

Enhancing Sublingual Tablet-Quality Through Quality-by-Design Principles: Current Trends and Insights

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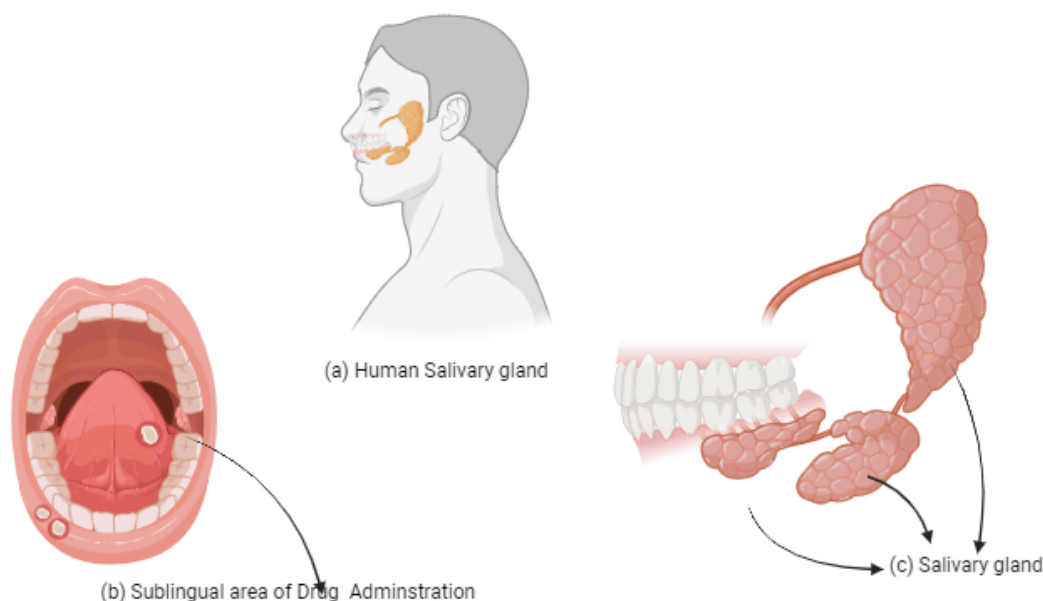
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Graphical Abstract



Abstract:

The field of pharmaceutical development has witnessed a significant shift toward implementing Quality by Design (QbD) principles to enhance the quality, safety, and efficacy of various drug delivery systems. As a promising alternative to traditional oral dosage forms, sublingual tablets have gained attention for their rapid onset of action and improved patient compliance. This review article aims to provide a comprehensive overview of the fundamental principles of QbD and its relevance in the context of sublingual tablets. It delves into the intricate relationship between Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), emphasizing the necessity of a systematic approach to achieving product excellence. Furthermore, the article highlights the benefits of implementing QbD in sublingual tablet development, potential challenges, and the regulatory landscape for QbD in pharmaceutical development.

Keywords: Quality by Design, Design of Experiments, sublingual tablet, optimization of formulations, stability testing

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Rationale, Purpose, and Limitations

The study is motivated by the pharmaceutical industry's shift toward Quality by Design (QbD) principles and the increasing interest in sublingual tablets due to their potential benefits.

Its purpose is to educate the reader about the principles of QbD, their application to sublingual tablets, and the associated implications and challenges. The paper aims to provide a comprehensive understanding of how QbD can be applied to sublingual tablet development, emphasizing the need for a systematic approach.

This knowledge will benefit others in the field by guiding them in optimizing pharmaceutical products for enhanced patient outcomes, thereby addressing an unmet need for a systematic framework in sublingual tablet development within the context of nanomedicines.

