Practical Information

All Fields are compulsory

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Towards Quality by Design in Pharmaceutical Manufacturing: Modeling and Control of Air Jet Mills

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The pharmaceutical industry is dominated by batch production processes which lack the flexibility required for the *fit-for-patient* and *fit-for-purpose* formulations. This has led to a trend of moving towards continuous manufacturing technologies which are driven by quality considerations which have to be strictly enforced. The Quality by Design (QbD) paradigm is a scientific, holistic, and risk-based approach towards pharmaceutical development. The QbD philosophy mentioned in the ICH Q8 Guidance states that "quality cannot be tested into products, i.e. quality should be built by design" [1]. The idea behind QbD is to identify each and every characteristic of the final product which is critical from the consumers' quality perspective and translate them to the important attributes of the drug product, and then to identify critical process parameters which can be varied to consistently deliver the drug product with required attributes. Relating these critical process parameters (CPPs) to the critical material attributes (CMAs) requires a thorough understanding of each and every step in the pharmaceutical manufacturing process by means of mathematical modeling and continuous monitoring of the process. The various tools proposed for QbD, thus include – design of experiments necessary to determine relation between CMAs and CPPs, process analytical technology (PAT) required to monitor the CMAs, effective control strategy to steer the process such that the required quality is always delivered.

Milling is an important step in pharmaceutical manufacturing as it not only determines the final formulation of the drug product, but also influences the bioavailability and dissolution rate of the active pharmaceutical ingredient (API). In this respect, the air jet mill (AJM) is most commonly used in the pharmaceutical industry as it is a non-contaminating and non-degrading self-classifying process capable of delivering narrow particle size distributions (PSD). Keeping QbD in mind, the CPPs of the AJM have been identified to be the pressures in the milling chamber and the injector, and the feed rate which affect the PSD, surface charge and the morphology of the product (CMAs). Laser diffraction (LD) is the widely used and approved technique to determine the PSD of the final product. However, the in-line implementation of LD provides many challenges due to the extremely large concentration of particles which leads to multiple scattering. This needs to be overcome, before any meaningful data can be obtained from the online monitoring. Once, the data is available the next step is to obtain a detailed model of the process. Most often the population balance method (PBM) provides a suitable framework to model particulate processes [2]. The idea behind PBM is to discretize the PSD in a number of bins and write a mass balance over each one. The breakage of particles is defined by the *breakage parameters* which define the probability of breakage of a particle of particular size. With an appropriate model, the process can be controlled using techniques like model predictive control which allow imposition of constraints directly in the controller. This is important, because avoiding operating regimes which lead to a change in morphology is of utmost importance as well. Finally, it has to be kept in mind that a mill in the pharmaceutical industry processes almost 500-600 different products in a year. Thus, the model for the mill should have easily identifiable parameters which can be obtained by minimum experimental efforts.

References

[1] ICH Guideline, Q8(R2) Pharmaceutical Development (November 2009)

[2] Ramkrishna, D., & Singh, M. R. (2014). Population Balance Modeling: Current Status and Future Prospects. *Annu. Rev. Chem. Biomol. Eng*, *5*, 123–46.