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A Novel Imaging Technique to Investigate the Influence of Atomization Air Pressure on Film–Tablet Interfacial Thickness

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A novel X-ray photoelectron spectroscopic (XPS) technique combined with principal component analysis of spectra-to-image datasets was employed to study the effects of atomization air pressure used during the coating process on film–tablet interfacial thickness. Placebo tablet cores were prepared and coated with Eudragit® RL 30 D. Atomization air pressure was varied from 10 to 20 psi, whereas all other processing parameters were held constant. Higher air pressures generally produced thinner interfaces, although the interfacial region was not uniform across the tablet surface and was dependent on the sampling location. These results demonstrate the suitability of this XPS technique to study the coating–tablet interface. Moreover, the variability in the interfacial thickness illustrates the need to further study such systems.

Keywords film coating; film–tablet interface; X-ray photoelectron spectroscopy; processing parameters; atomization air pressure

INTRODUCTION

Polymeric film coatings have been applied to various solid dosage forms to improve aesthetic qualities (Felton & Wiley, 2003), mask an unpleasant odor or taste (Cerea, Zheng, Young, & McGinity, 2004; Pearnchob, Siepmann, & Bodmeier, 2003), facilitate swallowing upon ingestion, improve product stability (Felton & Timmins, 2006; Ruotsalainen, Heinamaki, Taipale, & Yliruusi, 2003), and alter drug release characteristics (Dashevsky & Mohamad, 2006; Siepmann, Siepmann, Walther, MacRae, & Bodmeier, 2006; Zheng, Sauer, & McGinity, 2005). The process of applying thin polymer films to solid substrates is a complex, multi-step process involving the atomization of the polymer solution or dispersion, the impingement of the polymer-containing droplets onto the solid surfaces, spreading of the droplets, and finally film coalescence (Carlin, Li, & Felton, 2008). During the coating process, atomized droplets cause dissolution of the outermost surface of the tablet. Drugs and excipients from the tablet can migrate into the film coating, influencing the mechanical, adhesive, and drug release properties of the polymer (Felton & Perry, 2002; Felton et al., 1996; Missaghi & Fassihi, 2004). Our understanding of such interactions between the substrate core and the film coating, however, is quite limited and further scientific study is needed for more efficient drug development activities.

Various analytical techniques have been employed to understand scientific mechanisms and facilitate the selection and optimization of formulations, predict process scale-up, and determine properties of raw and processed materials. For example, attenuated total reflectance-fourier transform infrared spectroscopy (FTIR) imaging was used to investigate the distribution of components within tablet compacts (Chan, Elkhider, & Kazarian, 2005). In another study, nuclear magnetic resonance (NMR) was used to determine the drug release mechanism of coated pellets (Ensslin, Moll, Paulus, & Mader, 2008). Terahertz pulsed imaging has been used to evaluate the dissolution performance of coated tablets as a function of coating processing scale (Ho et al., 2008). In this study, a new analytical approach for the characterization of the film–tablet interface was developed

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using X-ray photoelectron spectroscopy (XPS). The film–tablet interface is the region where components of both the polymer and the substrate are found (Felton & Perry, 2002).

XPS is a surface-sensitive technique that has been used to analyze solid surfaces both qualitatively and quantitatively (Buckton, Bulpett, & Verma, 1991; Burke, Wurster, Berg, Veng-Pedersen, & Schottelius, 1992; Davies et al., 1989). A previous study combined ion-sputter profiling with XPS to quantify the thickness of the film–tablet interface (Felton & Perry, 2002). The technique, however, required a complex and lengthy sample preparation. Moreover, the tablet core and polymeric film had to be constructed such that each contained unique chemical signatures for XPS analysis. This study investigated an alternative approach, using XPS in combination with image-to-spectra datasets and principal component analysis (PCA) to investigate the film–tablet interfacial region as a function of atomization air pressure used during the coating process.

MATERIALS AND METHODS

Dibasic calcium phosphate (Emcompress®) was donated by JRS Pharma (Patterson, NJ, USA). Cabot Corporation (Tuscola, IL, USA) supplied the colloidal silicon dioxide (Cab-O-Sil® M-5P). Magnesium stearate USP was purchased from Spectrum Corp (Gardena, CA, USA). Evonik (Piscataway, NJ, USA) donated the Eudragit® RL 30 D aqueous polymeric dispersion. Triethyl citrate was provided by Morflex (Greensboro, NC, USA).

