Electronic Supplementary Material (ESI) for Analyst.

Supporting Information

In-situ Analytical Characterization and Chemical Imaging of Tablet Coatings using Laser Induced Breakdown Spectroscopy (LIBS)

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1. Instrumentation

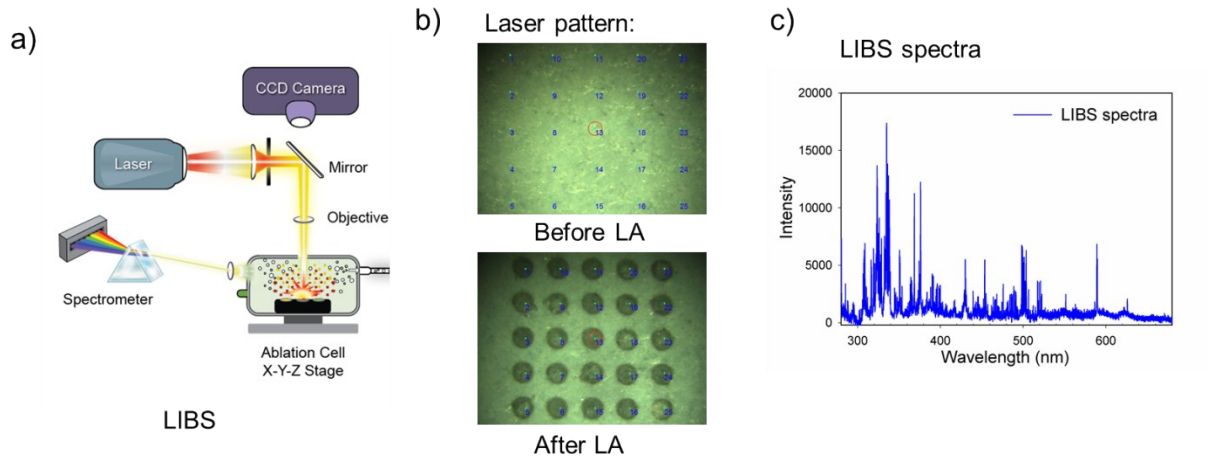

Figure S1. a) Schematic view of the LIBS experiment showing the laser ablation (LA) process. The emission light can then be detected by spectrometer. b) Example of laser pattern (grid of points) before LA and after LA. c) Example of LIBS spectra recorded for the blue tablet coating.

Tablet analysis was performed using a J200 Tandem LA/LIBS system (Applied Spectra Inc., Fremont, CA, USA). The J200 consists of a 266 nm Nd:YAG laser (ns) operated with 10 Hz repetition rate, a Czerny–Turner spectrometer with a CCD detector, and an x–y–z translational stage. Spot size, gate delay, and energy output were optimized for a high signal/noise (S/N) ratio while maintaining sufficient depth profiling resolution. A carrier gas (helium, 1 L/min) was utilized to reduce the re-deposition of the ablated material. All parameters were controlled within Applied Spectra's Axiom Software.

Two parameters of interest for LIBS are the ablation threshold and the spot size. The ablation threshold is usually determined experimentally, but it can be calculated if the material is well characterized and all the properties are known. Additionally, the spot size can be calculated theoretically based on the lens positions and distances, and also based on the aperture size. However, the actual spot size on the sample is usually determined by the energy and the sample's physical and chemical properties, e.g. a theoretical 100 µm spot size might be slightly bigger in some samples due to the heat affected zone as well as the energy dissipation.

In this work, there are six channels in the spectrometer and the gratings in each of the channels are as follows:

Ch 1: 2400 gr/mm
Ch 2: 1800 gr/mm

Ch 3: 1800 gr/mm
Ch 4: 1800 gr/mm
Ch 5: 1200 gr/mm
Ch 6: 1200 gr/mm

The resolution of the spectrograph is estimated as follows:

Channel 1 = .09nm
Channel 2 = .10nm
Channel 3 = .09nm
Channel 4 = .08nm
Channel 5 = .14nm
Channel 6 = .11nm

This resolution is sufficient to carry out atomic emission spectroscopic measurements.