Introduction:

Among all drug administration methods, oral drug delivery is the most usually utilized because of its identifiable benefits, including its

convenience, ability to improve patient compliance, minimal need for sterility, and a high degree of flexibility in developing the dosage form. Today's formulation research is overcoming shortcomings of conventional delivery systems to provide medications with improved performance and high bioavailability. [1]

The three main issues with orally administered medications are first-pass metabolism, bioavailability, and the onset of action, which are addressed by sublingual formulation because the sublingual mucosa is thinner than the buccal mucosa, drugs can be absorbed quickly and take effect quickly. [2] Sublingual tablets could be used as a substitute for the oral route to address the shortcomings of the oral tablets (Figure 1). Nowadays, several medicines are given sublingually, including nifedipine, several opioid analgesics, some barbiturates, benzodiazepines, and steroids. [3-8]

Traditional methods for developing pharmaceuticals predicated on quality through testing are no longer in use. [9]

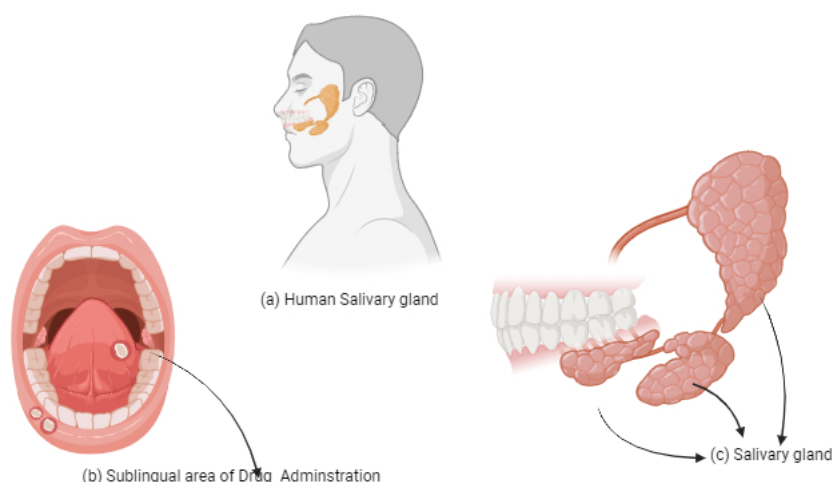


Figure 1. Sublingual route for drugs.

When using the quality-by-design approach, raw materials (such as drug substances and excipients) and manufacturing techniques are controlled to ensure the quality of the final product.

When finished products don't meet regulatory authorities' requirements, manufacturers must restart the process and determine what went wrong. [10-13] Testing techniques for quality are costly and can lead to variances that reduce

the safety of the finished pharmaceutical products (Figure 2).

Formulations and processes must be optimized through more scientific and systematic methods to address these challenges. To overcome this challenge, the Quality by Design (QbD) strategy is introduced to improve production procedures and ensure the quality and safety of finished products. [14-17]

QbD was given regulatory agency approval after publications of several International Conference on Harmonization (ICH) recommendations Q8, Q9, Q10, and Q11. For instance, the ICH Q8 guideline describes the QbD strategy as clarifying the process's initial goals, facilitating knowledge and control, and controlling quality-related risks. Consequently, QbD makes it possible to produce pharmaceuticals that are both safe and high-quality pharmaceutical products. [18] This review discusses the QbD principles and their applications to developing pharmaceutical sublingual formulations. [19]