Preparation of the Tablet Core

Dibasic calcium phosphate (99%) and colloidal silicon dioxide (0.5%) were passed through a 30-mesh screen and blended in a V-shell blender (Erweka USA, Inc. Milford, CT, USA) for 10 min. Magnesium stearate USP (0.5%) was sieved through a 40-mesh screen, added to the V-shell, and then the powders were blended for an additional 3 min. The powder blend was compressed into tablets using a Strokes B2, 16-station rotary tablet press (Stokes, Inc., Bristol, PA, USA). Flat-faced punches with a beveled edge were employed. The tablets (12.8 mm in diameter) weighed approximately 1,100 mg and had a hardness of 12 kg.

Coating of Tablet Cores

Tablets were coated with the commercially available Eudragit® RL 30 D aqueous polymeric dispersion. Triethyl citrate (20% wt/wt, based on dry polymer weight) was added to plasticize the polymer. Sufficient water was used to dilute the solids content to 20% (wt/wt). The polymeric dispersion was allowed to mix for 30 min prior to initiation of the coating process. Tablets were placed in a Vector LDCS coating apparatus (Vector Corp., Marion, IA, USA) with 1.3 L pan insert. The batch size was 400 g and the bed temperature was 30°C. A theoretical weight gain of 8% was applied to the tablets. The rotational speed of the pan was set to 15 rpm. The spray rate of the polymer dispersion was 3.2 g/min. Atomization air pressure for spraying was fixed at 10, 15, or 20 psi. All other processing parameters were held constant. Following the completion of the coating process, the tablets were placed in an oven at 40°C for 2 h to promote further coalescence of the coating, then stored in closed glass containers at ambient conditions.

Tablet Cross-Sectioning

For the initial spectroscopy experiments, tablets were cut approximately in half by placing a straight, single-edge blade into the tablet with sufficient force to make the cut. One of the halves was then placed into the sample bar holder of the XPS instrument for analysis. The surface created by the razor blade, however, was too rough for quantitative image analysis, and so alternate methods of cutting the tablet were investigated. A microtoming technique produced sufficiently smooth surfaces for characterization and was used for the imaging experiments. First, the coated tablet was cut in half using a commercially available tablet splitting tool. The exposed interior side was then secured to a microtoming stage using O.C.T. 4583 (Tissue-Tek, Sakura Finetek, Torrance, CA, USA) as an embedding medium and subsequently cut on a microtome a number of times. Before the final cut, the thickness of the shaved slice was set to 0.5 μm in order to produce the smoothest surface possible for subsequent analysis. Samples were then placed directly in the analyzing sample bar of the XPS unit and analyzed within half an hour of preparation. N_2 purge was used before ultra high vacuum (UHV) placement of the samples to eliminate adsorbed hydrocarbons as a possible contamination source.

X-Ray Photoelectron Spectroscopy Acquisition

All XPS data were acquired with a Kratos Axis Ultra photoelectron spectrometer (Kratos Analytical, Inc., Chestnut Ridge, NY, USA). A monochromatic Al K(α) X-ray source was utilized at 300 W (20 mA, 15 keV). Survey spectra and images were acquired with an 80 eV pass energy while high resolution spectra were obtained with a 20 eV pass energy. Charge compensation, required because of the non-conducting nature of the tablets, was accomplished by flooding the surface with low-energy electrons. Standard operating conditions for good charge compensation are −2.8 V bias voltage, −1.0 V filament voltage, and a filament current of 2.1 A.

Spectroscopy

Survey spectra from 300 × 700 μm areas were acquired for 2 min at each sample position. High-resolution spectra were acquired from the same areas with the following acquisition regions and times: C1s 300–278 eV for 180 s, O1s 540–524 eV for 180 s, Si2p 106–92 eV for 180 s, Na1s 1080–1062 eV for180 s, and S2p 170–156 eV for 300 s. Each sample was analyzed in triplicate. Spectra were charge-corrected to adventitious carbon, at a binding energy (BE) of 285.0 eV.

Imaging

The first set of C1s images were acquired at maximum signal intensity for the carbon C1s peak and had a BE of 283.2–283.5 eV, depending on the sample. Multivariate image datasets were constructed from a series of images acquired from the same position as a function of BE. High magnification images (250 × 250 μm) were acquired over the BE range of 295–278 eV with 0.2 eV/step for 2 min each, which resulted in 85 images. Images were charge-corrected using the same procedure as for the spectra data. PCA was performed on each multivariate image dataset prior to classification analysis.

