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A Nondestructive Image-Based Microstructural Characterization of Solid Oral Dosage Forms

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Abstract

Optimizing the performance of drug products requires a strong understanding of the interplay between material properties, manufacturing process parameters, and tablet performance. Microstructure is a crucial intrinsic property that details the spatial and material arrangement that can be examined in a rapid nondestructive scan. Here, we aim to demonstrate the development of a nondestructive, image-based microstructural characterization with potential to rapidly troubleshoot tablet performance with custom analysis. X-ray computed microtomography (micro-CT) is used alongside 3D advanced imaging techniques to examine the spatial distribution of tablet coating and porosity to then model the effect of porosity under simulated dissolution. The benefits of a developed microstructural analysis cannot be overstated, as it has the potential to routinely provide a mechanistic basis to understand, predict, and troubleshoot tablet performance.

Introduction

Performance of every drug product is assessed through extensive physical, chemical, mechanical, and pharmacological testing. However, performance behavior is complex and thus troubleshooting performance is a resource-intensive process, requiring large efforts from various groups and numerous test formulations which lead to extended development timelines.

One of the major keys to this root cause analysis and product optimization is developing a mechanistic understanding of the performance behavior. Specifically, mechanistic understanding can be gained through the advanced analysis of product microstructure. Tablet microstructure describes the arrangement of internal components, such as active pharmaceutical ingredient (API), excipient, coating materials, and pores/voids inside a tablet, due to material interactions and the manufacturing process [1]. Hence, the microstructure of drug products is directly related to drug release, disintegration [3], batch-to-batch consistency, and tensile strength [5]. Therefore, every dosage form, from solid oral dosage forms to depots and lyophilized product have potential to be better understood through an analysis of the internal microstructural characteristics of its form [8].

Microstructure

Material properties, manufacturing process, and tablet performance are inextricably linked through microstructure (see Figure 1). Porosity and pore size are known to have a direct impact on dissolution. The presence of a high porous surface area can facilitate faster dissolution in conditions where liquid intrusion on the outer layers is a rate-limiting step [1]. Simulation models have been used to establish dissolution mechanisms and understand non-standard results [12, 13]. Custom modeling yields potential understanding of the impact of the tablet on the phases of

