Effects of Core Tablet Size on the Functionality of Aqueous Delayed Release Coatings as Measured by SEM and LIBS

PURPOSES

The aim of this work was to develop a correlation between tablet surface area (size) and the minimum amount of coating weight gain/thickness of a functional coating necessary for enteric protection of tablets. Acryl-EZE®, aqueous enteric coating system, was used and the film coat thickness was determined via scanning electron microscopy (SEM) and laser-induced breakdown spectroscopy (LIBS).

METHODS

Tablet Characterization

Standard round concave tablets with diameters ranging from 6 to 10 mm were used for this study. The small tablets were placebos while the larger tablets were 325 mg aspirin cores manufactured by LNK, International (Hauppauge, NY). All tablets were examined for physical properties, including weight variation, thickness, hardness, and friability. General tablet physical properties were measured using an Erweka Multi-Check (Table 1). In this study, we focused on coating application as a function of theoretical weight gain of coating applied to the tablet. Since it is also common to quantify film coating amount as mass/surface area, we also determined film coating amount as mg/cm2 using a rudimentary calculation for surface area, assuming the tablet is a perfect cylinder:

$$SA = 2(\pi r2) + 2\pi rh$$

SA is the surface area r is the radius of the tablet and h is the height or thickness of the tablet.

Table 1. Tablet Physical Characteristics (Prior to Enteric Coating)

Tablet Property	*6mm Placebo*	*10mm Aspirin*
Average diameter (mm)	5.60	10.32
Average weight (mg)	84.30	380.80
Average thickness (mm)	3.14	4.72
Calculated surface area (mm2)	104.50	320.32
Average hardness (kp)	8.90	8.00
Friability after 100 drops (%)	0.00	0.79
Friability after 400 drops (%)	0.00	1.58

Enteric Coating & Acid Resistance

Tablets were coated in an O'Hara Labcoat II fully-perforated coating pan. Two sets of trials were conducted for each tablet size, one batch without and one batch with a seal-coat (1% w/w) of a clear Opadry®, complete film coating system (Colorcon, Ltd.). This was to examine the effects of a seal-coat on enteric coating functionality. All tablets were coated with Acryl-EZE®, aqueous enteric coating system (93O Series, Colorcon, Ltd.) up to a 14% theoretical weight gain. Samples were taken after 6, 8, 10, 12 and finally 14% theoretical weight gains. Functional acid resistance (a measure of enteric protection) was determined via weighing tablets (n=6) before and after 2 hrs in 0.1N HCl in an Erweka ZT x20 disintegration tester.

Film Coat Thickness

Film coating thickness was determined using scanning electron microscopy (SEM) and laser-induced breakdown spectroscopy (LIBS). For SEM, tablets were manually bisected and gold sputter coated using a Quorum Technologies SC7620 sputter coater (Ashford, England). Samples were analyzed using a scanning electron microscope manufactured by FEI Phenom (Eindhoven, Netherlands). Measurements were taken in three locations across the cross-section of the tablets: crown, corner, and edge, as shown in **Figure 1**.

PharmaLIBS 250 (PharmaLaser, Montreal, Canada) has proven to be a rapid and easy-to-use tool for studying tablet coating thickness and uniformity.1,2 cLIBS data consisted of measurements of spectral signal intensity, in this case, titanium from titanium dioxide, coming from tablets impacted by multiple laser shots at predetermined locations. For each coating batch, measurements were taken on 20 tablets at each weight gain increment. Tablets were assayed in 19 locations across the face of the tablet (**Figure 2**) with 30 laser pulses at each location. In this work, the focus was on the center point of the tablets, to correlate with the SEM measurement of film thickness at the crown of the tablets.

Figure 1. Schematic of a Bisected Coated Tablet

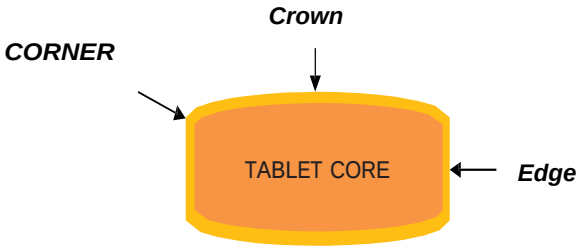
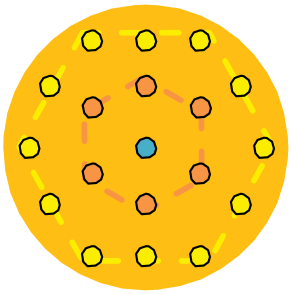


Figure 2. Schematic Diagram Showing the Top-View of a Tablet.