Data Analysis

Principal Component Analysis

PCA is generally used to evaluate correlations and variations in large datasets. PCA is a linear transformation that converts data into a new coordinate system where coordinates are principal components (PCs). The results of the analysis are scores (image-like maps) and loadings (spectra-like graphs), as shown in Figure 1, where the first PC accounts for the majority of variance in the dataset, and the second component accounts for the next greatest variance, and so on. In this study, PCA reduced the dimensionality of the 85 images of the C1s region to three PCs that captured a 99% variance in the original data set. No additional processing was applied to the data in order to keep the original intensities within the dataset. The PCA utilized the PLS_Toolbox Version 3.5 for MATLAB (Eigenvector Research, Wenatchee, WA, USA).

Chemical identification of PC images calculated from the C1s dataset is generally possible based on the comparison of their loadings with the spectral envelopes (photo peaks) of C1s high-resolution spectra acquired from the same area. Based on the examination of the first PC1 image, three peaks corresponded to photo peaks present in the coating and in the tablet core (C1s high-resolution spectra, Figure 2), therefore representing the topography of the analysis area. The PC2 image in Figure 2 was a combination of two intense negative peaks from images acquired at 289.0 and 285.0 eV BE which appeared at the same BE in the high resolution C1s spectrum of the coating. Therefore, the PC2 image captured chemical variation in the coating region (spectroscopy section for C1s spectra of coating and tablet core). For the samples prepared using a razor blade to cross section the coated tablet, PCA extracted topography was used as the most common variable within the dataset and it was not possible to classify chemical interfaces based on topographical information. In contrast, samples prepared by microtoming did not exhibit topography and the first PC image contained chemical information. A classification procedure was further used to quantify the distribution of carbon chemical species specific to the coating and the tablet.

Classification

Classification is the process of assigning data to one of a fixed number of possible classes (Artyushkova, 2002, 2004). Classification converts the image data into descriptive labels that categorize different materials present. Similarity between pixels or groups of pixels is a fundamental concept of classification, since labels are assigned to areas on the sample that have similar chemical or physical characteristics. In this study, carbon C1s images were chosen for classification as the C1s

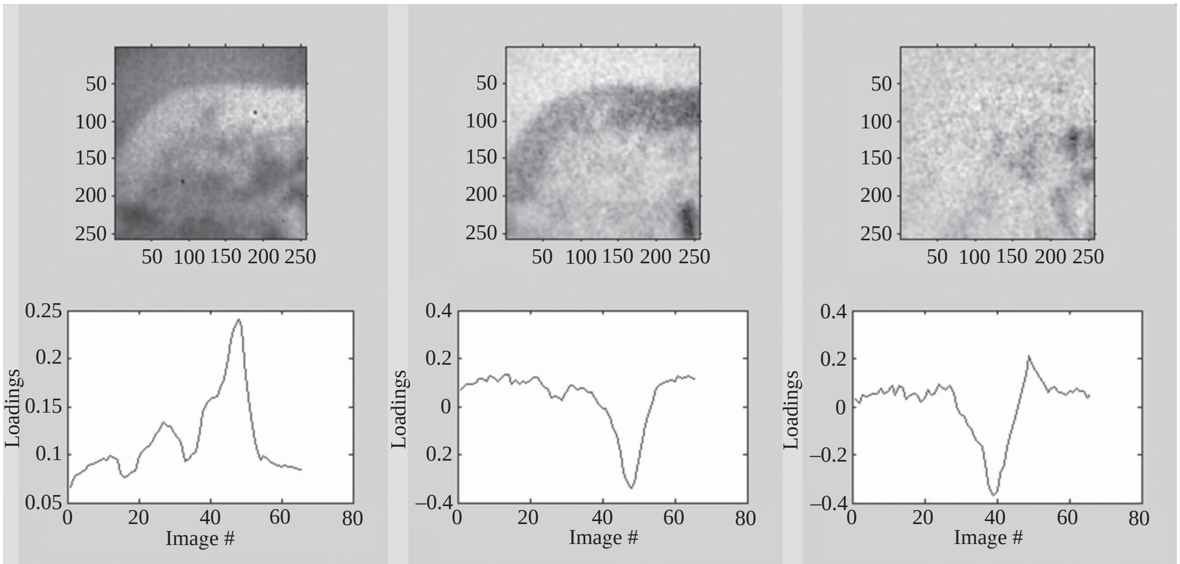

FIGURE 1. PCA results on 10-psi C1s dataset acquired from razor cut interface with scores (on top) and loadings (on the bottom).

