Characterization of Tablet Film Coatings Using a Laser-Induced Breakdown Spectroscopic Technique

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ABSTRACT

Laser-induced breakdown spectroscopy (LIBS) was evaluated as an early phase process analytical technology (PAT) tool for the rapid characterization of pharmaceutical tablet coatings. Measurement of coating thickness, uniformity, and photodegradation-predictive potential of the technique were evaluated. Model formulation tablets were coated with varying amounts (2%-4% wt/wt) of red and yellow Opadry II, and a pulsed laser was used to sample at multiple sites across the tablet face. LIBS was able to successfully detect the emissions of Fe and Ti in the coated samples, and a proportional increase in signal with coating thickness was observed. Batch-to-batch variability in the coating procedure was also easily monitored by LIBS. The coating thickness was non-uniform across the tablet surface with higher thickness at the edges, likely due to the concave shape of the tablet. Film coating levels and color of the film had been subjected to photostability studies according to the International Conference on Harmonisation (ICH) guideline to determine effectiveness of the film coats. LIBS measurements of coating thickness provided a good correlation ($R^2 > 0.99$) to photodegradation as measured by high-performance liquid chromatography (HPLC). Last, the concentration of Fe in the coating was varied and monitored by LIBS. Increasing photostability was observed with increasing levels of ferric oxide, providing a new understanding of the photoprotection mechanism in the coated formulation. Determination of levels of ferric oxide and coating thickness by LIBS demonstrated its utility as a good PAT tool for the determination of photoprotection of the drug, thereby enabling facile optimization of the coating process.

KEYWORDS: LIBS, coating uniformity, coating thickness, photostability, photoprotection.

INTRODUCTION

In recent years, laser-induced breakdown spectroscopy (LIBS) has emerged as an innovative tool for quantitative and qualitative elemental analysis of pharmaceutical materials. LIBS, a laser based technique, uses a high power laser that ablates the surface of the sample medium to form a plasma plume of finely dispersed material. It is in the plasma that the ablated constituents are vaporized and dissociated into ionic and atomic species that are ultimately, excited. The ions and excited electrons in the atoms relax to their ground state as the plasma cools and emit light at wavelengths characteristic of the elements present in the material. Some of the more common applications of this technique are the quantitative elemental analysis of materials in metallurgy,[1-4] art conservation,[5] and environmental samples.[6-8]

New initiatives from the Food and Drug Administration (FDA) have described process analytical technology (PAT) as a novel approach in improving pharmaceutical processes.[9] This has contributed to an increasing interest in LIBS technology as an analytical technique for rapid detection and quantitation of pharmaceutical materials. Several pharmaceutical applications using LIBS include examples such as the determination of pharmaceutical excipients used in the formulations[10-12] quantitative analysis of the drug substance (active pharmaceutical ingredient [API]) in solid dosage forms,[13] determination of magnesium stearate distribution in powder blends,[14,15] tablet coating thickness and uniformity determination of enteric-coated tablets for at-line measurements,[16] and effects of physical attributes in LIBS measurement.[17]

Mowery et al[16] have illustrated the potential use of LIBS for rapid characterization of film coatings in pharmaceutical products. Film coating is often used in the pharmaceutical solid dosage form for several reasons including protection of the drug from air, moisture and/or light, masking of unpleasant taste, and improvement of product elegance and ease of swallowing.[18] Studies have shown the photostabilizing effect of film coating with pigments on tablets with photosensitive active drug substance susceptible to light degradation.[19] Thus, characterization of tablet film coatings may become critical. Improved photostability often depends on the thickness of the film or the amount of pigment used in the coating suspension; therefore for functional film coats, uniformity and thickness of the coating on the tablet surface is important. When coatings are applied for photoprotection, not only the appropriate thickness but also the amount of pigment needs to be determined. At present, no direct procedures are available to determine the characteristics of film coatings.

