Real Time and Noninvasive Monitoring of Dry Powder Blend Homogeneity

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One of the most common unit operations in preparation of pharmaceutical solid dosage forms is the physical blending of the active drug substance with one or more excipients. The end point of this process is material homogeneity as measured by sampling and off-line analysis of the powder. Removal of samples is currently done with a sampling probe called a thief to withdraw samples from different locations of a blender. A sample thief is a probe designed to extract and collect small volumes of powder from a chosen representative cross-section of a blender. The resulting samples are then assayed using the same methods used to analyze the finished product. Content uniformity is established if the drug content of the samples conform to predetermined criteria (Berman and Blanchard, 1995; Muzzio et al., 1997). This method is influenced by the skill of the operator and often provides false representation of the sample due to desegregation and disruption of the powder bed during sampling and transport. Thus, both sampling and analytical errors are likely to incur in these procedures (Berman et al., 1996; Harwood, 1964; Harwood and Ripley, 1977; Schofield, 1976). Furthermore, sampling and off-line analysis causes long cycle time for operating and optimizing the blending process. Because blending validation is mandatory, due to the FDA's 1996 proposal to amend the good manufacturing practice regulations (FDA, 1996), commercial-batch final blends need to be tested routinely for blend homogeneity. For this reason, there is an opportunity for new technology to fulfill and perhaps replace the conventional thieving method with a more rapid and consistent technique of measuring blend homogeneity.

An interest in noninvasive monitoring of powder blend is seen in the work with near-infrared (NIR) spectroscopy to monitor blend homogeneity (Hailey et al., 1996; Sekulic, 1996; Wargo and Drennen, 1996). NIR relies on the use of a complex reflectance spectra specific to the substance analyzed and register extensive data analysis to reduce the spectra to a representative pattern for the mixture. This approach can provide a basis for monitoring the convergence of the expected aggregate spectra to establish blend homogeneity. Because reflectance NIR is usually a weak signal, except for water, there is a limitation to the sensitivity of this method for high potency drug formulations where drug content may be below 1% w/w in the mixture.

As an alternate optical method, we developed a laser-induced fluorescence (LIF) technique to monitor homogeneity of solid powder mixtures during component blending. LIF has been successfully deployed in diverse applications such as the automotive (Beer, 1995) and biomedical industries (Alfano, 1998) to monitor fluorescence of gases and liquids. Recently, Unger and Muzzio employed the LIF technique for quantification of mixing liquids in impinging jets (Unger and Muzzio, 1999). The operations of LIF involve irradiating samples at a suitable wavelength for excitation and evaluating the emission at another wavelength. An examination of many drugs in the marketplace suggests that a majority of them are likely to fluoresce when excited at the proper wavelength. Hence, there is a broad opportunity for employing LIF for monitoring dry powder blend homogeneity of pharmaceutical products. The analysis is rapid and usually on the order of microseconds. If a continuous light source is used, then the limit to data acquisition is the limit of computing speed. This rapid, on-line method allows one to examine quickly, in real time, the details of blending kinetics, and thus the effect of blending conditions, such as blender type, physical particle characteristics, and order of component addition.

The primary goal of this research is to develop a method to implement both process and product verification in real time for blending of the dry active pharmaceutical ingredient (API) with excipients. It is expected that success will facilitate process development and validation, open the possibility to reduce cycle time by eliminating the need for routine off-line analysis of blend homogeneity, and further assure product quality by measuring component homogeneity in a way that

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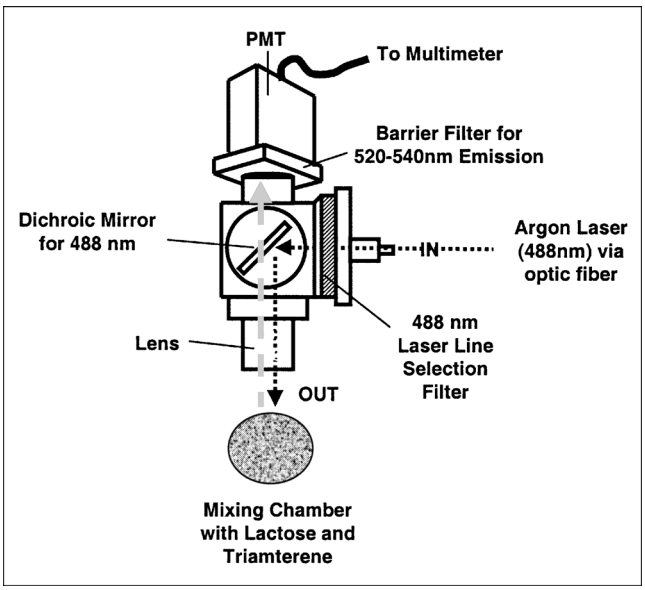

Figure 1. LIF sensor.

avoids the possibility of sampling error. There is also the benefit of permitting better equipment utilization by shortening cycle time and reducing labor costs associated with this unit operation. Although the work here described processing of pharmaceutical powders, this technology is applicable for all types of powder mixing processes in other industries.

