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Quality by Design (QbD) Approach for Formulation Development and Evaluation of Fixed-Dose Combination Tablets: A Comprehensive Review

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Review Article

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ABSTRACT

Quality by Design (QbD) is a systematic approach to developing, producing, and controlling pharmaceutical products that emphasize understanding and controlling the Critical Quality Attributes (CQAs) of the product and process. QbD helps to ensure that a product meets its intended quality and performance characteristics and can help to identify and prevent potential manufacturing problems. Instead of providing quality through product testing, QbD aims to ensure pharmaceutical quality by incorporating quality into the products from the start. The purpose of this current study is to provide an overview of the QbD approach for formulation development and evaluation of Fixed Dose Combination (FDC) tablets. The paper further covered dosage forms, fixed dose combination drugs, and the principles and elements of pharmaceutical quality by design. It also examined the distinctions between Quality by Testing (QbT) and Quality by Design (QbD). The article discussed QbD tools, the evaluation of FDC tablets, and the challenges of the QbD approach in pharmaceutical development. The goal of pharmaceutical development is to create high quality products, and the manufacturing process should be carefully planned to ensure that the product performs consistently as expected.

Keywords: Fixed dose combination tablets; Quality by Design; Critical quality attributes; Design of experiment; Design space; Content uniformity test; Risk assessment; Process analytical technology

INTRODUCTION

Joseph Moses Juran, a well-known specialist in quality, provided a summary of the idea of quality by design. He argued that a product's quality may be planned and that issues with a product's quality can be traced back to the initial planning process. The product is expected to turn out as it was initially planned. Customer satisfaction in terms of service, product, and process is what quality entails. Quality activities must detect quality concerns early enough to take action without compromising cost, time, or quality. Quality by Design (QbD) is a systematic risk-based development approach established on available scientific evidence and quality risk management that begins with predefined objectives and emphasizes product and process understanding and control through the organisations of design space. In the 21st century, FDA initiated Quality by Design (QbD) and Process Analytical Technology (PAT) principles in 2003, intending to build the quality of the drug product right from the onset. QbD is described in ICH Q8, Q9 and Q10 guidance documents. A decade ago, the traditional Quality by Testing (QbT) approach was used to ensure the quality of drug products by checking them against regulatory specifications. It has been realized that quality must be built into the drug from the beginning rather than tested after it is manufactured. QbT is focused on testing finished products to ensure they meet established standards, while QbD is focused on understanding and controlling the critical quality attributes of the product and process throughout development and production to ensure that the product meets its intended quality and performance characteristics [1].

Using QbD principles enables the production of high quality medicines and their evaluation throughout their lifecycle, benefiting patients greatly. The fundamental tenet of QbD is that quality must be integrated into products from the onset rather than being tested into them. By assessing the factors that could affect quality, QbD seeks to ensure the intended level of product quality [2-8].

QbD can be applied in developing fixed dose combination drugs to achieve desired quality and therapeutic effect on patients. It has been reported that fixed dose combination drugs have drug interactions and pharmacokinetic and pharmacodynamic mismatch issues. They, however, lessen patients pill burden by requiring fewer pills to be taken, reduce the risk of adverse reactions compared to higher doses of monotherapy, and are believed to be more effective than higher doses of monotherapy. Drug substances, excipients, container closure systems, production processes, and quality control tests are all important factors that affect the final product's quality during the drug development process. Critical formulation attributes and process parameters are typically defined and regulated to ensure quality, which is another crucial responsibility. This current review aims to provide a comprehensive overview of the QbD approach for formulation development and evaluation of Fixed Dose Combination (FDC) tablets. This will help pharmaceutical companies and health service providers put a lot in planning to achieve their desired products, ensure efficient treatment and achieve patient's demands [9].

LITERATURE REVIEW

QbD approach for formulation development

The Quality by Design (QbD) methodology enables a systematic approach to drug development to enhance quality through analytical and risk management methods during the design, development, and production of new drugs. The ability to adapt techniques to avoid potential disruptions and manufacturing problems can be achieved by building a knowledge bank as the drug substance or product progresses through its lifecycle. The principle of continuous improvement underpins the QbD approach. The Quality by Design implementation strategy advocates a systematic approach to product development, starting with predefined goals and emphasizing product control and process understanding based on sound science. The Design of Experiments (DoEs) and Response Surface Methodology (RSM) are valuable components of this paradigm for producing a design space for the formulation's input variables. Currently, the concept of QbD can be used to optimize the majority of pharmaceutical unit operation operations. As with spray drying, hot melt extrusion, roller compaction, and homogenization processes, each unit operation has its unique input material characteristics, process parameters, and quality characteristics [10].