(Nineteen sites were analyzed with beginning at the center of the tablet and expanding into two concentric hexagons.)



RESULTS

Enteric Performance

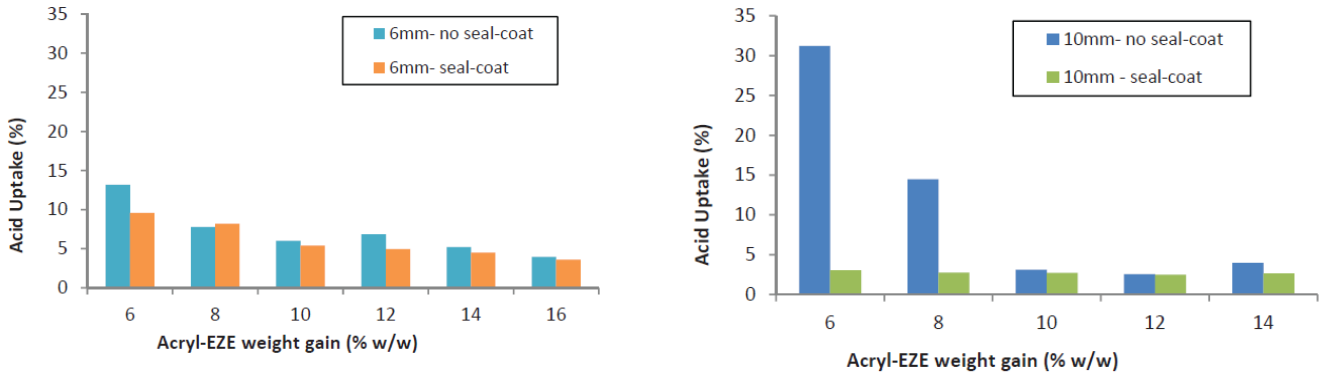
Figure 3 shows the acid resistance testing results of both sets of tablets, with and without seal-coat. It has been reported that up to 10% acid uptake by enteric coated tablets is acceptable for enteric functionality. Generally, the minimum amount of enteric coating weight gain required to achieve satisfactory acid resistance increases with increasing surface area of the cores. Therefore, smaller cores tend to require higher weight gains. However, the following results indicate that tablet mechanical robustness plays a large part in the quality of an enteric coating as well.

In the case of the larger, more friable aspirin cores, application of a seal-coat made a substantial difference in the amount of enteric coating required to provide acid resistance. At 6% weight gain of the Acryl-EZE, the 10 mm standard, round, concave tablets without seal-coat showed more than 30% acid uptake compared with less than 5% acid uptake after addition of a seal-coat. To achieve the same level of acid resistance, these friable cores required a 10% weight gain of Acryl-EZE. While this process would be a one-step process, material costs and processing times would far exceed those needed for a 1% seal-coat and 6% weight gain of enteric coating.

In both cases, addition of a seal-coat of a clear Opadry (1% w/w) reduced the overall amount of Acryl-EZE necessary to achieve enteric protection. For the small, robust tablets, acid resistance was achieved at 8% weight gain of Acryl-EZE without a seal-coat, and 6% weight gain of Acryl-EZE with a clear Opadry seal-coat.

In this study, the coating amounts in terms of both weight gain (as a percentage of uncoated tablet weight) and weight (or mass) applied per surface area (in mg/cm2) were quantified. Previous work has recommended 6 mg/cm2 for acrylate-based enteric coatings.

