

# Monitoring Blend Uniformity with Effusivity

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The authors describe the measurement of the effusivity of blended and unblended commercial pharmaceutical formulations to

effectively differentiate between materials and then to determine if the effusivity changed with blending time. Eight components of a commercially available formulation were tested to determine if their effusivity values were unique enough to permit them to be distinguished. Two aliquots were tested, and the variance between the two was  $<1.6\%$ . The effusivity values indicated that the blend of the eight components was sensitive to uniformity. The eight components then were blended and samples were extracted at times ranging from 2 to 60 min. The results, when compared with assay results from the drug manufacturer, showed excellent agreement in terms of uniformity determination.

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When powders are blended during drug production, the blending time is critical to the quality of the product. Typically, four to six powder components are added into the top of a blending machine. Ideally, the rotation stops when the mixture is uniform, usually after 10 to 30 min. However, no method currently exists that detects uniformity during the blending process, and as a result the true optimum endpoint rarely is realized. If blending is excessive, then the particles will segregate (demix or deblend) on the basis of particle size and mass. In addition, temperature increases that occur during blending can damage some of the sensitive components and eliminate the potential for continued blending to return the mixture to a homogenous state.

Blend uniformity is a function of both the formulation and the mixing action. Once the formulation is optimized from a theoretical process standpoint, blend uniformity then must be validated during piloting and scale-up. Validation involves stopping the blender, extracting a sample, and analyzing the active-ingredient content. After the blend time has been derived and adopted in production, usually it is reevaluated only if poor content uniformity of the tablets has been detected. Variations from the determined ideal blend time result from the influence of factors such as environmental temperature and humidity, feedstock grade, and component particle distribution and blender type, all of which may vary from batch to batch. By moving the uniformity monitoring back to the blender phase, these issues can be identified early and then be controlled.

FDA wants to ensure that pharmaceutical manufacturers stop the blending process when a homogenous mixture is obtained. From FDA's perspective, poor uniformity poses potential threats to public health. From a manufacturing perspective, poor uniformity generates unacceptable amounts of discarded product, resulting in a significant loss of revenue. Thus FDA drafted a regulation for abbreviated new drug applications that established acceptance criteria for blend uniformity analysis before the final preparation of a drug formulation (1).

This article examines a relatively new thermal-analysis technique for effusivity to determine if it can be used to differentiate between powder mixtures on the basis of uniformity. The technique was evaluated because of its ability to be placed on the blender for in-process control should the results indicate

the method's ability to differentiate on the basis of uniformity.

## The experiments

### Materials and methods.

Eight individual powder components of a commercially available formulation were evaluated. Several grams of each material were deposited into individual vials. Blends that comprise the eight components then were selected. The powders were mixed in a V-blender and sampled at times ranging from 2 to 60 min.

**Thermal inertia (effusivity).** The thermal inertia of the samples was measured using a TC Probe (Mathis Instruments, Fredericton, NB, Canada) (2). 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 instrument's heating element is a function of the thermal effusivity, as demonstrated in the following equation

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

in which  $k$  is the thermal conductivity ( $\text{W/m} \times \text{K}$ ),  $\rho$  is the density ( $\text{kg/m}^3$ ), and  $c_p$  is the heat capacity ( $\text{J/kg} \times \text{K}$ ). Effusivity is sensitive to composition because materials differ in value from  $5 \text{ Ws}^{1/2}/\text{m}^2\text{K}$  for air to several thousand for advanced composites. The TC Probe is designed to test liquids, powders, and pastes. Blend uniformity, homogeneity, miscibility, concentration, voiding—delamination, and moisture content are examples of industrial applications that effusivity can measure. The underlying principle is that if  $A$  and  $B$  have different effusivities, then the desired or undesired mixture properties can be measured.

**Procedure.** The powder sample was placed in a container so that the material overflowed (see Figure 1). The TC Probe sensor was inverted and placed in contact with the powder, and a weight was placed on top of the sensor (1000 g was used, but later work indicated that this threshold weight must be optimized for various materials [3]). The weight and the overfilled container ensured that the packing was consistent. The sample was tested with a heat input duration of 10 s, although later work indicated that 2 s was sufficient.

## Results and discussion

**Phase 1: Component sensitivity.** Each point on the graph in Figure 2 represents the result of triplicate tests conducted on one aliquot from the vial. The triplicate tests had an average relative standard deviation (RSD) of 0.6%. The barely visible bars on the graphed results represent one standard deviation. Two aliquots were tested, and the variance between the two was  $<1.6\%$ .

The two color components were indistinguishable, but the next-closest effusivity value was 225% higher. The effusivities spanned

