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Rapid at-line analysis of coating thickness and uniformity on tablets using laser induced breakdown spectroscopy

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Abstract

Because of the functionality of controlled release tablet coatings, it is desirable to have a rapid means of optimizing coating conditions and predicting the performance of a batch at-line, prior to exhaustive lab analysis. In this paper, Laser Induced Breakdown Spectroscopy (LIBS) was utilized for the first time as a rapid means of simultaneously determining the thickness and uniformity of an enteric coating on compressed tablets. In these studies, the core tablets contained a high concentration of calcium, and the coating contained titanium, silicon, and magnesium, all of which are excellent analytical targets for LIBS. The emission spectra of all four elements were simultaneously monitored as a function of the number of laser pulses in the same spatial location, literally drilling through the coating and into the core tablet. The depth penetration of individual laser pulses was calibrated using profilometry, and the thickness of the coating was determined by the incidence of calcium signal and simultaneous decrease in emission from the other probe elements (titanium, silicon and magnesium) as the laser penetrated the coating. Coating thickness measurements were evaluated by sampling coatings ranging from 5 to 21% (100 mg tablet weight basis). Additionally, LIBS spatial resolution capabilities were exploited to evaluate the film coat thickness uniformity across the tablet faces and edges. Furthermore, tablet to tablet uniformity differences were readily assessable. The results indicate that a change in coating application of less than 2 wt.% on a 100 mg tablet can be easily detected. The rapid analysis times for this technique (10 tablets were analyzed in under 15 min) makes it applicable for in-process evaluation of coating thickness, as well as intra- and inter-tablet coating uniformity on compressed tablets.

Keywords: Laser induced breakdown spectroscopy; Enteric coating; Coating analysis

1. Introduction

Laser Induced Breakdown Spectroscopy (LIBS) is the application of a high energy pulsed laser to a solid, liquid, or gaseous sample. Each laser pulse ablates the sample material and forms a

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plasma in which elements present in the matrix are excited. The subsequent atomic emission of these elements is then detected and is proportional to the concentration of the elements in the sample [1–3]. Most commonly, LIBS has been applied to the elemental analysis of materials such as steel [4–6], rubber [7], alloys [8,9], ores [10,11], and environmental [12,13] samples. However, given the rapid analysis times possible, minimal sample preparation, wide range of target analytes, and spatial selectivity, LIBS also shows promise for the in-process analysis of pharmaceutical intermediates and finished products.

Evaluating the properties of pharmaceutical coatings such as intra- and inter-tablet thickness and uniformity is important for demonstrating adequate process controls and for ensuring the optimal performance of the final product. This is especially true for functional coatings such as an enteric coating which is designed to protect the tablet from the acidic environment of the stomach, resulting in drug release in the higher pH environment of the small intestine. Inter-tablet coating uniformity is important to ensure that the coating is homogeneously distributed on each tablet throughout the batch; furthermore, the intra-tablet uniformity is crucial, since the overall performance of the film will likely be limited by the thinnest location on the tablet. Techniques are currently available for coating analysis which provide the spatial resolution necessary for intra-tablet uniformity measurements. These include scanning electron microscopy, atomic force microscopy, and conventional optical microscopy. However, these techniques are somewhat tedious and not amenable to rapid at-line analysis of a large number of samples in order to obtain reliable statistics on coating uniformity. Alternatively, techniques that can potentially be used for routine in-process testing of coatings, such as near infrared spectroscopy, do not provide the spatial resolution necessary for intra-tablet coating uniformity analysis. LIBS has the potential to provide both rapid at-line analysis of multiple samples as well as the spatial resolution necessary for intra-tablet uniformity determination.

