Industry 4.0: Digital technology for advanced continuous pharmaceutical tablet manufacturing

Problem statement

Currently, Industry 4.0 concepts are being applied to pharma industry to achieve Pharma 4.0 paradigm. Pharma 4.0 reduces the time and resources needed for continuous pharmaceutical manufacturing and also improves the product quality and production consistency. It has many advantages but also have bigger challenges on the applications of artificial intelligence (AI)/machine learning (ML), material traceability, optimization, advanced process control, cyber-physical security, and data management side because of the different levels of complexities involved [1-7]. The predictive capabilities and the quality of the pharmaceutical products can be improved significantly via employing the artificial intelligence and the advanced model predictive control (MPC) system if an appropriate cyber-physical security defense is in place.

Methodological approach and status

In this work, seven components of industry 4.0 namely artificial intelligence (AI)/machine learning (ML), modelling, material traceability, optimization, advanced control, cyber-physical security, and data science have been developed and implemented into the continuous pharmaceutical manufacturing process.

Four machine learning (ML) models have been trained to predict the response of continuous pharmaceutical manufacturing process and the performance of these ML models has been compared. The investigated ML methods are long short term memory (LSTM), 1D convolution neural network (CNN), random forest (RF), and artificial neural network (ANN). The best performing ML model is then implemented into the continuous pharmaceutical tablet manufacturing process for real time prediction. A digital twin model of continuous pharmaceutical tablet manufacturing process has been also developed.

A systematic framework including the methods and tools have been developed for material traceability. A corresponding software tool has been also developed to automate the material traceability procedure. The heart of the material traceability toolbox is the RTD model. The applications of the developed methods and tools have been demonstrated for material traceability of continuous pharmaceutical manufacturing process.

A systematic framework including the methods and tools has been developed for dynamic optimization of the feeder refill strategies. The deviation of the outlet mass flow of the feeder from the targeted flow rate has been minimized to obtain the optimum value of the feeder refill parameters. The material properties also affect the refill strategy meaning that the feeder refill strategy need to be frequently optimized if there are any changes in the materials and plant. Therefore, the developed feeder model and dynamic optimization tool can save the time and recourses as well as can improve the product quality significantly.

An advanced model predictive control (MPC) system has been implemented in the continuous pharmaceutical manufacturing (CPM) pilot-plant. The CPP’s and CQA’s are controlled in real

time. The critical control variables that have been controlled using model predictive control (MPC) system are drug concertation, powder level before tablet press, main and pre compression forces, tablet weight and hardness. A novel control strategy for powder level control in a chute placed in between blender and tablet press unit operation of continuous tablet manufacturing process has been developed, implemented and evaluated.

A systematic framework including the methods and tools have been also developed for proactive identification and mitigation of potential cyber-physical attack risk on continuous pharmaceutical manufacturing plant [2]. The cyber-physical security relevant software tools such as Snap 7, Wireshark, and Tripwire have been applied to CPM. A novel software tool named CPS (Cyber-Physical Security) has been developed for cyber-physical security of the continuous pharmaceutical manufacturing. The integrated commercially available and developed (in house) cyber-physical security tools have added an extra layer of security of our continuous pharmaceutical manufacturing pilot-plant for any unexpected attacks.

All the relevant data generated during continuous manufacturing has been systematically collected, stored and organized in a data hub (OSI PI) and cloud system as per industry 4.0 standard.

Contribution to the state of the arts

The research conducted in this work is novel and an original contribution to System Dynamics and systems thinking field. The developed models, methods and tools have been used to analyze the dynamics of continuous tablet manufacturing pilot-plant. The dynamic analysis has been useful for designing the control system of the actual manufacturing pilot-plant. The control system has been implemented in the pilot-plant for real time quality assurance using feedback control mechanism and model predictive control algorithm. The control system implementation methodology has been previously reported [4].

References

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