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Nondestructive and On-line Monitoring of Tablets Using Light-Induced Fluorescence Technology

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Chee Kong Lai,[1] Aina Zahari,[1] Bayen Miller,[1] Wendy E. Katstra,[2] Michael J. Cima,[2] and Charles L. Cooney[1]

[1]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139
[2]Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139

ABSTRACT

A system using light-induced fluorescence (LIF) technology was developed for rapid and nondestructive analysis of active pharmaceutical ingredients on tablet surfaces. Nonhomogeneous tablets with defined layer of active ingredients were made by 3-Dimensional Printing technology to determine penetration depths of the light source and the resultant fluorescence responses. The LIF method of analysis showed penetration to depths of up to 3 mm into tablets. A correlation between LIF signals from analysis of tablet surfaces and the total drug content of the respective tablets was established. This method of surface analysis was verified with UV spectrometric methods for the total drug content of each respective tablet. The results from a small sample population of tablets made from both homogeneous and nonhomogeneous powder mixtures established good correlation between LIF surface monitoring and total tablet content. The use of on-line monitoring of the individual tablet for surface content demonstrated consistent LIF profiles from simulated production rates up to 3000 tablets a minute. The instrument was also field tested successfully on a tablet analyzer.

KEYWORDS: pharmaceuticals, tablets, surface analysis, production profile, PAT

INTRODUCTION

Typically, small batch subsets of core tablets are sampled following production and analyzed off-line for batch-specific characteristics such as unit dosage, content uniformity, dissolution, and other properties. On a laboratory scale, these tablets are pulverized, and the resulting powder is subjected to chemical, chromatographic, and spectrometric tests. This process is not only time consuming, but the solid dosage forms are destroyed. Tablets from the batch of formulation will normally be completed before the results of quantitative analysis for content uniformity of the tablets are known. If the analysis on unit dosage or content uniformity fails to satisfy the acceptance criteria, then no remedial action can be taken except to regrind, remix, and repress the tablets.

Hence, it would be useful if a nondestructive analysis method were available as it would provide an additional dimension for tracking and characterizing historical and shelf-life properties of the solid dosage forms. With the improved production rates of tablets (>3000 tablets per minute) and the development of higher potency drugs (eg, less than 1% active pharmaceutical ingredient (API) wt/wt), there is a need for both faster and more sensitive monitoring technology for on-line analysis. A portable light-induced fluorescence (LIF) sensor that can perform quantitative analysis of solid samples and surfaces rapidly and nondestructively has recently been described by Lai et al.[1,2] By examination of the vast sources of drug-like chemical structures, a large proportion of pharmaceutical active ingredients are predicted to fluoresce when excited at the appropriate wavelength,[3] while most excipients such as calcium phosphate, lactose, microcrystalline cellulose, starch, and many others remain nonfluorescent. A review of the chemical structures of the top 200 pharmaceuticals from the Rx Web site[4] also showed that greater than 60% of the compounds are potential candidates with fluorescence property. By a careful selection of excitation and emission bandwidth filters, specific concentration-dependent fluorescence signals can be quantitatively measured in a rapid fashion. From the fluorescence emission of the excited sample, information about the constituent makeup of the surface of the sample can be measured. Hence, a large number of tablets can be quickly and easily analyzed for content (eg, at a rate of 60 Hz or more), especially when the content of the active principle in the final dosage form is detectable by this method. This provides possibilities for determining content uniformity, not only from randomly drawn samples but also for the total tablet production batch using on-line monitoring. The analy-

Corresponding Author: Chee Kong Lai, Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139; Tel: (978) 486-9074; Fax: (815) 333-1946; Email: cklai@rcn.com

sis is nondestructive, and measurements as well as statistical calculations may be fully automated and good manufacturing practice (GMP) conditions maintained while samples are tested. This technique is expected to reduce both validation time and cost, and improve the quality of the test results.

Novel and innovative methods are being developed to fabricate pharmaceutical solid dosage forms to produce tablets containing potent drugs at a very low dose and in a more controlled and consistent fashion. Some examples of these methods involve deposition of the active ingredient by electrostatics[5] or by a 3-dimensional ink-jet printing technology.[6,7] In this article, we present studies on conventional tablets as well as those fabricated by the 3-Dimensional Printing (3DP, Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA) method. Some preliminary results on a laboratory simulation of on-line monitoring of tablets moving at up to 3000 tablets per minute are discussed.

MATERIALS AND METHODS

The LIF Sensor

The LIF portable sensor has been previously described in detail.[1,2] The light source is generated from a flashlamp (LS 1130-2, EG&G Optoelectronics, Montgomeryville, PA) with 125 millijoules maximum flash energy at 160 Hz (600 VDC) that covers an optical range from 190 to 1100 nm. Narrow light bandwidth of specific excitation wavelengths can be selected by the use of commercially available optical bandwidth filters (Omega Optical, Brattleboro, VT). The detector is a solid-state photomultiplier tube (PMT) and is a proprietary unit obtained from Hamamatsu Corporation (Bridgewater, NJ).

