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THERMAL EFFUSIVITY AS A PROCESS ANALYTICAL TECHNOLOGY (PAT) TO OPTIMIZE BLEND UNIFORMITY:

A Case Study in On-Line Monitoring of a Pharmaceutical Blend in a Bin Blender.

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What is the goal of the Process Analytical Technology (PAT) initiative?

In October 2003, FDA released a draft guidance that introduced PAT to the pharmaceutical manufacturing industry [1]. PAT is a science based approach that focuses on 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 robust process and hence more consistent end product.

Why monitor blend uniformity on-line?

Powders are normally blended together to produce pharmaceutical products and the consistency of those powders is critical to the quality and the efficacy of that product. Typically a blender is charged with four or more individual components and they are blended using parameters of fixed 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 is still facing the problem that slight variations in the chemical or physical properties of these components can potentially have a huge impact on the final product. Variation of the components could be attributed to several factors. Some of these include: environmental conditions, humidity, feedstock grade, and

particle size distribution. Presently the blending is validated as a fixed process (e.g. blend for ten minutes). If variation is introduced into a fixed process, the only possible outcome is product variability. Fixed processing conditions do nothing to dampen or buffer the influence of incoming variability.

On-line monitoring of a blending process uses a somewhat different approach. Real time measurements and feedback provide a "process check" operation that occurs within the actual unit operation being performed. The knowledge gain during the process does not in itself improve the incoming variability, but by measuring and modifying a process in response to measured fluctuations of incoming materials, it is possible to achieve processing, and hence, product consistency. On line measurements also add the benefit of eliminating thieving time and bias.

How can thermal effusivity measurements help?

This study introduces thermal effusivity as a means to monitor the blending process in order to improve this critical stage of the manufacturing process. The technique is non-invasive, quick and easy to use. Furthermore, no method development is needed.

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

$$Where:$$
$$k = thermal\ conductivity\ (W/m \cdot K)$$
$$\rho = density\ (kg/m^3)$$
$$c_p = heat\ capacity\ (J/kg \cdot K)$$

Effusivity varies with powders due to their differing ability to transfer heat (see sidebar). This ability in each powder is due to differences in heat transfer through and between particles and is therefore effusivity is a function of particle size, particle shape, density, morphology, crystallinity and moisture [2,3]. But this alone does not aid in the detection of blend uniformity. The use of effusivity sensors on-line hinges on the fact that effusivity is being measured in multiple locations. The effusivity values are compared and it is the relative standard deviation in the measurements that is related to the uniformity.

At the onset of blending, the material at each effusivity sensor is different and therefore the effusivity measurement is different. As blending time progresses and uniformity is achieved, the measurements will converge and the RSD will decrease. In this case, the RSD is a proxy for blend uniformity and will approach zero for a perfect mixture. [4]

The thermal effusivity of a powder sample will be driven by the properties of the sample composition and the properties of the inter-particle material (typically air). The thermal effusivity of air is very low with a value of 5 $Ws^{½}/m^2K$ whereas the thermal effusivity of solid pharmaceutical powders typically varies between 150 and 800 $Ws^{½}/m^2K$. For this reason, powder samples with small particles will show higher effusivity values than samples of the same material with comparable density and larger particles.

On-line blend monitoring in a bin container using thermal effusivity

Bin containers are widely used in several industries such as, the pharmaceutical industry, for everyday process operations. They give the ability to store, blend, transport, and discharge powders more efficiently as all these functions occur in the same container. The benefits of this include minimizing potential powder segregation

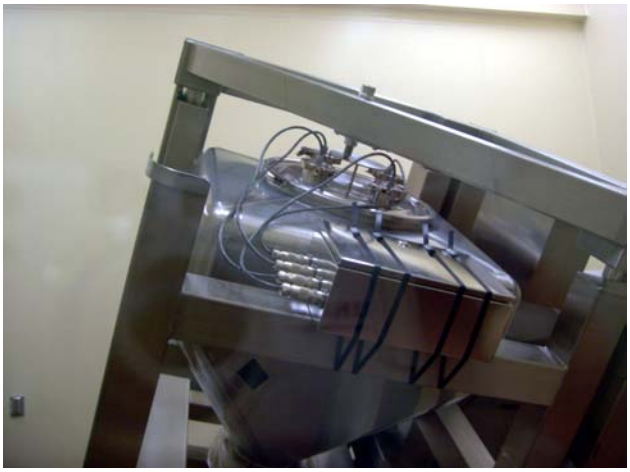
throughout the process, as well as providing a high degree of product containment for employee safety.

