Institution: University College London

Unit of Assessment: 3B - Allied Health Professions, Dentistry, Nursing and Pharmacy: Pharmacy

Title of case study: Developing methods to measure and quantify amorphous content in micronised particles, leading to improved manufacture and performance of inhaled drug delivery devices

1. Summary of the impact

Graham Buckton's work at the UCL School of Pharmacy has involved the development of new techniques, which are now industry standards, for assessing the amorphous content of materials in inhalation products. This work has had a significant influence on both manufacturing quality control and regulatory requirement, including informing FDA policy, to the effect that this type of assessment is now a requirement for licensing of powder inhalation medicines in the US and Europe. Benefits to drug companies include cost savings and more reliable production. Furthermore, the associated School of Pharmacy spin-out company, Pharmaterials, offers these assessments as a core part of its commercial activity, with a large client base of industrial partners who require such assessments for their inhalation and other products. The overall result of this work has been changes and improvements in the design, control and manufacture of inhalation products.

2. Underpinning research

The drug and excipient powders used for inhalation aerosols have to be of specific size in order to allow appropriate drug deposition in the lung, hence they are often processed using techniques such as micronisation to control the particle properties. However, it is well recognised that this process may cause unforeseen changes in performance; linked in to this is the issue of batch-to-batch variation, whereby seemingly identical materials perform very differently. The research of the group of Buckton has focused for the last 20 years on understanding the underpinning reasons for these performance changes and developing methods whereby such alterations may be identified and quantified. More specifically, he has produced a considerable body of work demonstrating that subtle changes in surface properties, notably including the generation of surface amorphous material, may give rise to significant changes in performance. However as the surface only constitutes a very small proportion of the bulk of a solid material, detection of such changes requires the development of sophisticated and sensitive methodologies. It is in this area of methodology development that Buckton's work has made, and continues to make, a particularly significant contribution.

In the 1990s Buckton's laboratory was extremely active in developing the use of isothermal microcalorimetry for the detection of surface amorphisation, whereby by inducing crystallisation in the material, the associated heat change could be detected with enormous sensitivity, thereby allowing very small amounts of amorphous material to be detected. In particular, his group were instrumental in developing a modified calorimetry cell whereby humidity could be controlled and hence used to induce crystallisation. A key development was a publication in 1994, in collaboration with scientists in Astra Draco (now AstraZeneca), which showed that this method was able to detect minute quantities of crystallisable amorphous content present in micronised materials **[1]**. It was then possible to remove the amorphous material by annealing, resulting in a material that would be consistent in performance.

The development of isothermal microcalorimetry, through a series of publications in which Buckton's group played a leading role (e.g. **[2]**), led to this being used as the method of choice by the industry for the determination of amorphous contents in micronised materials. The group continued to develop innovative methods for amorphous content detection including gravimetric **[3]** approaches, solution calorimetry **[4]**, a novel gravimetric-near IR instrument (constructed in house) **[5]**, and the development of a novel inverse gas chromatography approach **[6]** and fast scan differential scanning calorimetry **[7]**. The combined output of this research revealed not only that

micronisation can generate partial amorphicity in otherwise crystalline materials but also that by appropriate measurement it was possible to detect quantities well under 1% of the total particle mass. The research described above was carried out from 1993 until the present date through a variety of collaborations with industrial companies, all of whom now apply this research concept. The co-authors on the publications cited include a number of industrial collaborators, as well as members of Buckton's group.

3. References to the research

[1] Briggner L, Buckton G, Bystrom K, Darcy P. The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders. Int J Pharm. 1994;105:125-35. http://dx.doi.org/10.1016/0378-5173(94)90458-8

[2] Ahmed H, Buckton G, Rawlins DA. The use of isothermal microcalorimetry in the study of small degree of amorphous content of a hydrophobic powder. Int J Pharm. 1996;130:195-201. http://dx.doi.org/10.1016/0378-5173(95)04288-1

[3] Buckton G, Darcy P. The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powder. Int J Pharm. 1995;123:265-71. http://dx.doi.org/10.1016/0378-5173(95)00083-U