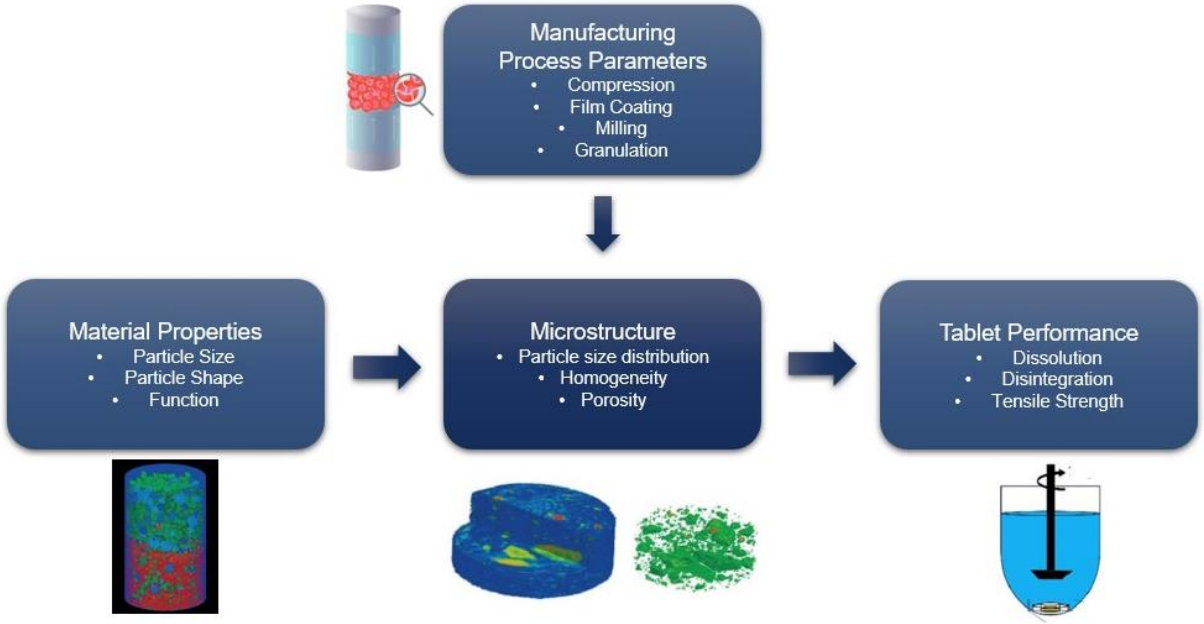

***Figure 1**. Microstructure bridges knowledge between material properties, process parameters, and tablet performance. Adapted from Jia [14] (material properties and microstructure), Skelbæk-Pedersen [16] (process parameters), and Jain[15] (tablet performance).*

dissolution such as disintegration, intrinsic dissolution rate, dissolution rate, and percentage dissolved. In a simple case, one study found that one microstructural descriptor, the quadratic mean and equivalent diameter of the excipient, could effectively describe drug release rate [6]. Stress conditions at high humidity can introduce porosity, material swelling (e.g. MCC and disintegrants), but can also be correlated with decreased dissolution and tensile strength [10]. Similarly, compaction pressure and speed directly introduce particle rearrangements, including deformation and fragmentation [6].

Microstructural Imaging

Chemical imaging (CI) methods, such as Raman spectroscopy, offer spatial resolution of chemical composition and are routinely used for chemometric analysis. The particle-level chemical resolution can be used to determine API polymorphism, material distribution, and agglomerate detection (particle size) [7]. Scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM-EDX) is also used for elemental analysis and evaluation of surface topology.

While these CI techniques can relay chemical distributions in space, they are limited by penetration depth and are destructive in nature. In the case of tablets, the surface must be cut to analyze deeper layers, the method by which is a source of measurement bias [7]. Recent technologies developed in x-ray computed microtomography (micro-CT) fill this gap, providing a complete high-resolution spatial reconstruction in one non-destructive scan, allowing resolution depth up to 3um. Materials with different molecular weight and densities have different attenuation of absorbed X-rays. This creates a high-resolution gray scale scan that is colored with respect to distinct materials, enabling a 3D reconstruction of the tablet, along with the distribution of all components (API, excipient, coating materials and pores/space) internal to it. This digital reconstruction of the tablet can then be used for several computational characterizations of the tablet. The coating layer can then be characterized nondestructively to determine local thickness and roughness profile; pore networks and density distributions can inform mechanical strength; and API can be segmented to determine content uniformity [2].

While the impact of microstructure on performance is well documented, this phenomenon lies in academia and limited fields outside of drug development. Similar publications in the pharmaceutical industry include Zhang [11] with spray dried dispersions, to Nagaputi [8] with long acting injectables (LAIs), and a white paper on enteric tablet coating [9].

In this proceeding, we demonstrate the development of a custom image-based microstructural analysis with potential for troubleshooting of performance in solid oral dosage forms. We show that pore quantification, tablet coating, and spatial porosity can mark differences between tablets. This serves as a steppingstone to introduce mechanistic analysis via microstructure that can be applied to any solid dosage form in development.

Methods

Micro-CT Imaging

Formulated tablets were subjected to accelerated stress conditions (e.g. open dish, high humidity, elevated temperature).

Tablets were analyzed by X-ray µCT acquired on a SkyScan 1272 with rotation step of 0.2 degrees over 360 degrees, Exposure time of 658ms, and X-ray source tuned to 60 kV and 140 mA with an Al 0.25mm filter. The scans were corrected for ring artifacts, beam steering and reconstructed using NRecon software from Bruker. The scale bar for the image scans is depicted in Figure 2.