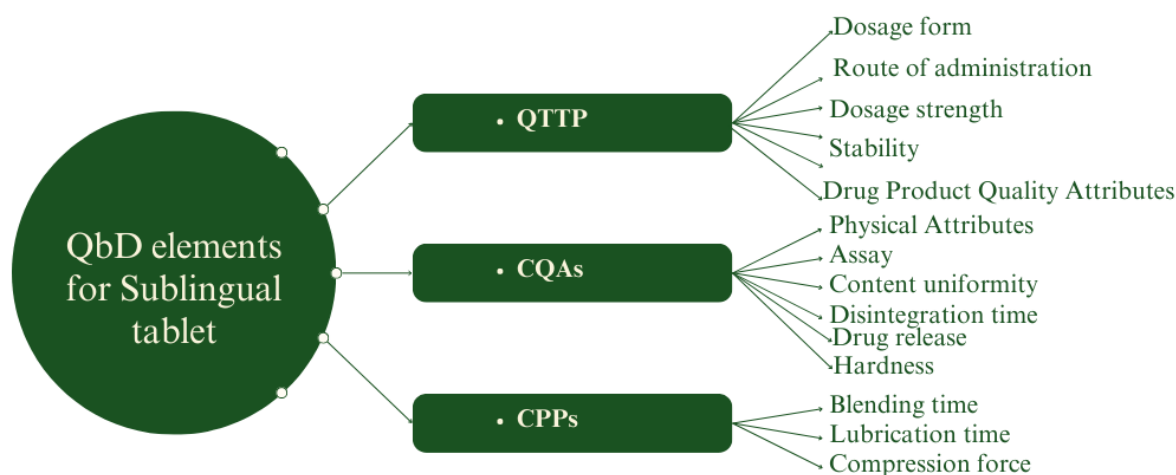


Figure 2. QbD elements for sublingual tablet.

According to ICH Q8 (R2), “Quality must be integrated into a product or manufacturing process because it cannot be tested or inspected into a final product.”

The level of effort, formality, and documentation of the QRM process should be proportionate with the level of risk, according to ICH Q9, which specifies that “the assessment of the risk to quality should be built on scientific information eventually relating to the protection of the patient.” [24-28]

The primary objectives of ICH Q10 are to realize the product, establish and maintain a condition of control, and facilitate continuous pharmaceutical product improvement. It presents a thorough model for an efficient pharmaceutical quality system based on ISO quality ideas and involves required GMPs. [29]

Discussion

QbD Principles

QbD is “a systematic approach to pharmaceutical development that starts with predefined objectives and focuses on product and process understanding and process control, based on quality science and QRM.” [20]

ICH Guidelines

- ❖ ICH Q8 (R2) – Pharmaceutical development.[21]
- ❖ ICH Q9 – Quality Risk Management (QRM). [22]
- ❖ ICH Q10 – Pharmaceutical quality system.[23]

Comparison of the Traditional Quality by Testing (QbT) Approach with the Modern QbD

The traditional regulatory evaluation system involves the evaluation of the performance and quality of the product by restricting flexibility in manufacturing processes and end-product testing. Thus, the QbT approach mainly involves evaluating all product parameters equally, resulting in more review time for low-risk products and removing necessary resources from high-risk products. [30-31] Table 1 compares the systematic QbD approach with the classic QbT approach.

The quality-by-design approach

Because the QbD technique involves quality assurance during production, it is necessary to identify essential patient needs-related qualities before developing a pharmaceutical product. In

this regard, QbD defines the standards that ensure the quality of the final product, which must be assessed throughout the development of the pharmaceutical product. The ICH Q8 defines the most often used QbD elements, which include Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs). It is based on risk identification, defining the design space after doing the Design of Experiment (DoE), and risk analysis. A control measure is used throughout the process to guarantee that products have a constant and predetermined quality.[32]

Quality Target Product Profile (QTPP): concerns the product's safety and efficacy; the QTPP is a prospective description of the ideal quality attributes of a drug product that will be achieved to assure the required quality.

Critical Quality Attributes (CQAs) are the physical, chemical, biological, or microbiological properties of drug substances, excipients,

intermediates (in-process materials), and products that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Material Attributes (CMAs): substances that must be within specific ranges to ensure the quality of the drugs, excipients, and other substances utilized.

Critical Process Parameters (CPPs): are dynamic process variables that impact CQAs and should be observed or controlled to ensure the desired quality.

Risk assessment methods like risk filtering and fishbone diagrams (Figure 3) and prior experience and knowledge obtained from the literature are used to identify QTPP, CQAs, CMAs, and CPPs. Analysis of variance (ANOVA) and multiple linear regression are usually used to evaluate the experimental results when conducting risk analysis.