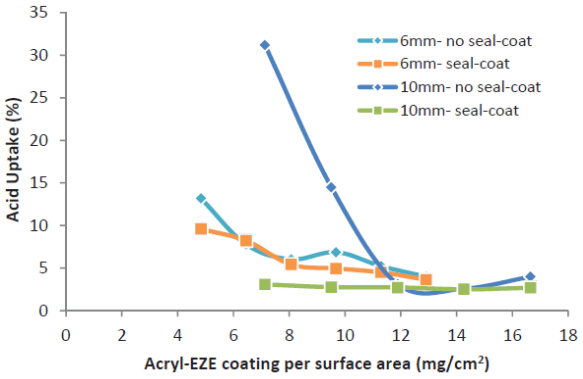
Figure 3. Effect of Enteric Coating Weight Gain on Acid Uptake (%) for a 6 mm Placebo and a 10 mm Aspirin Core



Looking at the acid resistance as a function of amount of coating per surface area (**Figure 4**), this is a good recommendation for the small, robust cores and the seal-coated friable cores. However, for the friable aspirin core without

a seal-coat, the required amount of enteric coating (12 mg /cm2) was necessary to achieve satisfactory acid uptake results. Mechanical robustness of the tablets played a significant role in the amount of enteric coating required.

Figure 4. Enteric Performance as a Function of Amount of Coating Applied Unit Surface Area (mg/cm2)



MEASUREMENT OF FILM COATING THICKNESS

Scanning Electron Microscopy

Figure 5 shows typical micrographs of the corners of bisected tablets. In this particular case, we examined the cross-section of 10 mm aspirin tablets (a) without and (b) with a seal-coat of a clear Opadry, and coated with Acryl-EZE 8% weight gain (w/w) in both cases. Micrograph 5a revealed a weak point in the coating at the corner of the tablet without the seal-coat. Addition of a seal-coat of a clear Opadry allowed the functional coating to be more evenly applied across the entire surface and corners of the tablet, enhancing enteric protection of the tablet using the same amount of functional coating.

Figure 5. Cross-Section of a 10 mm Friable Aspirin Core Coated with 8% w/w Acryl-EZE Aqueous Enteric Film Coating: (a) without Seal-coat; (b) with 1% w/w Application of a Clear Opadry Seal-coat

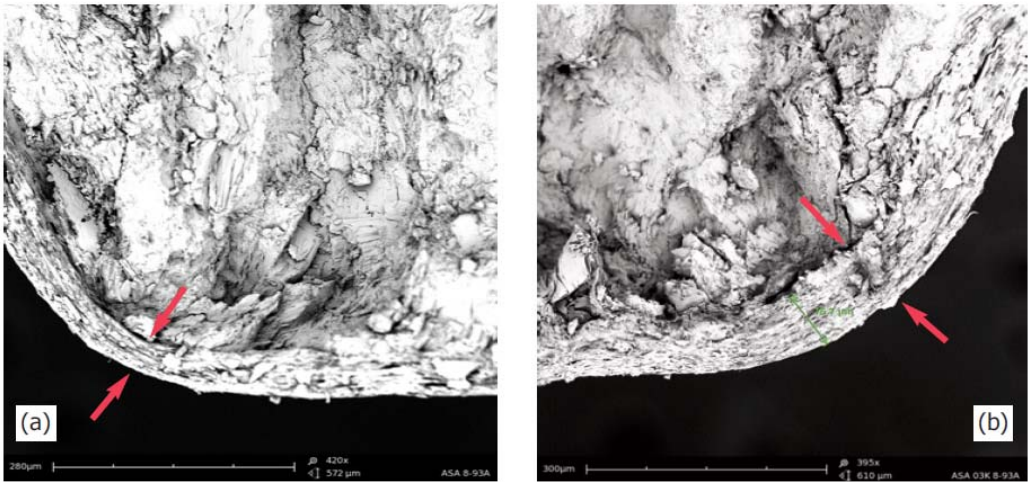
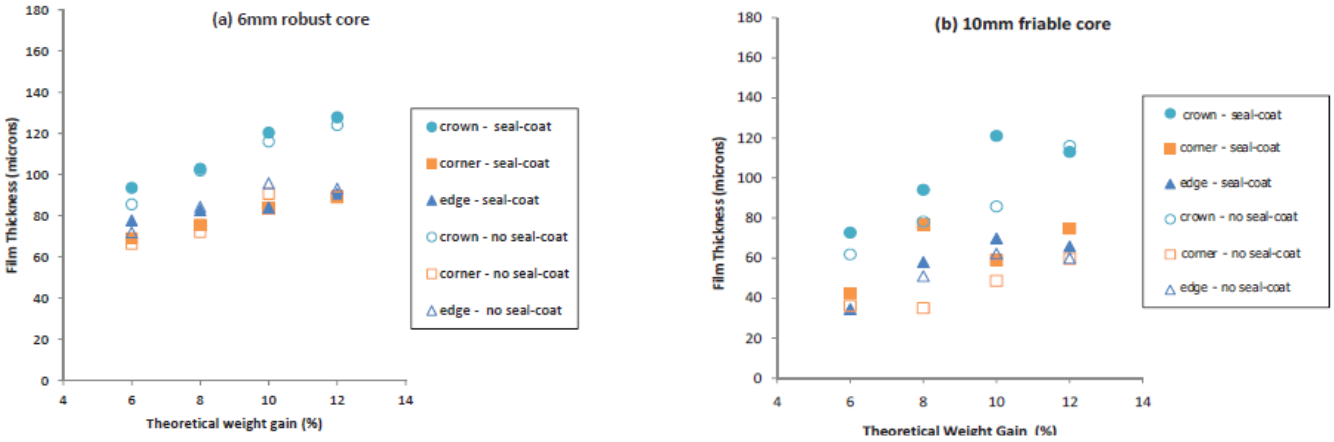