[4] Hogan SE, Buckton G. The quantification of small degrees of disorder in lactose using solution calorimetry. Int J Pharm. 2000 Oct 10;207(1-2):57-64. http://dx.doi.org/10.1016/S0378-5173(00)00527-5

[5] Hogan SE, Buckton G. The application of near infrared spectroscopy and dynamic vapor sorption to quantify low amorphous contents of crystalline lactose. Pharm Res. 2001 Jan;18(1):112-6. http://eprints.pharmacy.ac.uk/3237/1/APPLICATION_OF_NEAR_RED.pdf

[6] Newell HE, Buckton G, Butler DA, Thielmann F, Williams DR. The use of inverse phase gas chromatography to measure the surface energy of crystalline, amorphous, and recently milled lactose. Pharm Res. 2001 May;18(5):662-6. http://eprints.pharmacy.ac.uk/3236/1/use_of_inverse_phase.pdf

[7] Saunders M, Podluii K, Shergill S, Buckton G, Royall P. The potential of high speed DSC (hyper-DSC) for the detection and quantification of small amounts of amorphous content in predominantly crystalline samples. Int J Pharm. 2004 Apr 15;274(1-2):35-40. http://dx.doi.org/10.1016/j.ijpharm.2004.01.018

4. Details of the impact

The inhalation device market is predicted to reach a value of approximately $20 billion by 2017 **[a]**. This approach provides essential, and often life-saving, therapy for the management of a range of diseases including asthma and chronic obstructive pulmonary disease. Inhalation therapies are in development for both treatment of infection and gene therapy for cystic fibrosis, as are many systemic delivery therapies for conditions such as migraine, sexual dysfunction and pain control. The need for control and understanding of inhalation products is therefore critical.

Inhalation particles are inevitably small (less than 5 microns is the norm) or at least of low aerodynamic size. The large surface-area-to-volume ratio of small particles makes them very sensitive to changes in surface properties. In the 1980s and early 1990s there was an awareness that batch-to-batch variation in performance was common, but at that time, all the available analytical techniques (such as differential scanning calorimetry and powder X-ray diffraction) would show every sample to be identical. There was an urgent need to develop analytical methods which were at least as sensitive as the product in terms of a material's properties.

The understanding, developed to a large part from the work described above, that micronised material will have amorphous content and that the presence of that amorphous content will give

rise to variability in the manufacture and performance of inhalation products is now well established. In particular, isothermal microcalorimetry is now a standard means of measuring amorphous content, as pioneered by Buckton. Widespread use of this method has had a profound effect on sales of related instruments within the pharmaceutical industry. A microcalorimetry expert associated with instrument sales stated: "*The realisation that the instruments can detect small quantities of amorphous material changed [the] sales profile totally and annual sales to this sector increased 5 fold in the period from mid-1990s onwards and maintained at this level for a decade. The market is even more buoyant now with new applications but the core solid state pharmaceutical market is still the basis of our market leading position. Key to the solid state application is Graham Buckton's initial amorphicity studies where the methods he developed are still used, almost unchanged, today*" **[b]**. In addition, the use of gravimetric vapour sorption, new scanning calorimetric techniques and spectroscopies have all contributed to the science and understanding of partially amorphous materials.

The methods developed in the work described above allow for reliable quantification of amorphous content in micronised powders. The impact of the body of work has therefore been to profoundly influence the current industrial practices associated with quality control of powders for inhalation as well as the choice, development and indeed sales of methodologies associated with measuring small quantities of amorphous material. A materials scientist working in product development at GSK said: "*the work he has conducted has influenced the way in which we characterise inhaled products (a major market at GSK worth some £7.3b in 2012). The key findings that we picked up at GSK were the development of methodologies in which very small amounts of amorphous material could be measured…we developed our material characterisation procedures with his papers very much in mind*" **[c]**. Furthermore, a drug product design scientist at Pfizer has confirmed: "*The work performed by Graham's group on using a range of techniques to detect these small amounts of amorphous material has been seminal in developing the control strategy for pharmaceutical materials. We currently have isothermal microcalorimetry and solution calorimetry instruments for precisely this purpose and have developed the use of the approaches developed by Graham into material characterisation and drug product design*" **[d]**.

