A NOVEL TECHNIQUE FOR DETERMINATION OF REAL TIME BLEND UNIFORMITY USING THERMAL EFFUSIVITY.

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Abstract

Purpose. To introduce a new technique for monitoring powder blend uniformity in a manner that allows on-line control. The existing blenders can be retrofitted to allow for real time monitoring without removing material from the blender.
Methods. This technique is based on heat transfer properties, specifically effusivity. Effusivity combines thermal conductivity, density and heat capacity. Effusivity is dependent on the material and changes during the blending process. The blending end point is reached when samples from different positions in the blender gives minimum variability. Effusivity was measured non-invasively with a test time of 2 seconds.
Results. An example of output below shows the ability to detect convergence to a uniform blend for a commercially available product. The first sample drawn at 2 minutes had a large scatter in the results due to the non-uniformity that existed. As the time progresses toward 15 minutes, the repeatability improves as an indicator of the uniformity.
Conclusions. Variation in effusivity measurements in multiple locations is a powerful and simple method to monitor blend uniformity.

Introduction

Powders are blended together for pharmaceutical product manufacture and the blending time is critical to the quality of the product. Typically four or more individual components are added from the top into a blender and the blending process begins. Ideally, the rotation or mixing process stops when the mixture is uniform (typically after 10-45 minutes) but there is currently no method to detect uniformity during the blending process and, as such, the true optimum end point is rarely realized. If blending is excessive, there is potential for the individual components to segregate based on particle size or density.

Blend uniformity is a function of the formulation as well as the mixing or blending process. Once the formulation is optimized from a theoretical process stand point, blend uniformity must be validated during manufacture of pilot batches and scale up. The validation process usually involves stopping the blender, extracting a sample and analyzing for active ingredient content. After a blend time has been derived and adopted in production, it is typically only reevaluated if poor content uniformity (on the

tablets) is detected. Such variations from the determined ideal blend time could be due to several factors some of them include, environmental temperature, humidity, feedstock grade, component and particle size distribution. By moving the uniformity monitoring back to the blender, the goal is to catch these issues early and better control the process.

In addition according to an Aug'99 FDA Guidance for the Industry, the FDA recommends that information submitted to support applications must include in-process controls to determine blend uniformity of the drug product. The guidance further recommends an acceptance criteria of 90.0 % to 110.0 % with a RSD of not more than 5.0 %.

The work presented in this study evaluated a novel innovative thermal analysis technique, which utilizes measuring the effusivity of individual components an the blend during the blending process to determine its applicability to differentiate between powder mixtures on the basis of uniformity. The technique was evaluated because of its potential ability as a non invasive tool that can monitor the blend uniformity, real time during the blending process.

Materials & Method

A formulation under development was used in this study. The formulation was a directly compressible formulation that consisted of a mixture of 8 individual ingredients. For the purpose of this study an 18 Kg. batch was mixed in a 1 cu.ft. "V" blender. Samples from the blender were withdrawn at predetermined time intervals of 2, 5, 10, 15, 30 and 60 minutes. At each time point samples were withdrawn from the left top and right top of the "V" blender and effusivity measured for each in triplicate.

Thermal Inertia (or Effusivity):

The thermal inertia of the samples was measured using a Mathis Instruments TC Probe™. This instrument is an interfacial device that contacts and detects heat flow from the same side of the sample. The rate of heat transfer from the instruments heating element is a function of the thermal effusivity. Effusivity is sensitive to composition because materials differ in value from 5 $Ws^{½}/m^2K$ for air to several thousand for advanced composites. The underlying principle is that if A and B have different effusivities, then the desired or undesired mixture properties can be measured.

$$Effusivity \; ? \; \sqrt{k ? c_p}$$

$$Where:$$

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

$$? \; ? \; density \; (kg / m^3)$$

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

Effusivity measurement procedure:
The powder sample was placed in a weigh boat, the Probe™ sensor was inverted and placed in contact with the powder and a weight of 1000 g was placed on top of the probe. This weight ensures a good contact between the sample and the Probe™. The sample was tested with a 10 second heat input duration. Additional experiments carried out later confirmed that a 2 second heat input duration also gave consistent results.

RESULTS AND DISCUSSION:

Component Sensitivity

Each point on the plot in Figure 1 is the result of triplicate tests conducted on one sample. The triplicate tests had an average relative standard deviation of 0.6%. Multiple aliquots from the same lot of raw material when tested gave a variance of under 1.6%.

The two color/die components were indistinguishable because both of them were aluminium lakes, but the next closest effusivity value for flavor was 225% higher. The effusivities spanned from 180 to over 600 $Ws^{½}/m^2K$ which indicated that the effusivity of

the blend of these eight components would be sensitive to uniformity. Each formulation will vary in its sensitivity to effusivity as a measure of blend uniformity. Once components are tested on their own, the expected sensitivity of the blend will be a function of the amount of each and the range of effusivity values.