For on-line effusivity measurements, the sensors are retrofitted directly onto the bin lids for two reasons. Firstly, this is inexpensive and less intrusive than modifying bin walls, and secondly, this allows for consistent applied load pressure on the sensors during measurements intervals. This means that the bin containers do not need to be retrofitted with holes and ferrules. The typical process involving bin measurements would include:

- Filling the bin container;
- Moving the bin into the blending room;
- Placing the "effusivity cover" on the vessel;
- Blending with real time monitoring of effusivity to desired endpoint;
- If blending several bin of the same formulation, use the same "effusivity cover";
- Cleaning of the “effusivity cover” and proceeding with next product.

The control system is mounted on the rotating unit (see figure 1). The number of sensors used depends on the bin cover size, but typically 4-8 sensors is appropriate. The lowest number of sensors is related to the available surface area. Larger numbers of sensors generate more data points at each blending intervals and increase the statistical confidence level in the process results.

Figure 1 – IBC bin with Mathis BT-04 unit. The bin lid is retrofitted with four thermal effusivity sensors and the control box is attached to the blender.



Thermal effusivity for blend uniformity in a bin blender: A case study

Thermal effusivity of powder was measured using a Mathis Instruments BT™ unit. [5,6,7] This instrument is an interfacial device that is in direct contact with the sample and is used to measure heat flow. The rate of heat transfer from the instrument’s heating element is a function of the thermal effusivity of the sample material. For additional information on the method and apparatus, refer to the ASTM E55 standard or USP Chapter 1073 [8,9]. The ability of the BT™ unit to measure the uniformity of powder blends and lubricated blends was evaluated by testing a powder blend composed of

microcrystalline cellulose (PH 102) and lactose, monohydrate (316) before and after addition of magnesium stearate. The composition of the blend as well as the measured thermal effusivity value of individual components is presented in table 1.

Table 1 – Thermal effusivity values of the individual components

Ingredients			Thermal Effusivity	Quantity added to the final blend	Concentration in the final blend
Product	**Brand name and grade**	**Supplier**	**($Ws^{1/2}/m^2 K$)**	**(kg)**	**(%, w/w)**
Microcrystalline Cellulose	Avicel PH 102	FMC International	246.5	50	49.0
Lactose Monohydrate	Regular 316	Foremost Farms	375.1	50	49.0
Magnesium Stearate		Mallinckrodt Baker Inc.	155.5	2	2.0

The cover of a 375 L bin was retrofitted with four thermal effusivity sensors. The bin container was mounted on a rotating bin blender that had the effusivity controller attached to the frame. The speed of rotation was set at 12 rpm. The bin was charged with 100 kg of the unlubricated powder mixture resulting in a load of 70% of the total capacity. The initial two component mixture was blended for 30 minutes, following which 2 kg of magnesium stearate was added to the blend. The lubricated mixture was then blended for an additional 54 minutes for a total blend time of 84 minutes.

The thermal effusivity measurements were taken at 3 minutes intervals during the two component excipient blending (30 minutes total), at 2 minutes intervals for the lubrication blend time period between 30 and 54 minutes and then for 3 X 10 minutes intervals for the remainder of the 84 minute trial.

The thermal effusivity values of the blend for each sensor are presented in table 2 and 3 for the unlubricated and lubricated blends respectively. During testing, sensor 2 was not flush mounted with the inside of the cover that resulted in an indentation of approximately 2-3 mm inside the ferrule. As a result, sensor 2 was reading systematically lower effusivity values compare to the other 3 sensors that were flush mounted. This could be due to the reduced powder pressure on its surface or the formation of air pockets as a result of the ferrule indentation (air has an effusivity of 5 $Ws^{½}/m^2K$). For this reason, the readings from sensors 1, 3 and 4 are used to evaluate the blending parameters and uniformity using bin blenders.

