Monitor, Control, Optimize
Heat Balance Calorimetry…. the ideal PAT tool

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In the five years since the birth of the PAT initiative, we have seen a vast number of developments in analytical tools. There are now an array of monitoring tools available that can provide valuable information about what is happening throughout a process. The majority of these tools have been developed as enhancements to existing laboratory equipment.

The main improvement we have seen, thanks to the driving force of the PAT initiative, has been the ability to collect data in real time. Thus being able to see what is happening, and when. For many products this has enabled process times to be optimised. For example, through the improved accuracy of end point detection, processes no longer need to over run, saving valuable lab time. These tools provide valuable information, however they are highly susceptible to process changes. This requires multiple calibrations and complex modelling, making standard procedures rather cumbersome. Many of these tools are often best suited to final production stages where changes are less likely to occur, minimising the time spent calibrating equipment.

Temperature – a fundamental parameter

One of the key forgotten variables in the drive for greater process understanding, is temperature. Calorimetry is the measurement of temperature and represents the purest form of change in any reaction. Every reaction produces an exothermic and / or endothermic change. By measuring in this change, the level of understanding of a process can be dramatically improved. Furthermore, having the ability to control the temperature of a process accurately can have significant effects on product quality, not to mention the safety benefits.

The most suitable and robust technique is heat balance calorimetry which unlike other calorimetric techniques is not affected by changes to process conditions. The only restriction on implementing this technique to date has been the large fixed volume jackets of the traditional rector design which generate huge background signals making it incompatible for monitoring relevantly small changes in the process signal.

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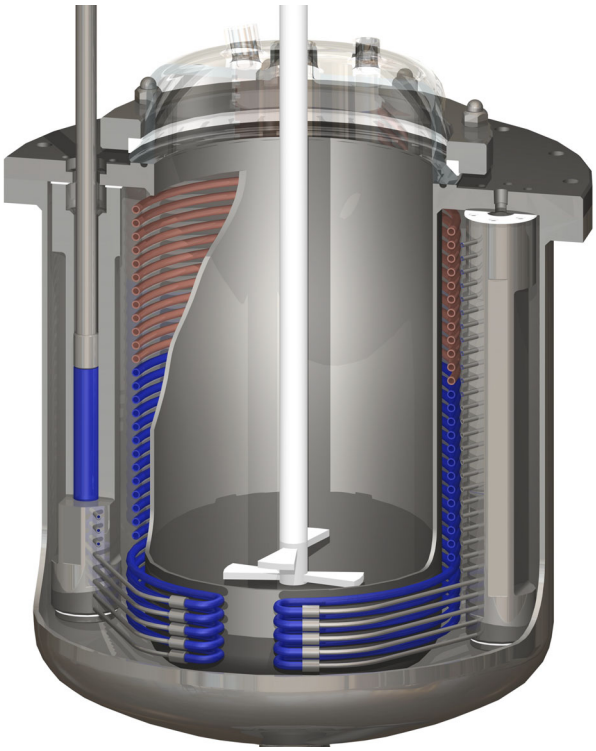
Jacket Design

By re-examining the traditional jacket and employing a different technique for controlling temperature, the thermal inertia associated with a traditional jacket design can be effectively removed. Based on this concept Coflux[tm] technology utilizing a number of independent coils or jackets, is, (see diagram below). With a minimum volume of heat transfer fluid (HTF) an instant response to temperature change is possible, allowing accurate measurement and control of any process.



PSL ChemFlux jacket design

ChemFlux intelligent reactors incorporate Coflux[tm] technology and offer the unique opportunity to monitor and control a process simultaneously by using thermal fingerprints to provide a unique process specific signature. Utilising this reduced volume jacket design, reactors of any size can, not only significantly improve the performance characteristics of the reactor itself, but also provide a simple and easy to use method for real time monitoring of any chemical or biological process. At lab scale, reaction calorimetry is simplified and improved, at production scale it can be used as a versatile PAT tool. There is the additional benefit that, by utilising the jacket for monitoring and controlling, the method is non-intrusive.

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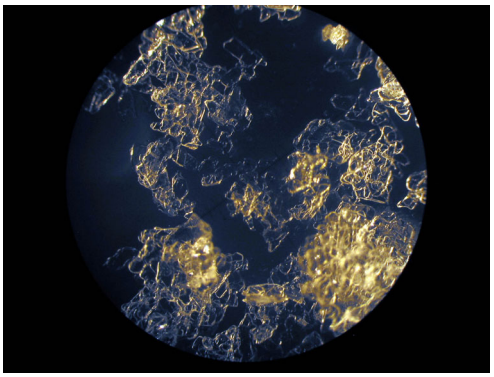
This design enables extremely responsive temperature control, not to mention its improved energy efficiency. The reactor wall will not have dead spots in heat transfer surface, nor will it apply heating / cooling to dry surfaces above the process fluid, preventing burning or icing. As the quantity of HTF required is just 10% of that of a normal jacketed reactor, the responsiveness of the temperature controller is greatly improved.