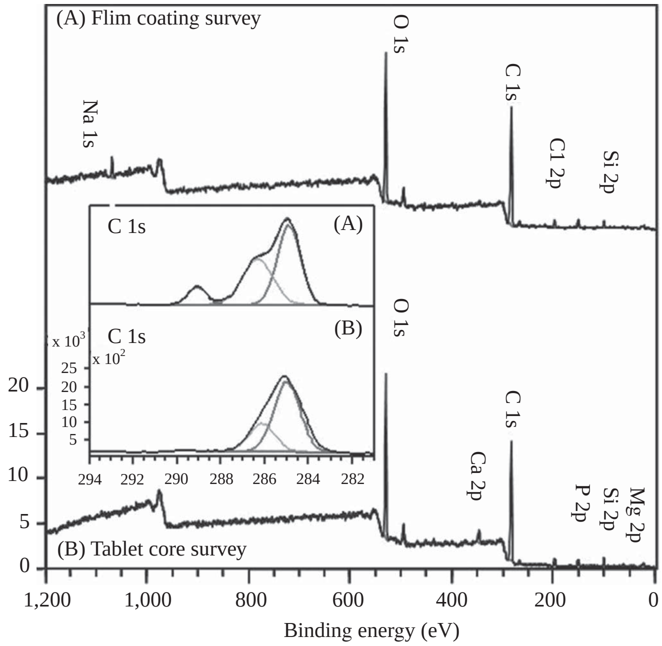

FIGURE 2. XPS of the coating and tablet core survey and C1s high-resolution spectra. (A) Coating and (B) tablet.

chemical shifts are well documented (http://www.nist.gov/srd/nistweb20v4.htm).

Image classification algorithms have been described in detail (Artyushkova, 2002, 2004) and here we briefly describe the algorithm utilized in this study. PCA was used to reduce the number of images to three PCs: PC1, PC2, and PC3. Next, training pixels were identified in order to classify regions in the images into categories of interest. Finally, the rules developed during training were used to assign all pixels in the image to one or more of the training categories. The output map consisted of one label for each pixel and classes were formed if the neighboring pixels had the same labels. For this project, external knowledge of the coating and tablet core location on the images was used for the supervised classification algorithm. Supervised maximum likelihood was selected to characterize the carbon images-to-spectra datasets. This algorithm allowed the analyst to select regions in the image which were then used to develop categories of pixels for additional image classification. The classification analysis was performed using ENVI (ENVI, The Environment for Visualizing Images, ITT Visual Information Solutions, Boulder, CO, USA).

RESULTS AND DISCUSSION

The composition of the film coating and tablet core was determined from the XPS spectroscopy data (Figure 2). Elemental analysis of three areas per sample was performed and compositions are reported in Tables 1 and 2. Experimental mass percentage was then correlated with theoretical mass percentage.

TABLE 1
Comparison of the Theoretical and Experimental (XPS) Elemental Concentrations for the Film Coating

	Elements				
Coating Composition	O	C	Na	Cl	Si
Theoretical (at.%)	35.0	62.5	–	1.8	–
Experimental[a] (at.%)	27.2	66.7	1.4	1.3	3.3
SD	0.8	0.9	0.1	0.1	0.1
%RSD	2.9	1.3	7.1	7.7	3.0

[a] Average from three areas per sample.
RSD, relative standard deviation.

TABLE 2
Comparison of the Theoretical and Experimental (XPS) Elemental Concentrations for the Tablet Core

Tablet Core Composition	Elements					
	O	C	Ca	P	Si	Mg
Theoretical (at.%)	46.7	23.7	12.9	10.2	2.2	4.4
Experimental[a] (at.%)	43.0	26.1	13.5	9.8	3.8	3.8
SD	2.7	2.8	2.0	2.2	1.5	1.2
%RSD	6.2	10.7	14.8	22.4	39.5	31.6

[a] Average from three areas per sample.

According to the chemical composition of the coating (ammonio methacrylate copolymer/triethyl citrate as 83.3/16.7 wt %), the elements present should include O, C, N, and Cl, with O and C present in the highest concentrations. All primary elements were detected by XPS with the exception of N, whose theoretical concentration was near the limit of detection. The composition of the coating was uniform, as the concentrations of the primary elements changed less than 5% in relative *SD* at the three sampling points (Table 1). The spectra, however, exhibited photopeaks that were not associated with the theoretical composition of the coating, including Na and Si (Figure 2). Na was present at very low concentrations (1 at.%) and was attributed to the NaOH included in the aqueous polymeric dispersion as an alkalizing agent.