Table 2 – Thermal effusivity* (Ws$^{1/2}$/m^{2}K) *values of a Lactose and Microcrystalline cellulose mixture at different stage of blending in a bin blender.

Sensor	Blend time (minutes)									
	3	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**26**	**28**
1	280	285	273	271	270	276	275	280	276	277
2	263	265	249	253	255	265	273	255	267	267
3	272	284	272	272	271	272	273	275	275	277
4	265	293	276	262	263	265	264	263	273	267
Average	270	282	267	265	265	269	272	268	2733	272
%RSD	2.8	4.1	4.7	3.3	2.7	1.9	1.8	4.3	1.6	2.1
Without sensor 2										
Average	272	287	274	269	268	271	271	273	275	274
%RSD	2.7	1.6	0.7	2.0	1.6	2.0	2.2	3.3	0.7	2.0

(Data courtesy of Patheon Inc.)

Table 3 – Thermal effusivity* (Ws$^{1/2}$/m^{2}K) *values of a lactose and microcrystalline cellulose mixture with the addition of magnesium stearate at different stage of blending in a bin blender.

Sensor	Blend time (minutes)														
	30	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**62**	**72**	**82**
1	286	298	323	330	326	337	344	344	346	346	350	343	353	342	349
2	278	289	303	313	316	326	316	325	326	335	350	324	321	322	329
3	288	296	319	324	335	337	346	341	344	338	354	329	337	338	333
4	279	291	317	328	337	340	345	345	350	347	358	341	354	350	349
Avg.	283	293	315	324	328	335	337	339	341	341	353	335	341	338	340
%RSD	1.8	1.4	2.8	2.3	2.9	1.9	4.3	2.8	3.1	1.6	1.1	2.7	4.6	3.5	3.1
Without sensor 2															
Avg.	284	295	319	327	333	338	345	343	347	343	354	338	348	343	344
%RSD	1.7	1.2	1.0	0.9	1.7	0.6	0.3	0.5	0.8	1.4	1.1	2.2	2.9	1.7	2.7

(Data courtesy of Patheon Inc.)

Data analysis reveals a blending pattern typical of an unlubricated powder blend, as well as the subsequent influence of magnesium stearate on the blend effusivity measurements as the powder is further mixed with the lubricant. As shown in figure 2 the most favorable uniformity of the 2 component mixture is achieved after 9 minutes of blending when the RSD was low and the average effusivity value stabilized. Figure 3 illustrates the average effusivity measurement at each interval and the corresponding increase in thermal effusivity of the blend after the addition of magnesium stearate. This phenomenon was observed by Closs and al. [10] in earlier work on a different system in a V shell blender, but these results further that study as they show the plateau that occurs at longer blending times.

Figure 2 – Effusivity trend while blending a two-component mixture.