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The objective of this work was to (1) develop a LIBS method for the rapid evaluation of thickness and uniformity in tablet coating used for photoprotection, (2) use the LIBS technology to better understand the photoprotection mechanism in the coated formulation by means of a novel approach for the quantitative determination of the coating depth profile (via calculation of an area under the curve [AUC] of the signal intensity as a function of the number of shots), and (3) evaluate the feasibility of using LIBS as a tool for determination of photostability of the drug substance as compared with the results obtained using high-performance liquid chromatography (HPLC).

MATERIALS AND METHODS

Materials

Core Tablets

A photosensitive active pharmaceutical ingredient (compound A) was used as a model compound for preparing the core tablets. Microcrystalline cellulose (Avicel PH102, FMC Biopolymer, Philadelphia, PA), sodium carboxymethylcellulose (Ac-Di-Sol, FMC Biopolymer), anhydrous lactose (Quest International Sheffield Products, Chicago, IL), and magnesium stearate (Mallinckrodt Chemical, Phillipsburg, NJ) were the pharmaceutical excipients used in the tablet manufacture.

Film Coating Solution

The film coating solution was prepared from Opadry II HP (85F15362 and 85F12231, Colorcon, West Point, PA) containing 2 main elements, titanium and iron, which can be detected using the LIBS analysis.

Methods

Preparation of Core Tablets

Tablets containing the API and excipients were compressed to 100-mg weight using the Korsch PH106 tablet press with one-quarter-inch round standard concave tooling. These tablets were then coated according to the procedure mentioned below.

Film Coating Process

The film coating process was performed in a Hi-Coater (Vector/Freund, Marion, IA) coating pan with a capacity of 200 to 300 g. The process parameters used were as follows: inlet temperature was set at 65°C, spray rate was between 4 and 5 g/min, atomizing air pressure was set between 1 and 4 psi, and the pan speed was set at 30 rpm. The levels of tablet coating applied were 2, 3, and 4% wt/wt, and color
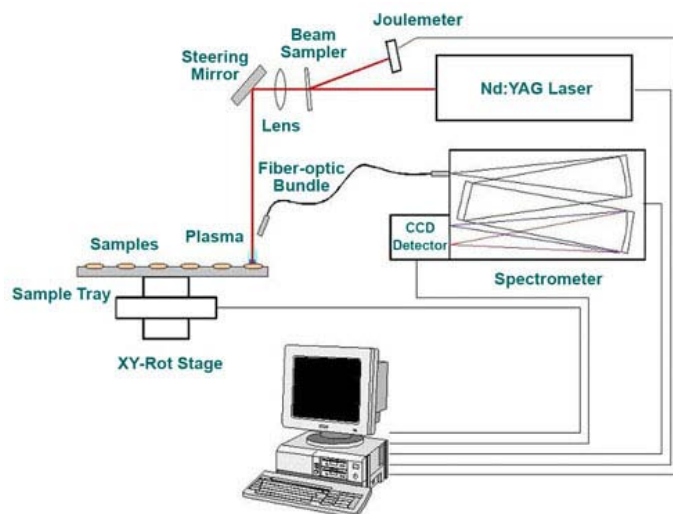

Figure 1. Schematic representation of LIBS instrument. LIBS indicates laser-induced breakdown spectroscopy; CCD, charged coupled device.

pigments used in the formulations were red and yellow. Each pigment used in the coating contained 3 varying contents of Fe_2O_3: 2% wt/wt, 4% wt/wt, and 7% wt/wt.

