White Paper

INDUSTRIAL TOMOGRAPHY SYSTEMS plc

Scale-up of Crystallisation

Application of process tomography as a tool for monitoring and scale-up of crystallisation

Introduction

Electrical resistance tomography (ERT) is able to monitor conductivity at in excess of 200 points in a vessel at rates of 20-40 times per second.

There is a substantial change in conductivity as ions move from solution to solid form. The chart below shows the tracking of crystallisation of paracetamol using ERT, compared to FBRM. It shows that ERT is able to pick up crystallisation much closer to nucleation (as it does not require the build up of particles). It is well known that as scale moves from millilitres to litres, mixing and flow processes can allow different regions of a vessel to have different concentrations and conditions. This means that scaling up processes can lead to different product characteristics.

ERT offers the opportunity to monitor how crystallisation develops in different regions of a vessel and as a result provides a useful tool for process scale-up.

Experimental

The precipitation of barium sulphate (surface addition of barium chloride to sodium sulphate) was observed at:

- Two scales (7 and 170 litres)
- Three mixing speeds
- Three different concentrations (all equimolar)

The reaction was scaled up matching power per unit volume and addition time.

Results

Process tomography conditions were observed using ITS p2000 instrument which takes data from up to 8 measurement planes (each with 16 electrodes in a circular array). In addition particle size and micrographs were taken of the precipitate. The tomography data was used to determine:

- Reaction progress through averaging all electrical measurements
- Homogeneity of reactant conditions through analysis of standard deviation of vessel cross-sectional conductivity maps
- Reaction conditions through analysis of tomograms of vessel conditions

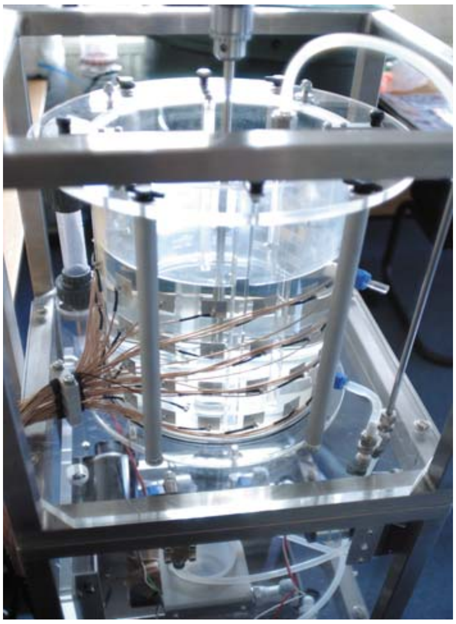

Figure 1: Seven litre experimental ERT

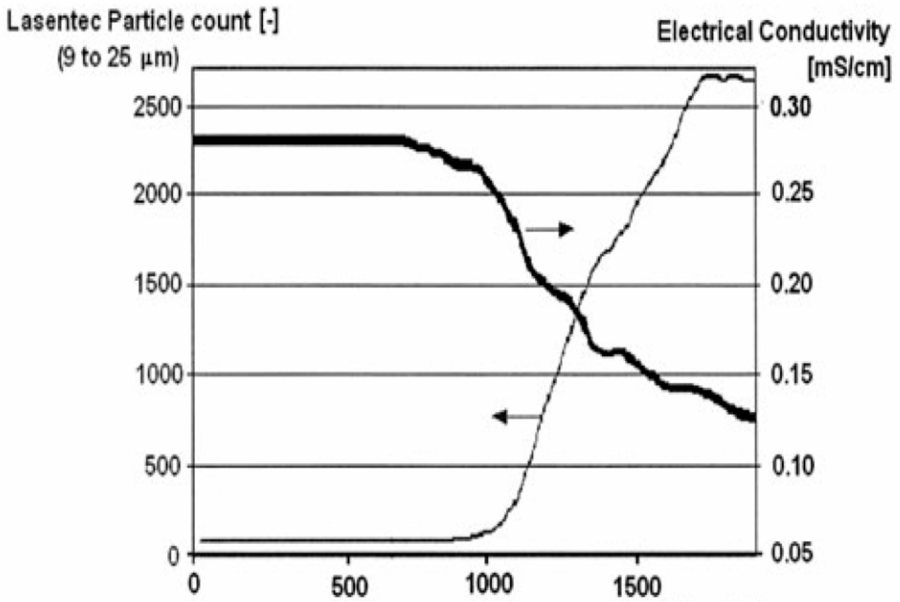

Figure 2: Chart plotting FBRM and ERT measurements during crystallisation (Ricard et al., 2005)