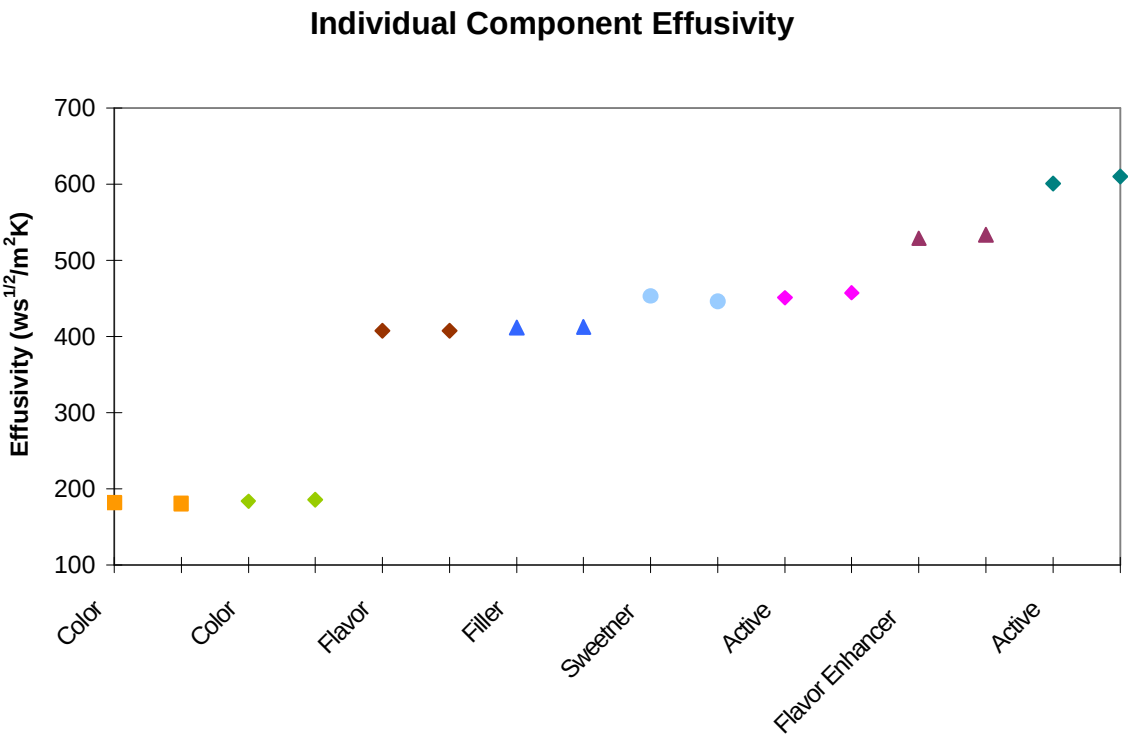

Figure 1: Individual Component Effusivity

Inter lot variability

Table 1 below gives the effusivity measurements for twenty commonly used pharmaceutical excipients. The mean given represents the average of six individual measurements on each of three lots of raw materials. The RSD for effusivity measurements is below 3 % indicating good reproducibility between lots of the same raw materials.

Table 1

Inter lot variability for commonly used pharmaceutical excipients

	Mean of 3 Lots	SD	RSD		Mean of 3 Lots	SD	RSD
Avicel 101	369.21	2.14	0.58	Prosolv 50	319.79	2.48	0.78
Avicel 102	353.08	1.20	0.34	Prosolv 90	253.08	7.49	2.96
Avicel 103	333.79	1.71	0.51	Emcocel 15	297.08	2.24	0.75
Avicel 105	335.67	0.38	0.11	Emcocel HD 90	433.51	2.32	0.54
Avicel 112	382.04	2.16	0.56	Emcocel 50 M	298.93	6.59	2.2
Avicel 200	355.22	1.70	0.48	Emcocel 90M	265.91	8.46	3.18
Avicel 301	364.73	1.72	0.47	Emcocel 90 XLM	306.32	2.16	0.71
Avicel 302	448.78	1.75	0.39	Emcocel LP 200	229.72	1.46	0.63
SuperTab	446.38	1.18	0.26	Emcompress	122.78	0.36	0.29
Acdisol	308.04	3.00	0.97	Emdex	192.69	3.62	1.88

Blend Time

Figure 2 zooms in on the first 15 minutes of blending and shows the six individual results rather than the average. The first sample drawn at 2 minutes had a large scatter in the results due to the non-uniformity that existed between the samples. As the mixing continues the blend becomes more uniform and hence the effusivity measurements for the samples are all close together. Figure 3 further illustrates this theory. This figure has a plot of standard deviation between the 6 measurements verses time. The lowest SD at 15 minutes indicates that the blend is most uniform at this point.