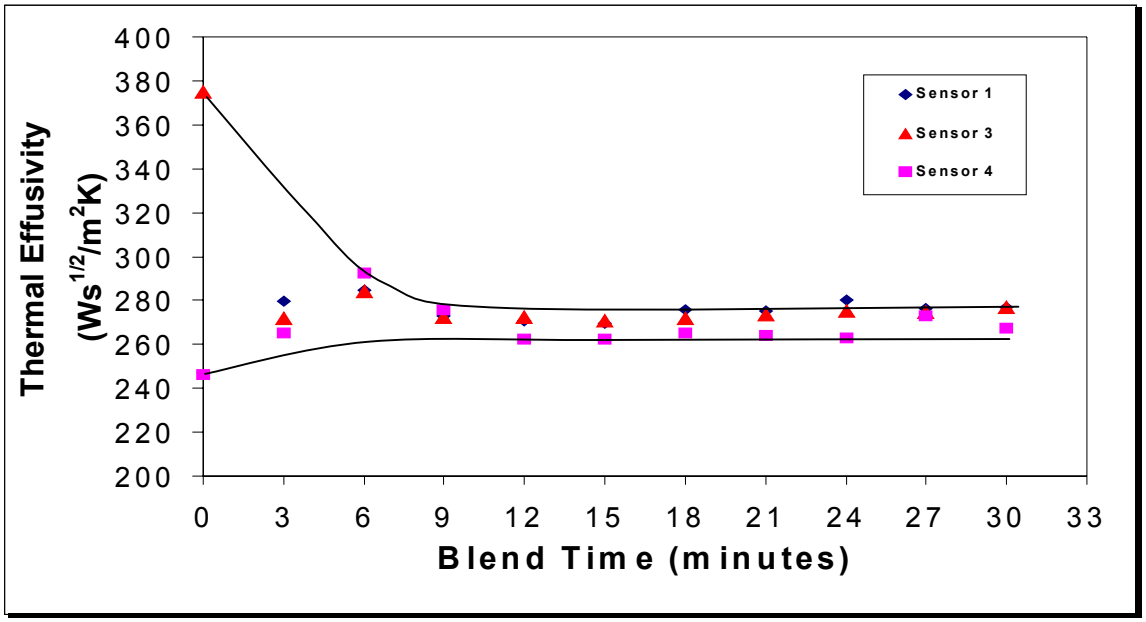
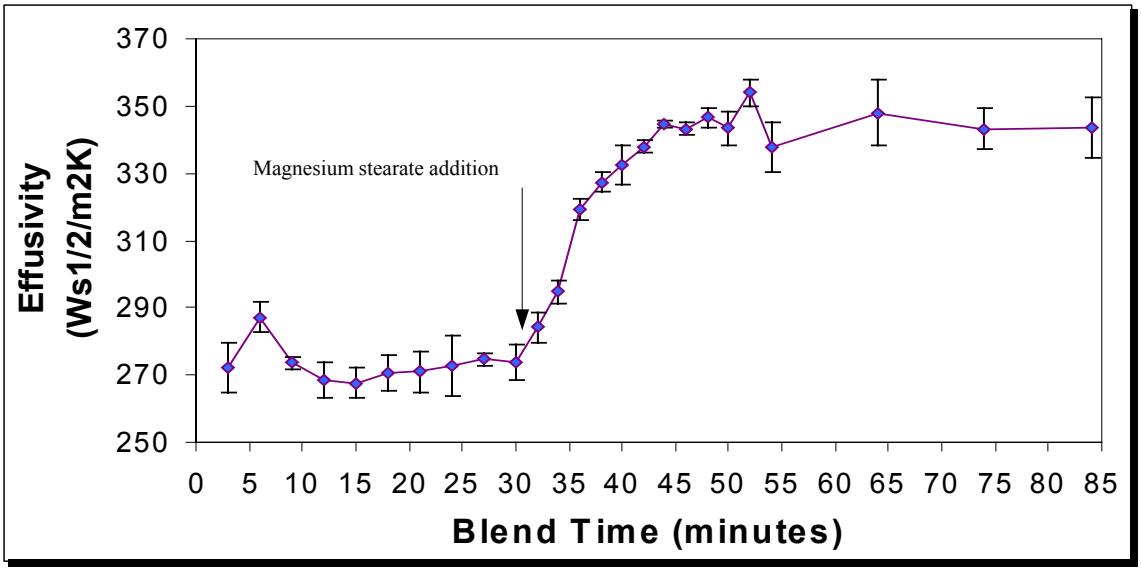


Figure 3 - Influence on effusivity of the addition of magnesium stearate



Conclusions

These preliminary results indicate that thermal effusivity is an effective PAT tool for monitoring product uniformity on-line in a bin blending operation. The most favorable uniformity of the 2 component mixture is achieved after 9 minutes blending.

Lubrication blend data confirms the "magnesium stearate effect" on the thermal effusivity of powders in which lubrication of the blend decreases the interspatial air between particles and thereby causes an increase in average blend effusivity. Analysis of blend effusivity during lubrication could potentially assist in identifying uniform blend lubrication and over lubrication states. Further testing and correlation with compression test data should be able to evaluate this potential application.

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