Experimental Studies

LIF sensor

The sensor (Figure 1) uses an argon laser as the excitation light source (Omnichrome Air Cooled Argon Laser Model 532). The laser beam is directed into a fiber-optic cable connected to the Photosensor Module containing the lens and the detector (Hamamatsu HC120 Photomultiplier Tube). Inside the photosensor module, a dichroic mirror (Omega Optical 505DRLPO2) reflects the laser beam at 90 degrees to the sample. The fluorescent signal that is emitted from the sample is collimated by the lens and passes through the dichroic mirror and an emission filter (Omega Optical 530DF30) to the detector. Signals are converted to voltage and recorded by a multimeter (Hewlett-Packard 34401 A), which is interfaced to a computer via the RS-232 and hyperterminal. Reflected light (at 488 nm) is prevented from reaching the detector by the dichroic mirror and the emission filter.

Materials

Triamterene (2,4,7-triamino-6-phenylpterine) is the active pharmaceutical ingredient (API) used in all experiments. It is an oral diuretic and antihypertensive agent typically formulated as Dyazide capsules and is a gift from Smithkline Beecham. This API is a cohesive powder of particle size 10–30 μm and bulk density of 0.3 g/cc. The solid-state fluorescence spectra of triamterene is obtained at its tap density using front-face optics in a FluoroMax-2 (ISA Jobin Yvon-Spex) equipped with modified Czerny-Turner spectrometers and DataMax software. When excited at 488 nm, triamterene produced two distinct emission peaks at 526 nm and 561 nm. Direct compaction anhydrous lactose (Sheffield Products, New York) of a mean particle size of 100 μm and bulk density of 0.6 g/cc is used as the primary bulk filler for all subsequent blending studies.

LIF sensor operation parameters

For instrumentation optimization, it was essential to explore parameters to maximize the measured signal over the background. We would explore the effect of sample distances, sample angles, laser power, detector sensitivities, and process variable such as bulk density during powder blending. Signal responses to sample distances from the sensor were determined with triamterene in a 1-cm quartz cuvette at 60 μW laser power and detector sensitivity at 300 V. The range of the measured distance was ± 15 mm from the focal distance of the lens. Evaluation of sample angle variation effects was conducted at $\pm 10^\circ$ intervals from a reference point 90° to the laser beam. Laser-power output was reduced from 60 μW to 16 μW using a neutral filter to determine the effects on the API signal over the background with respect to detector sensitivity using a 50-V stepwise increase from 350 V up to 700 V. Laser-power output was measured at the start of each set of experiments and may vary due to changes in alignment to the optic fiber.

Process variables

Powder bulk density variations were achieved by gradual compaction of a fixed sample of 10% w/w triamterene powder mixture. LIF signal response was determined corresponding to each change in density. Blend homogeneity experiments were conducted in a 20-mL glass microblender with 60% filled capacity (~ 8 g) of a formulation containing 10% triamterene in anhydrous lactose. This is a typical case for mixing of a low dose and fine cohesive powder with a fast-flowing bulk filler. All blends were run for a duration of 20 min at 20 rpm and raw data were acquired as distinct data points and presented without further manipulation. The laser beam was directed either one-third from the top or bottom of the powder level to determine consistent signal stability. An infrared switch was used to control and synchronize data acquisition only when powder was present.

Powder mixing kinetics

The same triamterene-lactose formulation as just cited was used in two separate experiments to demonstrate the sensitivity of the LIF sensor toward the kinetics of mixing when the API was either placed at the top or bottom locations of the blender. Mixing proceeded under conditions identical to these just given.

Monitoring of the mixing process of formulations of different powder concentrations

Several batches containing 10%, 5%, 1%, 0.5%, 0.1%, and 0% triamterene–lactose formulations were prepared as earlier. Their blend kinetics profiles and homogeneity endpoints

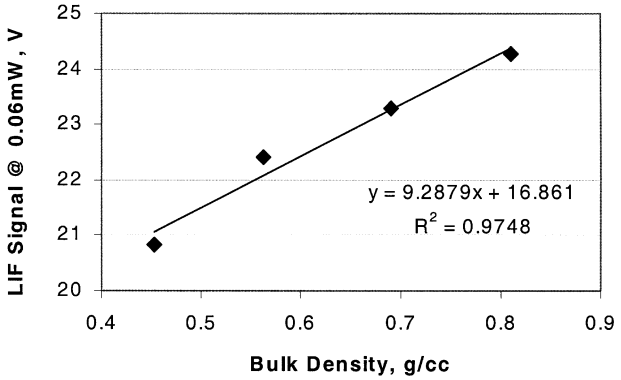

Figure 2. Effects of powder bulk density on LIF signals.