LIBS Instrumentation

The PharmaLIBS 200 instrument (PharmaLaser, Montréal, QC Canada) is shown schematically in Figure 1 and employs a pulsed laser with high power to form a plasma plume of finely dispersed material directly from the surface of the sample medium to be examined. The instrument was equipped with an neodymium doped yttrium aluminum garnet laser (New Wave Research Inc., Fremont, CA) that operates at 1064 nm with an adjustable energy of up to 200 mJ and 10 Hz repetition rate. Plasma emissions are transmitted to an imaging spectrograph of Czerny-Turner configuration by a fiber optic bundle with 3 gratings; namely, 600 g/mm, 1200 g/mm blaze (visible), and 1200 g/mm blaze (>750 nm), which were then detected by an interline readout charge-coupled device (CCD). The optimized instrument conditions used for this work are shown on Table 1. The grating used allowed for a 20-nm detection window in order to simultaneously monitor the elements of interest, and the tablets were placed in an XY rotational stage. In addition, the film-coated model formulation tablets were sampled across 33 sites, with 25 laser pulses per site. The sampling plan of the model formulation was optimized for the resolution of the laser shot. The titanium and iron emissions from these coatings were evaluated using LIBS. The change in signal intensity with number of shots was profiled. The AUC of the elemental signal intensity as a function of the number of laser shots was then calculated using the WinNonlin Professional Version 4.1 software from Pharsight Corporation (Mountain View, CA).

Table 1. Summary of the LIBS Parameters for the Coating Thickness and Uniformity Studies*

Parameters	Values
Laser energy (mJ)	100
Repetition rate (Hz)	2
Delay (ms)	1×10^{-3}
Exposure (ms)	3×10^{-3}
Grating	1200 g/mm blz vis
Binning	25
Number of sites and shots/site	33 sites, 25 shots/site
Analytical lines (nm)	Fe: 405; Ti: 391
Function	Net signal, peak height

*LIBS indicates laser-induced breakdown spectroscopy; ms, millisecond.

Figure 3. Analyte signal intensity as a function of laser energy of tablets coated with 4% wt/wt red Opadry II.

High-Performance Liquid Chromatography

An Agilent 1100 HPLC UV system (Palo Alto, CA) was used for the determination of the degradate levels when exposed to ICH photostability conditions. The data were collected using Atlas Labware systems software from Thermo Electron Corporation (Waltham, MA). The HPLC parameters included a 150 mm × 4.6 mm inner diameter (ID) Symmetry C18 column (Waters Corp, Milford, MA) with a 3.5-μm particle size, 30ºC column temperature, flow rate of 1.2 mL/min, 55%:45% 0.1% trifluoroacetic acid (TFA) in water: acetonitrile (vol/vol) mobile phase ratio and a detection wavelength of 255 nm.

RESULTS AND DISCUSSION

Instrument Optimization

Selection of Optimal Laser Energy

The presence of such metals as iron and titanium in the coating produce a complex spectrum with their characteristic atomic emission lines. Thus, this is observed in the film-coated tablet but not in the core. This finding confirms the s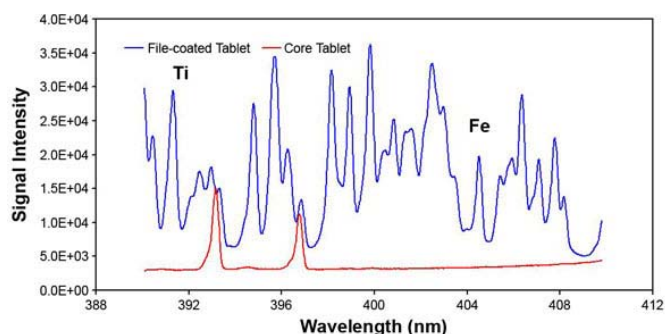electivity of the LIBS approach for the determination of these metals (Figure 2). One of the critical operation parameters in LIBS is the laser energy. In order to ensure maximum analyte signal intensity and depth resolution of the sample surface, optimization of this laser energy is required. The effect of laser energy on analyte signal was studied using tablets coated with 4% wt/wt red Opadry II containing 7% wt/wt iron, which contained the highest level of iron, these samples were used to monitor the LIBS signal over a range of laser energies. In order to minimize redundancy, only results from the iron emission have been reported. Figure 3 shows the average signal intensities from every site as a function of the laser pulse number for different laser energies. The signal was observed to change as the laser drilled through the tablet from the surface into the core. The results in Figure 3 showed that measurable signal intensity can be achieved with minimum laser energy of 25 mJ. However, the signal intensity was also shown to increase with increasing laser energy up to a value of 150 mJ, where a saturation of emission lines was observed with the instrument's charged coupled device detector as shown by Figure 4. Therefore optimal laser energy of 100 mJ was selected as it provided the highest response for the analyte signal intensity without saturation. In addition, at the 100 mJ laser energy, the possibility of complete ablation of the coating after a