On the CCD detector, the gate delay (when the acquisition starts) can be controlled down to nanosecond times. The gate width is predetermined by the CCD and is usually 1.05 ms. Although this value can be extended, this parameter was set to a minimum since this is both optimal and sufficient.

2. Coating Material Composition

2.1 Description of Blue and Green Tablets Coating Process

Prepare a suspension of the Opadry® II Blue/Green film coating material in purified water. Charge the tablet cores to a pan coater and spray the film coating suspension to the tablet cores.

Table S1. Batch formula for blue and green tablets (amount (kg) per batch):

Component	Blue tablet	Green tablet
Drug Substance	1.30	4.33
Lactose Monohydrate	10.27	7.24
Povidone	0.65	0.65
Croscarmellose Sodium	0.65	0.65
Purified Water*	-	-
Magnesium Stearate	0.13	0.13
Theoretical Core Tablet Batch Size	13.00	13.00
Film-coating suspension		
Opadry® II 85F90660	0.52	0.52
Purified Water*	-	-
Theoretical Coated Tablet Batch Size	13.52	13.52
Theoretical Batch Size (# of Tablets)	108,333	108,333
*Evaporates during processing		

2.2 Description of Mini and Adult Tablets Coating Process

Table S2. Adult tablets (100mg) composition:

Component	mg/tablet	% w/w
Drug Substance	100.0	9.709
Hypromellose Acetate Succinate	400.0	38.83
Aceton	-	-
Purified Water	-	-
Lactose, Monohydrate	215.0	20.87
Cellulose, Microcyrstalline	215.0	20.87
Croscarmellose Sodium	60.0	5.825
Colloidal Silicon Dioxide	5.0	0.485
Magnesium Stearate	5.0	0.485
Total core tablet weight	1000	97.09
Film-coating suspension		
Film Coating System	30.0	2.913

Carnauba Wax	0.031	0.0030
Purified Water	-	-
Total Theoretical film coating tablet weight	1030	100.0

Table S3. Film Coating System Composition for Adult Tablet

Components	**Weight%**
Hypromellose	45.00
Titanium Dioxide	25.00
Lactose Monohydrate	22.00
Triacetin	8.000

3. SEM Measurements

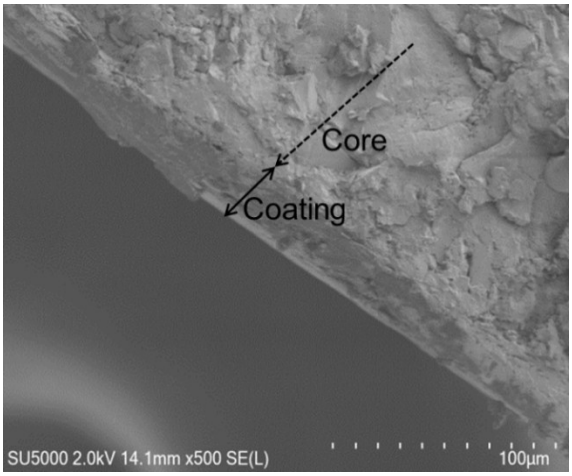

Figure S2. SEM image of blue tablet, showing the coating and core.

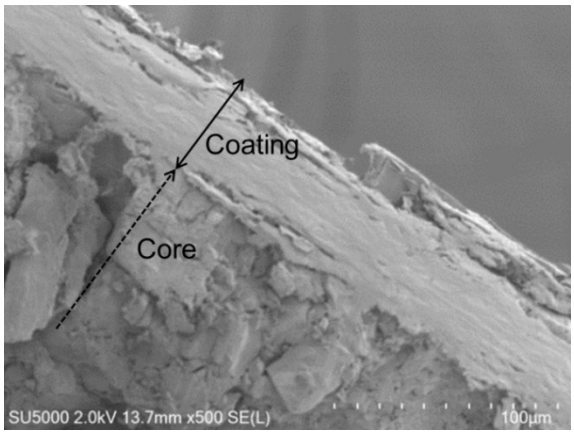

Figure S3. SEM image of green tablet, showing the coating and core.