The objective of these studies was to demonstrate the feasibility of LIBS for measuring the thickness and uniformity of an enteric coating on finished tablets with the ultimate goal of having a rapid at-line predictor of batch performance. The functionality of the enteric coating mandates a fast and accurate means of assessing the coating process. Using LIBS to perform depth profiling of the coatings, the emission intensity of various probe elements was monitored as the laser drills through the coatings and into the core. The emission from magnesium, silicon, titanium, and calcium was monitored simultaneously. In doing so, a plot of emission intensity versus laser shot number is generated with the shot number being proportional to the coating thickness. LIBS has been utilized previously to analyze thin metal films [14–18], and for elemental surface mapping [19–23] but has not been previously demonstrated for coating analysis on pharmaceutical tablets.

2. Experimental

Coating of the experimental tablet formulation was carried out in a 19″ O'Hara coating pan (O'Hara Technologies, Toronto, ON). Core tablet weight was 100 mg, compressed in $\frac{1}{4}$″ standard concave, round image; batch size was approximately 6 kg. A 2% (w/w) subcoating of hydroxypropyl cellulose, hydroxypropyl methylcellulose, and titanium dioxide in a 10% (w/w) aqueous dispersion was applied to the core tablets. The subcoating served two primary functions: to prepare the tablet surface for the subsequent enteric coating, and to prevent possible interaction between the core tablet and the enteric polymer. Sureteric™ (Colorcon, West Point, PA) pseudolatex dispersion was used as the enteric coating

Table 1
Enteric coating conditions

Process parameter	Set point
Exhaust temperature	37 °C
Pan speed	14 rpm
Process air flow	300 cfm
Spray rate	35 g/min
Atomization air pressure	25 psi

material, and was applied to a weight gain of up to 21 wt.% based upon the subcoated core mass. Target coating conditions are shown in Table 1. Samples were collected between weight gains of 5 and 21% and analyzed by LIBS. The enteric coating contains various probe elements amenable to LIBS analysis including titanium, silicon, and magnesium. In addition, calcium ions present at high levels in the core tablet provide an excellent LIBS signal. The change in emission species from titanium, silicon and magnesium to calcium indicates the transition from coating material to tablet core.

The LIBS instrument (Pharma Laser Inc., Montreal, QC) used a Nd:YAG laser (1064 nm) operated at 2 Hz. Laser pulses of 100 mJ were focused just below the tablet surface, generating the excitation plasma. The laser is focused below the surface in order to minimize plasma formation and subsequent analysis of particles in the air (dust, ablated tablet material, etc.). The light emitted from the excited atoms in the plasma is collected through a fiber optic bundle into a spectrograph of a Czerny-Turner configuration containing a 1200 grooves/mm grating and imaged onto a gated CCD array detector. The grating used in this experiment provided a 20 nm detection window in which calcium (393.3 and 396.8 nm), magnesium (383.2 and 383.8 nm), silicon (390.5 nm) and titanium (390.0 and 391.3 nm) could be monitored simultaneously. Because the emission lifetimes of the elements of interest in the plasma varies, the detector delay is set to maximize the emission intensity of the lines of interest (typically 1 μs) and remove background contribution from continuum emission (white light). The tablets were placed on an XY rotational stage. Seven sites were tested on each tablet face in a hexagonal close packing configuration, and each site was sampled with 24 laser pulses. In addition, the sides of the tablets were also measured using 24 pulses per site. Ten tablets were analyzed for each coating thickness, yielding an estimate of inter- and intra-tablet variability.

The depth penetration of each laser pulse into the coating and core material was measured using profilometry. Craters were created in a tablet coating using different number of laser pulses (Fig. 1), and the depth of each crater was measured. The laser pulses resulted in craters that were approximately 1 mm in diameter. The results of profilometry measurements indicated that the depth penetration per laser pulse was approximately 10 μm in the coating and 100 μm in the tablet core.

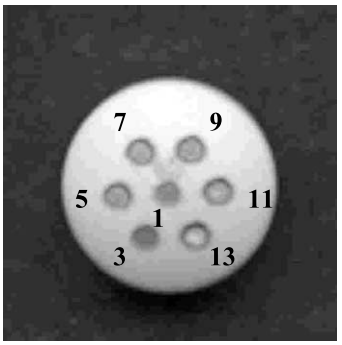

Fig. 1. Tablet image showing the typical hexagonal pattern used to sample each tablet. The numbers designate the number of laser pulses used for each spot with the center spot being one laser shot.