Fabrication of Compressed Tablet Wafers

Triamterene, the active pharmaceutical ingredient used in most of the studies, was obtained from GlaxoSmithKline (Philadelphia, PA). It is a highly fluorescent pharmaceutical powder, and its spectral properties have been previously described.[1,2] Standard triamterene powder formulations for direct compression were mixed in the same manner as described in the references.[1,2] A typical 300-mg tablet wafer was made by depositing the powder mixture into a square cardboard tablet holder (25 mm × 25 mm × 3 mm deep) with a 10-mm diameter circular cavity. Powder deposited in the cavity was compressed at 2000 psi between 2 stainless steel plates with a Carver hydraulic press (Carver Laboratory Equipment, Wabash, IN) to form a wafer of 2.5-mm thickness. In a similar manner, standard wafers comprising triamterene concentrations of 0.1%, 0.3%, 0.5%,1.0%, 2.0%, 3.0%, and 5.0% wt/wt were made. This method constituted a simple and rapid way of producing compressed powders for analysis. The tablet wafers were scanned at focal distance (17 mm) for maximum signal output. A correlation of LIF signal to surface content of the API was determined.

Tablet Fabrication Using 3-Dimensional Printing Technology

Cylindrical tablets were fabricated from circular horizontal layers with incremental thickness of 200 μm. The schematic for this process was described by Katstra et al[6] and Rowe et al.[7] The tablets used in this study contained 1 active-containing layer at different vertical positions.

Lactose powder first was distributed evenly on the tablet platform by the use of a rotation spreading bar hydraulically set to 200-μm gap spacing. During a second stage, active ingredients and/or a binder dissolved in ethanol were deposited on the powder surface. Depositions were done via very fine sprays with a minimum tolerance of 200 μm. The sprays move in an X-Y direction. The third dimension (thickness) was constructed by lowering the platform and spreading fresh layers of untreated lactose powder. Layers of spray patterns could be deposited in this way to form a 3-dimensional structure. By controlling the deposition of active pharmaceutical ingredient onto a specific layer, 3DP tablets were made with specific layers of a fluorescent ingredient deposited at different depths of each tablet.

These tablets measured 4 mm in height and were 10 mm in diameter. A layer of the fluorescent ingredient (approximately 200 μm) was deposited on each tablet. The fluorescent layer level differed from one tablet to the other by an increase of 400 μm in depth. Photographs taken under a UV lamp (displayed in **Figure 1**) showed the distinct layer of fluorescence from each tablet. These tablets were scanned with LIF from the top surface of the tablet at a focal distance of 17 mm.

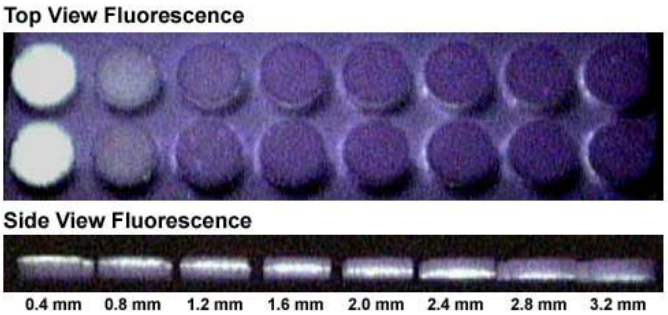

Figure 1. 3PD tablets with a specific layer of fluorescent ingredient deposited on each tablet.

Total Surface Content Recognition

Monitoring of total content uniformity requires recognition of the total content of each tablet regardless of the pattern distribution of the drug on the surface of the tablet. We constructed tablets with the same total concentration of the active pharmaceutical ingredient distributed specifically into different patterns on the tablet surface. These tablets were constructed using the precision of the 3DP technology that was discussed above. Specific patterns (shown in **Figure 2**) were initially designed using computer-aided design (CAD) software. Four uniform squares of 1-mm^2 each were designed to form 5 different patterns. Tablets with each pattern were printed in duplicates as described previously.

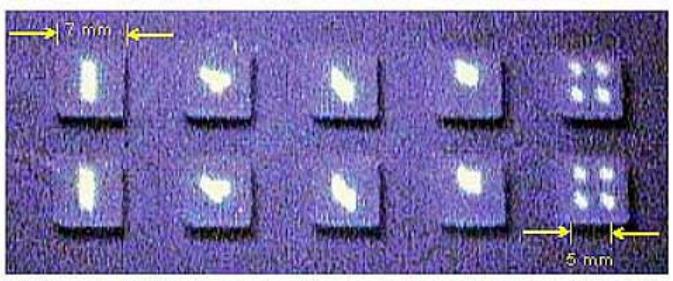

Figure 2. 3DP square tablets containing the same total drug content but with different surface pattern distribution.

The overall bulk of the "drug" in 4 designs was distributed around the center of the tablet. The pair of tablets shown on the far right of **Figure 2** had the active ingredients deposited at the 4 corners of the tablet. These tablets were scanned using LIF at 2 different beam sizes, one at 5 mm and the other at 10 mm. The 5-mm beam was generated at the focal distance (17 mm) between the tablet surface and the lens, while the 10-mm beam was generated off-focus at 50 mm away from the tablet surface.