Figure 6 shows the film thickness as a function of coating weight gain for both 6 and 10 mm tablets. The coating thickness on the crown of the tablet was consistently greater than that on the corners or edges of the tablets. SEM was unable to distinguish the clear Opadry seal-coat from the Acryl-EZE functional coating, and, therefore, the thickness of the seal-coated samples represents total film coating thickness. At lower levels of coating weight gain, film thicknesses were

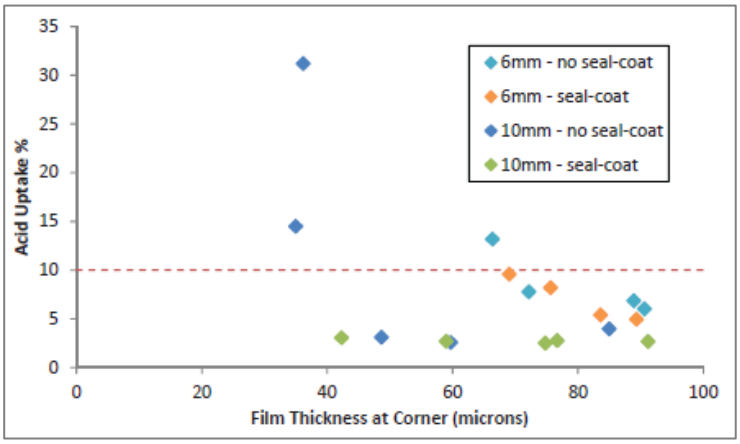
as low as 30 microns for the larger tablets vs. nearly double on the smaller tablets. A larger difference in film thickness was also seen on the 10 mm tablets with the application of a seal-coat.

Figure 6. Film Thickness as Measured by SEM on (a) 6mm Robust Cores and (b) 10mm Friable Cores



SEM revealed that the corners of the tablet show the least amount of coating on a consistent basis so we attempted to establish a correlation between minimum corner film thickness and satisfactory acid uptake values (**Figure 7**). However, the results were not consistent. For the 10 mm tablets, a corner film thickness of approximately 40 microns provided sufficient protection, but, for the 6 mm tablet without seal-coat, a corner film thickness of more than 60 microns still resulted in suboptimal acid resistance. This suggests that there are more factors than simple film thickness that affect the enteric performance of the film coating such as process conditions, the use of a seal-coat that could improve mechanical integrity, and the quality of the applied film.

Figure 7. Comparison of Acid Resistance and Total Coating Film Thickness at the Corner of the Tablet



Laser-Induced Breakdown Spectroscopy (LIBS)

While SEM allowed for physical measurement of the film coating thickness, sample preparation was extensive, and evaluation of many samples can be time consuming. LIBS offered a means of determining the relative film thickness of tablets in a rapid and easily automated fashion without any special sample preparation. One drawback to the LIBS technology is that the current configuration only allows for measurement across the face of the tablet at preset locations and does not allow for examination of the film coating at the corners, edges, or other such locations which may prove to be significant, such as debossed logos or visual defects.

