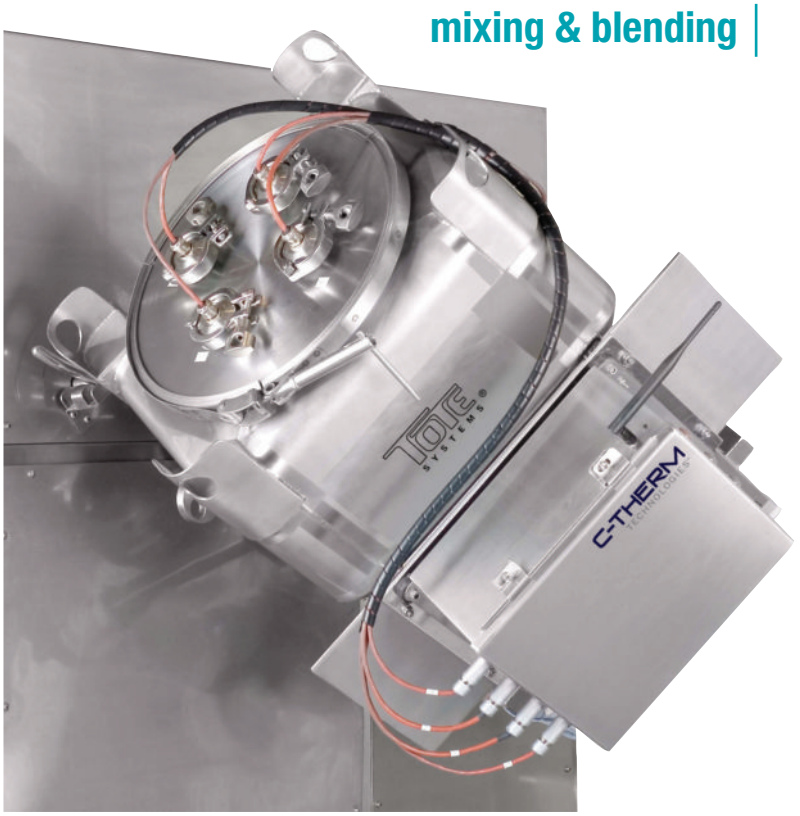
In-line monitoring of blending processes



Stephen Closs, manager pharmaceutics and process technology, and **Austin Freedman**, director, pharmaceutical development services, of Patheon (Whitby), discuss the benefits of monitoring blending operations in-line

In September 2004, the US FDA released a draft guidance that introduced Process Analytical Technology (PAT) to the pharma industry.[1] PAT is a science-based approach to the improvement of manufacturing efficiency and product quality. PAT tools perform real-time, on-line measurements of evolving quality parameters to ensure optimal processing conditions are maintained throughout the manufacturing process.

PAT tools provide the means to gain new understanding and knowledge of the process critical control points and facilitate better control of process variation further upstream. The variability of inputs to the process may still exist, but knowledge of their existence and impact allows the process to be accommodating to these differences, resulting in a more consistent end product. This increase in process understanding and process control through use of real time data collection is a cornerstone of the Quality by Design (QBD) initiatives revolutionising pharmaceutical development and manufacturing today.

Figure 1: ESP tote from C-Therm

in-line monitoring

Powders are normally blended together to produce pharma products and the consistency of those powders is critical to the quality and the efficacy of that product. Typically a blender is charged with individual components which are blended for a fixed period of time and speed. A fixed blending process does not take into account the variability of the components and this can lead to variation in the product. Despite the fact that a lot of effort has been committed to reduce the lot-to-lot variability of the components, the industry still faces the problem that slight variations in the chemical or physical properties of these components can have a huge impact on the final product. Component variation could be attributed to: environmental conditions, humidity, feedstock grade, and particle size distribution. Presently blending is validated as a fixed process (e.g. blend for 10 minutes). But fixed processing conditions do nothing to dampen or buffer the influence of incoming variability.

In-line monitoring of a blending process uses a different approach. Real time measurements and feedback provide a 'process check' operation within the actual unit operation being performed. The knowledge gained during the process does not in itself improve the incoming variability, but by modifying a process in response to measured fluctuations of incoming materials, it is possible to achieve processing, and hence, product consistency.

Thermal effusivity of samples is measured using a C-Therm ESPwireless unit. This instrument is an interfacial device that is in direct contact with the sample and is used to measure heat flow. Thermal effusivity is a material property that combines thermal conductivity, density and heat capacity. Hence, it can differentiate between solids, liquids and powders in a system based on heat transfer. Each material has its own thermal effusivity determined by the properties of the sample, as shown in Equation 1. ▶

Equation 1

$$Effusivity = \sqrt{k \rho c_p}$$

Where:

k = thermal conductivity ($W / m\,K$)

ρ = density (kg / m^3)

c_p = heat capacity ($J / kg\,K$)

Table 1 – Individual component and concentration used

Ingredients	Concentration in the final blend			
Product	(%, w/w)	Brand name and grade	Supplier	Weight (kg)
Ibuprofen	10	n/a	Mallinckrodt Baker	0.50
Microcrystalline Cellulose	35	Avicel PH 102	FMC International	1.75
Lactose Monohydrate	40	Fast Flo	Foremost Farms	2.00
Pregelatinised Starch	15	Starch 1500	Colorcon	0.75

