ABSTRACT

The pharmaceutical manufacturing industry has seen significant growth and advancements in recent years, driven by a combination of factors, including increased adoption of new technology, advances in computing and information technology, and growing demand for innovative medicines. The Food and Drug Administration (FDA) has realized the benefits of implementing new initiatives in pharmaceutical product development and manufacturing. It has published guidance on Process Analytical Technology (PAT) implementation in the mid-2000s and continuous manufacturing in 2022. Product quality is the most crucial aspect of pharmaceutical manufacturing. The manufacturing of pharmaceutical oral solids products, such as tablets, requires precise control over the active pharmaceutical ingredient (API) concentration to ensure product efficacy and safety. It is critical to have a robust manufacturing process that can repeatedly deliver high-quality products that meet all critical quality attributes of the formulation. Real-time process monitoring of these critical quality attributes is also a challenge for quality control.

Continuous manufacturing (CM) of oral solids is one of the most important emerging technologies in the sector. This innovative approach involves the seamless integration of multiple unit operations into a continuous process, leading to more efficient, cost-effective, and scalable production. CM process development is knowledge-intensive, and the first component of CM implementation is an accurate in-line, real-time process monitoring (RTPM) tool. Vibrational spectroscopy techniques such as Raman spectroscopy can provide RTPM of oral solids manufacturing processes. Raman spectroscopy offers excellent molecular specificity and high sensitivity and can be used to identify and quantify Active Pharmaceutical Ingredients. It, however, suffers from the interference of fluorescence background. Many pharmaceutical ingredients are fluorescent in nature and can affect the Raman spectra of the blend of ingredients. Hence, the adoption of Raman spectroscopy has lagged behind the acceptance of its complementary technique, Near Infrared (NIR) spectroscopy.

In this dissertation, the use of Raman spectroscopy to measure the API concentration at the feed frame tablet press in real time is studied. A novel way of removing the fluorescence interference, a significant drawback of Raman spectroscopy, is established. The method is used to build mathematical models to predict API concentration in real-time. The model predictions using the novel strategies are compared to the model with no fluorescence interference. The effect of photobleaching on the Raman spectra of pharmaceutical ingredients and ways to reduce its influence is also studied. The study shows that by utilizing these strategies, Raman spectroscopy can be used to build models with good predictions, even in the presence of high fluorescence background. Other considerations are also investigated, such as the effect of change in feed frame RPM on the real-time API concentration predictions and alternative strategies to build calibration models utilizing a fraction of the material.

Like RTPM, the homogeneous distribution of API is another crucial aspect of the oral solids process development. Formulations with low API concentrations are especially challenging

in achieving adequate blend uniformity. Omeprazole Sodium Bicarbonate formulation (OSBF) for suspension is one such low-API drug commercial formulation. It contains a very low API drug load (0.3% w/w) and suffers from the issue of non-homogeneous distribution of API. The API is cohesive in nature and has small particle size and poor flow properties, further aggravating the complexity. To overcome this issue of non-homogeneity in low drug load products, OSBF is used as a case study, and the improvement in product quality and manufacturability by utilizing wet granulation is investigated. Implementing the wet granulation strategy resulted in better homogeneity, lower variation in API concentrations and a more robust process. The impact of direct blending and wet granulation strategies on drug stability is also studied by loading the samples in stability chambers in different conditions and monitoring the quality over a period of six months. Linear mathematical models are prepared to predict the impurity levels of samples in different stability conditions, and the predictions are compared with high-performance liquid chromatography (HPLC) results. The wet granulation process increased the cohesion between ingredients, which helped improve blend uniformity. The strategic selection of components for granulation and extra granular blends and the implementation of wet granulation resulted in a homogenous blend of API in five excipients. The impurity levels with the wet granulation strategy are higher than that with the direct blending strategy.

The second case study on blend uniformity is based on researching a new blending strategy. The current modes of blending – batch blending and continuous blending – have their own limitations. This study presents a new approach of the semi-continuous blending of pharmaceutical ingredients. The potential advantages of using semi-continuous blending over the other modes of blending are conceptualized. The blend uniformity results utilizing a semi-continuous mode of blending are shown in the study. The results show that blends with good blend uniformity can be prepared using semi-continuous blending. Of the three important process parameters – impeller rotation per minute, blending time and fill level inside the blender, impeller rotation per minute has the most significant impact on the blending performance. The semi-continuous blender has a higher line rate of 12.5 kg/hr than a similarly sized batch blender at 3.6 kg/hr. Semi-continuous blending provides an excellent alternative to the existing modes of blending. This thesis demonstrates the implementation of Raman spectroscopy in a challenging environment and the improvement in the blend uniformity in two separate formulations, enhancing the real-time process monitoring and product quality in pharmaceutical oral solids manufacturing.