Figure 2. LIBS emission spectrum of core and coated tablets (400 nm wavelength, 100 mJ laser energy). LIBS indicates laser-induced breakdown spectroscopy.
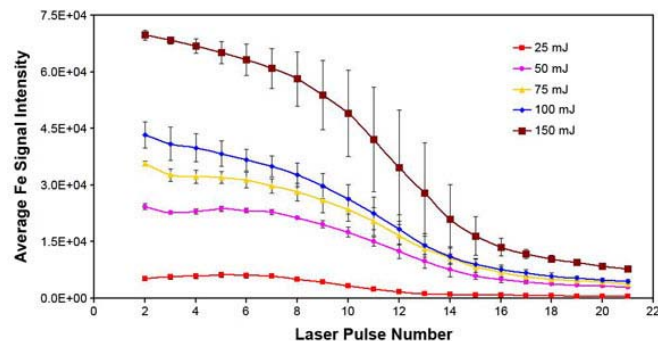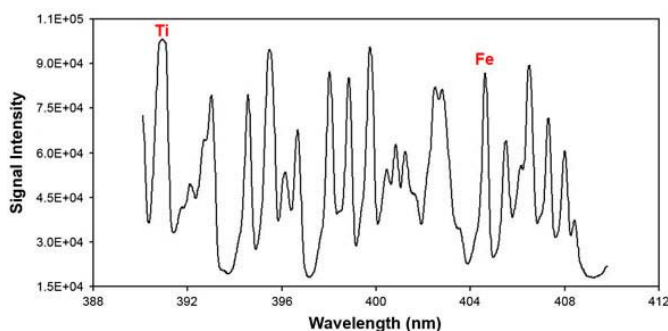

Figure 4. LIBS emission spectra of a tablet with red coating (7% wt/wt ferric oxide) at 4% wt/wt (150 mJ laser energy). LIBS indicates laser-induced breakdown spectroscopy.
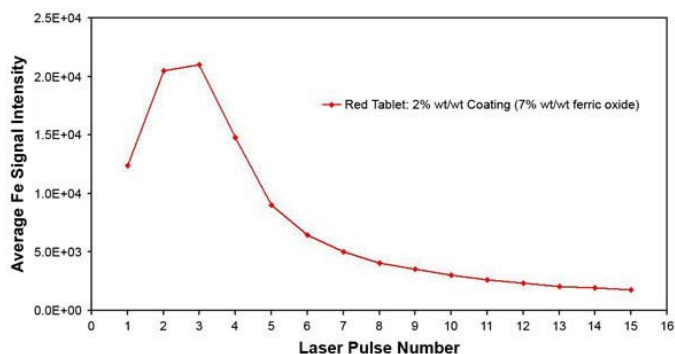
Figure 5. Plot of Fe emission vs the number of laser shots for red tablets (7% wt/wt ferric oxide) coated at 2% wt/wt (400 nm wavelength, 100 mJ laser energy).

single shot was minimized as compared with that of 150 mJ as determined by visual inspection.

Figure 3 also showed a decrease in LIBS signal with increasing number of laser shots. The decrease in signal corresponds to the penetration of the laser into the film coating, thereby providing a method for profiling tablet-coating thickness. Since the spot size of the laser is small (~150 μm), the measurement of individual tablet surface homogeneity is also possible with the LIBS approach.

