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Mini Review

Stability by Design (SbD): A proposal of application of Quality by Design (QbD) concept to physical stability as a control strategy

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Key words: Stability Control Strategy, Analytical Quality by Design, Stability Acceptable Design Region, Stability by Design and Quality by Design.

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Abstract

The ability to begin with the end in mind is a vital aspect of the Quality by Design (QbD) concept. The application of the concept to the process of pharmaceutical manufacturing, the first most requirement lies in developing a rather quality product. Also, the QbD concepts can be utilized in designing and developing product stability by assessing the reportable value of the given product as an analytical procedure for stability. Thus, a Stability Target Profile (STP) ought to be developed as it forms the foundation for stability development about the Stability Control Strategy (SCS). Contrary to the routine approaches, the SbD has to be initiated with a thorough comprehension of STP as well as risk evaluation for all the method variables that are likely to affect the response. An in-depth understanding of QbD will, therefore, be useful in the identification of the vulnerabilities and risks that relate to drug production, storage, and usage which will help in making informed choices and in return support the implementation of a control strategy.

Abbreviations
Quality by Design (QbD), Stability by Design (SbD), Stability Control Strategy (SCS), Analytical Quality by Design (AQbD), Continuous Stability Monitoring (CSM), Analytical Target Profile (ATP), Critical Quality Attributes (CQA), Stability Acceptable Design Region (SADR), Method Operable Design Region. (MODR), Design of Experiments (DoE), International Conference of Harmonization (ICH), Drug Substance (DA), Food and Drug Administration (FDA).

Introduction

With respect to contemporary drug discovery and development, the main concern is the physical and chemical stability of small-sized molecules pharmaceuticals. The stability of chemicals is essential for compounding across all the pharmaceutical research and development stages. Physical stability, on the other hand, relates to the overall stability of solids and is supported by certain properties like free energy, heat, and melting. In that, physical stability refers to the capability of materials to retain their physical structure over some time for manufacturing, usage and storage purposes.

The main purpose of QbD is to replicate the variety of products, enhance the process efficiency minimize the expenses across all stages. The approach usually improves the speed of manufacturing and availing them in the market and also improves the quality throughout the process through systematic R&D [1-2]. The approach through which pharmaceutical companies have to achieve QbD are briefly highlighted by the FDA guidance like pharmaceutical development (ICH Q8), quality risk

evaluation (ICH Q9) and pharmaceutical quality system (ICH Q10) [3].

Due to the growing need for quality pharmaceutical products with minimal effects on the overall individuals' wellness, QbD has become an important topic in the industry in developing robust manufacturing processes and products [4]. QbD refers to the systemic technique of product development which starts with prior developed aims and normally emphasizes understanding the process and products as a way of controlling quality [5-6]. The approach is mainly concerned with ensuring the predetermined specification is met by assessing the materials composition and the process of manufacturing drug products [7]. Following the QbD the quality of pharmaceutical products is guaranteed since the process and variables of manufacturing are considered. Hence, the execution of the paradigm in drug production under the QbD framework will be helpful to the pharmaceutical industry, the regulation parties and the public who act as the consumers [8].

SbD concept is characterized by risk assessment and science strategies that apply the familiarity and understanding of the merchandise in developing the most appropriate product plan stability leading to an amplified protocol as indicated below (Table 1) [9-11].

Stability by Design (SbD) clarification

Stability by design (SbD) refers to a risk-based strategy that places focus on time points and meaningful attributes. Further, the strategy may comprise the technical adjustment to stability protocols and in other cases, the strategies earmarked for the improvement of efficiency and expediting results without compromising the safety and quality of products.

The development of insights into the degradation pathways of compounds, whether in their physical or chemical form, offers the opportunity of the rational design of a strategy for stabilizing the compound. The studies are tailored and structured to ensure customer specifications are achieved.