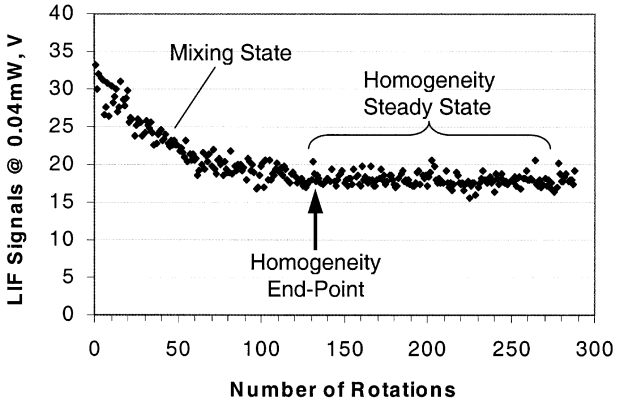

Figure 3. Synchronized LIF data acquisition for blending a 10% w/w triamterene/lactose mixtures.

were monitored in the usual manner. Triamterene was added at the bottom (near the laser beam) in all cases, so that we could track the reduction in signal even at the low drug powder concentration.

Results

LIF operation parameters

The LIF signal response of the sensor was maximum at the focal length of the lens with a first-order exponential decay in signal $\pm$ from the focal distance. Since fluorescence emission is radial in nature, a $\pm 30°$ tolerance to the incident angle of the excitation beam to the sample was observed without loss of signal. The fluorescent signal from triamterene saturated at a detector sensitivity of 400 V at 60-μW laser output power. Signal saturation was extended by reduction of the output power to 16 μW with the aid of a neutral-density filter. The signal to background fluorescence response was more favorable at lower laser power and lower detector sensitivity.

Process variables

Changes in bulk density of the powders in the blender corresponded to a proportional change in LIF signals. For an evenly mixed sample, there will be more API for each unit surface volume excited by the laser beam with increasing packing density (see Figure 2). This suggested that bulk-density variation during the blending process may elevate background noise. Hence, it is favorable to consider monitoring blend homogeneity within the blender at a location where bulk-density changes were minimal. Synchronized data acquisition was made at the selected location of the blender when powder was present and where the bulk density remained relatively constant. Data collected at a position one-third the distance from the bottom of the powder bulk (Figure 3) resulted in a clean first-order mixing kinetics profile.

Powder blend kinetics

Distinct differences in the early mixing phases were demonstrated when the API was loaded at different locations of the blender. When the API was loaded at the bottom, the initial signal was high due to close proximity of the LIF sensor near the bottom. When loaded on top of the blender, the initial signal was low since the sensor was responding only to lactose during the first few rotations. In both cases, the LIF signals reached an equilibrium state of blend homogeneity at the same value with signal deviations of less than 5% (see Figure 4).

Monitoring of the mixing process of different powder concentration formulations

Blend homogeneity was reached after 70 rotations for all the triamterene powder concentrations investigated, with each endpoint at signal values proportional to their API contents. An example of the sensitivity of the LIF technology is illustrated in Figure 5 for blending profiles of API contents of 0.5%, 0.1% and 0.05%. The results are summarized in Table 1, where the relative standard deviation for all mixing experiments was less than 5%.

A correlation curve generated from these data was fitted by a polynomial equation with R^2 of 0.9984 (see Figure 6). The nonlinearity of the correlation is believed to result from saturation of the PMT response at the higher concentration level. Linearity was observed at the lower concentration ranges from 0 to 1% triamterene with an equation of $y =$

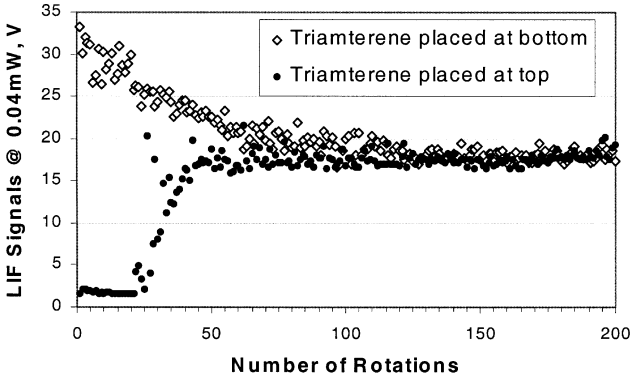

Figure 4. Sensitivity of LIF blend kinetic profile to the location of adding active pharmaceutical ingredient in the blender.

