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Accelerating pharmaceutical dry granulation through digital twins and application of chemometrics.

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In industrial practice, the development of pharmaceutical tablet manufacturing processes typically involves time- and resource-intensive development campaigns supported by equally resource demanding laboratory analysis. These campaigns are designed to construct the safe operating space to deliver the desired product quality for our patients. GSK is driving the digitalization of tablet manufacturing via the use of digital twins and chemometrics through the implementation of real-time metrology. In this study, we explore the integration of a digital twin and chemometrics on dry granulation and their impact to industrial manufacturing.

Pharmaceutical dry granulation is performed through roller compaction (RC) which can be operated in two different modes: (i) controlling the gap between the rolls (gapcontrolled) and (ii) controlling the screw speed (screw speed-controlled) (Bano, et al., 2022). The Johanson model (Johanson, 1965) applied on a gap-controlled operation relates the material properties of the powder and the roll operating conditions with the produced ribbon relative density and unit operation mass throughput. To generate a holistic systems model, this first principal model was combined with a tablet compressibility model, a tablet compactability, tablet disintegration and in-vitro dissolution models. The systems model was calibrated and validated with experimental data and enabled the identification of target values and in-process limits of the intermediate and final drug product to ensure compliance with the dissolution targets. It was also used to define the operating space where the target values and in-process limits can be met reducing the scope and extent of development campaigns required for a new drug product.

Ribbon porosity is a key quality attribute during dry granulation as it impacts the properties of the produced granules and finally the end-product tablet behavior (Dong, et al., 2024). In comparison to the traditional material displacement techniques, Terahertz spectroscopy enables fast, non-destructive and detailed porosity analysis of the ribbons capturing inter-ribbon variability. Intra-ribbon variability created by patterned rollers impacts the analysis result. This was addressed by the creation of a convolutional neural network (CNN) using Terahertz spectral features and classifying them according to the ribbon pattern. Upon classification, each porosity measurement is corrected for by a factor specific to the respective pattern feature providing an accurate bulk porosity value for the ribbon. This at-line approach provides a fast, accurate and non-destructive technique reducing the required sampling volume and analysis time. The combination of these tools enables the reduction of both drug product development timelines and analytical resource requirements.

Type of presentation

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