Institution: Imperial College London

Unit of Assessment: 12 Aeronautical, Mechanical, Chemical and Manufacturing Engineering

Title of case study: 15. Advanced Sorption Instruments for Powder Characterisation

1. Summary of the impact (indicative maximum 100 words)

Novel vapour sorption experimental methods for the characterisation of complex particulate materials have been developed in the Department of Chemical Engineering. This research and expertise resulted in the creation of Surface Measurement Systems Limited (SMS), whose Dynamic Vapour Sorption (DVS) and Inverse Gas Chromatography (IGC) instruments are now found in >500 laboratories around the world. They are recognised standard research and development tools in the global pharmaceutical industry (DIN 66138). SMS has contributed >270 man-years of employment and generated £27M of turnover, whilst SMS instruments have generated over £300M of economic value, over the REF period.

2. Underpinning research (indicative maximum 500 words)

The growth in the development of new solid state pharmaceuticals during the past 20 years revealed a significant knowledge and understanding gap in the physicochemical stability, and especially the moisture stability, of these complex organic solids. This is important as these materials underpin a £10Bn UK industry, and this knowledge deficiency in turn represented a bottleneck in development of new solid state dosage forms.

Research on the use of vapour molecules as a method for characterising solid state materials is a key research interest of Dr. Williams (in post 1993-date). His initial research focused on refining the technique known as Inverse Gas Chromatography (IGC). In this technique an unknown powder is packed into a small column the size of a pencil, and its surface and bulk properties are determined by eluting known vapour molecules through the column using a gas chromatographic approach. PhD students who worked on IGC and related techniques included N.Zafeiropoulos (1998-2002), P.Yla-Maihaniemi (2001-4) J.Heng (2002-5), R.Ho (2005-8) and , J.Khoo (2006-2010). Funding for IGC related work in this period included EPSRC, Unilever, Syngenta, Givaudan, Du Pont, GSK and Astra-Zeneca.

The research performed at Imperial College resulted in breakthroughs in the refinement of new vapour adsorption instrument approaches as well as identifying the key industrial research problems for these new measurement approaches. They key breakthroughs in the instrument approach were: (i) translation from chromatographic to a gravimetric measurement method [1]; and (ii) the discovery of the sensitivity of these methods to molecular structure and morphology [2]. These molecular adsorption based experimental techniques can provide a unique and important insight into the physicochemical properties of particulate materials such as pharmaceuticals. In turn, the availability of these new research tools within the Department of Chemical Engineering opened up a range of new research opportunities with industry.

Early work on the moisture stability and performance on pharmaceutical powders [1] first demonstrated the significant benefits of the DVS method of measurement in 1994. Specific knowledge on the surface properties of complex materials such as inhalable drug particles and polymers was then shown to accessible using the IGC technique [2,3,4]. It has also been found to be a very powerful way of looking at the effects of processing history on final product performance [4], while new scientific methods for determining surface heterogeneity of such materials have been pioneered using the IGC method [5,6].

3. References to the research (indicative maximum of six references)
* References that best indicate quality of underpinning research.

[1] P.V. Marshall, P.A. Cook, D.R. Williams, "A New Analytical Technique for Characterising the Water Vapour Sorption Properties of Powders" in Proceedings of the International Symposium on Solid Oral Dosage Forms, Sweden (1994) https://getinfo.de/app/A-New-Analytical-Technique-for-Characterising-the/id/BLCP%3ACN004364181

[2] P.S. Thomas, D.R. Williams, "The Characterization Of Thin Polymer-Films Using Igc ", Abstracts Of Papers Of The American Chemical Society Vol: 207 Pages: 222-PMSE Part: 2 (1994) ISSN: 0065-7727

*[3] N.E. Zafeiropoulos, C.A. Ballie, F.L. Matthews, D.R. Williams, "Engineering and characterisation of the interface in flax fibre/polypropylene composite materials. Part I. Development and investigation of surface treatments", Vol 33, pp. 1083-1093, (2002) ISSN:1359-835X DOI: 10.1016/S1359-835X(02)00082-9

*[4] J.Y. Heng, F. Thielmann, D.R. Williams, "The Effects of Milling on the Surface Properties of Form I Paracetamol Crystals", Pharmaceutical Research, Vol 23, pp. 1918-1927, (2006) ISSN:0724-8741 DOI: 10.1007/s11095-006-9042-1

*[5] P. Ylä-Mäihäniemi, J.Y. Heng, F. Thielmann, D.R. Williams, "An Inverse Gas Chromatographic Method for Measuring the Dispersive Surface Energy Distribution for Particulates", Langmuir, Vol 24, pp. 9551-9557, (2008) DOI: 10.1021/la801676n

[6] R. Ho, S.J. Hinder, J.F. Watts, J.Y. Heng, D.R. Williams, S. E. Dilworth "Determination of surface heterogeneity of D-mannitol by sessile drop contact angle and finite concentration inverse gas chromatography", Int. Journal of Pharmaceutics, Vol 387, pp. 79-86, (2010) DOI: 10.1016/j.ijpharm.2009.12.011

4. Details of the impact (indicative maximum 750 words)

Surface Measurement Systems Limited (SMS) was formed by Drs. Briscoe and Williams from the Department of Chemical Engineering and in 1994, working in collaboration with Pfizer Research UK, invented a novel gravimetric instrument for water sorption analysis of powders called Dynamic Vapour Sorption (DVS). The DVS instrumentation approach is closely linked to the IGC research work pioneered by Dr Williams at Imperial College funded by an industrial research contract with Du Pont Fibres. Dr Williams remains the Managing Director of SMS and in 1997-1999 spent 0.5 FTE working with SMS (the balance of FTE in post at Imperial College), promoting the DVS product and working on its commercialisation.