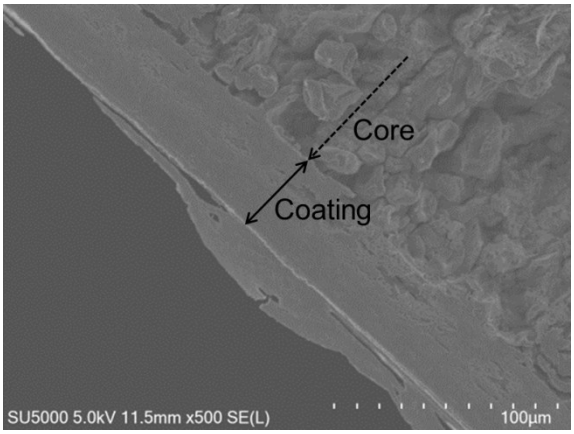

Figure S4. SEM image of mini-tablet, showing the coating and core.

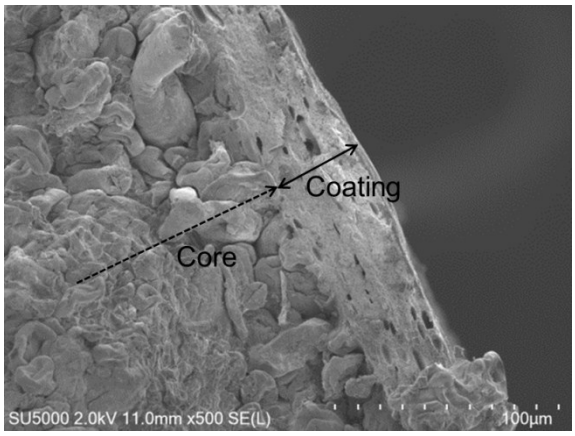

Figure S5. SEM image of adult tablet, showing the coating and core.

Table S4. Coating thickness (µm) from SEM measurements.

	1	2	3	4	5	6	Average	Uncertainty	RSD(%)
Blue tablet	32.2	31.3	32.0	31.2	27.6	33.2	31.2	1.9	6.2
Green tablet	39.5	41.6	40.2	38.2	36.9	39.3	39.3	1.6	4.1
Mini-tablet	38.9	39.8	38.6	44.2	38.9	38.5	39.8	2.2	5.5
Adult tablet	38.2	43.5	35.7	34.7	33.3	37.0	37.0	3.6	9.7

4. Coating Thickness Measurements for Tablet Coatings with Different Weight Gain

The developed protocol for the measurement of coating thickness by LIBS was successfully applied in a case study. Green tablets were coated to different weight gain (1%, 2%, 3%, 4%, 5%, and 6%), which is the increase in dry weight of tablets after coating.[1] Then they were measured under the same condition previously. From Figure S6 and Figure S7, a clear trend was observed. As the weight gain increases, the laser shot number needed to penetrate the coating also increases, with a correlation factor of 0.966. Case study demonstrated here confirms that LIBS is an accurate and rapid method for the measurement of coating thickness.

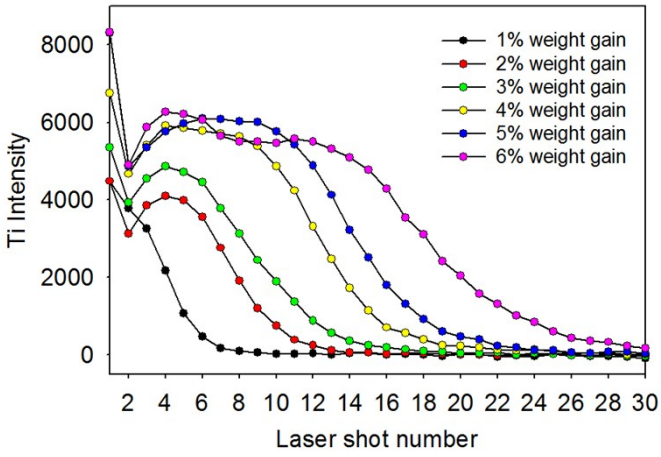

Figure S6. Plot of averaged Ti intensity vs laser shot number for tablet coatings with different weight gain (1%, 2%, 3%, 4%, 5%, and 6%).