Image Processing

Image processing and analysis were performed locally using python 3.11. Open-source packages such as SciPy, scikit-image, and CC-3D were used to supplement analysis. Values from each slice can be stacked to analyze the scans as a 3D matrix.

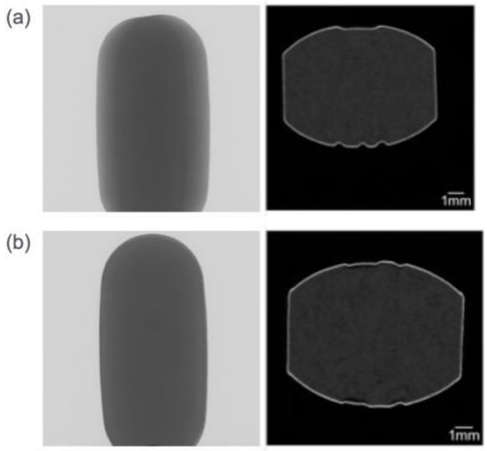

Figure 2. *micro-CT scan images of (a) unstressed and (b) stressed tablets with whole and single-slice tablet views. Unstressed tablet slices are shape (1324, 1324), and stress tablet slices are shape (1228, 1228).*

Results

Micro-CT imaging yielded over 1700 slices per tablet scan. With corrections for artifacts (such as beam steering and ring artifacts), we were able to build multiple 3D models of each tablet with granular information on the internal structure, including distributions of different materials, and localization of phenomena such as pore networks and coating distribution. Resulting images taken from the micro-CT are shown in Figure 2.

Segmentation

X-ray electron densities manifest in images as grayscale intensity, with zero representing air and 255 having strong attenuation. Segmenting the tablet CT scan poses a challenge by way of having an (unclear) indeterminant set of internal components that are very close in pixel values. Advances in computer vision have made segmentation more accurate and efficient on many tasks [17-19]. While it was clear to trained eyes that intensities could be

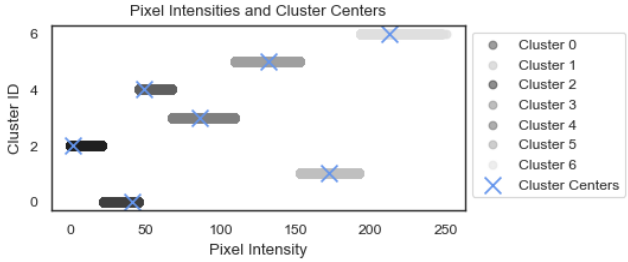

Figure 3*. Centers of k-means color clustering and quantization, k=7. The intensity values clustered into each group are represented horizontally. The centroid of each clustered is marked. Calculations are based on a down sampled 2D array of the scan.*

binned to achieve good segmentation, we also attempted statistical approaches for future automation. Of the algorithmic approaches attempted, k-means was one of few that segmented the internal structure. The result of k-means is several overlapping bins; two for the internal structure and four for the coating (Figure 3). The darkest four groups have significant overlap, though not all represent meaningful distinctions. Furthermore, unsupervised methods require some amount of human intervention– in the case of k-means, to determine the number of clusters; and for others, to seed starting points or bounding boxes– which can be difficult to perform on these images. When performed with experts, manual thresholding is simple, effective, and quick. Thresholding performed on one image can generally apply to the rest of the set, as the materials and scanning parameters are constant. While components may not fall neatly into intensity bins, they can be probabilistically estimated as one component. A sliding scale application was built to compare binned ranges against the original image, serving as the basis for downstream spatial analysis (Figure 4).

