

SCIENCE CHAIRMAN'S ADDRESS

The nation's experts on medicines

By *Graham Buckton, PhD, FRPharmS*

In his address to the British Pharmaceutical Conference on 16 September, the Science Chairman Professor Graham Buckton spoke about the divide between pharmacy practice and science, and pressures on research funding. He also mentioned the types of research being undertaken at his laboratory in the School of Pharmacy at the University of London

The Quality Assurance Agency for Higher Education has a benchmarking document for pharmacy which starts with the sentence "Pharmacists are the nation's experts on medicines".¹ It goes on: "They work, either directly or indirectly, to benefit patients, carers or other health professionals." These opening words cover the context of pharmacy, which sadly often seems to split along the axis of these two sentences, the expertise on medicines being the home of the scientist and the caring for patients being the domain of practice. The space between those who are medicine-centric and those who are patient-centric is often described as "the science-practice divide". The statement is, however, correct and it is essential for our future that pharmacy is the link between patient care and the science of medicines.

The QAA benchmarking document also gives a definition of a medicinal agent as being "a chemical compound . . . which has an effect when given to a patient" and a medicine as being the preparation containing the medicinal agent. It then notes that the terms "medicine" and "medicinal agent" are often used interchangeably. This is indeed true, for example an article in *The Pharmaceutical Journal*, entitled "Food and medicines",² covered only a passing mention of medicines (giving a brief comment on some foods that may delay gastric emptying) and concentrated on food-drug interactions. It is, of course, important to study drug-food interactions (and this is certainly not a criticism of the cited article), but this is an example of where pharmacists could benefit from knowledge of how food can affect the medicine. In the *PJ* article there was mention of food affecting the bioavailability of theophylline, but nothing about how different foods can alter the bioavailability from the different modified release products of theophylline that are available. Many clinical studies exist comparing different modified-release formulations and, given an understanding of the mechanisms of modified-release, it is certainly possible to realise why different foods can influence bioavailability.³

Surprisingly there are few articles in the *PJ* about medicines, and those which do appear (eg, "Tablet crushing and the law"⁴) tend to centre on issues other than the pharmaceuticals behind the subject. Indeed the only report I have seen with a pharmaceuticals content in the *PJ* in recent months has been in advertisements for a colon delivery product. My plea is for the profession, its Council and *The Journal* to further, value and pro-

mote the importance of a sound knowledge of the medicine and its fate (as well as the medicinal agent) in the primary care arena.

SCIENCE DIVORCING FROM PRACTICE?

There are pressures, whether real or perceived, on the science community that tend to draw the work away from practice.

Research funding One such factor is the sources and availability of funding for research. Research in pharmaceuticals can suffer from being regarded as close to market by research councils, which means that they believe it should be funded from industrial sources. There are now fewer sources of industrial money, due to the many mergers of companies, so the pool of industrial funding has diminished.

The research councils have not previously had drug delivery as a priority area. However, recently, the Biotechnology and Biological Sciences Research Council has funded specific aspects of drug delivery, but only a very small part mostly relating to bio-

logical barriers. The Engineering and Physical Sciences research Council has not had a drug delivery priority area and the nature of drug delivery work is that it tends to cross the traditional disciplines that make up the EPSRC committees. Thankfully, with help from the Royal Pharmaceutical Society, we are now moving to a situation where the EPSRC and the BBSRC may be able to recognise drug delivery projects.

It is good to have the research councils represented at the BPC in a session that will allow public discussion about the future research needs for drug delivery and how these can be met. Even with the hope of improved research council funding, it is clear that funding will follow research adventure. This is right and proper, but within our community there is also a need for directed research that helps patients today. It may be that this research is perceived as developmental, but when we consider the plight of vulnerable patients who have need today it is clear that there must be action.