UV Spectrometric Assay of Total Tablet Content

A UV calibration curve was generated from standard triamterene solutions. Each sample was dissolved completely in 95% formic acid (10 mL). The solution was filtered, and 5 mL was used for 10-fold serial dilutions with 10% formic acid for 3 iterations to reduce the absorption within 1 absorption unit. This is representative of triamterene concentrations between 0.000 125% and 0.001% wt/wt respectively. UV absorption was measured using a standard 1-cm quartz cuvette with a Hewlett-Packard 8452A diode array spectrophotometer (Hewlett-Packard, Palo Alto, CA). A linear calibration curve of $y = 824.77x - 0.0082$ with $R^2 = 0.9998$ was generated and used to determine total triamterene content of the individually dissolved tablets.

Fabrication of Regular Compressed Triamterene Tablets

Homogeneous powder standards containing various concentrations of triamterene in anhydrous lactose for direct compression were obtained, and tablets of these standards were made using a twin station semiautomatic tablet press by Carver (Carver Laboratory Equipment) at 2000 psi. Tablets of 10 mm in diameter and 4 mm in height were pressed at 50 rpm. The tablets averaged 320 mg in weight. These standards contained 4.75%, 3.22%, and 1.64% of triamterene in anhydrous lactose with 0.1% each of colloidal silicon dioxide and magnesium stearate. Ten tablets from each concentration were randomly chosen for surface scanning using LIF to generate a correlation curve. The tablet scanning distance of 50 mm was chosen to generate a 10-mm beam large enough for total coverage of the tablet surface. A filter set (XF22, Omega Optical, Brattleboro, VT) with excitation at 485 nm (bandwidth 22 nm), emission at 530 nm (bandwidth 30 nm), and detector sensitivity at 563-mV applied voltage was used. For determination of actual total triamterene content for each tablet, the respective tablets were weighed, dissolved in 10 mL of 95% formic acid, and then diluted 3 times at 10-fold dilutions with 10% formic acid. UV analysis of the filtered formic acid solutions was performed at 362 nm, and correlation curves for UV analyses were generated.

Fabrication of Unmixed Compressed Triamterene Tablets

Three batches of triamterene powders of concentration from 4.75%, 3.22%, and 1.64% described in the previous section were combined and added together into the Carver tablet press without prior mixing. This was an attempt to produce a failed batch of tablets that represented either an undermixed or segregated blend process with possible variations in the powder content uniformity throughout the tablet. Tablets were produced in the usual manner with this powder mixture. Fifteen tablets from this batch were randomly chosen for surface scanning with LIF using the procedure described in the previous section. LIF scan results were recorded. The individual scanned tablets were weighed and dissolved in formic acid; then UV analysis of the formic acid solutions was performed to determine the actual total API content of each respective tablet. The results were correlated to the surface scan obtained using LIF.

On-Line Monitoring of Simulated Tablet Production Profile

The speed and resolution of the LIF technology provides the possibility of examining individual tablets for the surface

content uniformity profile of the entire tablet production batch. Tablets of triamterene with known content in anhydrous lactose, described above in "Fabrication of Regular Compressed Triamterene Tablets," were used and placed on a rotating table of 42-cm diameter (**Figure 3**) to simulate monitoring of tablets during production at a tablet press.

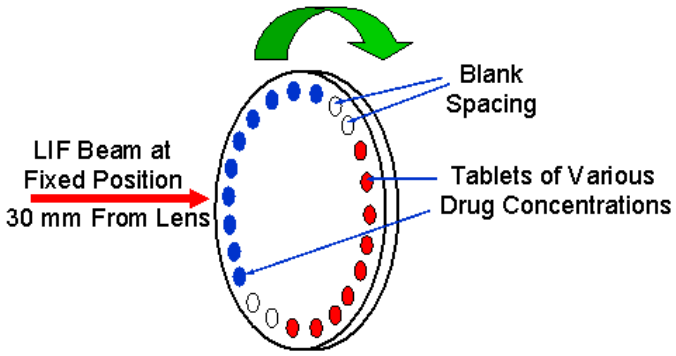

Figure 3. Illustration of a tablet analysis platform.

In the first experiment, a batch of 27 tablets at 4.75% wt/wt triamterene and a batch of 34 tablets at 1.64% wt/wt triamterene were placed on the tablet scanning platform. For each batch of tablets, the individual tablets were spaced 1 cm apart from each other. A blank space was allotted between the 2 groups of tablets. The LIF instrument was positioned to monitor at a fixed position at the circumference of the rotating table at a distance of 30 mm (beam size ~7 mm) between the lens and the tablet surface and with detector sensitivity at 620 mV. Monitoring of the tablets was conducted with continuous data acquisition mode at a flash rate of 25 milliseconds per strobe. The rate of rotation was increased from 5 to 25 rpm with a representative rate of 305 to 1525 tablets per minute.

In the second experiment, a batch of 40 tablets of 1.64% wt/wt triamterene and a batch of 70 tablets of 4.75% wt/wt triamterene were used. Each batch of tablets was placed next to each other in a continuous string with no spacing between them. The batch of 4.75% tablets was divided into 2 equal sections, where one of the batches was "spiked" with a few of the lower concentration tablets. A blank space was allotted between the 3 groups of tablets. The LIF instrument was set up as before with identical run parameters. Monitoring of the tablets was conducted with continuous data acquisition mode with a flash rate of 25 milliseconds. The rate of rotation was increased from 5 to 50 rpm with a representative rate of 550 to 5500 tablets per minute.

