QbD for Industrial Pharmacy in Costa Rican Academy

Subjects: Others

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The Quality by Design (QbD) model stands out as a great methodology for carrying out research projects regarding Pharmaceutical Sciences, but especially for Industrial Pharmacy, where it has contributed in terms of formulation development, manufacturing, and quality control. Academic research based on this model enables the training and development of practical, scientific, and leadership skills in Industrial Pharmacy students. The generated knowledge can be shared in classrooms, which represents an ideal environment to communicate research results and to foster collaborative work between researchers, professors, and students. Moreover, research performed through a QbD approach increases the confidence shown by the industrial sector and health regulatory authorities in the quality of the research, products, and knowledge that are developed and created in an Academy. As a result, the implementation of the model has allowed the creation, transfer, and materialization of knowledge from the Costa Rican Academy to different local pharmaceutical industries.

academy formulation development industrial pharmacy

1. Model’s Basic Characteristics

The ICH guideline Q8 (R2) defines the Quality by Design (QbD) model as a systematic approach to Pharmaceutical Development, which begins with predefined objectives and places special emphasis on understanding the product, the process, and its controls [1]. Moreover, the FDA considers that quality in a Drug Quality System cannot be evaluated or determined in a product but must be introduced and promoted from its design [2].

Despite the aforementioned, the quality of the products has been historically determined through “Quality by Test”, i.e., to evaluate the quality of the finished product without prior controls [3]. Nevertheless, the demand to produce medicines of the highest quality and to improve competitiveness within the pharmaceutical, industrial, and health fields forced many institutions to take on new measures to guarantee the quality of their products. Therefore, the adoption of the QbD is of great relevance, as the predictions made by the model are useful in the design of experimental investigations, time management, and the use of resources throughout the process [4].

The QbD model’s lifecycle [5] is directly related to the different constituent elements, such as the Target Product Profile (TPP), Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), and Design Space [6][7]. In addition, Quality Risk Management (QRM), Design of Experiments (DoE), and Process Analytical Technologies (PATs) are used as tools to guarantee

the quality of the products being developed [8]. These tools also make the QbD model an approach that meets the current demand for research processes, as it is considered cost effective in project development [9][10][11].

According to the ICH Q9 guideline on Quality Risk Management [12], CQAs, CMAs, and CPPs can be identified through adequate risk management, as it detects those problems in the development of the product and their associated risks [13][14]. In general, nine tools are recommended for risk management. However, among the most widely used tools are Ishikawa's fishbone diagram [9] and the Failure Mode and Effects Analysis (FMEA) [13][15][16]. These two tools are thoroughly explained to the Pharmacy students in Drug Analysis courses.

In addition, DoE allows researchers to use their knowledge regarding the product and/or process instead of merely applying the commonly known "trial and error" [17][18]. This tool is used to organize, conduct, and interpret the results of experiments efficiently, guaranteeing the collection of the greatest possible amount of useful information through the execution of a small number of tests. The main objective of an experimental study is to find the relationship between independent variables (i.e., factors) and dependent variables (i.e., responses) that affects a certain process and its final product [19]. An adequate DoE can help identify optimal conditions, CMAs, CPPs, and their impact on CQAs [20].

2. Implementation in Academic Research

QbD can be used in any section of the Pharmaceutical Development process, from the drug substance development stages to clinical trials[4].

Moreover, Orozco et al. previously described the Costa Rican innovation system as weak, mainly due to a poorly effective linkage of the universities with the industrial sector [21]. However, a direct benefit of the increase in students and the research groups' practical and scientific skills due to the implementation of the QbD approach is the confidence shown by customers, the industrial sector, and health authorities on the quality of the research, products, and knowledge that are developed and created in the Academy. The empowerment demonstrated by the students during the execution of their graduation projects, and the increase in learning engagement owing to the application of this methodology have also developed leadership and team-work skills, necessary to conduct research [22][23][24].

As a result, the QbD model has allowed the creation, transfer, and materialization of knowledge from Costa Rican universities to different local pharmaceutical industries, as discussed in the following sections. Different QbD approaches carried out regarding formulation, the manufacturing process design, and the quality control of drugs and natural products are addressed. An emphasis is placed on the different QbD elements and tools employed throughout the research.