I am pleased that a large section of the conference is devoted to paediatric issues,

Science Chairman



Professor Graham Buckton is professor of pharmaceuticals and head of the department of pharmaceuticals at the School of Pharmacy, University of London. His research relates to the amorphous state, powder processing, surface science, solid oral dosage forms, inhalation drug delivery and modified release dosage forms. He has published a book and more than 130 papers on these themes. He is editor of the *International Journal of Pharmaceutics* and is on the editorial boards of *Pharmaceutical Research*, *European Journal of Pharmaceutical Sciences* and 'The excipients handbook'.

Professor Buckton is vice-chairman of the chemistry, pharmacy and standards sub-committee of the Committee on Safety of Medicines and is a British Pharmacopoeia Commissioner.

both in plenary session and through the session run through the link between the Academy of Pharmaceutical Sciences and the UKI Controlled Release Society. At the School of Pharmacy in London we have established a Centre for Paediatric Research with the Institute of Child Health and Great Ormond Street Hospital. This unit, headed by Ian Wong, will link practice and science as never before and the recently appointed Pfizer lecturer in paediatric pharmaceuticals (Catherine Tuleu) will be a focus for providing delivery to babies and small children. Challenges that have been identified within the Centre for Paediatric Research include:

- Physicochemical testing of suspensions made from existing capsule products
- Dealing with delivery of drugs which do not exist as liquids (eg, crushing of nifedipine tablets)
- Developing slow-release liquid formulations
- Developing consistency of dose of drugs administered through nasogastric tubes
- Developing eye-drops that can reduce the number of daily administrations
- Taste masking
- Novel delivery methods (eg, needleless injections, considerations of transdermal delivery through immature skin, etc)
- New analytical methods for very small volume fluids

It is clearly not just children who need novel delivery solutions. To a greater or lesser extent this is a challenge that all hospitals have and to which pharmacists can provide the solution — by understanding medicines and linking science with practice.

Research Assessment Exercise issues The Research Assessment Exercise (RAE) is the quality control method used to judge research of individuals and thus departments. Inevitably, the RAE will be impressed with innovative science published in top research journals but, I fear, be less impressed with the development of a drug delivery solution to a special problem for a neonate. Ironically, then we can have a situation where a research group provides major benefits to patients, but this may not be weighed highly in the RAE. We must learn to value both fundamental and applied science contributions or else we do society a disservice. The best way to ensure this is to encourage the Medical Research Council to support research in drug delivery that will be of value to patients in the immediate or near future and which would be seen as positive by the RAE.

A related RAE concern is that of band-wagons. Certain subjects become instantly popular. For example, we now are all nanotechnologists, which is a trendy term for the microparticles that many have been making for years. In the past decade it has become socially unacceptable for academics to work on tablet technology, even though most administrations of medicines are tablets and much is still not understood in this area. The result is that few schools of pharmacy retain any presence in pharmaceutical technology.

The same was true for pharmacognosy. Again, few schools viewed this as an area to retain, yet we are seeing important new drugs from natural sources.

So, by the whim of opinion formers, whole areas of research can be cast aside to be replaced by the latest trend. For a while it was protein delivery and now it will be genetics/DNA delivery. This is not to say that we should not move forward and embrace the new goals and real challenges that face us. We must move on, indeed delivery research will be fundamental to the success of gene therapy, but we will be better placed to do so if we bring our traditional skills with us, through the application of physicochemical principles and processing technology. What we must achieve is a balance between the skills that make up our discipline. These skills will provide for improved medicinal agents of today and the novel needs of those of tomorrow, and for the consideration of the biological barriers as well as the methods of manufacture.

In keeping with these thoughts, the BPC this year covers a range of world class research; from fundamental work, which is removed from direct patient application, through to science to be used directly for patient benefit.

The drug delivery symposium, to mark the retirement of Professor Bob Davis from Nottingham University, brings together leaders in the field to provide an overview of the subject. The theme of cancer allows consideration of cancer drug discovery and the nature and basis of the disease. It is pleasing that we have such high-calibre speakers addressing the conference.

Pharmacology is a subject that has been under-represented at the BPC, as there are pharmacology conferences that attract the researchers, but it is good that we have a session to highlight some of the relevant work that is going on around the UK in seeking innovative solutions to chronic diseases.