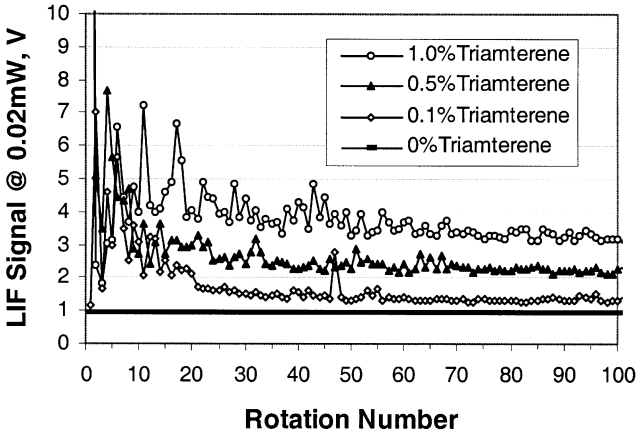

Figure 5. Monitoring of low-dose blending profiles.

Table 1. LIF Mixing Endpoints

% w/w API Concentration	10%	5%	1%	0.5%	0.1%	0%
LIF Signal, Volts	12.25	8.58	3.29	2.25	1.34	0.96
Std. Deviation	0.30	0.29	0.12	0.07	0.05	0.01
% Deviation	2.42	3.38	3.70	3.08	4.00	0.54

$2.212x + 1.0493$ and an R^2 of 0.9947. Endpoint blend homogeneity was determined at as low a triamterene powder concentration as 0.1% (1:1,000).

Discussions

We have optimized the design and operating parameters of the LIF sensor. The laser power source, the detector sensitivities, and the excitation wavelength can independently control signal intensity. The laser output power needs to operate at levels below the saturation limit that is necessary for quantitative correlation of the fluorescence signal to the amount of compound present.

The primary process variables that impacted the signal quality are void volumes and differences in bulk densities during the mixing. These issues are handled effectively with the introduction of an infrared on-off switch to synchronize data acquisition only at positions when powder is present and by selecting a location for data acquisition close to the bottom of the vessel where the powder bulk density is relatively constant.

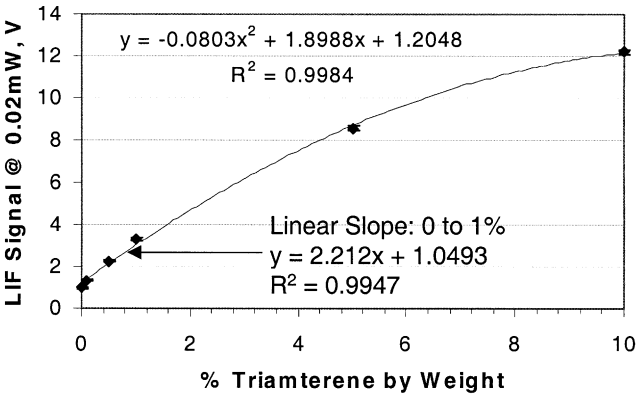

Figure 6. Correlation of LIF signals to triamterene concentration at mixing endpoint.

Each API concentration provides a unique mixing profile with endpoints of less than 5% deviations. A correlation of the LIF signal at homogeneity to the API concentration was determined to a triamterene powder concentration of 0.1%. This low level of detection demonstrated potential usefulness to monitor the blending process in the manufacture of high-potency drug formulations.

In all of the cited experiments, data were obtained only from one location during each rotation. We made the assumption that monitoring one location of a mobile powder mixture throughout the process would closely represent the bulk composition due to the constant turnover of powder at that location. This was clearly demonstrated in Figure 4 by the experiment on blend kinetics where in one experiment, the active ingredient was placed on the top in the blender. In the second experiment, the same formulation was used where the active ingredient was placed at the bottom of the blender. Both experiments were mixed similarly with LIF monitoring at a fixed location of the blender. Although the mixing kinetics was different during the mixing stage, both experiments reached the same homogeneity steady state, indicating good turnover of powders within the blender.

This LIF technology can be applied to all types of mixing procedures, provided that the critical component of that mixture contained a measurable fluorescent signal at the concentration of interest. It can be used to study and monitor powder mixtures irrespective of the physical characteristic of each particle. Blend homogeneity is established when the LIF signal at steady state is the same from one turnover of powder to the next for each mixing rotation. The monitoring process is considered as a snapshot of the powder content at each rotation. The signal derived from each snapshot is a quantitative representation of the number of fluorescent particles distributed within that area of analysis. Changes in that number of fluorescent particles within that area of analysis will result in changes in fluorescence signals that indicate a nonhomogeneous state. Any presence of a dead spot would result in an overall change in the API concentration. This change in concentration would result in a change in signal when steady is established.

The application of LIF to noninvasively monitor blend homogeneity during dry pharmaceutical powder mixing allows one to acquire real-time data on kinetics and the endpoint of mixing. This approach eliminates errors introduced by the use of thief sampling and off-line assay techniques.

Acknowledgments

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