For coating thickness evaluation, it is desirable to have the least amount of coating penetration per laser shot in order to maximize depth resolution. However, there is a trade-off in that lowering laser power to decrease penetration depth also decreases the atomic emission efficiency. In this case, a minimum laser energy of 50 mJ was necessary to achieve a measurable emission intensity. Further experiments to evaluate the effect of the laser energy on the penetration depth revealed that the penetration depth was nominally independent of laser energy within the range of 50–150 mJ. As a result, an intermediate laser energy of 100 mJ was selected for these experiments. Although penetration depth was independent of laser energy in this case, the penetration depth is highly dependent on the coating chemical composition and physical properties. For example, tablets coated with a methacrylic acid copolymer enteric coating (Eudragit) were completely ablated in a single shot, even at low laser energies.

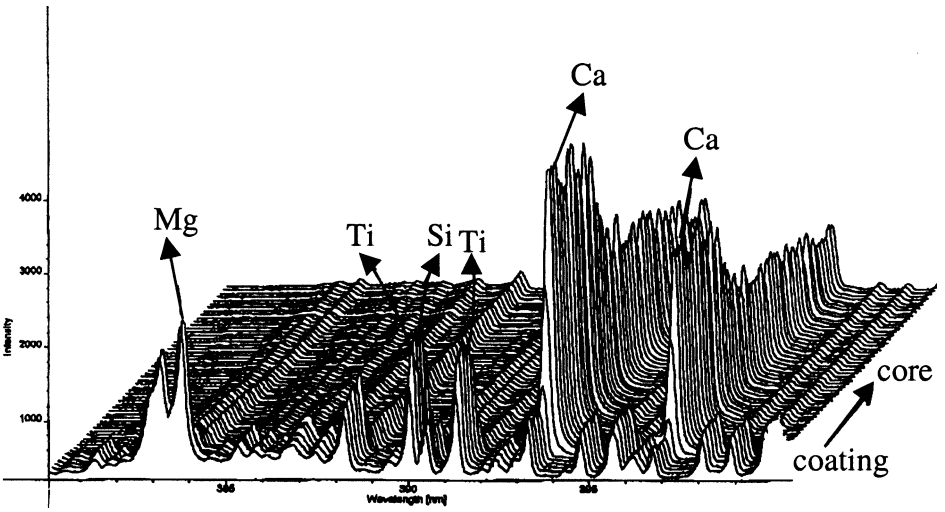

Fig. 2. LIBS emission spectra as the laser penetrates the coating and enters the core tablet.

3. Results and discussion

Fig. 1 shows an image of a tablet in which different numbers of laser pulses were used at each site. One can visually see that the appearance of the resulting cavity is a function of the number of laser pulses, and can be attributed to drilling through the film coatings into the core tablet. When the laser ablates the coatings, they are charred and turned black, however, when the laser is sampling the core a white color persists. Fig. 2 shows a typical set of emission spectra as the laser penetrates through the coating and enters the core tablet. The magnesium, silicon, and titanium signals are the most intense when the laser is sampling the coating material. The signal from these elements decays and the calcium signal increases as the laser samples the core tablet. The presence of titanium dioxide in the subcoating causes the titanium signal to persist beyond the silicon and magnesium signals.

Theoretically, the LIBS response as a function of laser shot number (penetration depth in the coating) should resemble a step function with the emission intensity changing abruptly as the laser samples the coating in one shot and the core in the next. The predicted LIBS response of the coating used in these studies is depicted in Fig. 3. This figure represents a relative profile of the concentration of individual elements in a cross section of the tablet and coating. In this case, the magnesium, titanium, and silicon emission intensities would all be high as the laser samples the enteric coating material. Because there is a subcoating applied to the tablets which contains titanium, one would expect a slight increase in signal as the laser samples the thin sub-coat. Finally, as the laser begins to sample the core tablet, the silicon and magnesium fall to a low value (there is a slight amount of magnesium present in the core tablet). In addition, the large concentration of calcium in the core would result in a large increase in the calcium signal.