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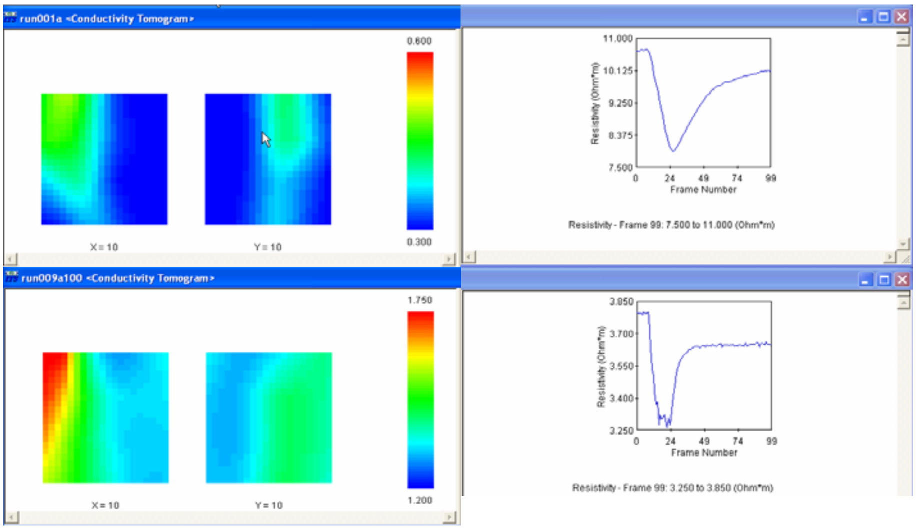

Figure 3: Slow (top) and Rapid (lower) mixing conditions for small scale

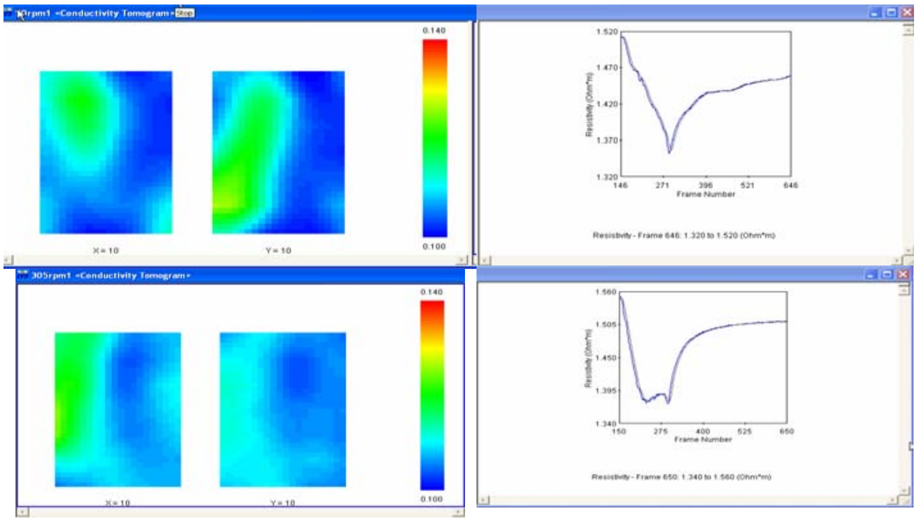

Figure 4 Slow (top) and Rapid (lower) mixing conditions for large scale

The images on the left show two orthogonal ‘conductivity’ slices through the mid point of the vessel during the feed addition and the graph on the right shows the mean resistivity plotted from the entire process volume plotted over time. It can be seen from the conductivity slices that the key differences between the reaction conditions is whether the high conductivity regimes are running along the baffles (rapid mixing) or at the centre of the vessel (slower mixing).

These conductivity images provide a snapshot of the highly conductive region where crystallisation occurs (rapid in centre, slow along baffle) and the conditions during the reaction (slow with variable conditions and extended time to complete, rapid with relatively constant conditions and reaching completion more rapidly).

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Analysis

As the high conductivity region is observed at the centre of the vessel in slow mixing conditions and at the baffle in rapid conditions, the average measurements from these zones were compared to characterise these two conditions.

Figure 5 and 6 shows these average measurements for the fast and slow experiments respectively.