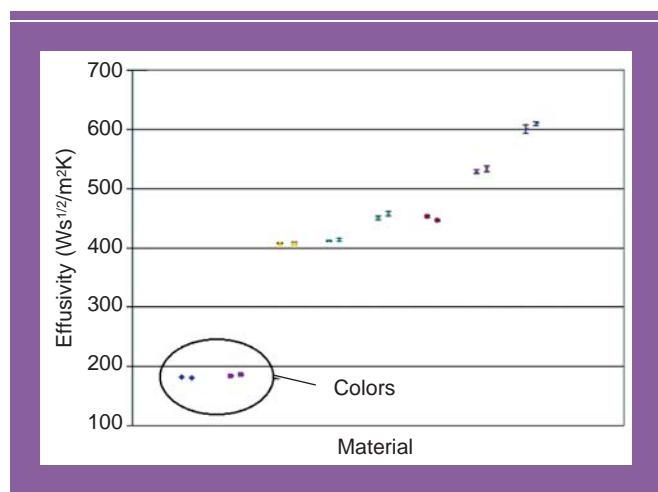


**Figure 1:** The TC Probe sensor is inverted on top of a container of powder sample.

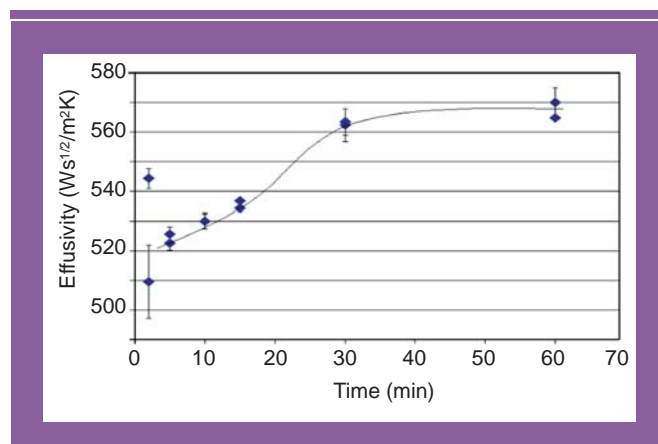
from 180 to  $>600 \text{ Ws}^{1/2}/\text{m}^2\text{K}$ , which indicated that the effusivity of a blend of the eight components would be sensitive to uniformity. Each formulation would vary in its sensitivity to effusivity as a measure of blend uniformity. Once components were tested on their own, the expected sensitivity of the blend would be a function of the amount of each and the range of effusivity values.

### Phase 2: Blend time.

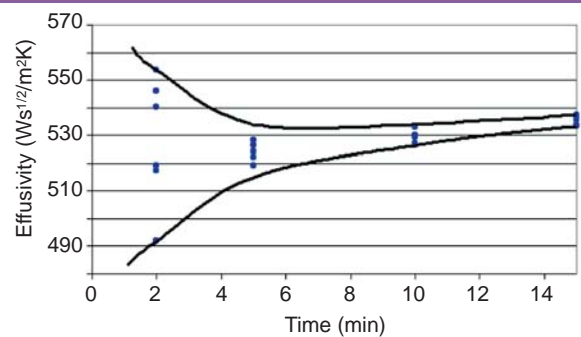
Figure 3 shows the results of testing the second set of samples extracted at various times from a commercial blender. As shown for the previously described method, each point on the graph represents the result of triplicate tests conducted on one aliquot from the vial. The triplicate tests had an average RSD of 0.6%, which agreed exactly with the component-testing phase. The



**Figure 2:** Component effusivity. The components of this product range in effusivity from 180 to 600, indicating that the product will be sensitive to blending effectiveness.



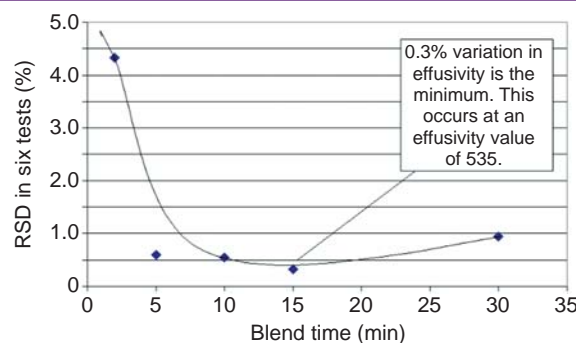
**Figure 3:** Blend-time variations. Effusivity increases with blend time and then plateaus. The error bars, which indicate one standard deviation, are large at the beginning as a result of nonuniformity.



**Figure 4:** Blend-time variations. The individual data points converge as uniformity improves. At 2 min, a 13% difference exists between the highest and lowest of six samples. This is reduced to 0.8% at 15 min.

trend in the average results is to increase and then level off. The increase is suspected to result from improved packing, which removes air from the volume of material tested. Two aliquots were tested, and the variance between the two ranged from 6.4% to as little as 0%. This variance is the significant portion of the results.

Figure 4 represents the first 15 min of blending and shows the six individual results rather than the average. The first sample, drawn at 2 min, had a large scatter in the results because of



**Figure 5:** Minimization of scatter. When the RSD of the six data points is plotted, the minimum at 15 min is 0.3%. The precision is representative of a uniform blend.

the nonuniformity that existed. As the blending time progressed toward 15 min, the repeatability improved as an indicator of the uniformity. This outcome also is shown in Figure 5. The minimum indicates a uniform blend.

### Future work

Further study of other formulations must be performed to confirm the findings described in this article. In addition, study must be conducted to determine the influence of grade, particle size, temperature, and humidity on the effusivity results. This work has begun within a blend uniformity group that comprises pharmaceutical manufacturers and blending equipment OEMs. The work is necessary to support the validation of the effusivity technique for blend uniformity measurement. Once validated, effusivity testing can be conducted in the blender by placing the sensors at strategic locations as an easy retrofit.

### Conclusion

The TC Probe represents a fast nondestructive method to evaluate powder-blend uniformity in an off-line manner for the materials investigated. The method has the attributes to warrant further study to determine the suitability for on-line testing to address FDA requirements.

### References

1. *Code of Federal Regulations*, 21 CFR Part 10.90(b).
2. <http://www.tcprobe.com>.
3. C. Chandler et al., "A Novel Technique for Determination of Real-Time Blend Uniformity Using Thermal Effusivity," to be published in the Proceedings of the 2001 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition, Denver, CO, 20–25 October 2001. **PT**