Implementation of LIF On-Line Tablet Monitoring on a Commercial Tablet Analyzer

A commercially available in-line tablet test system, the Autotest 4 from Dr. Schleuniger Pharmatron (Manchester, NH) was used to install the LIF instrument on-line to demonstrate feasibility in providing a content uniformity profile for a batch of tablets to the success of this test may demonstrate potential use with any other tablet analyzers and tablet presses. The placement of the LIF instrument on the Autotest 4 was chosen on the side of the discharge trough. At this location, the tablets were perfectly aligned as they discharged down the inclined plane with the aid of a gentle vibration mechanism. The primary objective of this experiment was only to demonstrate the mechanism and the ability of the instrument to readily adapt to a commercial tablet analyzer for monitoring tablet characteristics. A batch of commercial core tablet samples from Aventis Pharmaceuticals (Kansas City, MO) was used requiring a specific filter set (XF13, Omega Optical) with excitation at 405 nm (bandwidth 40 nm) and broad emission band from 460 to 640 nm.

The rate of discharge was adjusted to a flow rate of approximately 150 tablets/min with the LIF instrument at continuous data acquisition rate of 25 ms/strobe. The distance of tablet from lens was about 24 mm. **Figure 4** shows in more detail the spot from the LIF beam when it strikes the tablet.

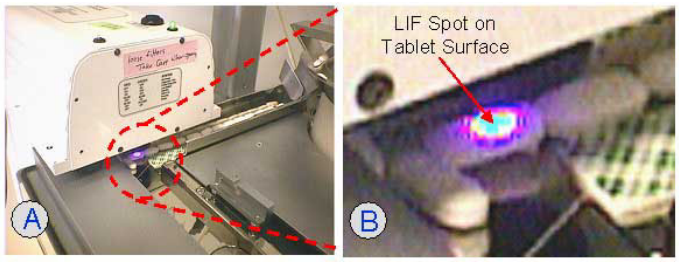

Figure 4. (A) A full view of the LIF instrument scanning the tablets as it passes by; (B) A close-up view of the LIF beam on a tablet.

RESULTS

Correlation of LIF Surface Scan Signals to Tablet API Concentration

The LIF-scanned results of tablet surfaces showed a correlation of the fluorescence signals to the known total concentrations of the respective tablets. This set of data (see **Figure 5**) fitted a nonlinear correlation curve typical for optical properties as described by Hargis.[8] Hence, linear correlation is usually characteristic only at the lower concentration range. In this case for triamterene, linear correlation can be

determined at concentrations below 2% wt/wt of triamterene.

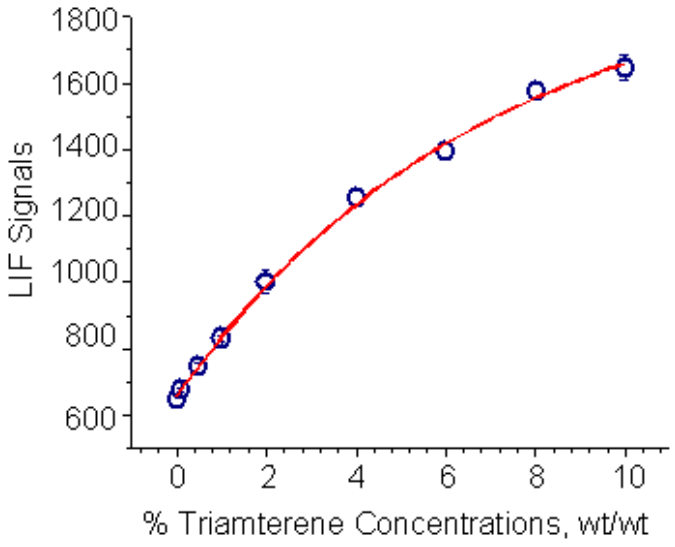

Figure 5. Correlation of surface LIF signals to tablet drug concentrations of tablet wafers. Excitation = 485 nm (bandwidth 22 nm); Emission = 530 nm (bandwidth 30 nm).

Penetration of LIF in Tablets Made by the 3DP Procedure

LIF scans of these tablets made by the 3DP procedure (**Figure 6**) showed that light penetration and the resultant fluorescence from the active layer of ingredient responded to at least 3 mm in depth. At 1 mm, response was 30% that of the surface. This response was similar to that for data obtained from layers of lactose powder packed at its bulk density.[2]

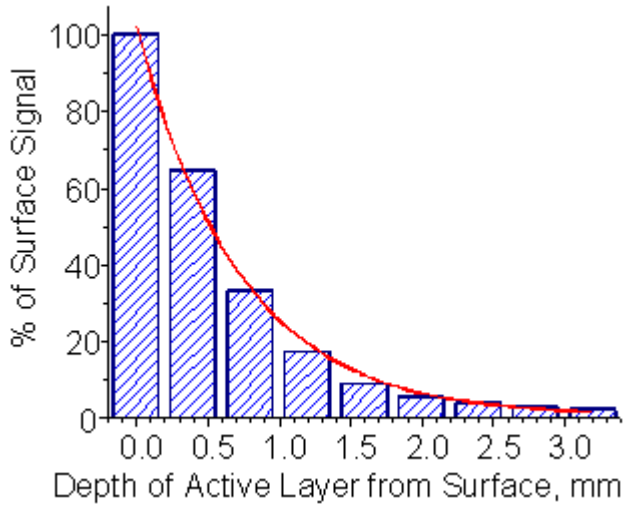

Figure 6. Penetration of LIF through 3DP tablets.

