibility of application to paracetamol.

Therapeutic proteins may be advantageously immobilised as dry particles and antigens may be bound onto insoluble adjuvant particles to improve the efficacy of vaccines. In both cases it is difficult to determine how the immobilisation process has affected the secondary and tertiary structure of the protein because the particles produced are not suitable for conventional circular dichroism analysis due to extensive scattering. **Ganesan et al** (University of Strathclyde) developed a novel rotating cell that ensures that particles remain homogeneously suspended during the measurement process. This was located in a conventional spectropolarimeter and positioned to maximise the collection of scattered light at the detector. Spectra were obtained of suspensions of protein-coated microcrystals in solvent and of protein bound to adjuvant in water. Changes to the structure of immobilised proteins could be successfully probed in both aqueous and solvent systems. This is likely to be of major benefit for improving formulations of therapeutic proteins and vaccines.

Removal of part or all of the protein hydration shell is thought to play a role in the instability of lyophilised therapeutic proteins. Knowledge of the content and distribution of water in the formulation is therefore critical. **Almutawah et al** (University of East Anglia) used FTIR (Fourier transform infrared spectrometry) and dielectric spectroscopy in combination to measure protein hydration *in situ*, with no requirement for extensive sample preparation or manipulation.

### New scientists

A podium session entitled "New scientists' short talks" enabled young presenters in the early stages of their careers, in industry or academia, to present their research.

**McInnes et al** (University of Strathclyde) used gamma scintigraphy to good effect to follow the disintegration of oral controlled release formulations in the canine gastrointestinal tract and were able to show that the *in vivo* performance of experimental formulations did not correspond with the *in vitro* behaviour.

**Fuller et al** (University of Leeds) built on previous work that had shown chitosan microcapsules can increase the permeation of drugs across *in vitro* cell monolayer models by opening tight junctions to demonstrate that yeast cells can be used as effective microcapsules for the delivery of drugs in a model system; the unique properties of the yeast cell surface act to enhance drug absorption by modulating epithelial tight junctions.

It has been suggested that the multidrug resistance phenomenon may be due to diffusing drugs being prematurely removed by transporter proteins. **Rauch and Pluen** (Manchester University) suggested a complementary hypothesis based on the lateral Brownian movement of drugs in the membrane. Once partitioned, a drug is not static but diffuses laterally in the membrane. The longer the lateral diffusive path, the higher the probability for a drug to meet and be extruded by a transporter.

**Ginty et al** (University of Nottingham) described a novel process using supercritical carbon dioxide for introducing live mammalian cells into biodegradable scaffolds for tissue engineering applications. Mammalian cells could survive and retain important aspects of functionality after a one-minute exposure to the fluid. The effects of the supercritical fluid upon gene expression in C2C12 cells after a one-minute exposure were minimal, with small down-regulations of eight genes indicating subtle changes at mRNA level that do not lead to significant cell death.

**Patel et al** (Pfizer Global Research and Development, Sandwich) showed that a nano-milled suspension of a model candidate drug yielded significant improvements in bioavailability averaging a fourfold increase compared with a standard suspension. Particle size analysis showed that particle reduction was a determining factor in this bioavailability improvement.

**McBride et al** (University of Strathclyde) reported on the development of a simple-to-operate, adaptable, economical absorption spectrophotometer applicable to the quantification of long-term sustained drug release, which does not tie up expensive equipment. Due to the simplicity of the design, multiple measurements can be run in parallel reducing the time needed for reliable repeated results. The instrument could also be used as an initial screening device for new sustained drug delivery methods permitting rapid elimination of unsuitable devices or formulations.