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Short communication

Importance of Quality by Design (QbD) approach during development of modified release film-coated tablet - objectives and challenges during implementation and preparation of dossier

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Introduction

The modern requirements aimed at the pharmaceutical industry impose a need for implementation of innovative approaches in the development of drug dosage forms. Such requirements are happened as results of the increasing number of new specific drug molecules (API), complex and increasingly sophisticated pharmaceutical-technological processes, as well as modern and extensive requirements from the pharmaceutical industry in order to confirm the quality, safety and efficacy of the manufactured products. Taking into account these facts, the pharmaceutical industry promotes the Quality by design (QbD) approach, as a new concept for development of pharmaceutical products and it was mentioned in ICH Q8 guideline, which states that "quality cannot be tested into products, i.e., should be built in by design". *QbD* concept has been involved as a systematic method of development strategy offering several benefits, such as high-quality drug products with operational flexibility within optimized ranges of critical factors, regulatory flexibility in drug product application approvals and post-approval management (Lee et al., 2022). The main goal of *QbD* may include: achieve meaningful product quality specification that are based on clinical performance; increased process capability and reduced product variability and defects by enhancing product and process design, understanding and control; increased product development and manufacturing efficiencies. To enhance root cause analysis and post approval change management (Yu et al., 2014). *QbD* is systematic step-by step approach which has predefined steps as definition of quality target product profile (QTPP), definition of critical quality attributes (CQA), identification and optimization of critical material attributes (CMAs) and critical process parameters (CPPs) for development of Design space (DS) through a systematic series of a design of experiment (DoE) along with the implantation of a control strategy with the adaptation of the continuous improvement through the drug product lifecycle (Simão et al., 2023).

Design and development process of generic drug product with modified release properties is process with a large number of unit operations involved in its manufacture require more intense validate control according to regulatory requirements. (Grangeria et al., 2020). Implementation *QbD* for development and optimization of manufacturing process of modified release tablets might reduce the number of experiments required to produce a cost-effective drug product with extended-release properties, give specific time-line information and high flexibility in drug product application approvals and post-approval changes.

Over the years, *QbD* has been involved in guidelines, appropriate documents and several literate reviews but in general these documents provide high level directions with respect to the scope and definition of *QbD* as it applies to the pharmaceutical industry. Unfortunately, many implementation details especially for development of generic drug products are not properly discuss and in general it is open to different interpretation. There is well known confusion among industry scientist, academicians and regulators despite recent publications.

The main objective of this work is to elucidate and provide a practical framework which can be used as postulate and/or starting point and will be suitable for the application of *QbD* approach for pharmaceutical

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development of generic modified release film-coated tablets prepared with wet granulation technology.

QbD approach as development strategy for modified release film-coated tablets

Definition of QTPP and CQA for modified release film-coated tablets

As first stage *QTPP* was defined, which can be defined as prospective summary of quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. Taking in consideration the fact that the final product is generic drug *QTPP* was defined in general based on reference drug characteristics. As next step in product development identification of *CQAs* was done. Once the *QTPP* and *CQAs* (hardness; identification; assay; dissolution profile; related and degradation products; residual solvents and microbiological purity) were established based on literature data, evaluation of reference drug and prior knowledge with similar products an initial risk assessment for influence of *API* characteristics, formulation variables and process parameters on final product quality was done. Once the initial risk assessment was established *API* characteristics, formulation design (type and concentration of polymer in formulation) and process parameters (granulation time/speed; compression force and compression force) that were evaluated as high risk were part of further evaluation.

Development of modified-release film-coated tablets

Evaluation of reference drug

The starting point of development of generic drug should be detailed evaluation of reference drug already available on the market as main source of information about the quality aspects of final product.

Compatibility study between API and excipients

A deep understanding of the compatibility between API and excipient in early development phase is essential due to the fact that any negative impact on the quality of the drug product may arise from the physical and chemical interaction between the API and excipient.

Formulation design and process parameters

Formulation design were defined through *OFAT* experiments based on previous experience and information from reference drug. This pathway was chosen as main strategy especially takin in consideration the need for proving *BE* with reference drug, experience with regulatory agencies and limited timeline for being on market earlier as much as possible. On the other hand, process parameters that were evaluated as high risk were screened and optimized through the *DoE* and based on results obtained experimental evaluation *DS* within which all *CQAs* meet their predefined specifications to ensure product *QTPP* were defined. In industry main focus is on process parameters due to the fact that main criticalities are shown during scale up and having *DS* for process parameters will enable knowing the product quality in detail and any change during life cycle with not need any regulatory variation submission which means no additional cost, time and etc.

Conclusion

Implementation of concept of *QbD*, which means design-based planning approach is valuable strategy for optimization the formulation and manufacturing process of drug products which will enable production of final product with predefined quality characteristics in all life cycle. Even in early development phase *QbD* concept can seems more time and money consuming, having detailed timeline which will enable prediction of all risks in early development phase and end with product which will have continuity of drug quality during whole life cycle will enable higher acceptance from regulatory agencies (easier for registration and decrease variation during life cycle) which will mean that can be cost and time effective in long term.

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