Depth of Laser Penetration

The coating thickness and depth of penetration into the film coating with the number of laser shots was evaluated by
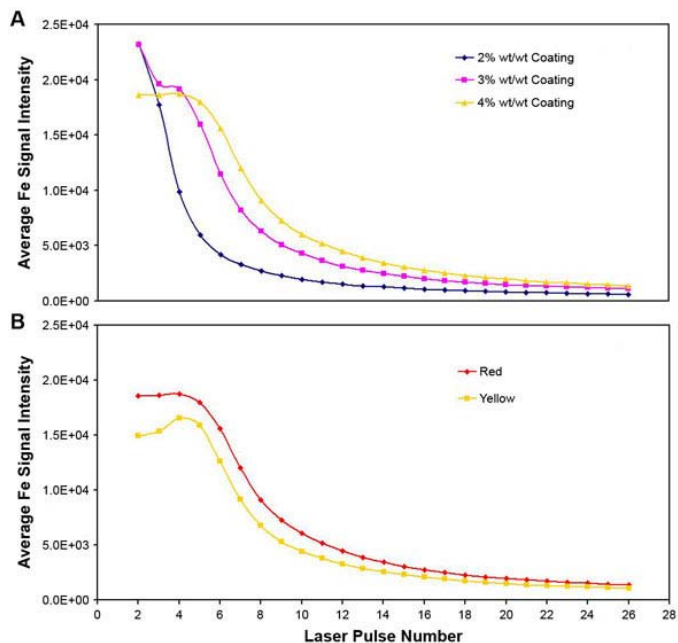

Figure 6. Signal intensity as a function of coating thickness (7% wt/wt ferric oxide): (A) tablets coated with different amounts of red Opadry II, and (B) tablets coated with different amounts of red and yellow Opadry II.
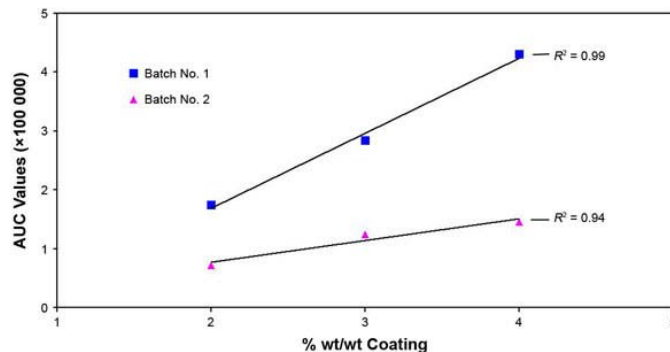

Figure 7. Batch-to-batch coating variability for different batches of tablets coated with red coating. AUC indicates area under the curve.

performing scanning electron microscopy (SEM) measurements on the 4% wt/wt film-coated tablets. After 10 and 15 shots, the depth of penetration into the tablet was determined to be ~250 μm and 300 μm, respectively. In addition, the coating thickness was observed to be ~25 to 30 μm at 4% wt/wt. The SEM values observed were compared with the coating ablation profiles obtained from LIBS, and it is evident that Ti and Fe emissions could be detected even after the laser completely ablated the coating. This finding could be attributed to the increase in diameter of the cavity caused by the laser or carryover particles in the sampling compartment of the instrument that can get re-excited in the plasma of the subsequent laser shot. Figure 5 shows the average Fe signal intensity as the laser penetrates the coating. The profile shows an initial increase in signal intensity as the laser penetrates the coating and, eventually, decreases as the laser penetrates into the core. The Fe signal, however, does not reach zero, which is most likely due to the carryover particles or over-sampling as previously mentioned. Similar observations were made for titanium.