The studies are significant in obtaining in-depth knowledge regarding the stability and links of various crystal forms. Further, the use of accelerated storage tests for chemical and physical components leads to changes in the identification of the best physical form. Additionally, accelerated stressing stability studies are conducted in accordance with the guidelines issued by the ICH.

Stability by Design (SbD) steps

1. Stability Target Profile (STP)

Refers to the prospective summary of the quality features regarding the physical stability that is to be achieved in ensuring the quality, efficiency, and safety of the pharmaceutical products. It, therefore, forms the design foundation in product stability development [12].

2. Stability Related Attributes (SRA)

The physical characteristics are considered as essential quality indicators. In this case, the manufacturing quality must demonstrate the ability to consistently develop a product with the utmost physical quality. The physical stability of the product must align with the storage specifications to ensure effective regulatory approval and filing of the marketing approaches [13].

3. Stability risk assessment

The risk assessment is important in determining the potential perils that are likely to affect the success of the entire development and the superiority of the product. The process is carried out through three stages which include risk identification, analysis and lastly evaluation [14].

3.1 Risk identification

The identification of risk helps in guarding the predefined stability of the design. From observation, several common risks can be identified and resolved before starting the process. For instance, materials with lower melting levels create challenges with regard to storage and therefore it is important to conduct phase changes throughout the manufacturing, storage, distribution and use phases to protect the quality. Proper packaging helps in protecting the products from the harsh environmental conditions such as heat or humidity as they are likely to distort the physical stability of the products.

Table 1. The comparison between the QbD, AQbD, and SbD.

Steps	QbD	AQbD	SbD
1	Quality Target Product Profile (QTPP)	Analytical Target Profile (ATP)	Stability Target Profile (STP)
2	Critical Quality Attributes (CQA)	Method CQA	Stability Related Attributes (SRA)
3	Risk Assessment	Risk Assessment	Stability Risk Assessment
4	Design Space	Method Operable Design Region (MODR)	Stability Acceptable Design Region (SADR)
5	Control Strategy	Method Control Strategy	Control Strategy
6	Continuous Improvement	Continuous Improvement	Continuous Stability Monitoring (CSM)

3.2 Risk analysis

It is also an important aspect of risk assessment as it helps in establishing the risk factors that would possibly lead an intense impact on the entire process and allows the trader to handle it with care. For example, if it is established that the heat will affect the physical stability, the entrepreneur is supposed to ensure that the product is stored under the specified room temperatures to preserve its quality and physical stability.

3.3 Risk evaluation

After consolidating the findings of the risk analysis phase, it is now time to evaluate the risks and their potential effects. The risk level of each factor is established by measuring its potential to occur and related consequences by focusing on the risk matrix defined in the table 2. There are risks with major impacts while others are minimal and can thus be controlled in general. The risks are categorized as major, minor or critical which depend on the anticipated impact on the stability, superiority, and usefulness of the product. While both major and critical risk factors are recognized to affect the well-being and efficiency of the products, minor risks are different as their effects might not be noticeable. The challenge is that the classification varies from one pharmaceutical product to the other. For example, in the case that the crystal structure of oral Bio-pharmaceutics Classification System (BCS) which has a high absorbency and solubility is changed and the new form meets the set solubility criteria, this means that the failure rate will be rated as minor. It is not until the solubility falls below the standard level that it will be classified as critical of major due to the physical instability that it will cause (Table 2) [15-22].

4. Design of Experiments (DoE)

The tertiary category of risks that is recognized from the risk evaluation assessment comprises contributory parameters and variables that can be explored with the assistance of DoE [23]. DoE is a methodical tactic for determining the association between the possible variables of the analytical method and how they affect the products [24]. The multifactorial design offers an opportunity for screening the number of specifications that are needed for minimal experiments. Stability Acceptable Design Region (SADR) refers to a rather multi-dimensional space that is established based on the outcomes of the DoE based on statistical calculation. Adjustments on the SADR can offer suitable approaches in meeting the physical stability performance [25-27].