The new scientists group of the Academy of Pharmaceutical Sciences has a session very much within my theme of bringing together practice and science: dealing with improvements in patient care through applied science. A further attempt to build links across the community is the session on small scale manufacturing. It is my hope that this will provide support for the many hospital pharmacists who work in manufacturing and quality assurance units and allow them to meet up with people facing similar challenges in research and industrial settings.

I mentioned above the decreasing number of multinational pharmaceutical companies. However, there are an increasing number of small companies being formed, often from the university sector. These small companies have been show-cased for a number of years at BPC and another batch will present this year, giving further proof of the vibrant pharmaceutical science base of the UK. Other sessions that provide high quality science, but which should have general appeal, are those relating to vaccine delivery and oral absorption. We live in a world that has a growing need to turn to vaccination, against nature and bio-terrorist threats.

Understanding oral absorption seems to me to be central to knowledge that pharmacists should have to understand the fate of the numerous medicines that they dispense.

MATERIALS SCIENCE

To round up the science programme we have sessions on analysis and materials science ("More from less" — understanding the physicochemical properties of the medicinal agents either before they have been synthesised or when they exist in only small quantities). The development of analysis and its application to understand and modify materials properties is my own area of interest and I will spend a short while describing this.

Professor Peter Elworthy's science chairman's address in 1971 was entitled "Dehydrated elephants and other matters".⁶ Some years ago I came across a cartoon with scientists standing around a mound of powder and a caption reading, "Of course no one wanted a dehydrated elephant, but it is nice to see what we can do". There is merit in work of this kind; we must explore and find out what we can do, simply to push back the frontiers of our science. With time, complicated processes (such as dehydrating elephants!) become routine. Indeed recently I read an article in which there were words to the effect of "it is not hard to dehydrate an elephant and grind it up to get a powder, the hard bit is to be able to add water and get the elephant back". This is how science progresses; someone tries to do something that seems to have little application and then it becomes a tool for a vital application. We certainly have a current need to dry proteins and rehydrate them with their structure and functionality intact.

In my laboratory, we look to develop new analytical methods, the goal being to be able to detect any change in the materials that can give rise to a meaningful change in the performance of the medicine. (By this I mean physical form rather than chemical, as chemical analysis methods are reasonably well developed.) Examples include changes in a material property that gives rise to variability in the processing of a product during manufacturing, which in turn could lead to a change in properties such as content uniformity, dissolution rate or stability. Having developed methods of detection (this being an ongoing process), we apply them to problems of unexplained batch-to-batch or supplier-to-supplier variability in materials. When we understand what gives rise to the variability then we can get an understanding of what constitutes a good and bad material property for the production and use of any medicine. If we get to understand what are the desired properties then we can move on to engineer materials that have these properties and hence optimise product quality and patient benefit.

The areas where the work is being applied at present include the development of techniques to enhance the efficiency and reproducibility of inhalation systems, to improve the dissolution rates of poorly soluble drugs and to help in stabilising macromolecules.

Figure 1: Particles of indomethacin/ polyvinylpyrrolidone solid dispersion produced using supercritical fluid technology, showing the porous structure at (A) 46x and (B) 387x magnifications

Of great interest in the field of pharmaceutical materials science is the study of polymorphism and the complicated issues involved in the study of the amorphous form. Many drugs become partially amorphous when milled and the extent to which this happens depends upon both the nature of the material and the energy of the processing. The amorphous regions have different properties to the crystalline ones, including changes in dissolution rate, water sorption potential, chemical stability and surface nature. Furthermore, the amorphous form is not thermodynamically stable so it will crystallise with time, and thus the properties will change with time. Consequently, it is important to be able to both detect and quantify the amorphous content in powders, to ensure reproducibility in the performance of the materials during manufacturing and subsequent use as a medicine. Over a number of years we have developed methods that allow the detection and quantification of the amorphous content of powders, including isothermal and solution calorimetry, gravimetry, near infrared (NIR) spectroscopy, the novel combination of water sorption and NIR, inverse phase gas chromatography and, most recently, hyper-differential scanning calorimetry. These provide a powerful armoury with which to study materials and to understand the causes of batch-to-batch variability. It is also possible to begin to optimise the materials to make them more efficient.