It can be seen that the scale-up criteria have effectively reproduced similar reaction conditions. These are borne out by the particle size data taken at the two different scales.

Figure 7 shows the conductivity variation between the two regions for the slow and fast mixing experiments. It is clear that the conductivity difference between the regions is much less for the fast mixing case when compared to the slow case.

Conclusion

Electrical Resistance Tomography provides an effective tool for characterising reaction conditions in crystallization. As such it can be an effective tool for PAT (Process Analytical Technology) in the pharmaceutical industry where particle size and characteristics are critical. It can be used to complement other on-line tools such as Lasentec FBRM.

Key benefits of ERT are the ability to detect conditions throughout a vessel and its sensitivity at stages close to nucleation where many particle characteristics are determined. In addition, the technique can be applied at different scales through both circular and probe based arrays.

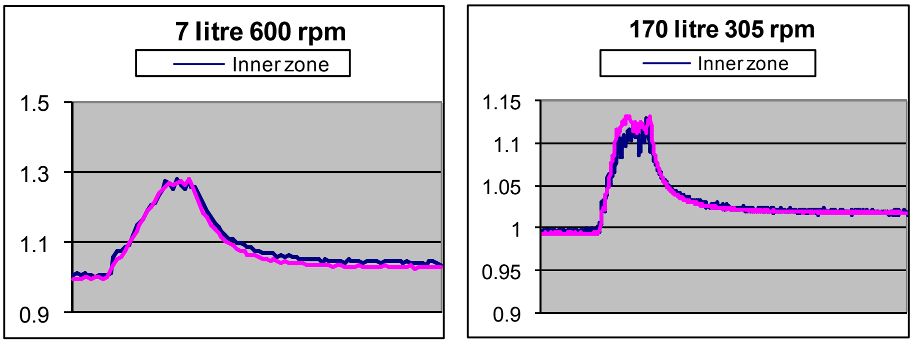

Figure 5: Relative conductivity for inner and outer region for rapid mixing conditions

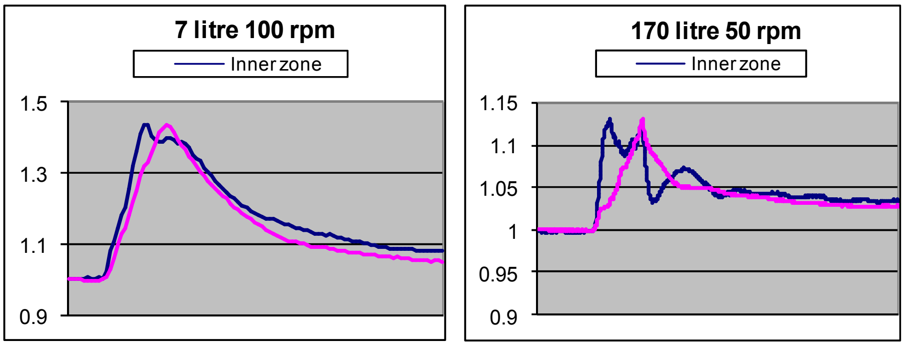

Figure 6: Relative conductivity for inner and outer regions for slow mixing conditions

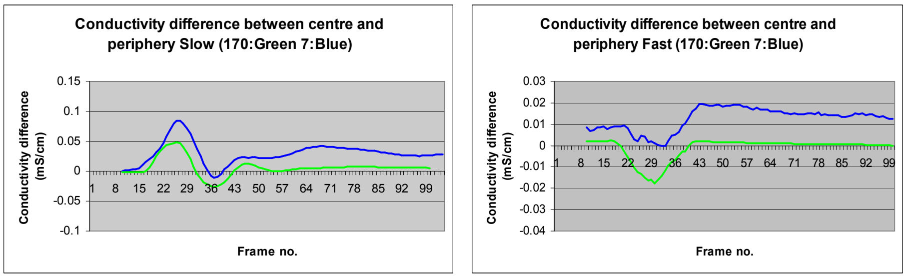

Figure 7: Conductivity difference (mS/cm) between centre and circumferential regions for rapid (left) and slow (right) mixing conditions

References

F. Ricard, C. Brechtelsbauer, X.Y. Xu, C.J. Lawrence, Monitoring of multiphase pharmaceutical processes using electrical resistance tomography, *Chem. Eng. Res. Des.*, **2005**, 83, 794-805.

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