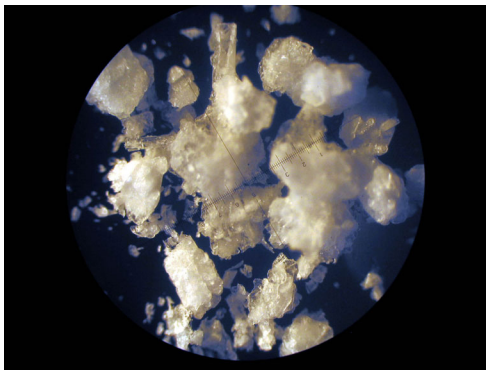
This presents many opportunities for supporting the PAT initiative in terms of process optimisation. The ChemFlux can reveal how fast a process change is taking place and how far through the change a process has gone. For example it can be used to monitor and control reaction end points, improving product quality and batch to batch variability as well as reducing processing times. By preventing reactant accumulation, repeatability of a process is greatly improved. Improved understanding of heat and mass transfer conditions also provides valuable information for process optimisation. All of these result in significant improvements to process understanding and repeatability, allowing real-time quality control of the product, improving yield and batch to batch variability. It has the potential, in principle, to be the most adaptable and flexible of all process analytical tools.

Crystal Clear

By utilizing calorimetry techniques to measure the temperature throughout a crystallisation process it is possible to accurately detect the point of crystallisation. Once this information is known, the product quality can be vastly improved by accurately controlling the temperature of the process. Knowing the exact temperature at which a crystallisation process begins can also reduce process time as the reactor can be crash cooled to within a few degrees of the predetermined temperature. This gradually reduces the temperature to the optimum rate throughout the crucial stages of the crystallisation process resulting in an improved product quality.



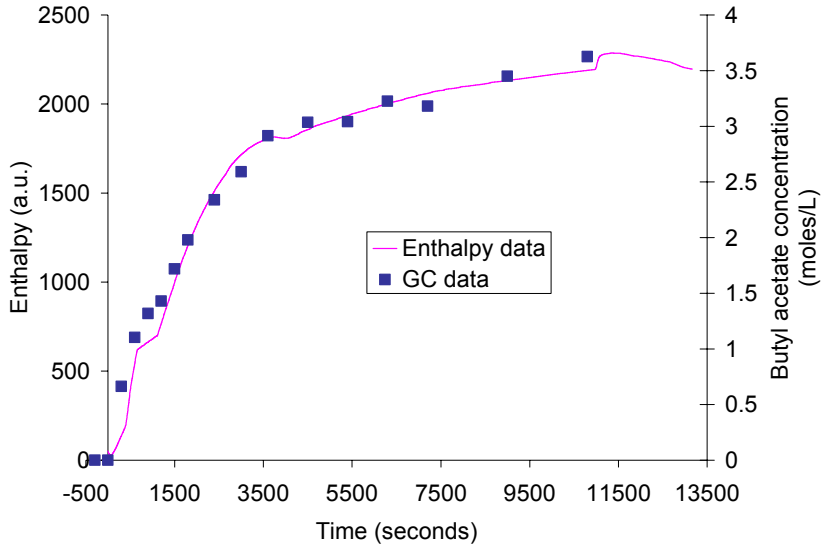
Coflux controlled cooling
0.1% impurity



Traditional reactor ambient cooling
0.3% impurity

GC Data Mapped

ChemFlux intelligent reactor systems can accurately measure the enthalpy throughout a process. A study carried out by Strythclyde University in Scotland, mapped the enthalpy data gathered in real time, against traditional gas chromatography (GC) data for an esterification process. See figure below. The benefits of gathering such data online are obvious, you can control the process, thus saving a batch that may traditionally have been allocated as out of specification. Even more dramatic is the idea that as confidence in this technology grows, the feasibility of running a GC lab with all associated costs may well come into question.



Who knows what the future holds?

The past five years have seen some tremendous developments in the production and formulation of APIs, and the FDAs PAT initiative has been a key driver in developing a deeper understanding of processes run in pharmaceutical development and production. But whatever the cause, any development that helps to get new and more effective drugs to market faster will always be welcomed. If innovation continues at its current rate, then who knows what the future might hold!

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