Si was detected in the coating at a concentration of 3.3 at.% and may be attributed to contamination during the coating process. It should be noted that Si was present in the tablet core as colloidal silicon dioxide. Although the concentration of silicon dioxide in the tablet core was low (0.5%), the density of the material is extremely low and the particle size quite small (Rowe, Sheskey, & Owen, 2006). The Si could readily aerosolize within the coating pan from abrasion during tablet rotation and thus contaminate the polymer film during the coating process. However, contamination of Si from tablet abrasion would be expected only until a critical coating thickness was applied, after which the polymeric film would protect the tablet core from further abrasion during pan rotation. Further investigation is needed to address this anomaly.

Survey spectra of the tablet core exhibited photopeaks corresponding to Ca, P, C, O, Si, and Mg (Figure 2), all elements from the excipients used. Interestingly, the composition of the tablet core at the three sampling points was not homogeneous, as can be seen from the high relative *SD*s listed in Table 2. The greatest variation was noted for Si (colloidal silicon dioxide) and Mg (magnesium stearate), the excipients that were present in very low concentrations. These results were not surprising for the magnesium stearate, since this excipient was briefly mixed with the other powders to prevent overblending of the lubricant. However, the variation in silicon dioxide concentration was unexpected and suggested that the initial 10-min blending with the dibasic calcium phosphate was not sufficient to uniformly mix the powders. Other researchers, however, have shown that the compression process itself can also induce segregation as a result of powder flow and compaction (Wray, Chan, Kimber, & Kazarian, 2008).

Deconvolution of the carbon photopeak, shown in Figure 2, was used to analyze the carbon present in both the coating and the tablet core. The C1s images showed a distinct boundary between the air and the sample. Although some unevenness in the images was observed, variation in topography was not considered significant. Because carbon was present in both the tablet and coating composition, differentiating between the core and polymeric film was straightforward using photoelectron imaging alone. This differentiation was accomplished using PCA followed by classification of the carbon species present.

Deconvolution of the carbon spectra from the tablet core revealed two major species of carbon: carbon bound to hydrogen (C–H) and carbon bound to oxygen (C–O, O–C–O). In contrast, three carbon species were identified in the coating (C–H, C–O, and O=C–OH). In subsequent experiments, the distribution of carbon species specific to either the core or the coating was analyzed. All samples were microtomed as described in the section "Materials and Methods" to produce a smooth surface for analysis. Microtomed surface quality was evaluated by examining the cross-sectional area under a light microscope before image-to-spectra acquisition by XPS. Two areas of the tablet face were chosen for analysis, where the thickness of the coating would presumably be consistent. Additionally, one area at the edge of the tablet was analyzed for each sample. The tablet edge is potentially the weakest part of the substrate, susceptible to both abrasion and erosion during the coating process.

Classification analysis was performed on the PC images, as discussed in the section "Data Analysis" (Figure 1). A number of algorithms, using varying numbers of classes, were tested for classification. Maximum likelihood supervised classification with five classes characterized regions in the PC images without introducing artifacts, such as pixilation, difficulty grouping pixels into classes, mixing of classes, and problems correlating physical position of the tablet with the assigned image. The resulting classes were identified as air, air–coating interface, coating, coating–tablet interface, and tablet, and were considered as the most realistic model for characterization.

As shown in Figures 3 and 4, the tablet–coating interface thickness varied significantly on all images and it was not possible to report a single value for each sample coated at a particular psi. In this study, interfacial thickness was estimated by drawing two parallel lines at the continuous tablet and coating boarders. The distance between the lines represented the maximum interfacial thickness and these values are reported in Table 3.

