

europaean pharmaceutical review

THE QUARTERLY REVIEW OF
EUROPEAN PHARMACEUTICAL
BUSINESS & TECHNOLOGY

Issue 1 2003



europaean pharmaceutical review

contents

THE QUARTERLY REVIEW OF EUROPEAN
PHARMACEUTICAL BUSINESS & TECHNOLOGY

Issue 1 2003

3 INTRODUCTION

Ken Leiper, Editor

7 CRM

Mobile solutions for pharmaceutical sales

Ojas Rege, VP of Product Management, AvantGo, Inc.

11 HTS

High-Throughput Screening for
Ion Channel Modulators

Margaret Falconer and Fiona Smith et al, Pfizer Global Research and Development



23 GENOMICS

Human Single Nucleotide
Polymorphisms (SNPs):
towards utility in research and development

Claes Wahlestedt, Chairman, Center for Genomics and Bioinformatics (CGB) Karolinska Institutet and Dr Salim Mottagui-Tabar, CGB

31 PROTEOMICS

Adding value in the target discovery and drug
development pipeline

*Dr Stephen R Pennington,
University of Liverpool
and Dr Michael J Dunn,
Institute of Psychiatry,
King's College London*



37 SHOW PREVIEW: DRUG DISCOVERY TECHNOLOGY

Science, business and IT for drug discovery

41 NIR

NIR microscopy of pharmaceutical dosage forms

*Fiona Clarke & Steve Hammond, Process Analytical
Support Group, Pfizer*

51 NEW TECHNOLOGY FORUM

Multivariate mathematical approaches

53 CHROMATOGRAPHY

Chiral thin-layer
chromatography – the role of
imprinted polymers

*Dr Charles M Heard, Welsh School
of Pharmacy, Cardiff University*

58 DISSOLUTION TESTING

Good Manufacturing Practices

*Vivian A. Gray, E. A. Gray
Consulting, Inc.*

63 SHOW PREVIEW: PITTCON 2003

Bringing together the elements of science



67 PACKAGING

Blister barrier materials

*Pierre Barkman, Global Packaging Technology & Development
(Europe), Lilly Clinical Operations S.A.*

71 LYOPHILIZATION

How important is the flatness of shelves in a freeze dryer?

Thomas A. Jennings, Ph.D.

74 SHOW PREVIEW: ACHEMA 2003

World forum for process industries

81 KNOWLEDGE MANAGEMENT

Informatics for the Life
Sciences industry

Loric Karnath

84 PROCESS TOMOGRAPHY

Improving pressure
filter performance

Peter Varey



86 PHARMACEUTICAL NEWS

New developments and products

Improving pressure filter performance

❖ Peter Varey, on behalf of Industrial Tomography Systems

Pressure filtration can be a very slow business. Separation of solid and liquid can take a long time and you simply cannot see what is going on, or what to do to speed things up. Now there is a possible solution to this problem: process tomography.

It's new technology and one of the pioneers, Industrial Tomography Systems (ITS) – a "spin-off" of Manchester University Institute of Science and Technology (UMIST) – is half-way through a four-year Government-funded LINK project seeking to prove that it works at commercial scale. Whereas most pressure filters do not have even rudimentary instrumentation to help you, tomography actually allows you to see what is going on inside the filter cake. And once you know, you can make changes, watch the effect they are having and improve filtration performance substantially.

Process tomography is the process industry equivalent of whole body scanning in medical imaging. An array of electrodes – typically 8 to 24 – are placed on a mesh at the base of the filter cloth. In other applications the electrodes may be placed around the inner circumference of a process vessel, i.e. a reaction vessel, or a pipe. The idea in all cases is to get electrodes in contact with the fluid but not disturb the flow pattern. With reactors or pipework you can place electrodes on the inside surfaces; when using pressure filters you have to be careful about the integrity of the filter when placing electrical leads, so the sensor array is placed across the bed.

How tomography works

When a current flows between a pair of electrodes on the filter cloth, the resultant voltage difference between remaining electrode pairs can be measured according to a pre-defined measurement protocol. Then apply current through the next pair of electrodes and repeat the voltage measurements. The procedure continues until all necessary measurements have been made. This protocol interrogates an entire slice through the measurement zone. If n is the number of electrodes, the protocol yields a

maximum of $n(n-1)/2$ measurements. But of these only $n(n-1)/2$ are independent. Furthermore, to avoid electrode/electrolyte contact impedance problems, the voltage is not measured at an electrode where current is injected and so the total number of independent measurements is reduced to $n(n-3)/2$. For instance, a 16-electrode sensor gives 104 independent measurements. This is enough to achieve a real-time picture of the resistance of the process fluid in that plane of the vessel.

Typically ITS equipment can take 100 readings in 25 milliseconds. A filtration process can take more than 24 hours, so these measurements can provide a picture of the process as it moves from stage to stage, including washing and drying. You can see where the filter cake is uneven and, most significantly, when a filtration end point has been reached (Figure 1).