Titanium (from titanium dioxide) in the Acryl-EZE coating was used as the marker element, and so thickness here is representative only of the enteric coating and not the clear Opadry seal-coat. In the LIBS methodology, the laser ablates the coating creating a plasma, which then emits light at wavelengths corresponding to the elements in the plasma. The intensity of the emitted light is directly proportional to the concentration of a given element in the plasma.

Figure 8 shows the titanium signal intensity after each of 30 laser pulses in the center of the 6 mm core (n=20) coated with 6% weight gains of Acryl-EZE. The intensity of the titanium signal quickly increases between 1 and 5 laser pulses (shots) and then plateaus at ~5-13 shots as the laser penetrates into the center of the coating layer. Beyond about 13 shots, the intensity of the titanium signal begins to weaken indicating that almost all of the coating has been ablated. Intensity vs. laser shot number values from each of the 20 coated tablets were then averaged. Based on this average curve, the number of shots required to obtain 50% of the maximum titanium signal intensity was determined and taken as a rough indication of the number of laser shots required to completely ablate the coating **(Figure 9**). This was repeated for each of the weight gains, with and without seal-coat. **Figure 10** shows a compilation of the data acquired for the 6 mm robust core at 6, 8, 10, and 12% weight gains. The ½ max values increased with increasing weight gain indicating that more laser shots were required to ablate the coatings as the coatings became thicker, as expected.

Figure 8. Example of LIBS Data for 20 Tablets at Center of Small, Round Placebo Tablet with 30 Laser Pulses

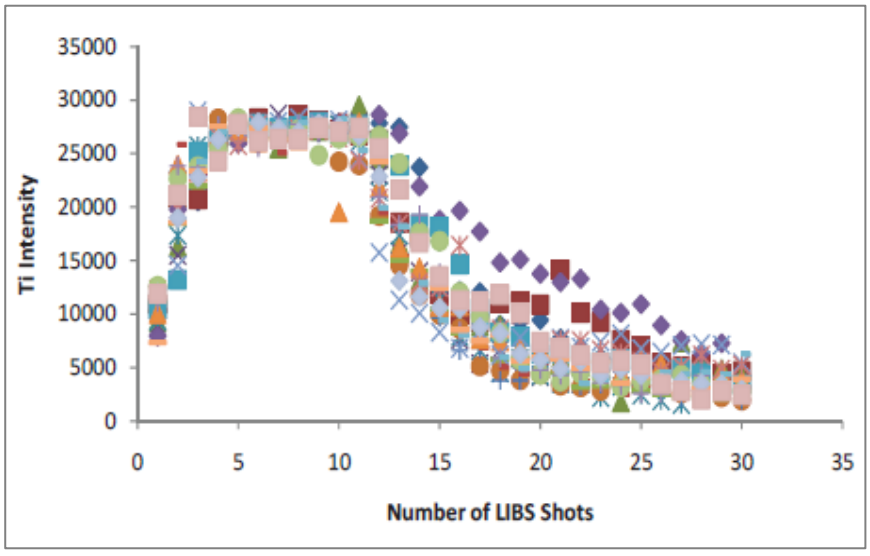


Figure 9. Titanium Signal Intensity for 6%

Weight Gain on 6 mm Core without Sub-coat.

(This serves to illustrate the determination of relative film thickness using the count value equal to one-half the maximum titanium signal intensity. In this case, it takes 14.6 shots to reach one-half the maximum.)