Tablet Evaluation

Variation in Coating Thickness

The thickness of the film coating was evaluated by averaging the analyte signal intensities from every site as a function of the number of laser shots needed to penetrate the coating. Red-coated tablets containing 7% wt/wt Fe_2O_3 were evaluated as shown on Figure 6A. The amount of coating was also varied from 2% to 4% wt/wt. In Figure 6A, the number of laser shots needed to penetrate the coating until no detectable iron signal is plotted. It was observed that the number of shots required for coating penetration was directly proportional to the coating thickness (Figure 6B). A similar trend was observed for the yellow-coated tablets. In addition, taking the AUC of the depth profiles, starting from the first shot to the last detectable shot obtained, also demonstrated that the AUC is linearly proportional to the amount of coating on the tablet as shown in Figure 7. Two different
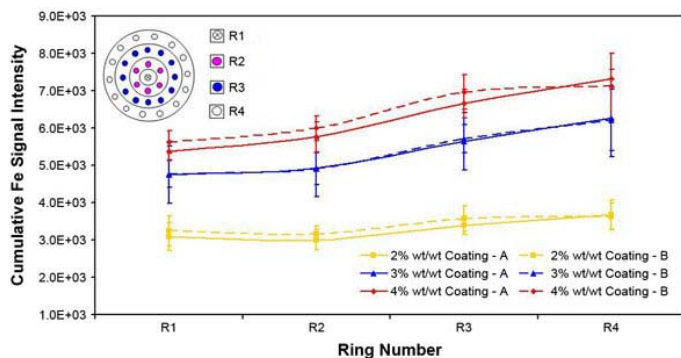
Figure 8. Cumulative Fe emission signal at different sites across the tablet surface (% wt/wt ferric oxide). Inset is the sampling plan of the model formulation.

batches coated at 2%, 3%, and 4% wt/wt of red-coated tablets were evaluated, and different AUC values were observed. Similarly, from the yellow-coated tablet data, different AUC values were also observed for the different batches. Since differences were visually evident between coatings for each batch, these results confirm that AUC obtained by LIBS can be successfully used to rapidly determine batch-to-batch variability.

Evaluation of Coating Uniformity

An assessment of the tablet coating uniformity would provide a quick means of optimizing the coating process during formulation development. The uniformity of the coating thickness on the tablet surface would also have a significant effect on the coating performance (such as photoprotection). The coating uniformity was evaluated by plotting the cumulative emission signal for iron in the 4% wt/wt containing 7% wt/wt Fe as a function of the different locations (sites) across the tablet surface. The locations evaluated were sampled and designated as concentric rings, wherein R1 is the

center of the tablet and R4 is the ring along the outside edge (inset, Figure 8). Some statistically significant differences in the thickness were observed with the coating on the edges being slightly thicker than that at the center. As shown in Figure 8, the coating uniformity between the 2 sides (A and B) of each tablet seemed to decrease with coating thickness with highest variability in case of the 4% wt/wt coating. Note that sides A and B were randomly chosen as there were no markings on either side of the tablet. Some variability in Fe response was observed, indicating differences in the coating of the tablets analyzed. Similar results were also observed with the yellow coating. In addition, these studies also showed that there was a good correlation between the number of laser shots required to completely penetrate the coating and the amount of coating that was applied (in this case 2%-4% wt/wt).

Photostability of API

In order to determine which color and amount of film coating were needed to provide a suitable level of light protection, photostability testing based on the ICH guidelines[20] of the tablets coated with red and yellow Opadry II at different amounts of coating and % wt/wt Fe content was performed. The level of photodegradation in the tablets exposed to light was analyzed by HPLC. This was then correlated to the results from the LIBS analysis, wherein the signal intensity was obtained as a function of the number of laser shots and therefore coating thickness. Table 2 summarizes the AUC values obtained from LIBS of the coated tablets and the photodegradation levels by HPLC. As expected, photoprotection increased with increasing coating thickness (ie, decrease in %LC of the degradate peak) was determined using the LIBS.

