doi:10.1017/S1431927622005773
Microsc. Microanal. 28 (Suppl 1), 2022

Application of X-ray Computed Tomography for High-Throughput Analysis in Drug Product Development at Micrometer and Nanometer Scale

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Microscopy is a fundamental characterization tool needed for all the stages of drug product development - from research to manufacturing. Confocal microscope, optical microscope and scanning electron microscope are some of the many techniques that are used ubiquitously for root cause analysis and problem solving at the surface level. However, in addition to surface properties, other factors like - particle size distribution, 3D microstructure, porosity etc. also have a tremendous impact on downstream processing behavior of drug products such as tabletability, flowability, stability etc. Therefore, investigation of just the surface is not adequate for developing a complete understanding of structure-property-performance relationships in materials and a thorough analysis is needed of the bulk both at micrometer and nanometer scale. In this talk, we discuss the advances made in characterizing drug product through X-ray computed tomography. X-ray computed tomography is a non-destructive technique used for 3D microstructural reconstruction of materials. The advent of lab based X-ray tomography instruments has made this technique more accessible to researchers as they no longer need to rely on synchrotron sources. These instruments have proven to be extremely beneficial for the pharmaceutical industry where they have not only been employed for high-throughput problem solving but also for enhancing the depth of understanding of materials in an environment of ever evolving and complex pipeline. In this talk, we will demonstrate that it is critical to study the 3D microstructure of SDI (spray dried intermediate) for its correlation with the downstream processing behavior. Spray Dried Intermediates have become a highly utilized formulation approach for enhancing the bioavailability of poorly soluble drugs (BCS class II and IV). Extensive studies have been performed towards formulation and characterization of SDIs to understand the effect of drug loading and choice of polymer on dissolution behavior and solid state physical stability. However, the impact of particle size, microstructure and morphology is not yet fully understood. XRCT scans were performed on SDIs with different morphology, wall thickness etc. and its impact on downstream processing behavior was studied. Additionally, through XRCT, multi-component systems were also investigated in various dosage forms. Distribution of each component was studied qualitatively and quantitatively. This study further enabled the understanding between the processing and performance parameters. In this talk, we also demonstrate the use of XRCT for developing a method for calculating ribbon density of roller compacted ribbons. Ribbon density varies based on formulation and process parameters such as roll pressure. Historically, ribbon density has been calculated by using powder displacement technique. However, this technique is not very reliable and has user-induced errors. XRCT, owing to its micrometer resolution provided an easy and reproducible method for calculating ribbon density.

In addition to obtaining quantitative and qualitative data, it is also important to develop high-throughput methods for getting relevant statistics and ensuring timely release of manufactured drug products such as oral compressed tablets, dry filled capsules, implants etc. In this talk, we discuss about making XRCT an easy-to-use tool and maximizing output by developing high-throughput methods. An algorithm was

developed that allowed the automation of detection and quantification of cracks present in oral-compressed tablets that had shown elegance failure. Oral compressed tablets were put on stability at elevated temperature and humidity conditions. Several tablets were placed in the bottle and scanned together. After which, Merck-developed algorithm was used for detecting cracks in the tablets. The algorithm uses deep learning via convolutional neural networks and helps in assessing the presence, as well as the extent, of crack formation inside the tablets in a quantitative and consistent manner, enabling a high-throughput analysis. This algorithm has enabled users who are not subject matter experts to utilize XRCT to solve time sensitive problems in their programs. Through these examples we wish to elucidate the importance and relevance of X-ray tomography in not only critical problem solving but also in increasing the depth of knowledge in pharmaceutical industry.

https://doi.org/10.1017/S1431927622005773 Published online by Cambridge University Press