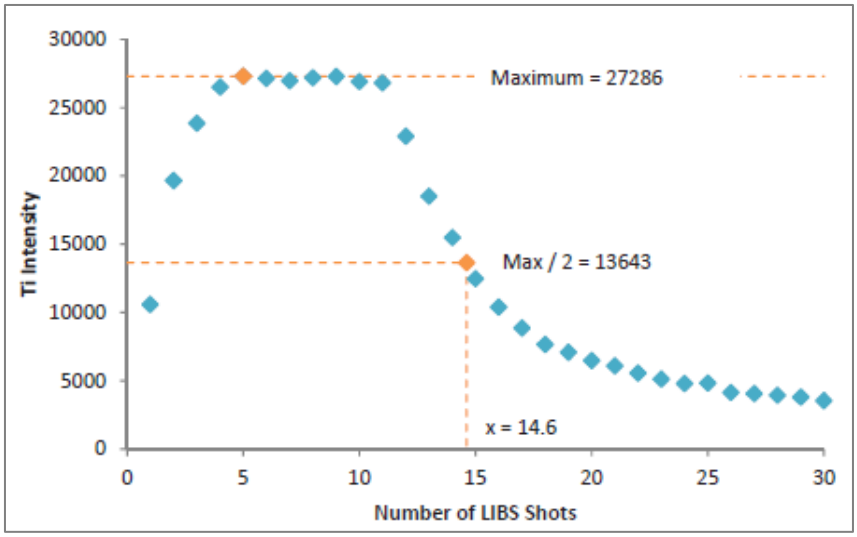
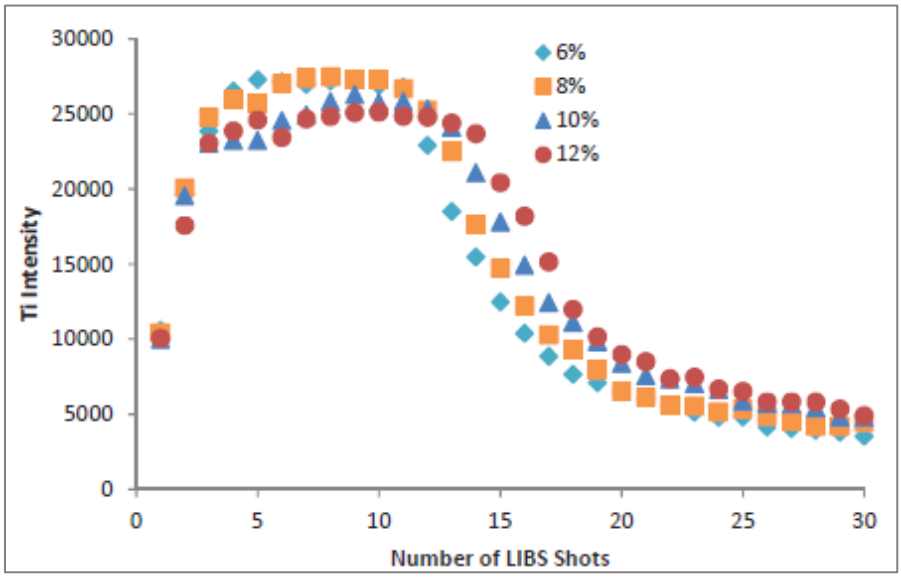


Figure 10. LIBS Map of Titanium Signal Intensity

at the Center of the Tablet Face for Varying

Weight Gain on a 6mm Round Placebo.

(Values are averaged over 20 tablets.)



By determining the number of laser shots required to reach ½ signal maximum and comparing those values vs. the theoretical weight gains, we constructed **Figure 11**. This figure shows that with increasing weight gain, a higher number of laser shots were required to penetrate through the entire enteric film coating.

These readings were obtained for all 4 sets of tablets: 6 and 10 mm tablets, with and without seal-coat. Again, using the amount of coating applied per unit surface area, we removed the variable of tablet size from the equation and constructed

a correlation between the depth or thickness of the enteric film coating as determined by LIBS and the amount of coating applied (**Figure 12**). Three of the 4 tablet groups form a very tight correlation between the number of LIBS shots and the amount of coating applied per surface area. At this point in time, it is unclear as to why the data for the 10 mm tablets without seal-coat appear to be outliers.

Figure 11. Comparison of Weight Gain and Laser Shots to Penetrate the Acryl-EZE Coating for the 6 mm Robust Core Without Seal-coat.