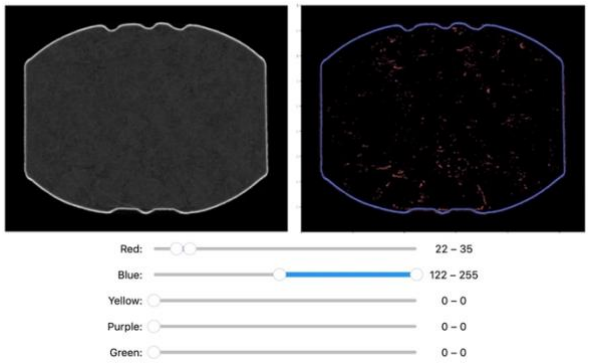

Figure 4. *An interactive application to dynamically segment image regions for each scan. Shown above are the segmentations on one slice for the coating and pores. The selected ranges from this app can be used for further reconstruction analysis downstream.*

Coating

Once tablet coating and pores were segmented, we can obtain summary statistics and specific local characterizations of the respective components. Coating thickness was measured here as the distance between the closest points on the inner and outer coating boundary. In addition to providing summary quantifications, this method can be used to determine local patterns of coating irregularity. Each point on regular 50th slice intervals were measured. Frequent sampling serves to capture local variations of coating due to factors such as compression, migration, and debossing. The average coating thickness was determined to have increased 8.89 µm, and the standard deviation also increased by 2.8 µm (Figure 5b). Still, the relative standard deviation overlaps. Comparing the equality of distributions using a two-sample Kolmogorov-Smirnoff test, we can determine statistical differences between the coating thicknesses ($p<0.01$). Similar measurements of coating thickness were observed using optical microscopy. From the normalized histogram of coating measurements in Figure 5a, we can see how the unstressed tablet clustered around 50 µm. The few peaks are indicative of the relatively small variation around the few tablet sides. On the other hand, the stressed tablet shows a rightward drift in coating thickness. Combining the aggregated thickness measurements with the local difference plots goes beyond traditional global measurements and investigates coating at a high spatial resolution.

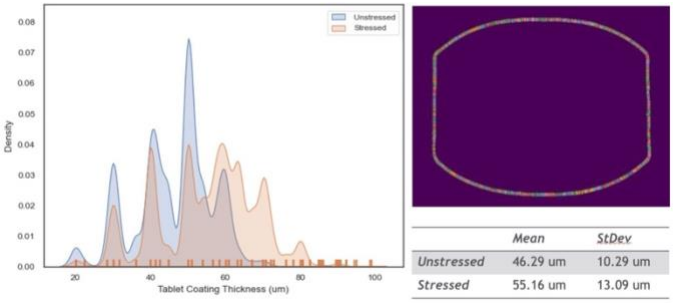

Figure 5. *Kernel density estimate of coating thickness in minimum inner-outer boundary distance aggregated over multiple slices of the tablet. The thickness density is represented as a continuous probability density curve. The tablet representation in the top-right shows all the points from where coating thickness is measured in one slice of the tablet.*

Porosity

Analyzing the tablet as a 3D array allows for a detailed investigation into the spatial distributions of the pores and how they evolve over time. Open pores are exposed to the environment and can interact with surrounding medium, increasing the available surface area. One-dimensional statistics show the tablet's total porous volume increased from 1.1% while unstressed to 3.7% for the stressed. The total number of pores increased by 37% with the vast majority being closed, doubling the initial closed pore count.

To map the porous networks, we applied a 6-connected binary 3D connected components algorithm by Seung Lab [20]. Skeletonization was applied to each pore in 3D space, reducing the thickness of each network to 1 pixel which facilitated visualizing the porous network. By plotting each point interactively in 3D, it becomes evident that a significant portion of the initial tablet's pore networks are concentrated around the debossing. This may be a result of the force of compression applied during the manufacturing process. Additionally, smaller porous regions were observed on the same curved tablet face, though the core and sides of the tablet have less porous regions. After subject to stress, there was similar patterns of debossing and surface porosity, however there was significant porosity at the core of the tablet. Many of these pores were closed and did not extend to the surface.