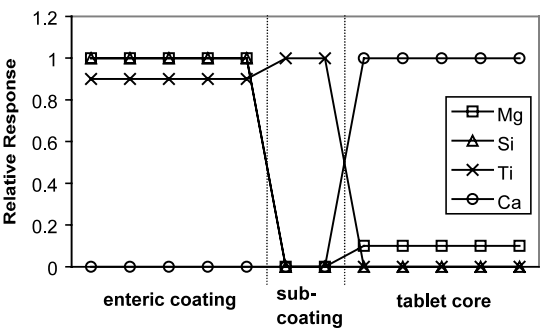

Fig. 3. Theoretical LIBS response for the four probe elements as the laser sequentially ablates the enteric coat, sub-coat, and core.

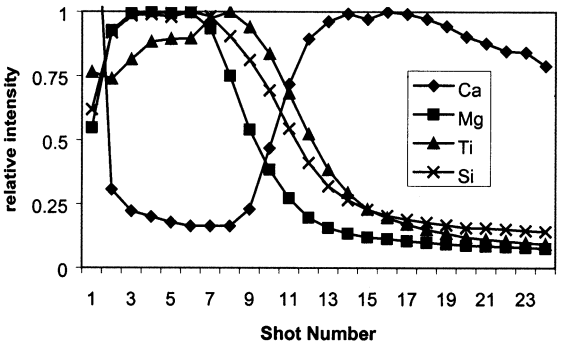

Fig. 4. Plot of the average relative intensity of each probe element versus the laser shot number for 10 coated tablets at the 10 wt.% coating level. Each signal is normalized to the maximum intensity for that particular element.

The actual experimental average relative intensity of each probe element as a function of laser pulse number is shown in Fig. 4. The magnesium, titanium and silicon are at relatively high concentrations in the coating and their intensity decreases as the laser penetrates into the core. Simultaneously, the calcium signal is low initially and increases as the laser penetrates the coating and enters the core. The large calcium signal in the first shot is due to calcium contamination on the surface of the tablets which occurs during routine handling. The onset of the rise in the calcium signal can subsequently be related to the coating thickness for that particular location on a tablet. The decrease in the calcium signal with increasing penetration depth into the core is a measurement artifact with LIBS and is not related to an actual decrease in calcium concentration. Rather, this decrease in signal results from reduced emission throughput to the fiber collection bundle because of the increasing depth of the crater in the sample. The magnesium signal in the coating diminishes noticeably earlier than either the silicon or titanium signals. One would expect the titanium signals to be larger in the region near the core tablets because the sub-coat contains a relatively high level of titanium dioxide. The cause for the higher levels of silicon (as compared to magnesium) near the core is not clear, but it could be related to inhomogeneity in the enteric coating or an intermingling of the coating layers during the coating process. The observed deviations from the theoretical LIBS response as a function of shot number are due to a number of factors including the curvature of the core tablet and non-ideal geometry of the crater drilled by the laser. In this paper, for further evaluation of the enteric coating thickness and uniformity, the calcium signal will be used because it has the largest absolute intensity and changes in the emission signal intensity are straightforward to detect and monitor. Because the calcium is located solely in the tablet core, potential inhomogeneities in the coating components will not impact thickness measurements.