Recent examples of material modification from my own laboratory include the production of particles with adapted surface properties, such that they can form better suspensions in pressurised metered dose inhaler formulations and the modification of physical form through an understanding of spray drying processes. These include surface modified salbutamol sulphate particles, produced by spray drying.⁷ The addition of different proportions of a range of surfactants resulted in particles with a wide range of surface energies which alter the quality of dispersions in suspensions. This is an approach to the optimisation of metered dose inhaler formulation, with potential to yield more efficient and reproducible drug administration. The modification of particles for dry powder inhalers is extremely

complex, but it has been possible to find improvement by changing the surface nature, for example by making the surface partially amorphous, with the surprising results that a partially amorphous surface conditioned particle gave improved drug delivery.⁸

In order to increase the dissolution rate of poorly soluble drugs, particles have been processed using supercritical carbon dioxide, to form amorphous solid dispersions of indomethacin and polyvinylpyrrolidone with a very porous structure (Figure 1). These particles were seen to have extremely fast dissolution rates compared with the drug alone and also with conventional (non-porous) solid dispersions of drug in PVP.⁹

In my view, the study of physical properties of materials, the understanding of which of these properties are desirable for optimising performance, and then engineering materials to achieve best performance, will be a valuable approach to improving drug delivery in the years ahead. Indeed, the reduction in the numbers of new drugs arriving from discovery will mean that optimisation and innovation in formulation processes will be critical to enhance the effectiveness of the drugs that are currently available.

CONCLUSION

Pharmaceutical science is diverse. It covers a wide range of subjects through a physical to biological spectrum, but pharmacy requires strength across this spectrum. The apparent tension between practice and science has to be removed; rather than diverge, it is vital that science and practice move together to overlap. In doing this there will always be scientists who are far from practice and practitioners who are detached from day-to-day science, but there must be a substantial core in between.

Everyone will have their own area of expertise, but the fascination of our subject comes from the consideration of a range of scientific disciplines and the empathy with the users of medicines.

ACKNOWLEDGEMENTS Science at the BPC is strong, largely because the Academy of Pharmaceutical Sciences provides an excel-

lent infrastructure. It is a joy to see the development of this organisation to a strong body with a wide membership. I am grateful to the board and other members of the academy for their support. I must also mention Dr John Clements, who worked tirelessly to ensure the programme came together.

My personal thanks go to my colleagues, collaborators and research students, who are the ones that keep the science and interest flowing.

REFERENCES

1. Quality Assurance Agency for Higher Education. Pharmacy. Gloucester: QAA; 2002. Available at: www.qaa.ac.uk/crntwork/benchmark/phase2/pharmacy.pdf (accessed 12 September 2003).
2. Mason P. Drug-food interactions (1): Food and medicines. *Pharm J* 2002;269:571-3.
3. Buckton G. Sustained release (SR) theophylline preparations: A review of biopharmaceutical influences on in vivo and in vitro drug absorption/release data. *J Biopharm Sci* 1991;2:81-96.
4. Griffith R. Tablet crushing and the law. *Pharm J* 2003;271:90-1.
5. Ahmed H, Buckton G, Rawlins DA. The use of isothermal microcalorimetry in the study of small degrees of amorphous content of a hydrophobic powder. *Int J Pharm* 1996;130:195-201.
6. Elworthy PH. Dehydrated elephants and other matters. *Pharm J* 1971;207:265-9.
7. Columbano A. Modification of particle surfaces by use of alkylpolyglycoside surfactants [PhD thesis]. University of London: 2000.
8. Al-Hadithi D, Buckton G, Brocchini S. PCT/GB03/02044 [Patent] filed 12 May 2003.
9. Viboontiat R. Methods to prepare amorphous material for rapid dissolution solid dosage forms [PhD thesis], University of London: 2002.