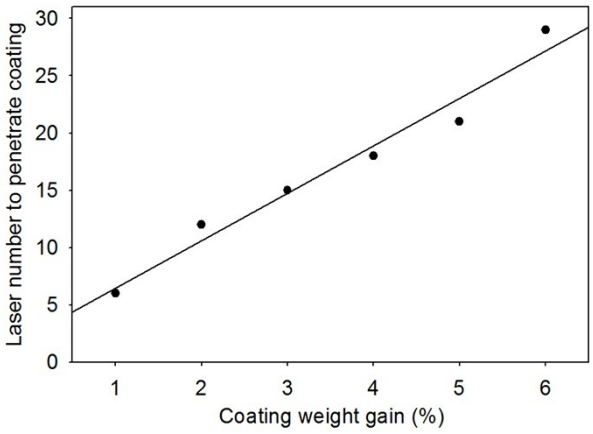

Figure S7. Correlation between the laser number required to penetrated coating and the coating weight gain with $R^2 = 0.966$.

5. Photostability Test of the Mini-tablet and Adult Tablet

Table S5. Photostability study procedure:

Sample Position:	To maximize light exposure, the tablets should be placed arranged as follows: • Open Dish Configuration: tablets should be lying flat in dish with no overlap and one layer deep • Bottle Configuration: bottle should be placed lying on its side within the chamber in attempt to minimize tablet overlap
Temperature:	The chamber temperature should be controlled to 25°C ± 2°C
Humidity:	The chamber humidity should be controlled to 60%RH ± 5%RH
Exposure Conditions:	As per the ICH guideline, samples will be exposed to a minimum of 1.2 million Lux Hours visible light and a minimum of 200 Watt Hours/m^2 near ultraviolet (UV) light.
Visible Light:	Samples will be initially exposed to visible light to meet the ICH minimum requirement. The chamber should be set to approximately 12.00 x 10^3 Lux Required Exposure = 1.2 x 10^6 Lux Hours x 1.258 (expanded uncertainty) = 1.51 x 10^6 Lux Hours Required Exposure Time = (Required Exposure / Light Controller Set Point) = (1.51 x 10^6 Lux Hours / 12.00 x 10^3 Lux) = 126 Hours
Near Ultraviolet Light:	After exposure to visible light, the samples will be exposed to near UV light to meet the ICH minimum requirement. The chamber should be set to 16.00 Watts/m^2. Required Exposure = (200 Watt hours/m^2) x 1.290 (expanded uncertainty) = 258 Watt hours/m^2 Required Exposure Time = (Required Exposure / Light Controller Set Point) = (258 Watt Hours/m^2) / (16.00 Watts/m^2) = 16.2 Hours

Tablet S6. Photostability study of adult tablets.

Coating Level	Sample minus Control	Full ICH Light Exposure Samples			Foil-wrapped Control		
		Rep 1	Rep 2	Average	Rep 3	Rep 4	Average
Control	3.15%	3.03%	3.57%	3.30%	0.15%	0.15%	0.15%
Coated	0.17%	0.27%	0.33%	0.30%	0.13%	0.12%	0.13%

Above chemical stability data indicates that the film coating provides additional protection from light exposure and minimizes the risk of photodegradation above ICH limits if the product exposed to light. The coating system contains hypromellose, titanium dioxide, lactose monohydrate, and triacetin.

Reference:

1. C. Cahyadi, B. X. Tan, L. W. Chan and P. W. S. Heng, *AAPS PharmSciTech*, 2012, 13, 785-792.