5. Control Strategy

Perhaps the most important aspect of developing a physical stability control strategy understands the underlying mechanisms of physical instability. This usually requires understanding the properties and variability of individual mechanisms, and the product in general. Some CQAs may be indirectly related to the causative physical changes. For example, the dissolution behavior of an oral dosage form could be affected by multiple underlying physical changes, such as changes in tablet breaking force and interactions between the DS and excipients [5].

The potential physical instability of a product should be considered throughout the product development process. Ideally, it should be addressed as early as the point at which the DS form is selected. If solubility, purity, crystallinity, and mechanical properties are not limiting the manufacture and bioavailability of a DS, the solid form that exhibits better physical stability should be selected [4]. For example, the polymorph of a drug that is thermodynamically stable at ambient conditions is usually chosen to minimize the chance that a physical form change could occur during normal storage and use.

Specifically, the potential physical changes include melting point, appearance, color solution and clarity, particle size, moisture, and crystal modification. All the potential physical instabilities are highlighted in the table below in table 3.

Continuous Stability Monitoring (CSM) is the last SbD stage. The management of the product life cycle is normally achieved by evaluating the performance of the method over a given time in order to ensure that the predetermined specification for quality and physical stability is achieved. The monitoring process can be achieved by controlling the charts to follow the method of performance limitations. Constant monitoring allows scientists to actively identify the stability based on the specifications.

Table 2. Illustration of risk evaluation.

	Rare	Unlikely	Possible	Likely	Certain
Critical	✓✓				
Major		✓✓			
Minor			✓✓		
Insignificant				✓✓	

Table 3. Illustration of the possible physical instabilities for different dosage forms.

Preparations	Potential physical instabilities	Effects
Oral Solutions[28-30]	Flavor and taste changes Dye loss Discoloration Precipitation	Changes in color, smell, and taste
Parental Solutions[31-33]	Discoloration as a result of oxidation Precipitation Whiskers manifestations	Appearance changes
Suspension [34-36]	Caking Crystal development Settling	Loss of product uniformity Elegance loss
Emulsion[37]	Viscosity changes Creaming	Elegance loss Content uniformity loss
Semisolids[38-39]	Particle size changes Bleeding Caking	Content uniformity loss Elegance loss
Tablets [40-42]	Hardness Dissolution Appearance change	Drugs release changes
Capsules [43-46]	Changes in strength, dissolution, and appearance	Drugs release changes

Potential benefits of SbD

SbD is a strategy applied in formulation and product development. Therefore, the use of SbD can be linked to the following benefits:

- SbD enhances and offers valuable knowledge regarding a product, and therefore, it facilitates the establishment of reasonable specification and expiry.
- The vastness of product knowledge gained because of SbD is important in the reduction of the impact of raw material variability.
- The strategy offers a faster and more efficient process scale-up based on the insights gained from stability testing.
- SbD enhances the creation of a robust product as it facilitates the scrutiny of areas of vulnerability at a point in the lifecycle leading to optimization of production.
- The use of SbD in product development could be more beneficial if the approach is extended to stability studies, and therefore, product stability could be reinforced.
- The approach might also be applied in the determination of stability predictions and in other cases, it carries the potential for the aggrandizement of the extent of stability testing needed for the establishment of the shelf life and storage conditions of a product, which would lead to time and cost-efficacy for the pharmaceutical industry.

Conclusion

Risk assessment strategies are normally promoted across all the different pharmaceutical development. However, physical stability still lags behind when it comes to utilizing the opportunities. Physical stability is widely recognized as an important aspect of the entire pharmaceutical development. Physical stability helps in determining the safety, quality as well as the efficacy of the drugs product and the related life cycle. Regardless of the level of the change in the performance, quality, life cycle, and product formulation, it is important to understand the factors that lead to instability. The knowledge acquired by comprehending the QbD technique is likely to help in identifying vulnerabilities that are involved in drugs products production, use, and storage. The understanding is also vital in making informed decisions that seek to guard the safety, superiority, and effectiveness of the products.

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