As well as influencing industrial practice, the work outlined above was also central to the creation in 2000 of Pharmaterials Ltd, a spin-out company from the School of Pharmacy **[e]**. This company provides consultancy and expertise to large and small pharma and related industries, with a particular (initial) specialisation being the physical characterisation of drugs, excipients and dosage forms based on the body of work developed by Buckton. The company has since grown to include formulation, analytical sciences, stability and manufacturing of clinical trial supplies and at the present time is involved with all aspects of product development. In January 2008, Pharmaceutics International Incorporated USA (PII) acquired a majority shareholding in Pharmaterials **[f]**. *[Text removed for publication]* **[g]**. The company have invested *[Text removed for publication]* on equipment since acquisition **[h]**, and there has also been substantial spend on the new building **[i]** reflecting the manner in which the characterisation research has translated into commercial activity.

The company provides a service for GMP-compliant measurement of amorphous content for many companies, including active ingredient manufacturers, SME development companies and large multinationals. Initially, this service was offered in a problem-solving capacity, but with the changing regulatory environment (see below), the data generated by Pharmaterials are now used in the development of product specifications and are submitted to regulatory authorities around the world. Pharmaterials now uses the knowledge of this materials science in order to provide a full inhalation development service. *[Text removed for publication]* **[g]**.

In addition to these activities, the research has also influenced regulatory processes. In 2002, the US Food and Drug Administration (FDA) invited Buckton to advise on developing a regulatory framework for amorphous materials **[j]**. It subsequently became a requirement for all new low molecular weight drugs for powder inhalation to be tested for amorphous material as part of the regulatory process. The US Pharmacopoeia followed the FDA's position in developing their standards and specify the use of microcalorimetry to measure amorphous content **[k]**. In the UK,

Buckton served on the MHRA's Committee on Safety of Medicines, where he similarly advised on amorphous materials. It is now also a requirement in Europe that inhalation materials are tested for amorphous content prior to licensing **[l]**.

5. Sources to corroborate the impact

[a] http://www.marketresearch.com/GBI-Research-v3759/Drug-Delivery-Device-Metered-Dose-6623023/

[b] Letter of support from Senior Account Manager, TA Instruments. Copy available on request.

[c] Letter of support from Materials Scientist and Technical Lead, product development, GSK. Copy available on request.

[d] Letter of support from Research Fellow, Drug Product Design, Pfizer available on request.

[e] Pharmaterials Webpage on amorphous materials, referencing Buckton's work: http://www.pharmaterials.co.uk/amorphous-content.html The webpage offers the following testimony to how the research underpins the commercial activity: "*Having worked in this field for some 15 years and published in the region of 100 research papers on the subject, Professor Graham Buckton has led the search for methods of characterisation and quantification of amorphous forms. The transfer of this experience into Pharmaterials allows us to provide the highest possible quality of service*."

[f] Press coverage of the sale of Pharmaterials to PII: http://www.drugs.com/news/pii-acquires-pharmaterials-ltd-7563.html

[g] Pharmaterials company details can be verified by Chief Operating Officer, Pharmaterials Limited. Contact details provided.

[h] Investment in new equipment by Pharmaterials, and see also [g]: http://www.pharmaterials.co.uk/details~144.html

[i] http://www.pharmaterials.co.uk/details~83.html

[j] Can be corroborated by a former Director of the section at FDA for this activity at that time supporting the role of Buckton's work in moving this policy forward. Contact details provided.

[k] FDA Guidance for Industry – Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documents. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf
The United States Pharmacopeial Convention. United States Pharmacopeia 36 - National Formulary 31. Characterization of crystalline solids by microcalorimetry and solution calorimetry.
http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/harmonization_february_2012_m99456.pdf

[l] EMEA document EMEA/CHMP/QWP/49313/2005 Corr "Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products"
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pdf