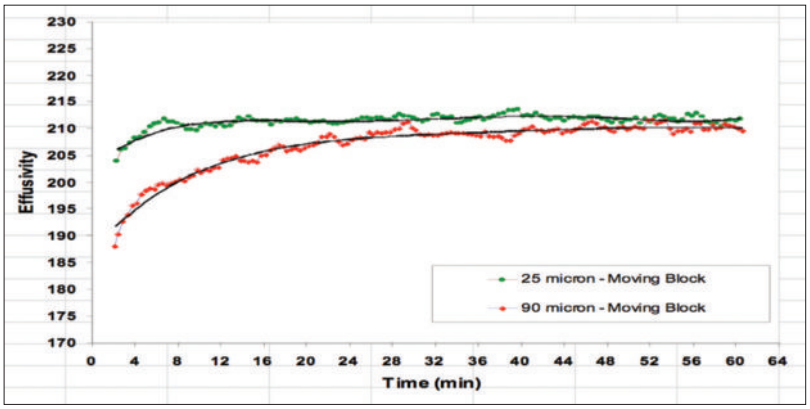


Figure 2: Thermal effusivity blend profiling using 25µm and 90µm ibruprofen

effusivity monitoring

Blending operations are integral to most solids pharmaceutical manufacturing today, whether used to achieve a state of API and excipient uniformity as in a direct blend application, or to provide optimal distribution of a functional excipient in an extra granular process stage such as final blend lubrication using magnesium stearate.

For in-line effusivity measurements, the wireless sensors are retrofitted directly onto the lids of the blending vessels. The number of sensors used depends on the vessel lid size, but four to eight is typical. The lowest number of sensors is related to the available surface area. The more sensors that are retrofitted, the more data points will be derived at each blending interval, increasing knowledge and confidence of the results.

The system synchronisation enables the sensors to dynamically obtain a real-time data stream from the rotating blender by 'firing' each sensor only when a minimum static contact is obtained. The selection of any empirical uniformity value may depend on several factors, including the nature of the materials being mixed. Based on previous works, blend consistency evaluation is based on a combination of stable averages and decaying relative standard deviation RSD%.

In other words, when the signal reaches a steady state over a moving block of measurements the blend is deemed to have achieved a state of physical uniformity.

The ability to measure relative differences in materials during processing provides useful information for process control. PAT instrumentation has been developed and used over the past decade that enables scientists and operators to open 'windows' on their processes and better understand blending operations in an attempt to achieve optimal mixing conditions and endpoints. Many types of instruments have been shown to be valuable for in-line determination of absolute values of an attribute of interest (i.e. quantitative NIR spectroscopy to determine chemical uniformity of an API in a pharmaceutical blend operation).

The FDA guidance states that PAT tools are 'measurements collected from these process analysers that need not be absolute values of the attribute of interest.'[1] The ability of the C-Therm ESP unit to measure the holistic physical uniformity of powder blends provides important real-time insight into the achievement of 'steady state conditions' during blending operations involving multi-component mixtures.

As noted from the earlier provided equation, thermal effusivity is affected by the thermal conductivity, density and inherent moisture of the materials being measured. Blend 'steady state' is achieved when the blend achieves a state of physical uniformity of all components, including API and functional excipients. This evaluation of blend physical homogeneity can aid in determining blend endpoints involving different pharmaceutical components that all contribute to the efficacy of the product and robust downstream manufacturing operations.

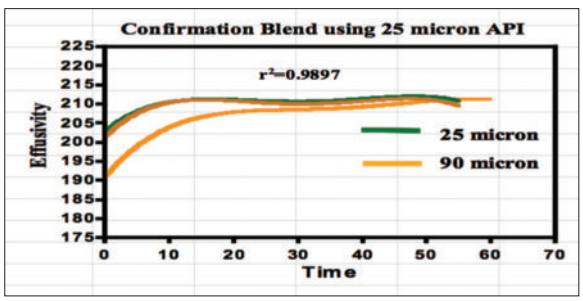
The following is an example of thermal effusivity being used to determine the blend 'steady state' achieved using a milled and unmilled version of an API marker compound (ibruprofen) in multi-component blends. The impact of variations in API particle size on physical blend homogeneity could be evaluated based on multiple data points collected from inline monitoring using four ESP wireless sensors. A 16qt V-shell (O'Hara Technologies) equipped with four ESP sensors in the blender lids (two per side) was charged with 5kg of material based the quantities listed in table 1.