A comparison of the bulk density of the 3DP tablets and a conventional compressed tablet was determined by measuring the porosity using a mercury immersion technique (WEK, unpublished data, 2002). By this method, the conventionally pressed tablet was determined to be approximately one and a half times denser than the 3DP tablet. These responses were not surprising because of the different production methods. The porosity of the 3DP tablets was the same as the loosely packed powders because these tablets were not compressed but were "fixed" in place with binders. Hence, light penetration of a regularly compressed tablet is expected to be less than that of the 3DP tablets.

Total Surface Recognition

The 5 square tablets containing the same amount of active ingredient were distributed differently on the tablets as shown by the different patterns. **Figure 2** shows that in the first 4 designs, the active ingredients were distributed relatively close together at the center. Scanning of these tablets with either a 5-mm or a 10-mm light beam would be large enough to illuminate the active components on these tablets. As a result, comparable LIF signals were observed for both 5-mm and 10-mm light beam diameter, except for tablets No. 9 and No. 10 (see **Figure 7**).

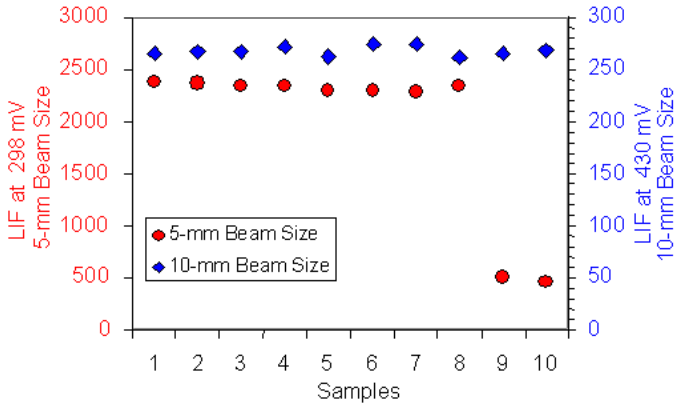

Figure 7. Scanning of 3DP patterned tablets with 5-mm and 10-mm diameter beam light source using the XF22 filter set. Excitation = 485 nm (bandwidth 22 nm); Emission = 530 nm (bandwidth 30 nm). For the 5-mm beam size, a detector sensitivity of 298 mV was used; for the 10-mm beam size a sensitivity of 430 mV was used.

Large differences in LIF signals for the pair of tablets, No. 9 and No. 10, were observed. Because the drug in this pair of tablets was distributed at the 4 corners of the tablets, the smaller diameter light beam (5 mm) could only partially illuminate some of the drug within the tablet. The partial excitation of some part of the total tablet results in a lower total signal. Increasing the beam size (to 10 mm) of the light source enabled total illumination of the total amount of drug

Table 1. Correlation of LIF Surface Scans and UV Spectrometry With Calculated Amounts of Triamterene in Tablets

	Triamterene Content 1	Triamterene Content 2	Triamterene Content 3
Calculated Values, % wt/wt Triamterene	4.75	3.22	1.64
LIF* Surface Scan, % wt/wt Triamterene	4.68 (RSD† 7.04%)	3.23 (RSD 6.41%)	1.61 (RSD 4.42%)
Total UV Spectrometry, % wt/wt Triamterene	4.75 (RSD 4.46%)	3.22 (RSD 4.87%)	1.64 (RSD 5.48%)

*LIF indicates light-induced fluorescence.
†Relative Standard Deviation.

distributed at each corner of the tablet. Hence, only total excitation of the active ingredients on the surface of these tablets could produce equivalent LIF signals that correlated with the other tablets.

Verification of LIF Scanning Technology With UV Spectrometry for Active Content in Tablets

The LIF signals obtained from scanning groups of tablet surfaces made from the 3 homogeneous triamterene powder samples (1.64%, 3.22%, and 4.75% wt/wt API) generated a linear correlation, $y = 843.78 + 93.57x$ ($R^2 = 0.992$), to the calculated total content of the triamterene in the tablets. Linear correlation was similarly observed and verified with UV spectrometry assays of the dissolved tablet with the following equation: $y = -0.006 + 0.237x$ ($R^2 = 0.999$).

The results from these groups of assays are shown in **Table 1**. The UV data have an overall relative standard deviation (RSD) of about 5%, while that for the LIF tablet surface scans varied from about 4% to 7%. Compilation of the analysis of data obtained from LIF surface scans and UV spectrometry for the various batch of tablets showed good linear correlation with an R^2 of 0.995 (**Figure 8**).

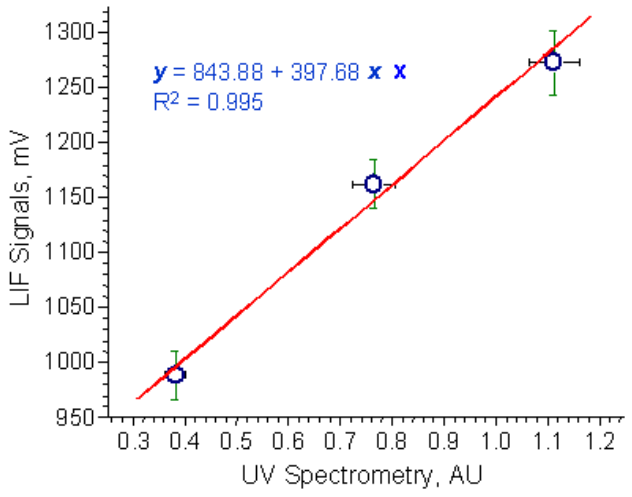

Figure 8. Verification of surface LIF signals to total tablet drug concentrations using UV spectrometry.