This new DVS approach allowed water sorption isotherms to be obtained 20 times faster, using 20 times less sample and 20 times more accurately [7] than traditional measurement approaches, thus transforming laboratory practice in this domain. This advance allowed stability testing, formulation development and polymorph screening studies to not only be significantly accelerated, but to be performed with a much higher degree of scientific certainty. The DVS method has now become a standard method used by all major pharmaceutical companies throughout the world, and has been formally adopted within the German DIN 66138 "Isotherm Measurement for Solids using Vapour Sorption" standard [8].

Advances in IGC research at Imperial College resulted in further developments at SMS. In 2000 SMS successfully released the world's first commercial IGC instrument. In 2011 a second generation instrument, called the Surface Energy Analyser (SEA) which incorporated many of the more recent scientific discoveries published by researchers at Imperial College [5,6], was launched. Over 50 of the new SEA systems have been sold in the first 24 months of sales.

Based upon Imperial College's research on the adsorption characterisation of solid state materials, instruments subsequently developed by SMS can now be found in over 500 research laboratories in over 25 different countries. All 20 of the world's largest pharmaceutical companies use SMS instruments as do over 100 universities globally. SMS instruments have accelerated the testing,

formulation and development of new solid state pharmaceutical products for nearly 20 years. Research described in [1],[4],[5] and [6] highlights some of the critical pharmaceutical research problems which have led the industrial demand for SMS products. These scientific applications are a key contribution to the commercial success of SMS, with SMS selling 60% of their instruments into the pharmaceutical industry.

SMS has contributed to the innovation capital of the UK, as the global technological market leader in sorption characterisation instruments. It has a significant patent portfolio [9, 10,11] as well as a significant proprietary base in key instrumentation technologies. SMS is an ISO 9001:2008 registered firm, and currently employs 50 staff globally, with offices in London, France, Germany and the USA. Manufacturing operations are based in the UK and the USA, with R&D activity based in West London. The company currently has 10 PhD qualified staff on the payroll, including a number of Imperial College graduates. It currently invests >15% of turnover in research and development and has an audited turnover of ~£5M. 90% of sales are exported from the UK. During the REF period of Jan. 1st 2008 to 31st July 2013, SMS has contributed > 270 man years of employment, generated £27M of turnover, £24M of export income and sold > 400 scientific instruments.

It is within the pharmaceutical sector that the instruments from SMS have had the greatest scientific and commercial impact. For the past 15 years many of the research and regulatory submissions globally on new drugs relating to moisture uptake and moisture stability will include data generated or elucidated using SMS instruments [12]. The impact of these instruments on the accelerating the development time for bringing new drugs entering market or in mitigating the risks of bring unstable products or formulations to market is best reflected by the fact that that every solid state and pre-formulation group in every major pharmaceutical company in the world will have DVS type instruments in daily operation; over 60% of these instruments are manufactured by SMS [7].

Senior Fellow at Novartis states [12]:

> *"DVS has been established over the past 15 years at Novartis development in Basel as a standard technique to measure water sorption in order to support physical stability studies and increase the understanding of phase transitions such as glass transition/ re crystallization and polymorphic changes, especially with the advent of the high throughput version."*

To estimate the economic impact of SMS instruments, one can use a commercial day price for 1 day of DVS or IGC contract test work of £500 (as charged by many universities as well as SMS to industry). Combined with the practical knowledge that DVS or IGC instruments are run 365/7/24 globally, and assuming a conservative 50% effectiveness, we can estimate that the current installed base of 700 SMS instruments generates an economic impact of over £60M annually. During the REF period this translates globally to over £300M of economic value being generated by SMS products.

5. Sources to corroborate the impact (indicative maximum of 10 references.)

[7] Surface Measurement Systems (SMS) www.smsuk.co.uk (Archived at https://www.imperial.ac.uk/ref/webarchive/zrf on 6th September, 2013)

[8] Deutsches Institut Fur Normung E.V. "Isotherm Measurement for Solids using Vapor Sorption" (2008) DIN 66138

[9] Williams, Daryl; Briggs., Michael; Jinting Gu, , Wrigley,. Ray "Method and apparatus for investigating the properties of a solid material" (2005) GB 2408800B, Filing Date: 24/10/2003

[10] Carl Levoguer, Dylan H Simpson, Daryl R Williams "Controlled sample environment for analytical devices" (2007) US 7160718 Filing Date: 30/05/2001

[11] David A. Butler, Carl Levoguer, Daryl R. Williams “Apparatus and a method for investigating the properties of a solid material by inverse Chromatography” (2002) US 6490910, Filing Date 08/10/1999

[12] Senior Fellow, Novartis Pharma AG, to confirm that many of the research and regulatory submissions globally on new drugs relating to moisture uptake and moisture stability include data generated or elucidated using SMS instruments.