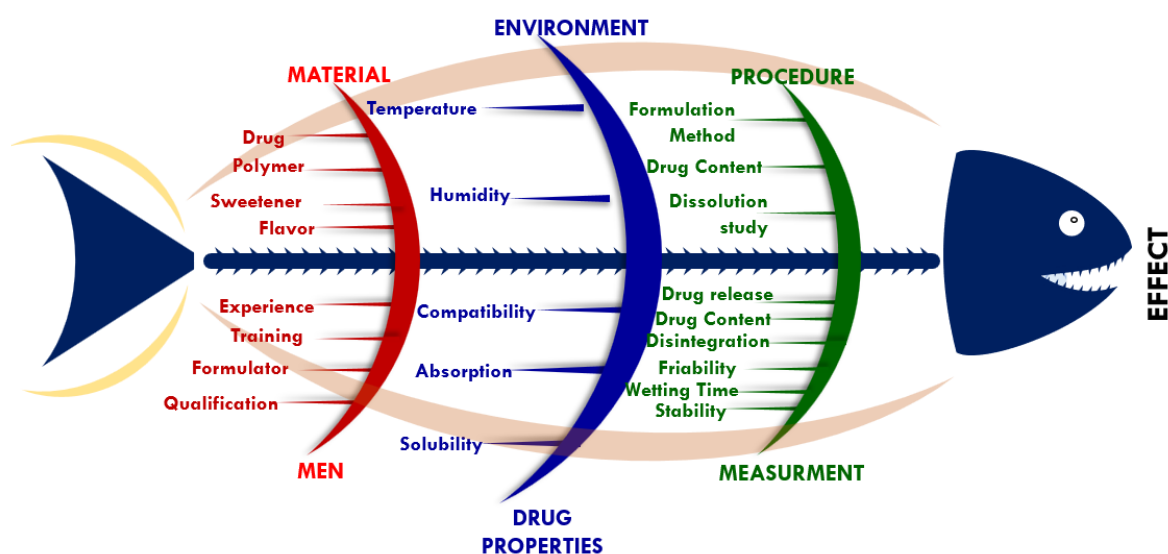


Figure 3. Ishikawa fishbone diagram shows the cause-and-effect association between the variables in the formulation and the process.

The input variables (such as material attributes) and process parameters that have been shown to ensure quality are combined and interacted in a multidimensional way to form the design space. Change is not considered when working within the design space. Exiting the design space is regarded as a modification that typically requires regulatory permission.

A control strategy is a planned set of controls that ensures process performance and product

quality. It is based on current product and process knowledge. The parameters and characteristics of the drug substances, the materials and components of the drug products, the operating conditions of the facility and the equipment, the in-process controls, the specifications of the finished product, and the associated monitoring and control methods can all be included in the controls. [33-38]

Applying the QbD approach is beneficial and important as it is still in the research phase for sublingual formulation development. The absorption and a lack of knowledge about pharmacokinetic factors are the main obstacles in the production of sublingual formulation. The QbD approach focuses on product and process understanding and aims to regulate product quality in accordance with the standards. Using QbD in the formulation design and production of a sublingual formulation is encouraging and promising (Figure 4).

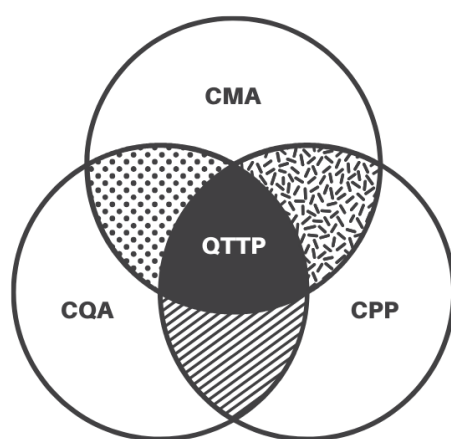


Figure 4, QbD approach diagram.

Development of Sublingual Tablet by Quality by Design Approach

- To create a QTPP for the sublingual tablet.
- Determination of the sublingual tablets' CQAs.
- Risk assessment procedure to determine the CPPs drafted a preliminary DoE to establish the CPPs' ideal parameters.

Sublingual Formulations that are Based on Nanotechnology Addressing the Key Differences from Traditional Sublingual Formulation

1. Particle Size Enhancement: Nano-based sublingual formulations employ particles at the nanoscale, notably smaller than those found in conventional formulations. This reduction in particle size significantly amplifies the available surface area for absorption, consequently elevating the drug's overall bioavailability.