Verification of the LIF Surface Scanning Technology With Tablets of Unknown Drug Concentrations to Simulate Undermixing or Segregation

Using the analytical data from the previous section as standard calibration curves, the concentration of triamterene in each unknown tablet made by the process described above in "Fabrication of Regular Compressed Triamterene Tablets" was determined. Drug concentration was determined first by LIF surface scanning technology, and then each respective tablet was weighed and totally dissolved for UV spectrometry analysis for quantitative triamterene content determination. The overall LIF signal showed that the unknown triamterene tablet measurements were all within the 1.64% to 4.75% drug range. UV spectrometry data for the totally dissolved tablet were used as the true value for the total content of drug in each tablet. The results summarized in **Figure 9** showed good agreement of the LIF surface-scanned values with that obtained from UV spectrometry for total drug content of the individual tablets.

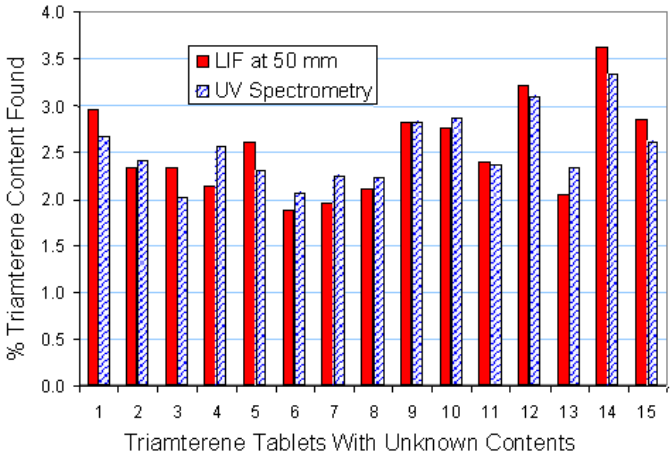

Figure 9. Comparison of surface LIF scan and total UV spectrometry analysis for determination of content uniformity in unknown triamterene tablets.

The number of tablets (15) used in this sampling is not sufficient to be considered for any significant statistical analysis. These tablets are made to simulate a failed production batch caused by segregation or undermixing of the formula-

tion components. In a worse-case scenario, a tablet analyzed may contain nonuniform distribution of triamterene throughout the entire tablet. The distribution of tablets within the population of tablets selected is illustrated in **Figure 10**. The triamterene concentration content reference is based on UV analysis of each individual totally dissolved tablet on the assumption that UV analysis provides an accurate determination of the total triamterene content in the tablet. By comparison, the LIF surface scan of these variable tablets correctly predicted the actual total drug content within an error of ±15% for 93% of the population, within ±10% for 60% of the population and within ±5% for 40% of the population, respectively. These results were based entirely on LIF analysis of tablet surfaces only.

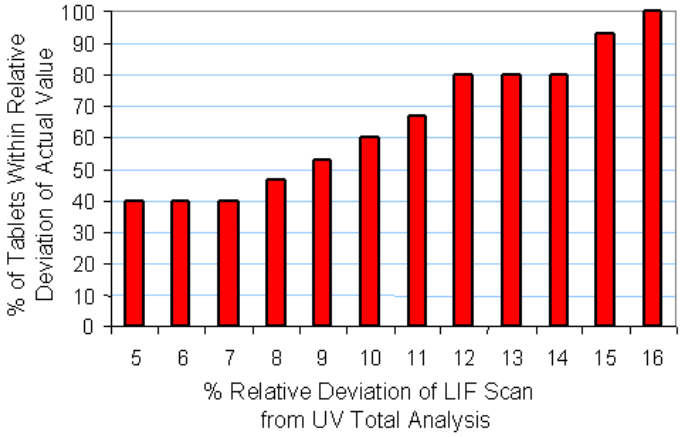

Figure 10. Distribution of variance of tablet LIF surface analysis from actual total content determined by UV spectrometry.

Verification of On-line LIF Surface Scanning Technology With Triamterene Standard Tablets

The results of the first set of experiments are shown in **Figure 11**. Due to the continuous mode of data acquisition, the profile of the data was displayed as a series of peaks and valleys that are representative for each tablet. The peaks represent the maximum fluorescence signal when the whole tablet was imaged, and the valleys represent the blank spacing between each of the tablets. From these results, the signals acquired for each tablet were shown to be consistent and within its representative API content throughout the scans. With increasing scan rates, the same signal consistencies were maintained from a scan rate of 305 tablets per minute to 1525 tablets per minute. A reduction in resolution was observed because less data were obtained for each tablet at the higher scan rate.