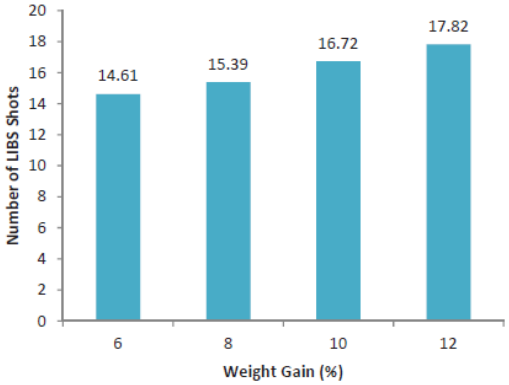
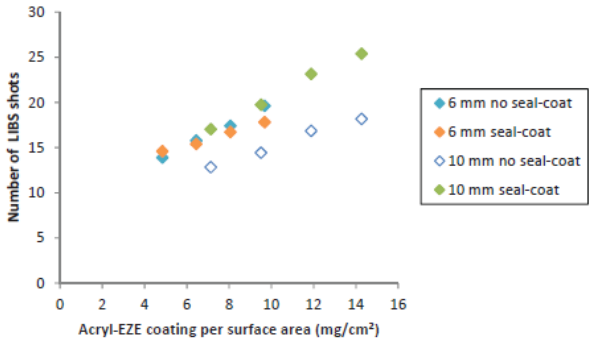


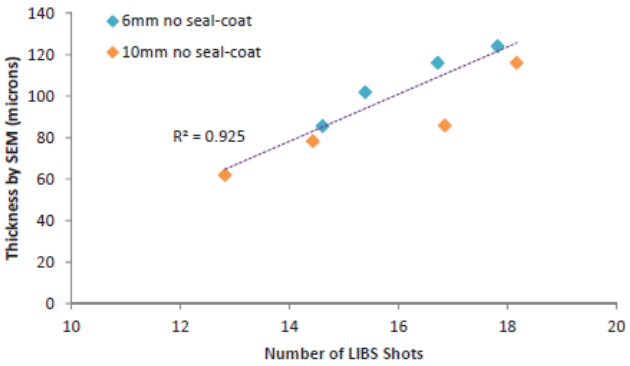
Figure 12. Plot of Relative Enteric Film Thickness, or Depth, as Measured by LIBS Vs. the Amount of Coating Applied Per Unit Surface Area.



Combining SEM & LIBS

By examining the relative thickness in LIBS shots against thickness by SEM, one can begin to create a correlation between the two methodologies. This illustrates LIBS' potential as a predictive on-line tool to determine functional coating endpoint. The correlation was developed by combining the two data sets for the non seal-coated tablets, resulting in a satisfactory R2 value of more than 90 (**Figure 13**). Further evaluations must be conducted across other coatings and substrates to create a robust calibration curve.

Figure 13. Correlation Between Acryl-EZE Film Thickness as Measured by SEM and LIBS



CONCLUSIONS

Experimental work with tablets of 2 sizes (6 and 10 mm standard, round concave) revealed an application of an Acryl-EZE aqueous enteric coating at 6mg/cm2 for a robust tablet will provide adequate acid resistance. However, in the case of a friable tablet, much higher levels are needed to compensate for the poor coverage of any corner or abnormalities in the tablet surface, as evidenced through SEM. Addition of an Opadry seal-coat added strength to the cores and allowed more even film thickness of the enteric coat across the tablet surfaces.

SEM provided a detailed view of the tablet film coating but required extensive sample preparation while LIBS offered a rapid measurement of relative film thickness with virtually no sample preparation. Further development of LIBS may provide a valuable rapid tool for accurate measurement of functional film thickness.

REFERENCES

1. Dubey A, Portillo, P, Muzzio FJ. “Study of tablet coating thickness uniformity using LIBS, DEM, and compartment modeling.” AIChE Annual Meeting, 2008.
2. Dubey A, Portillo P, Muzzio FJ. “A study of tablet coating uniformity using LIBS.” IFPAC, 2009.
3. Ali R Rajabi-Siahboomi & Thomas P. Farrell. Editors: Linda Felton and James McGinity, Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, 3rd Edition, 2008.
4. Cole G, Hogan J, and Aulton M. (2008) Pharmaceutical Coating Technology. (pp. 433-434). New York: informa healthcare.

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