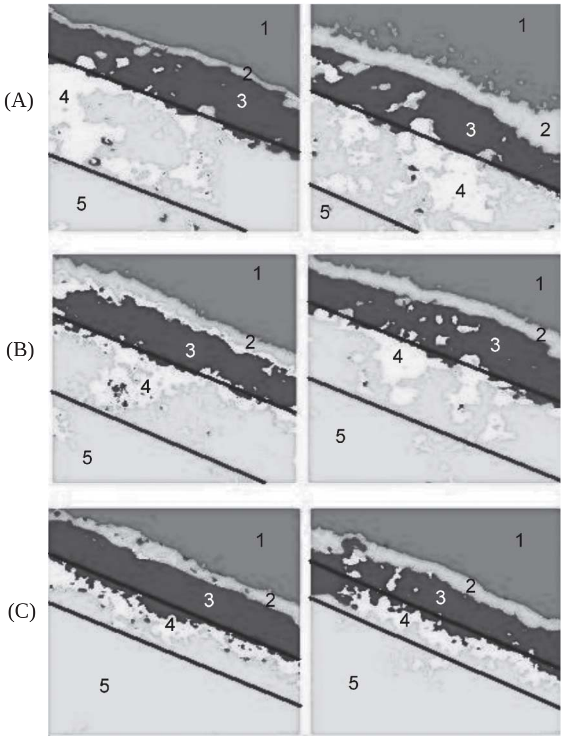

FIGURE 3. Classified images of tablets coated at various atomization air pressures following classification analysis. (A) 10 psi; (B) 15 psi; and (C) 20 psi. Color interpretation for images: 1, air side; 2, air–film interface; 3, film; 4, film–tablet interface; and 5, tablet.

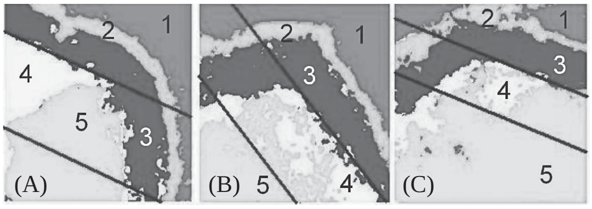

FIGURE 4. Classified images of the edge of tablets coated at various atomization air pressures following classification analysis. (A) 10 psi; (B) 15 psi; and (C) 20 psi. Color interpretation for images: 1, air side; 2, air–film interface; 3, film; 4, film–tablet interface; and 5, tablet.

TABLE 3
Interface Thickness Measured as the Maximum Distance Between Two Sides of the Coating/Tablet Core Region in μm

	Interface Thickness (μm)		
Sample (psi)	Sample 1	Sample 2	Sample 3 (tablet edge)
10	109	98	112
15	81	77	88
20	46	39	58

The film–tablet interfacial region decreased with increasing atomization air pressure. This trend is clearly observed for all regions including the tablet edge area. Tablets coated at 10 psi atomization air pressure exhibited a significantly greater interfacial region than tablets coated at higher air pressures (p = .004; one-way ANOVA). Lower atomization pressure likely produced larger droplets of the aqueous polymeric dispersion, which resulted in greater surface dissolution and physical mixing at the interface before subsequent water evaporation.

The interface at the tablet edge was much thicker and quite non-uniform compared to the areas along the tablet face. However, the film–tablet interfaces at the tablet edge exhibited a similar trend in thickness variation, with interfacial thickness decreasing as atomization air pressure was increased. Because the tablet edges are mechanically weak, there was likely more physical mixing at the interface during the coating process due to both surface dissolution and abrasion.

A previously reported sputter-depth profiling XPS method determined the interfacial thickness of a coated tablet to be 34 μm (Felton & Perry, 2002). In that study, 12 psi was used to atomize the aqueous polymeric dispersion, while the tablet core and coating formulations were the same as in this study. In this study, a visual image of the sample was created by PCA/classification, which demonstrated substantial variation in interfacial thickness (Figures 3 and 4). In contrast, the depth profiling XPS method determined interfacial thickness at a single point and was not able to detect variations in the interface that was shown in this study. Moreover, the depth profiling method required both ion sputtering and a labor-intensive sample preparation that could damage the sample and disturb the interfacial region of interest.

CONCLUSIONS

The combined method of PCA analysis followed by classification of image-to-spectra datasets obtained from XPS can be used to study the film–tablet interfacial region and offers several advantages over the previously reported sputter-depth profiling XPS technique. The method employed in this study was less labor intensive and provided images of the film–tablet interface rather than interfacial thickness at a single point from the sample. This study demonstrated a correlation between atomization air pressure used during coating processes and the resulting film–tablet interface thickness, with higher atomization air pressures producing more narrow interfacial regions. The interfacial region was much thicker at the tablet edges. The results from these studies suggest that processing parameters used during the coating process can impact the physical mixing between the polymer and the tablet core, and further studies are needed to determine the significance of such physical mixing on polymer properties.

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