Fig. 5 illustrates the calcium signal intensity as a function of laser shot number for coating thicknesses ranging from 5 to 21% (weight basis on a 102 mg subcoated tablet). Each curve is the average of 10 tablets at the given coating thickness and each tablet was analyzed at seven different locations on the tablet face for a total of 70 thickness measurements per coating level. These 70 measurements were collected in less than 15 min, illustrating the rapid response possible with this technique. For all tablets, the calcium signal is minimal until the laser penetrates the coating and begins sampling the core tablet. As is evident from Fig. 5, a small difference in coating penetration shot is observable between the 5 and 6% coating levels, and a change in coating thickness of 2.5% is clearly detectable. Numerous SEM measurements on tablets coated to a 10% weight

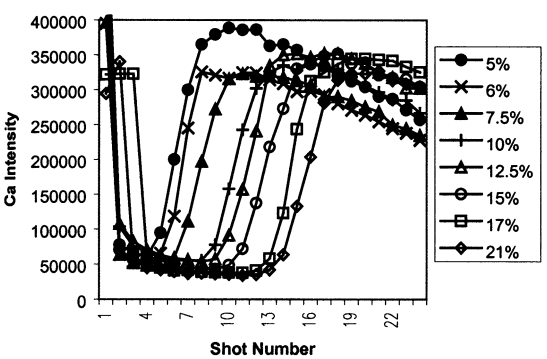

Fig. 5. Calcium signal intensity on the faces of coated tablets as a function of laser shot number for different coating thicknesses.

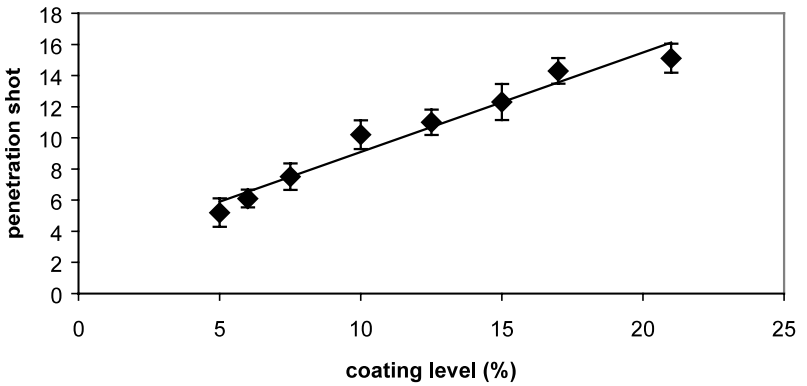

Fig. 6. Plot of the average number of shots necessary to penetrate the coating on the faces of the tablets versus the applied coating weight. Each point is the mean of 10 tablets and the error bars are ± 1 standard deviation.

gain indicated an average coating thickness of 100 μm, and profilometry measurements indicate that the laser penetrates approximately 10 μm per shot. As a result, for every 1 mg of coating applied, the thickness should increase by approximately 10 μm, equivalent to the depth penetration of one laser pulse, and resulting in a resolution limit of 1 wt.% (absolute) for the measurement of applied coating.

Fig. 6 is a plot of the penetration shot number versus the applied coating weight. In this case, penetration shot is defined as the first shot in which significant signal from the core is detectable (in this case, when the calcium signal is greater than 100 000). There is a good correlation between penetration shot and applied coating weight in the range of 5–21 wt.%, especially when considering the sources of variability in this measurement. The first and probably major source of deviation from linearity is the inherent variability in applying the coating. The second is the slightly non-linear change in coating thickness for each milligram of applied coating, due to the increasing tablet surface area as the coating thickness increases. This non-linearity also causes the non-zero y-intercept observed in Fig. 6, and would presumably cause further deviations with increasing coating thickness. Although, this slight non-linearity exists, for practical purposes the coating thickness in the range of 5–21 wt.% can be reasonably fit by a linear interpolation ($R^2 = 0.96$). Variability arising from slight variations in depth penetration per shot and from curvature of the tablet will also contribute to the measurement error.