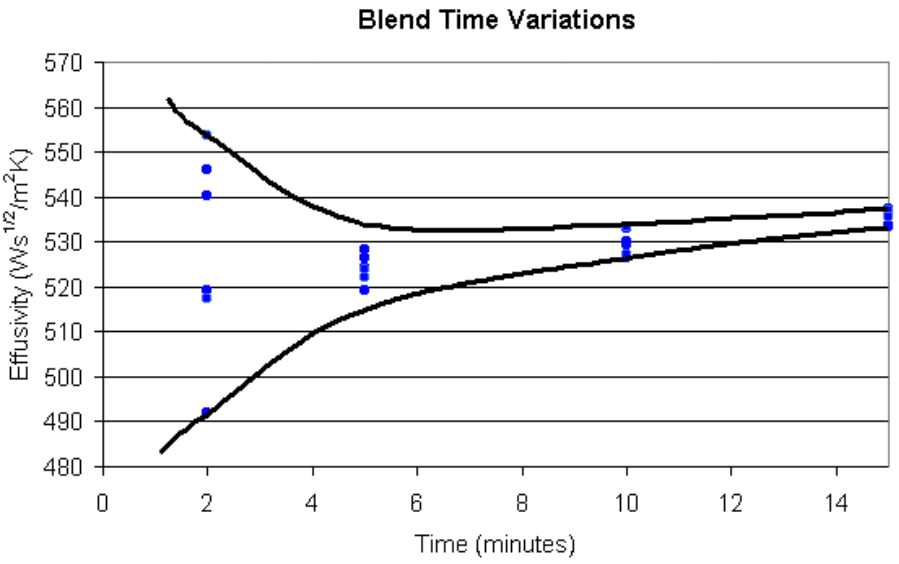

Figure 2: Blend Time Variations

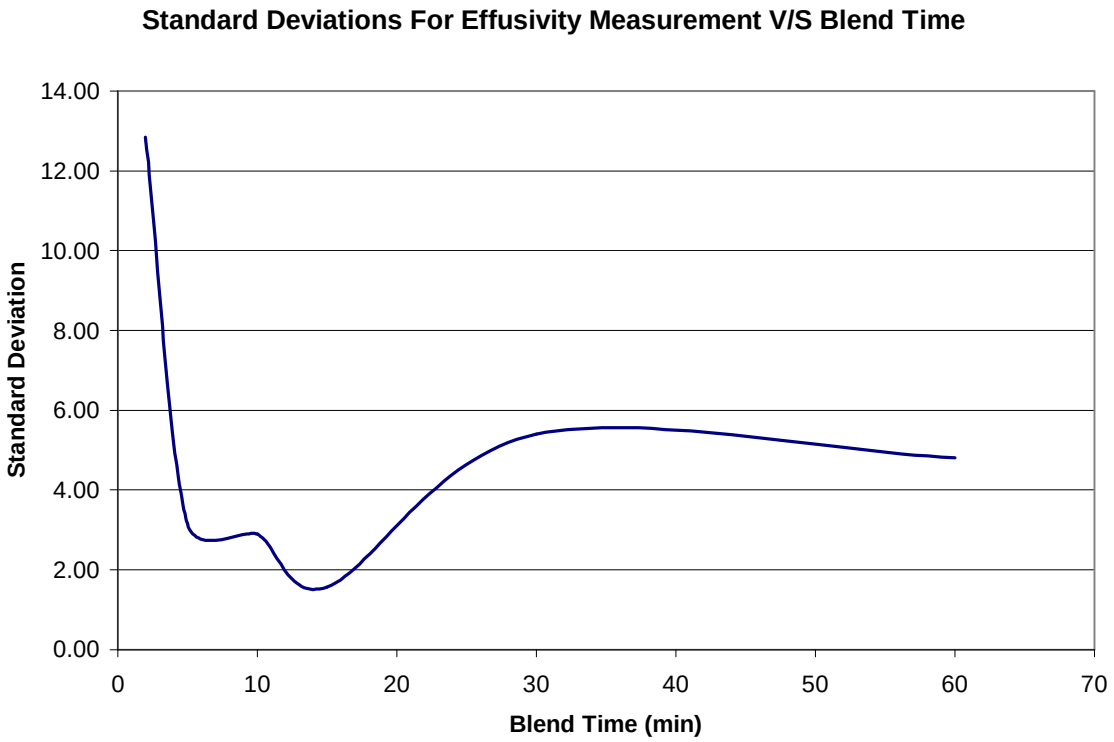

Figure 3: Standard Deviation For Effusivity Measurement V/S Blend Time

Conclusion:

This study confirms that thermal effusivity of a raw materials can be measured and that the measurements are within close tolerance and are reproducible. This study confirms that for blends that contains individual components with wide range of thermal effusivity, this new technique for the determination of blend uniformity can be used. Additional work is being carried out at Mathis Instruments to develop a TC probe™ that can be mounted on the blender and there by enable a continuous online measurement of thermal effusivity.