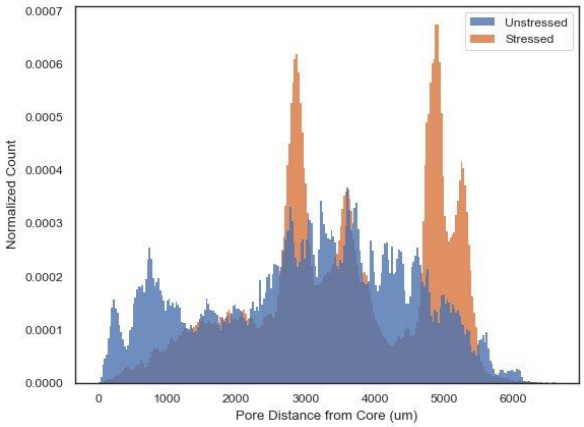

Figure 6. *Distance of each pore voxel to the y-axis center of the tablet. Histogram is normalized for the total porous volume. The total volume was ≈ 11M and ≈ 37M voxels for the unstressed and stressed tablets respectively.*

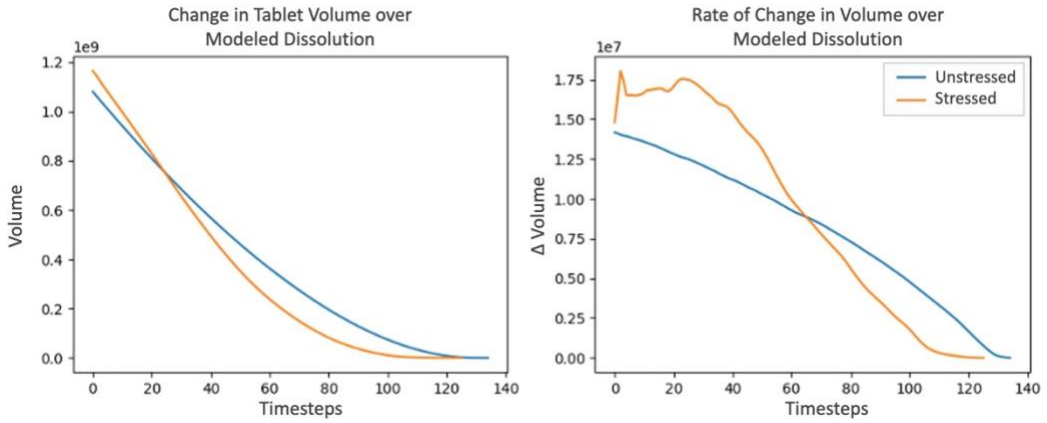

Figure 7. *Simulated dissolution via erosion modeling. (a) Successive changes in tablet volume and (b) change in release rate for each iteration of erosion.*

While most new pores were closed in sheer numbers, there was significant increases in the size of both open and closed pores under stress conditions. From Figure 6, the total volume of porous space largely increased, especially in the core tablet (radius = 3-4mm) and near surface (radius = 5-6mm).

Erosion Model

Erosion represents a fundamental model of drug release in gastrointestinal fluid or media. An erosion model was developed to gradually remove the outermost boundary of the tablet one layer at a time, including any open pores touching the surface. This process mimics the interaction of a dissolvable material with a liquid medium, such as gastrointestinal fluid or a type 2 dissolution apparatus. Other methods, such as the Higuchi and Navier-Stokes equations can be employed to mimic more complex mechanisms. While simple, erosion models mirror initial stages of drug release, where the outer layer plays an important role, and can inform how the spatial porosity affects liquid transport.

Our model treats the tablet as a homogenous porous object that erodes uniformly over time. Despite complex interactions and material differences among tablet components, we focus on the influence of porosity on the dissolution rate, and thus tablet performance. To achieve this, we assume that all solid components in the tablet matrix dissolve at the same rate.

The model tracks tablet volume over uniform time steps, such that we can predict the magnitude of the impact that porosity has on release rate (Figure 7a). For instance, the stressed tablet, which starts with a larger volume and greater porosity, releases as a rapid burst through time steps = 0 and 40, while the unstressed tablet has a much steadier and more gradual rate (Figure 7b). This also indicates that, while the number of open pores only increased slightly, the existing pores were exacerbated under the stress conditions, leading to greater exposed surface area. These enlarged pores contributed to the fast initial dissolution rate, contributing to a faster early release. As the stressed tablet volume decreases, its release rate slows significantly, suggesting that the initial rapid release moderates as the available surface area is reduced, matching the release rate of the unstressed tablet at around t=60. Still, the release rates differ in that the unstressed tablet follows a gradual, downward arching path, characterized by a steadier rate until completing at t=140.