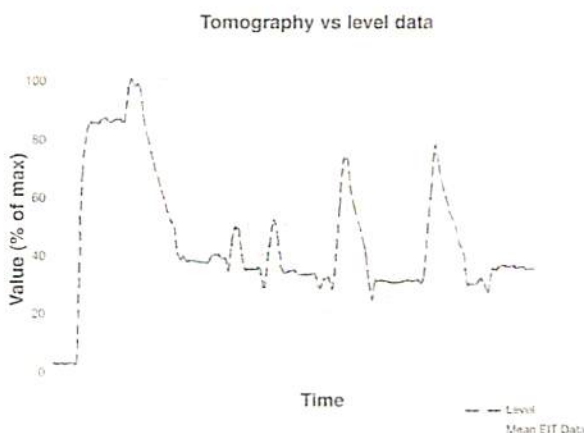


Figure 1. Tomography-assisted filtration: This graph of bed level against time shows bed height during filtration plus several washes (blue line) and indicates when liquid content has dropped to almost zero (green line, tomography)

The same technology lets you watch the cake being washed, rinsed and dried. During all this, the integrity of the product is of primary importance. In the ITS trials electrochemistry experts from Glasgow Caledonian University have been ensuring just that.

With other vessels and pipes, a 3-D representation of what is going on inside is possible. You place similar arrays of electrodes on a series of planes along the length of the whole vessel and an image

reconstruction algorithm reveals the flow pattern throughout the whole vessel.

Electrical considerations

In a pressure filter, electrodes are arranged on the filter mat but in other vessels they are arranged at equal intervals around the boundary of a circular vessel or as a vertical series. A co-axial cable connects the electrodes to the data acquisition system. This helps reduce the impact of outside environmental noise/interference. To reduce noise further, the outer sheath of the co-axial cable is coupled to the feedback path of a voltage buffer while the inner core is capacitively coupled to the voltage buffer input.

What are the electrodes made of? It depends largely on the process application. If they are more conductive than the fluids being imaged, it prevents problems due to contact impedance. Typically the electrode material is stainless steel, brass or silver/palladium alloy. Electrode dimensions are a function of the vessel diameter, range of conductivity to be measured and velocity of materials. A spare electrode – known as the ‘ground electrode’ and placed away from the measurement electrodes, but in electrical contact with the internal fluid – ensures that all voltage measurements are fixed against a common ground source.

In this application to commercial pressure filtration, the size of process vessel and media being used contribute to the engineering challenges. In the trial that yielded Figure 1, the pressure filter was particularly large and the selection of materials limited by the fact that the process liquor included acetic acid.

Collecting the data

The challenge to the data acquisition system is to track small changes in real time quickly and accurately. An image reconstruction algorithm can then provide an accurate measurement of the true conductivity distribution. In the ITS system, a sine-wave voltage output is fed into a voltage-to-current converter (referred to as a voltage-controlled current source, or VCCS). Current is used in preference to voltage as electrical probe because of the variation of contact impedance between electrodes and the fluid inside the sensor.

The VCCS maintains a constant amplitude over a wide range of resistance loads by employing two operational amplifiers and an analogue switch arrangement in the feedback path of one of them. To accommodate a wide range of material conductivities and to improve the accuracy when following slowly changing processes, a range of injected current frequencies is used, typically within the range 75 to 154 kHz in 12 steps.

Besides taking account of the chemically aggres-

sive nature of the process media, the instrumentation must also be intrinsically safe – that is, certified for use in an explosive atmosphere. The basis of the instrumentation for process tomography is the injection of electrical current into the process vessel and the creation of sparks is deemed to be an unacceptable hazard. In practice, the instrumentation is rendered intrinsically safe by using an array of zener diode barriers between the sensors and the measuring instruments in order to prevent surges of high energy from reaching the process.

Constructing the image

Once data has been acquired from the boundary of the object to be imaged, an appropriate image reconstruction algorithm is applied to the processed data. The reconstructed image contains information on the cross-sectional distribution of the conductivity of the contents within the measurement plane.

The choice of image reconstruction algorithm is a trade-off between accuracy of image and time required for reconstruction. Fast image reconstruction algorithms that can be used for the real time imaging of fast moving processes are much in demand. As a result, a large number of both non-iterative and iterative algorithms are available for electrical tomography. In the example case, a specialised algorithm was developed that would summarise local information on the filter cake, providing information on local dryness.

The results in Figure 1 come from a project carried out in one of several pressure filters belonging to bio-processing company Syngenta. The trials were assisted by ITS and UMIST.

Counting the benefits

Pressure filtration is a poorly understood process, but the trials have identified a number of benefits:

- opportunities to improve yield and quality
- reduction in use of raw materials like wash solvent
- safer operation due to less need for sampling
- reduced capital cost because optimising allows use of a smaller pressure filter

The LINK project has reached a point where additional UK-based demonstration sites are being assessed. The research group intends to invite a pharmaceutical company to test the technology on one of its pressure filters: support is available from DTI and EPSRC. Rosenmund will provide support in instrumenting the filter. ITS will provide tomography input and detailed technical advice is available from UMIST and Glasgow Caledonian University. ■

Industrial Tomography Solutions (www.itoms.com) was created by UMIST in 1997 to develop process tomography commercially.