2.1. Formulation Development

The QbD model satisfactorily deals with the challenges posed by the design and development of pharmaceutical formulations, being also able to accelerate them [25]. The thorough comprehension of CMAs, the assessment of physicochemical compatibility, the application of QRM, the performance of DoE, and the use of PAT to assess and predict stability are responsible for the great success experienced [26].

Castillo et al. employed QbD for the development of different pharmaceutical formulations. In 2017, a collaboration between UCR and the National Laboratory of Nanotechnology (LANOTEC) worked on developing an immediate-release formulation of rupatadine fumarate 10 mg tablets by direct compression. The research involved identifying the TPP in terms of the target population, administration route, posology, potency, composition, and desired performance regarding drug release and physicochemical stability compared to a commercialized reference product, Rupax® [9]. Later on, knowledge and technological transference to a local pharmaceutical industry resulted in the commercialization of the drug product.

Moreover, an adequate QRM during formulation can provide products of the highest quality and safety, thus becoming an excellent resource for the identification and control of possible quality problems during research [27]. This tool allows for better decision making when quality-related issues arise, making their justification easier and generating greater confidence in the research group [28]. In the rupatadine research, QRM was employed to identify the CMAs and CPPs, and it led to the definition of the CQAs, a safe process, and formulations with no physicochemical incompatibilities. Additionally, spectroscopic and thermal analysis techniques were used to assess the physicochemical compatibility and the suitability of the manufacturing process [9].

Following that, in 2021, another investigation involving students at UCR applied a QbD approach for pharmaceutical formulation development. Hanley et al. developed an oral suspension with anti-ulcer and gastroprotective effects. Remarkably, they reported the thickening agents' concentration as a CMA and the pretreatment of the drug using a wetting agent as a CPP. Once the previous aspects were identified, a DoE was designed and executed to determine the effect of these on the suspension's viscosity, which was defined as a CQA [29]. In general, DoE is conceived as an excellent tool that allows forsystematic manipulation of factors according to a design prior to the establishment of specifications [30][31]. The independent variables are usually formulation factors or manufacturing/test conditions, while the dependent variables are product properties or parameters that indicate the performance of the process [32]. Using this tool, Hanley's research results revealed that only one of the prototype formulations was suitable for development. In this case, the technology was transferred to another local pharmaceutical industry, which is currently in the process of registering the product and commercializing it in the country [29].

At a private university, Universidad Internacional de Las Américas (UIA), Ramírez, et al. developed a sustained-release tablet formulation of a non-steroidal and anti-inflammatory drug (NSAID) to treat chronic pain. In this approach, the research group sought to fulfill the CQAs established by the United States Pharmacopoeia (USP) and the British Pharmacopoeia (BP) for the product. The performed QRM was based on Ishikawa's diagram, FMEA, and the creation of an adequate strategy for risk control and mitigation [33]. Furthermore, other research projects are currently applying this methodology at UIA, such as in the development of a self-emulsifying drug

delivery system (SEDDS) to improve itraconazole oral bioavailability and chlorpheniramine/guaifenesin chewing tablets for cold treatment in children.

More recently, collaborative work between the Faculty of Pharmacy of UCR, LANOTEC, the Laboratory of Biopharmacy and Pharmacokinetics (LABIOFAR) of UCR, and the Laboratory of Polymers of the National University (POLIUNA) allowed the development of a topical chitosan-based thermo-responsive scaffold loaded with dexketoprofen trometamol (DKT). In this case, the TPP was defined as a function of the intended application for chronic and non-healing wounds caused by different diseases (e.g., diabetes), as well as for local pain and inflammation management. The scaffold was required to provide controlled release of DKT for 24 h use, having a small release rate at or below the normothermia and taking advantage of the local hyperthermia presented in wounds. The latter induces a sol–gel transition in the polymer's structure, which increases the drug's release rate. This QbD approach contributed to the avoidance of excessive DKT loading in the polymer matrix as most conventional drug systems do to achieve a concentration gradient for Fickian diffusion as the main release mechanism [34].