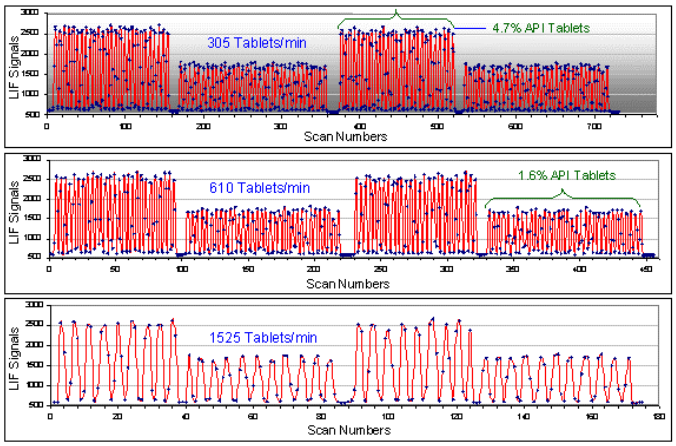

Figure 11. Monitoring of 2 batches of tablets containing 4.7% triamterene and 1.5% triamterene at different rates. Data were acquired at a flash rate of 20 milliseconds.

At the slower scan rate of 305 tablets per minute, details of surface API distribution for each individual tablet can be observed (see **Figure 12**). A greater number of scans could be performed on the individual tablet using the smaller beam size as the tablet moved across the beam at the slower rate. Hence, it may be possible to discriminated small changes in distribution of the API at each tablet surface.

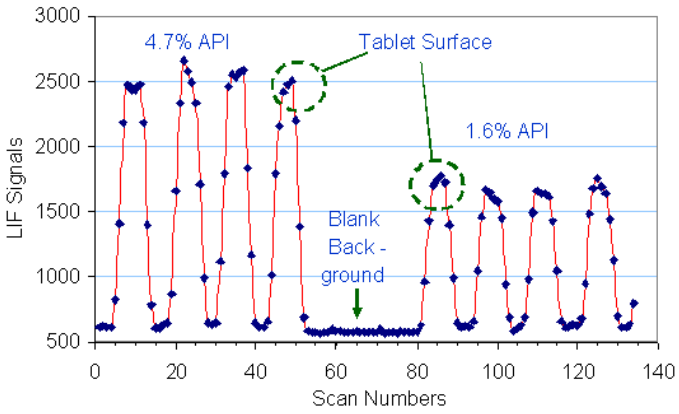

Figure 12. On-line monitoring of surface distribution of API on tablet surfaces at slower rate.

When the tablets were aligned in a continuous string, the resultant signal profile shown in **Figure 13** simulated synchronized data acquisition of each tablet without the interfering background noise produced by the blank space between the tablets. Some lower API concentration tablets were placed among these tablets to determine the sensitivity and ability of the system to pick up these tablets as variations in signals. The resultant profile showed depression in signals from the "spiked" lower concentration tablets that

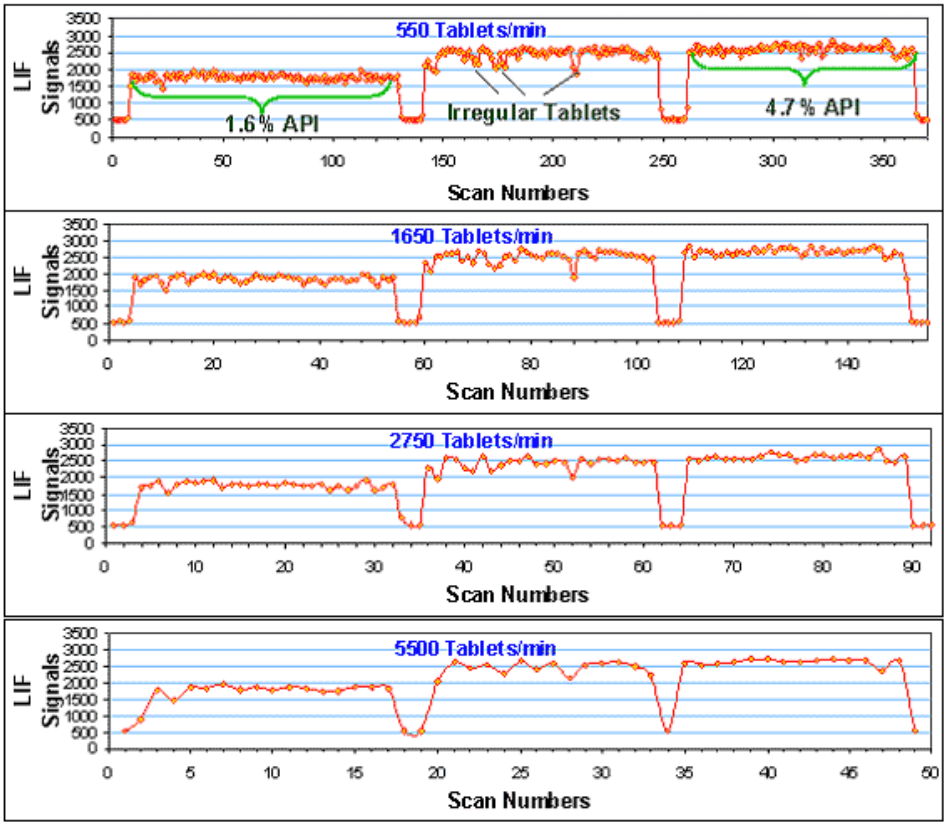

Figure 13. On-line monitoring of API content profiles of tablet surfaces simulating different production rates.

were observed throughout, from a monitoring rate of 550 tablets per minute to 5500 tablets per minute. However, as the rate of tablet movement increased, the number of relative data obtained decreased. Hence, the resolution gradually declined as was expected from results observed in the earlier experiment. Similar to the earlier observation, the signal profiles remained consistent, and the signal levels remained the same, respectively, for the 2 different levels of API contents in the tablets.