An additional concern for the application of functional coatings is potential differences in coating thickness as a function of tablet geometry. In this case, the tablets were round convex, and one might expect differences in coating thickness on the faces compared to the sides of the tablets. Representative measurements of the differences between coating thickness on the faces and sides of the tablets as measured by LIBS are illustrated in Fig. 7. The calcium contamination present on the face of the tablets is not observed on the sides, most likely because the sides are not handled as frequently. There is also a baseline offset between the two curves which is due to sample orientation

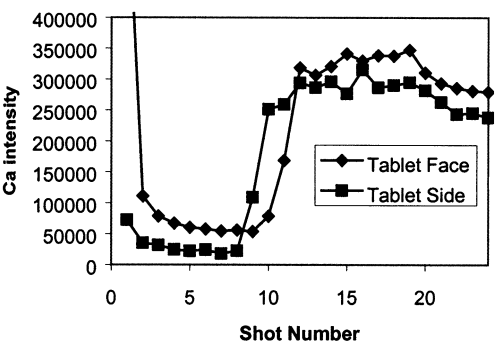

Fig. 7. Average calcium intensity versus laser shot number taken on both the tablet faces and sides for 10 tablets coated at the 10 wt.% level.

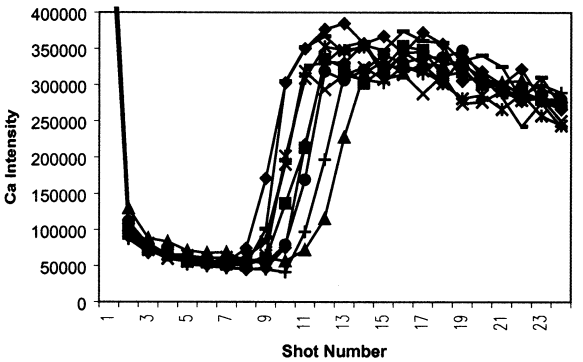

Fig. 8. Average calcium intensity versus laser shot number for 10 individual coated tablets with 10 wt.% applied coating (inter-tablet variability).

differences inherent in measuring the two tablet regions. The calcium intensity curves indicate slight differences in coating thickness, with the face being slightly thicker than the sides. The magnitude of the differences is near the depth resolution limit of the measurement (1 shot or 10 μm by profilometry), indicating that coating thickness on the side is slightly thinner, but within 10 μm of the tablet face.

An example of the inter-tablet (tablet-to-tablet) uniformity for the 10 wt.% coating level is illustrated in Fig. 8 and a complete listing for all coating levels is shown in Table 2. The inter-tablet uniformity, as indicated by the range of thickness measurements on the faces of 10 tablets, does not appear to be significantly dependent on coating thickness, with a measured variability of 30–40 μm (assuming 10 μm per shot). For the 10% coating level this indicates a coating thickness of 102 μm, in good agreement with the aforementioned SEM measurements of coating thickness. On a manufacturing scale, the inter-tablet uniformity is important for predicting the performance of the batch. If a minimum required coating level of 5% (50 μm) is predefined to achieve acceptable enteric coat functionality, then these measurements would indicate that coating thickness ranges observed at a 10% target coating weight should be sufficient to achieve acceptable acid resistance properties with very minimal failures. Using LIBS a single analyst can analyze hundreds of tablets in a single day to achieve reliable statistics on the coating variability of a batch as a predictor of acceptability. In contrast, obtaining reliable statistics on the performance of a batch via USP acid resistance testing would take a single analyst much longer to complete. As a result, the speed of LIBS can greatly accelerated the optimization of critical coating processes during development.

Theoretically, the spatial resolution of LIBS is limited by the laser beam diameter ($\sim$ 100 μm in this case). In practice, the high energy of the laser causes ablation of a much larger area on the sample, limiting the actual spatial resolution which can be achieved (in this case $\sim$ 1 mm). The area of the ablated crater in the sample will be dependent on laser energy and sample physical properties (hardness, friability, etc.). Here, the

Table 2
Thickness and variability for enteric coated tablets

Coating applied wt.%	Mean thickness (μm)[a]	Inter-tablet variability (μm)[a]	Intra-tablet variability (μm)[a]
5.0	52	30	9
6.0	61	30	8
7.5	75	30	13
10.0	102	40	14
12.5	110	40	17
15.0	123	40	16
17.0	143	30	20
21.0	151	30	21

Inter-tablet variability is the range in thickness measurements for the 10 tablets at each coating level. Intra-tablet variability is the mean ($n = 10$ tablets) of the of the thickness range of seven sites across individual tablets.

