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Short communication

Opportunity for real time release testing in liquid dosage forms

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Introduction

This paper will help to understand the opportunity of real time release testing in production of bulk product of liquid dosage forms**.** The possibility of even going to a continuous or semi-continuous processing of liquid bulk product for a faster and more reliable analysis before primary and secondary packaging od finish product. The use of PAT tools like reliable application and achieving state of control on the production and CQAs and CPP of the bulk product without QC testing on every batch. It will be less costly and more efficient in terms of time and expensive testing. The production will be more effective and more productive with a best quality product for the market (Medicines Agency, 2017).

Real Time Release Testing

A medicinal product must comply with the requirements stated in the authorized specifications for release and shelf life. RTRT is a system of release that gives assurance that the product is of intended quality, based on the information collected during the manufacturing process, through product knowledge and on process understanding and control. RTRT recognizes that under specific circumstances an appropriate combination of process controls (critical process parameters) together with pre-defined material attributes may provide greater assurance of product quality than end-product testing and the context as such be an integral part of the control strategy. Enhanced product knowledge and process understanding, the use of quality risk management principles and the application of an appropriate pharmaceutical quality system, as defined within ICH Q8, Q9 and Q10 provide the platform for establishing RTRT mechanisms for other applications, for new products as well as established marketed products. The application for RTRT should be supported by adequate validation of the RTR test method. The relationship between the RTR test, including acceptance criteria, and the end product test and associated specification should be well understood and, where applicable, supported by substantial comparative data at commercial scale (parallel testing) (7 Westferry Circus 2009).

Possibility of RTRT and control strategy in oral liquid dosage forms

Many processes for the production of solid pharmaceutical forms do not reach more than 60% of their design capacity and often require ten times more design time than liquid processes where they reach even 90% of the design space. This is primarily attributed to better development and implementation of advanced closed-loop control and control strategies in production of liquids. To implement a quality average control system are:
(1) the integration of control hardware, software and sensors into process equipment. This is a major challenge due to the lack of standardization of pharmaceutical equipment in terms of control perspectives.
(2) The differences in real-time data for online / inline process monitoring, which need to be controlled, is another barrier that it is a challenge for implementation of control systems.
(3) The most suitable control categories (PID, PI, MPC, feed forward controller, feedback controller) for liquids production processes are possible.
(4) There is no standard control package commercially available that can be used to implement a control system in a pharmaceutical plant. A systematic framework is needed, through which the control system can be easily designed on site and implemented in the plant with less resources and time (Allison et al., 2015).
The specific objectives of the proposed systematic framework are twofold: first, to provide step-by-step

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guidance for the integration of advanced control strategies, hardware / software control and analysis technologies (PAT tools); and second, to support the design and implementation of control strategies. It involves the installation of advanced sensors (eg NIR) within the process equipment to monitor variable process parameters in real time. Through the framework of advanced control strategy (hybrid MPC-PID) can be developed and implemented using the process automation system (eg Emerson's DeltaV PAS), and hardware can be integrated into the plant to allow manipulation in the closed-loop of the physical process. The control system uses PAT-based multi-variable data management platform (eg SynTQ) to integrate the control platform (eg DeltaV) with NIR analyzer and multivariate model. Through the commercial implementation of advanced control strategies and the integration of these strategies with control hardware and sensor technologies, this technology platform will lead to more efficient manufacturing operations, reducing labor and the volume of experimentation in introducing new processes, and also facilitating implementation of QbD in the pharmaceutical industry (Markl et al., 2020).

SCADA (supervisory control and data acquisition system) can be implemented for supervision, of process parameters, raw materials, as well as the quality of semi-finished products during the process, and attributes of the final quality of the product with a model of process dynamics for data harmonization in order to support RTRT. As a result of the high frequency of data collection, statistical methods for large samples can be applied to increase the level of confidence that the batch is in accordance with the desired quality. Batch calculations with RTRT should consider the observed variance in the critical quality attributes during production, which is an indicator of variability within the batch. This helps in analyzing the risk of PAT failure and procedures can be developed to identify contingencies for process monitoring and batch release. Procedures may include testing the final product or using surrogate measurements to prove that the product maintains an acceptable level of quality.

In addition, to make natural use of the RTRT methodology, increasing the amount of data and quality processes collected during continuous production facilitates the adoption of multivariate process monitoring approaches. Multivariate statistical process control (MSPC) is a process monitoring approach used to determine whether process variability is stable over time. It can be used to detect abnormalities in the process that could lead to adverse consequences if they are not mitigated and diagnostic information is provided for which variables in the process may be responsible for the event (Aulakh et al., 2021).

Conclusion

Manufacturing process for production of liquid dosage forms is very important step for ensuring production of high quality products which will be present on the market. Real time release testing can ease the time needed for the product to go to the market. The quality of the product depends from many factors but mostly from the characteristics of the raw materials, equipment and their performance and critical process parameters such as temperature, pressure/ vacuum, share speed and mixing and usage of additional parts as pumps, transfer lines and filing lines. All these parameters should be monitored during production process in defined ranges. Only fully controlled process the use of PAT tools, a significant state of control and real time release testing will insure that manufacturing of the product result with a high quality products according the specifications.

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