2. Solubility Advancement: Nanotechnology can bolster the solubility of drugs with limited water solubility—a challenge encountered in

traditional formulations. This heightened solubility translates to improved drug absorption and heightened therapeutic effectiveness.

3. Utilization of Carrier Systems: Nano-formulations for sublingual administration frequently harness carrier systems such as liposomes, micelles, and nanoparticles to encapsulate and convey drugs. These carriers offer controlled release mechanisms, safeguard drugs against degradation, and enable targeted delivery—a level of sophistication not commonly associated with traditional sublingual medications.

4. Precision Targeting: Nano-based formulations are amenable to meticulous targeting strategies. This involves functionalizing nanoparticles with ligands or antibodies that interact with specific receptors, a level of precision not typically attainable with traditional formulations.

5. Facilitation of Combination Therapies: Nano-formulations unlock the potential for amalgamating multiple drugs or therapeutic agents within a single formulation. This innovative capacity allows for the realisation of combination therapies, an avenue less explored in traditional sublingual medications.

Benefits of Implementing QbD in Sublingual Tablet Development

Implementing QbD principles in sublingual tablet development offers several significant benefits that contribute to the project's overall success and the final product's quality. Some significant benefits follow below. [39-42]

1. Enhanced Product Quality and Consistency: QbD encourages a thorough understanding of the relationships between CPPs and CQAs. This understanding allows for developing a robust and optimized formulation and manufacturing process that consistently meets desired product specifications.

2. Reduced Risk of Failures and Recalls: QbD involves proactive risk assessment and mitigation strategies. Identifying and addressing potential risks early in the development process minimizes the likelihood of unexpected failures and product recalls due to quality issues.

3. Efficient Resource Utilization: QbD focuses efforts on critical factors that significantly impact product quality. This efficient allocation of

resources saves time and reduces costs associated with unnecessary experiments and iterations.

4. Faster Development Timelines: With a systematic approach, QbD helps streamline the development process by providing clear guidance on which parameters and factors to prioritize. This leads to quicker decision-making and accelerated development timelines.

5. Optimized Formulation and Process: Through methods like DoE, QbD enables thorough exploration of various parameters and their interactions. This results in identifying optimal formulation and process conditions that meet target CQAs.

6. Enhanced Process Understanding: QbD encourages a deeper understanding of the under-

lying science and mechanisms behind the formulation and manufacturing processes. This understanding allows for more informed troubleshooting and continuous improvement efforts.

7. Regulatory Compliance: QbD aligns with regulatory expectations as agencies increasingly emphasize the need for a science-based approach to pharmaceutical development. Documentation of QbD efforts demonstrates a robust understanding of the product and process, which can facilitate regulatory approvals.

8. Improved Scale-Up and Technology Transfer: The knowledge gained through QbD-driven development facilitates smooth scale-up and technology transfer to larger manufacturing scales or different manufacturing sites.