2.2. Manufacturing Process Design

In many cases, the definition of scalable and consistent methods of drug preparation or manufacturing is hard to achieve. Nevertheless, a QbD approach can bring solutions to many of the related issues by making use of three key steps: (a) QRM, (b) DoE, and (c) the execution and analysis of studies to determine their impact on the process quality, as well as on the Design Space [35]. In addition, the ICH Q8 (R2) [1], Q9 [12], Q11 Development and Manufacture of Drug Substances [36], Q13 Continuous Manufacturing of Drug Substances and Drug Products [37], and the FDA Guidance for Industry on PAT [38] represent a magnificent framework for the manufacturing of pharmaceutical products [39][40]. In fact, the use of PAT and Continuous Manufacturing has been increasing in QbD-based developments. Both have enabled real-time measurements for process monitoring, higher operational flexibility, reducing batch rejection, faster manufacture, and fewer resources and efforts for regulatory compliance [41]. The reduction in R&D costs and time has also been associated with the implementation of QbD [42].

At UCR, Cantillo et al. designed a film coating process of tablets at a pilot scale for a local pharmaceutical industry. In this case, the group employed a full factorial design to evaluate the impact of the CMAs (friability, density, and tablet dimensions) and CPPs (drum's rotational speed, core bed temperature, and feed rate of the coating solution) on the weight increase and appearance of defects. In conclusion, they reported the drum's rotational speed, the core bed temperature, and the feed rate of the coating solution as the main effects, and created a control strategy for these process parameters [43].

2.3. Quality Control

QbD can also be expanded to analytical methods for the quality control of pharmaceutical formulations, also known as Analytical Quality by Design (AQbD), which is different from the classical approach for Analytical Method Development[44]. AQbD demands that the goal to be achieved is initially defined, i.e., the analytical target profile, as

well as properly selecting the analytical method from the different alternatives that are systematically evaluated. This allows a well-understood method to be obtained that not only exhibits the best performance but also has the possibility to be improved, if necessary. As the next step, a control strategy is designed and established to manage risks and guarantee robustness. Then, the validation of the method is developed, and finally, continuous monitoring is mandatory throughout the lifecycle [45].

Furthermore, AQbD facilitates regulatory flexibility in analytical methods. Given the fact that health regulatory agencies only allow minor modifications, the ease of changing parameters within a method operable design region (MODR) in the AQbD approach provides a multidimensional space based on the factors and settings that provide a suitable method performance [46].

Recently, at UCR, Murillo et al. developed and validated a bioanalytical HPLC method with a diode array for the simultaneous quantification in human plasma of carbamazepine and its active 10,11-epoxide metabolite. The risk assessment focused on the separation and recovery of the analytes from properly preserved human plasma, using a solid-phase component extraction strategy. For this critical parameter, three types of extraction cartridges were evaluated to optimize the process, which allowed more than 95% recovery of the analytes to be obtained. However, validating a bioanalytical method presents some issues posed by the biological matrix. Thus, applying the AQbD approach allowed them to optimize and save reagents and consumables in the execution of the validation process, as well as fulfilling validation criteria in terms of linearity, specificity, precision, and accuracy, among others, to ensure reproducible and reliable results. This was achieved by implementing the use of a 50 mm column with a particle size of 3.5 µm, obtaining good integration and a resolution higher than 2.0 for the chromatographic peaks [47].

QbD has also gained importance in natural product development and quality control due to the current high demand [48]. On top of that, the use of DoE in an AQbD approach for these products implies a higher contribution due to the intrinsic variability that occurs when working with natural raw materials. However, it is important to note that, according to QbD, risk management has priority over DoE [15][16][49].

For instance, Castillo et al. evaluated a sample's mass and temperature impact on the moisture content in *Camellia sinensis*, *Cassia fistula*, *Chamaemelum nobile*, *Lippia alba,* and *Tilia platyphyllos* using a gravimetric method developed through a 3^2 full factorial design. A response optimizer was used to define the test conditions that allow results to be obtained according to a target value from a certified method[50]. The designed model was able to explain the response variability for all samples based on the R^2 (adj), which led to the definition of the range of mass and temperature for the analyses based on each materials' properties, as well as considering the capacity, precision, moisture range, heating technology, and operational temperature range of the dryer and the available moisture balances.

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