[a] Assumes 10 μm per shot as determined by profilometry.

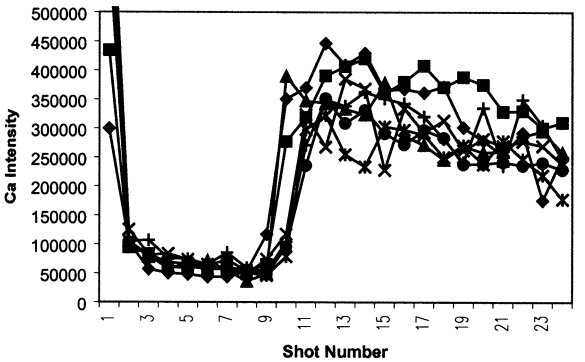

Fig. 9. Average calcium intensity versus laser shot number for seven sites on an individual tablet with 10 wt.% applied coating (intra-tablet variability).

seven different locations in the hexagonal close packing pattern (Fig. 1) were used to evaluate the film uniformity across individual tablets. The intra-tablet coating uniformity on a single tablet at the 10% coating level is depicted in Fig. 9. In this case, the six sampling locations on an individual tablet are displayed independently. As is evident by comparison of Figs. 8 and 9, the coating on an individual tablet is more uniform than the tablet-to-tablet coating uniformity, as judged by the consistency in the penetration shot of the coating. In contrast to the inter-tablet uniformity, the intra-tablet thickness variability did increase with increasing applied coating (Table 2). However, in general the intra-tablet variability is less than the inter-tablet variability. This result is encouraging in that coating thickness across an individual tablet should be very uniform in order to achieve effective and predictable acid resistance and coating stability properties. It also indicates that the main source of coating non-uniformity in a batch may be due to factors such as a non-uniform movement of tablets in the coating pan or non-uniform spray patterns.

Currently, the value of LIBS for coating analysis is as a rapid and reliable means of assessing batch coating uniformity, thereby accelerating the development process and providing an assurance of batch performance prior to exhaustive laboratory testing. For functional coating analysis the critical parameter of interest is the batch coating uniformity. The absolute coating applied can be accurately estimated from the spray rate and coating time. As a tool for coating uniformity determination, absolute thickness standards are not necessary for LIBS because the sample to sample variability in laser penetration shot provides an accurate measure of batch uniformity.

4. Conclusions

LIBS has been demonstrated to be a viable technique for rapidly determining coating thickness and uniformity on pharmaceutical tablets. In this case, the results indicated an approximate average thickness of 100 μm for a 10% coating weight gain, in good agreement with SEM measurements. A change in coating thickness of less than 2.5 wt.% could easily be detected, and a plot of the coating thickness versus laser penetration shot showed good correlation over the coating range of 5–21 wt.%. The inter-tablet uniformity was ± 3 shots or 30 μm (3 standard deviations), and the intra-tablet uniformity on individual tablets was better than the uniformity across tablets. There were only small changes in coating thickness detected between the faces and sides of the tablets with the coating on the sides of the tablets being slightly thinner. Furthermore, LIBS rapid at-line analysis of coating thickness on tablets can provide both spatially isolated and gross average thickness measurements from the same samples, information that is not currently available at-line. For example, in this case the inter- and intra-tablet homogeneity on 10 tablets was measured in less than 15 min. This combination is especially important for the analysis of functional coatings where both inter- and intra-tablet uniformity are important in determining the overall performance of a given batch. For enteric coatings, LIBS may provide a means to quickly predict the performance of the batch without acid resistance testing, thus limiting exhaustive lab testing and accelerating coating process development. The future direction of LIBS for coating analysis is to extend this work to other pharmaceutically relevant coatings, including an investigation of the relationship between laser energy, coating properties, and penetration depth. In ad-

dition, the application of LIBS for quantitating active compounds and excipients in tablets and powder blends is a promising area of active research where LIBS is also proving to be a valuable technique.

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