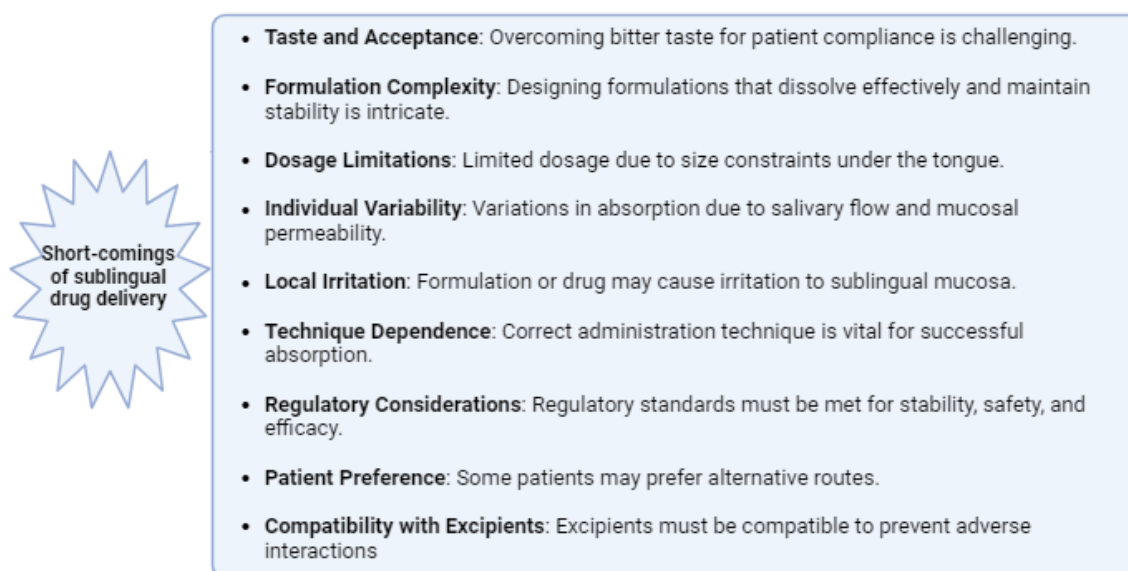


Figure 5: Shortcomings of sublingual drug delivery
Challenges

While implementing QbD principles in sublingual tablet development offers numerous benefits, there are also challenges that organizations may face, which are shown in Figure 5. Recognizing and addressing these challenges is crucial for successful QbD implementation. Some potential challenges are outlined below. [43-44]

- **Multiple Variables and Interactions:** Sublingual tablet development involves many variables, including active pharmaceutical ingredient (API) characteristics, excipients, disintegration agents, and manufacturing

parameters. Understanding the intricate interactions between these variables can be intricate, as they collectively affect the final product's quality.

- **Rapid Dissolution and Absorption:** Sublingual administration requires rapid dissolution and absorption of the tablet's contents.
- **Regulatory Acceptance of Innovative Delivery Routes:** Sublingual administration is relatively innovative, and regulatory agencies might have varying levels of familiarity and acceptance of this route of administration.

- *Taste and Palatability Issues:* Sublingual tablets are placed under the tongue, making taste and palatability critical factors for patient acceptance. Developing a formulation that delivers the desired therapeutic effect while being palatable can be challenging.
- *Patient Variability in Administration:* Sublingual administration depends on patients' correct placement and retention of the tablet under the tongue. Patient variability in administration can impact drug absorption and efficacy.

Regulatory Landscape for QbD in Pharmaceutical Development

Regulatory agencies, including the United States Food and Drug Administration (FDA)

and the European Medicines Agency (EMA), view and encourage the application of QbD principles in pharmaceutical development as a means to improve product quality, safety, and efficacy while ensuring a robust and science-based approach to manufacturing. [45] Both agencies recognize the benefits of QbD in enhancing the understanding of products and processes, reducing variability, and ultimately leading to better patient outcomes. Tables 2 and 3 show key aspects of the regulatory agencies and ICH requirements for pharmaceuticals for human use. [46-56]

Conclusions

Quality by Design is a systematic approach that ensures a deep understanding of the relationships between Critical Process Parameters and Critical Quality Attributes in sublingual drug product development — by proactively addressing risks, defining a design space, and optimizing processes through techniques like Design of Experiments, Quality by Design guarantees consistent product quality. It aligns with regulatory expectations, fosters a patient-centric approach, and supports continuous improvement. Collaboration across disciplines and anticipation of future trends contribute to its effectiveness. Quality by Design is essential for producing reliable sublingual drug products that meet regulatory standards and patient needs. This review analyses the fundamental principles and the importance of systematic approaches, as well as addresses challenges and regulatory considerations. As the pharmaceutical industry evolves, embracing Quality by Design for sublingual tablet development can provide improved drug delivery and enhanced patient care.

Abbreviations

Critical Quality Attributes (CQAs)
 Critical Process Parameters (CPPs)
 Design of Experiments (DoE)
 European Medicines Agency (EMA)
 International Conference on Harmonization (ICH)
 Quality by Design (QbD)
 Quality Target Product Profile (QTPP):
 Quality by Testing (QbT)

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Conflict of Interest

The authors declare no conflicts of interest. For a signed statement, please contact the journal office at editor@precisionnanomedicine.com.

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