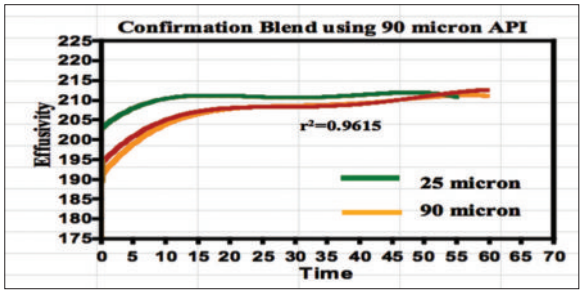
The initial blend was executed using ibruprofen with a mean particle size of 90µm. The second blend used a milled ibuprofen with a mean particle size of 25µm. The blender was rotated at 15 rpm and four thermal effusivity readings were taken at 24-second intervals. A moving block average of five measurements was plotted every two minutes in an effort to profile and contrast the two different blends. The thermal effusivity values for each of the blends are presented in figure 2.

The end experimental data indicates that the sensors are sufficiently sensitive to detect physical material changes during processing. The relationship between API physical characteristics and blend performance observed during this exercise provides important information relative to optimisation of materials and process. Blends showing more favourable physical uniformity profiles (consistency in material content, particle size, and density) are more likely to remain stable in downstream processing (ie, tableting) and help minimise segregation potential, flow problems and possible weight variation.

Blends made using 25µm API were quicker to achieve steady state physical uniformity (8–12 mins) than blends using 90µm API (>20 mins) and therefore the use of a reduced particle size ibuprofen is most likely integral to product success. Correlating thermal effusivity profiles with chemical uniformity through HPLC analysis or spectroscopic methods could be used in the creation of blend reference models for scale-up and optimisation activities. Confirmation ibuprofen blends produced at the same scale using the 25µm and 90µm variants showed good correlation with the original reference models (see figure 3).

Figure 3: Confirmation blends runs and comparison with thermal effusivity blend models





magnesium stearate effect

Physical blend profiling has also shown merit in the determination of blend lubrication states involving magnesium stearate.[2] Preliminary work with thermal effusivity in blend monitoring applications led to the discovery of what was coined the 'magnesium stearate effect'. In this occurrence, lubrication with magnesium stearate decreased the interparticulate void spaces with a resultant densification in the mixture as a whole, thereby causing an increase in the average effusivity measurement of the blend.

Figure 4 shows the effect of adding

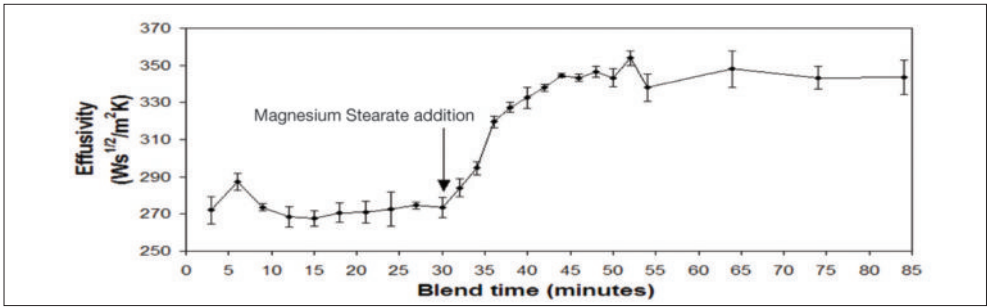


Figure 4: Influence of the addition of magnesium stearate in a pharmaceutical blend using thermal effusivity

magnesium stearate to a physically uniform binary mixture of Lactose Fast Flow (Foremost Farms) and Avicel PH102 (FMC Corp.). Upon achievement of 'steady state' physical homogeneity, the addition of magnesium stearate causes an increase in average thermal effusivity, resulting in a plateau some 20 mins after addition.

Unlike API or functional excipients, complete uniform dispersion of magnesium stearate does not always equal optimal lubrication conditions. The deleterious consequences of complete monomolecular coverage of particulate with the blend lubricant includes negative effects on downstream compressibility as well as a potential for a slowing of dosage dissolution rate. Correlation of thermal effusivity Δ change and blend lubrication states as defined by downstream operations (i.e. tablet compressibility) or tablet disintegration/dissolution values could provide a means to achieve consistent optimal lubrication. This would help mitigate the risk of blend under- or over-lubrication as well as enable adjustment of blending conditions to account for incoming raw material variability (e.g. particle size).

Recent published work by Okoye and Wu[3] correlated physical uniformity as defined by thermal effusivity blend profiles and chemical uniformity as defined by HPLC. They also were able to monitor thermal effusivity Δ change during blend lubrication using both magnesium stearate monohydrate and dihydrate. They were able to correlate these effusivity increases with downstream tablet compression and dissolution results and demonstate the benefits of the dihydrate versus the monohydrate form.

In summary, the monitoring of blend operations through the use of wireless thermal effusivity measurements has provided blend profiles that can be used to adjust process conditions and mitigate the risk of downstream manufacturing problems.

The creation of physical uniformity profiles aids in the determination of optimal blend conditions in which API and excipients reach a 'steady state' condition. The effect on blend effusivity values when mixing with magnesium stearate has allowed for the correlation of thermal effusivity Δ changes and downstream tablet compression and dissolution performance, helping to achieve the most favourable blend lubrication conditions for a product. ■

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2. Y. Roy *et al*, *Tablets and Capsules*, March 2005
3. P.Okoye and S. Wu, *Pharmaceutical Technology*, September 2007

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