This simulation highlights the impact of porosity on release in the evolution of a tablet. The stressed tablet had higher porosity at the beginning of simulation and released at a much faster rate due to large open pores but reached a much slower release rate as it eroded. In contrast, the unstressed tablet exhibited a more controlled and consistent release rate.

Discussion

Leveraging micro-CT and image processing to examine tablet microstructure revealed several key differences between the unstressed and stressed tablets. From one scan, we presented analysis on tablet coating and porosity; elementary analyses that provided rich insight into changes over time.

While the coating distributions showed difference between timepoints, there was no evidence of coating migration. More investigation could be done to determine the impact of the small increase in coating thickness. Further expansion of this analysis can be used to monitor coating migration, roughness, and in combination with modeling, permeability. Linking the environmental conditions and plotting the local increases in tablet coating can further determine potential causative agents of this change and predict the effects of stress conditions.

Compaction force in manufacturing likely led to increased porosity around debossing. While the stressed tablet saw significantly increased closed porosity around the core of the tablet, the open pores near the surface increased in volume. These structural changes have significant potential to impact tablet performance. Further experiments may aim to explore the role of media uptake on pores, and how closed pores impact the rate of drug release.

Erosion modeling provides a further link in the relationship between porosity and performance via drug release. From the change in volume over time, we were able to observe the effects of increased open porosity volume and increased number of closed pore networks. However, erosion modeling may only be appropriate for certain stages of dissolution, where layer by layer erosion is expected, and needs to be complimented by material properties reflecting the solubility and dissolution of the specific components. As the erosion model treats the tablet as homogenous, advanced models of dissolution (such as the Higuchi or Navier-Stokes equations) will be beneficial in taking in the physical properties of certain components and the dissolution medium [1][13]. Furthermore, scientific studies are required to build the equivalent *in vivo* and *in vitro* time scaling factors.

To establish a rigorous pipeline, however, several steps and considerations remain. While this analysis focused primarily on tablet coating and porosity, there is much to be gained in understanding the relationship between API and excipients. A

combination of imaging techniques could be used to isolate the component spatial distributions, and similar techniques can be applied for analysis.

More extensive research on tablet microstructure, and its relationship with popular excipients, may bolster mechanistic understanding and be a transformative routine analysis. The variety of excipients and blends, complexity of API polymorphisms, and various imaging techniques can make it difficult to create a standard platform/workflow for all tablet microstructures. Development of critical microstructural qualities or attributes can bridge this gap, making these workflows more translatable.

Conclusion

Here we presented the development of a nondestructive microstructural characterization analysis using scans from micro-CT. With this analysis, we can look at the spatial, material, and chemical arrangement and simulate its dissolution performance. With tablets under accelerated stress conditions, we were able to assess; tablet coating thickness, patterns in increased porosity, and simulate tablet dissolution. Findings from this analysis echo that which is documented in literature; the evolution of open and closed porosity in tablets has significant implications for drug release dynamics.

Current methods of troubleshooting and developing drug products using dissolution can be time and material intensive. Mechanistic understanding of the relationship between tablet formulation and dissolution contributes to decreased time in troubleshooting dissolution slowdown. The development of this custom analysis offers new methods to troubleshoot formulation and manufacturing issues, and possibly optimize solid oral dosage forms. The rapid and nondestructive nature of the method makes it even more valuable for iterative testing that can be used to screen a variety of conditions. Furthermore, it also potentially enables routine testing on any sample at minimal cost.

Future developments in this work will tie in chemical imaging to incorporate more components of microstructure, as well as developing models of dissolution that are fit for purpose. Scientific research studies are also required to incorporate empirical findings and physical properties of manufacturing and materials.

Acknowledgements

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