The initial evaluation of the red and yellow film coatings indicated that the photoprotection depended on the color of ferric oxide in the film coating. The 4% wt/wt red film coating

Table 2. Summary of ICH Photodegradation Levels and Corresponding AUC Values for Tablets Coated With Formulations Containing Various Ferric Oxide Levels*

	Coating % wt/wt	2% Fe		4% Fe		7% Fe	
		Degradate (% LC)†	AUC Values‡ ($\times 10^4$)	Degradate (% LC)†	AUC Values‡ ($\times 10^4$)	Degradate (% LC)†	AUC Values‡ ($\times 10^4$)
Red	2	1.4	2.49	1.1	5.35	0.8	7.20
	3	1.0	3.59	0.7	9.39	0.5	12.41
	4	0.7	4.87	0.5	9.45	0.3	14.54
Yellow	2	1.4	14.96	1.0	12.85	0.7	30.58
	3	0.8	17.22	0.4	19.04	0.3	30.29
	4	0.6	19.21	0.3	29.97	0.3	42.97

*ICH indicates International Conference on Harmonisation[20]; AUC, area under the curve; LC, liquid chromatography.
†Determined by high-performance liquid chromatography.
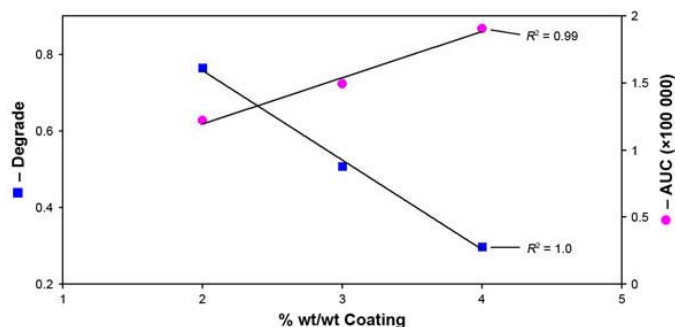‡Determined by laser-induced breakdown spectroscopy.

Figure 9. Drug degradate levels (% LC) and LIBS AUC values vs different coating range for the red tablets. LC indicates liquid chromatography; LIBS, laser-induced breakdown spectroscopy; and AUC, area under the curve.

provided better photoprotection than the yellow. However, the amount of ferric oxide in the red Opadry II (7% wt/wt) was determined to be higher than that of the yellow coating (2% wt/wt). When the ferric oxide level in these coated tablets was varied, a good correlation between photostability and ferric oxide content was obtained (Table 2). Thus, the differences in photoprotection provided by the commercially available yellow and red film coating formulations could be attributed to the differences in the ferric oxide content. The photostability of the API as indicated in Table 2 by the degradate level obtained by HPLC was improved, with an increase in the ferric oxide content. From the %LC results, the yellow ferric oxide showed a slightly better photoprotection than the red ferric oxide. Therefore, based on these results, a correlation of the AUC values (film thickness and ferric oxide) to the degradate levels can be used to determine the extent of photostability of a given compound. This finding is significant because it indicates that a thinner coating can be photoprotective if the ferric oxide levels in the coating formulation are sufficiently high. Use of a lower coating thickness can reduce coating times and costs.

Prediction of Photostability

A plot of the Fe signal intensities obtained from LIBS correlated to the amount of Fe_2O_3 content in the film coating and the degradate levels is shown in Figure 9. For this particular model compound, Figure 9 shows that the film thickness or AUC of the profiles was inversely related to the degradate level, which means that the higher the AUC values observed, the lower the degradate level and, therefore, better photoprotection is achieved. In addition, a linear correlation between the AUC and the amount of degradate vs percentage wt/wt of the coating was obtained for the API as observed from the plot. Therefore, using this approach, it maybe possible to determine directly the degradate levels of the API in the tablet using this technique, thereby accelerating the formulation development process.

CONCLUSIONS

In this work, LIBS has been demonstrated to provide a rapid means of evaluating the quality of film coatings in pharmaceutical solid dosage forms. A good correlation between the LIBS signal (AUC) and the amount of ferric oxide or coating thickness could be obtained. Furthermore, because both the ferric oxide content and the thickness correlated well with the photoprotection of the API, LIBS can potentially be used to determine the extent of photostability of the drug due to film coating. Therefore, this technique can potentially be developed as an early phase PAT tool for monitoring the tablet-coating process and, thus, accelerating the formulation development.

ACKNOWLEDGMENTS

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