Implementation of LIF On-Line Tablet Monitoring on a Commercial Tablet Analyzer

The purpose of mounting the LIF instrument onto a commercial tablet tester (the Autotest 4) is to demonstrate feasibility of monitoring tablet content characteristics on-line. Real-time display of the surface content from each tablet was presented. In the actual expanded display of the tablet-surface profiles, these data not only presented the content observed along the surface but also the variation in distribution of contents on the individual tablet surfaces. The sudden drop in signals observed are the gaps between tablets acquired as a result of continuous monitoring. Lower signals are typically observed at extreme ends of the oblong-shaped tablets. These drops in signals are due to illumination of only part of the tablet instead of the whole tablet (see video clip [online version] and "Total Surface Recognition" section).

At the discharge rate of 150 tablets per minute, the tablets are lined up in close proximity to each other to produce a nearly continuous profile of individual tablet surfaces monitored. As a result, the content profile of this batch of tablets can be mapped out.

DISCUSSION

There are obvious limitations in the use of this technology, and they need to be addressed. These limitations include the need for the API or excipients to have some measurable fluorescence properties with respect to other ingredients present so that signal variations can be distinguished between surfaces where the fluorescent components are distributed unevenly. Since the primary LIF signals of the API contents of the total tablet are derived directly from fluores-

cent measurements from within 1 mm of the tablet surface, the obvious limitation is in the confidence in correlating these results to the entire tablet. Hence, we have been careful only to claim qualitative correlation of production profile using this method prior to producing more statistical confidence data from a larger population of tablets. The small sampling of tablets from the study presented here is insufficient to provide the desirable statistical confidence in the results. The results presented here are intended to verify the feasibility of monitoring changes to the contents on tablet surfaces at a rate of up to 3000 tablets per minute and to provide the capability to determine consistencies in the production profiles for many more tablets than is currently possible. In order to provide feasibility for future use of this method for nondestructive and on-line quantitative analysis of tablet-content uniformity,[9] sufficient statistical confidence in this type of measurement needed to be produced. These are similar problems that faced most of the reflective optical analytical systems available today.

The LIF system had already shown feasibility as a process analytical technology (PAT)[10,11] tool for on-line monitoring of blend homogeneity in the pharmaceutical industry's drive to provide real-time information to characterize and control process variation of a manufacturing process. In this case, the measurement had proven to be quantitative as well.[1,2] We built on this technology to demonstrate feasibility for PAT application in terms of monitoring of a tablet-production profile qualitatively. PAT is specifically useful during earlier stage process development as it builds upon monitoring process knowledge in real-time that was not possible before. Starting from research and development, PAT may allow the mapping of a process history through scale-up to commercial manufacturing. The ability to follow this process to scale-up will increase process knowledge leading to higher quality products. Since PAT involves measurement science that is used to make processing decisions, the profile of the tablets monitored during a production run can provide real-time and in situ indications in the changes of the individual tablet content when it occurs. If the deviation from the release criteria is caught in time, remedial actions can be immediately made to control and save the batch of product. It is envisaged that in the near future tablet press manufacturers may implement this sensor together with a feedback loop to either change the parameters necessary to correct the profile or to reject tablets on an individual basis in real time. On-line and in situ analysis benefit the pharmaceutical industry by providing large reductions in process manufacturing cycle-time and by maintaining products within acceptable ranges. The result of all this can only lead to a reduction in production costs, greater efficiency in manufacturing, and an increase in the quality of the product.

CONCLUSION

The advantage of the LIF technology for rapid tablet content uniformity determination of batches of standard core tablets by surface scans had been shown and verified. Even tablets made from nonhomogeneous powders can provide comparable LIF results that were verified with UV spectrometry of the respective total tablet. These results showed that the LIF technology can be a rapid means for qualitative on-line determination of drug contents of direct compressed tablets. It would be feasible to implement this technology as a continuous, on-line and qualitative method of monitoring the production profile for the total batch of tablets. The rapid rate of acquisition of the current system allows for a scan rate of at least 3000 tablets per minute. For modern high-speed presses, we could envision synchronized monitoring of at least 10% to 20% of the total tablets produced. It is expected that any change in the total drug content of the tablet will likely affect a change in the drug content on the surface. This change may allow the rapid LIF scanning technique on surfaces of tablets to provide statistically reliable results.

Prior to actual implementation on a tablet press, the instrument was field tested for real-time monitoring of core tablets on a commercial tablet analyzer, the Autotest 4. A video clip of the process and the real-time display of the tablet profiles can be seen at this link [online version]. The tablet analyzer typically operates at a slower speed but was sped up several fold just to demonstrate the speed of analysis by the LIF instrument. The rate is slow for the LIF instrument even at 150 tablets per minute. As a result, it was possible to acquire several data points along the surface of each tablet. This data can provide additional information on the nature of distribution of ingredients on the tablet surface.

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