Objectives of QbD

Quality by Design (QBD) aims to:

- Design and develop products and processes that meet specific quality requirement. This entails determining the critical elements that influence quality, confirming that the design complies with requirements, and monitoring and regulating the final product's or process's quality.
- Identify and eliminate the root causes of quality problems. This enhances the general quality of the product or process and prevents recurrent quality problems.
- Improve process efficiency and effectiveness. This can result in cost savings, higher productivity, and higher customer satisfaction.
- Increase the predictability and reproducibility of the product or process. This helps to ensure that the final product or process consistently meets the desired quality standards [11].

Key characteristics of pharmaceutical Quality by Design (QbD):

The following are the key characteristics of pharmaceutical Quality by Design (QbD).

- QbD is concerned with identifying and comprehending the product and process's CQAs, as well as establishing controls to ensure that they are consistently met.
- QbD creates a design space within which the product can be manufactured consistently to meet the desired quality and performance characteristics.
- QbD employs a scientific and systematic approach to understanding the product and process, and this knowledge is applied to the product's design and control.
- QbD necessitates effective communication and collaboration among all stakeholders involved in the product development and manufacturing process, from research and development to manufacturing and regulatory affairs.
- QbD enables product design, manufacturing, and control strategies to be flexible in order to adapt to new technologies and market demands [12].
- QbD emphasizes continuous monitoring and evaluation of the product and process, as well as the use of that information to improve and optimize quality.
- QbD is incorporated into a quality management system, which ensures that all aspects of the product and process are consistently controlled and monitored.
- QbD complies with current regulatory guidelines and requirements to ensure product quality, safety, and efficacy [13].

Differences between QbD and QbT

QbT is a traditional method of testing finished products to ensure they meet established specifications. It is a retrospective approach, which means that it examines the final product to ensure that it meets the standards. The emphasis is on testing the product to ensure that it meets the established standards. QbD, on the other hand, is a more proactive approach that focuses on understanding and controlling the product and process's Critical Quality Attributes (CQAs) throughout development and production. This method entails a more in depth understanding of the science and technology at work in the product and process, as well as the application of this knowledge to design and control the product. The emphasis is on understanding the product and controlling the process to ensure that it meets the quality and performance specifications. Table 1 below highlights some of the key distinctions between quality by testing and quality by design [14].

Table 1. Differences between quality by testing and quality by design.

Quality by Testing (QbT)	Quality by Design (QbD)
Based on trial, error and understanding approach	Based on a systematic approach
Performance is guaranteed by product testing and validation	Quality is constructed in the robustness and reproducibility of the method built-in method development stage
The method is based on batch trial and validation report	Based on method performance to ATP criteria
The method is frozen and discourages changes.	The method is flexible and allows continuous improvement.
A rigid process that avoids changes; causing a burden to the FDA.	A flexible process that accepts changes within the design space; not required to add supplements to FDA.

Advantages and disadvantages of pharmaceutical quality by design approach

Although a promising approach for producing desired products, QbD has also got shortcomings which is summarized in Table 2 below.

Table 2. Advantages and disadvantages of QbD.

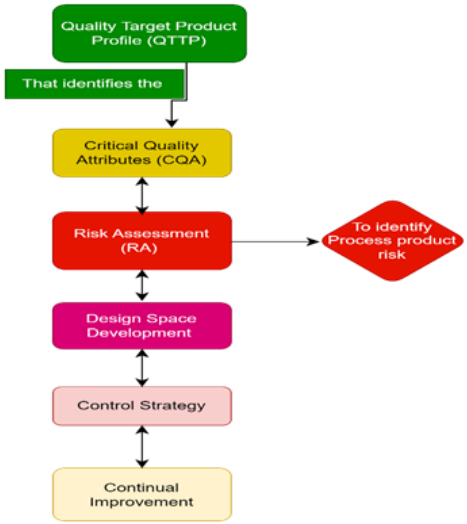
Advantages of QbD	Disadvantages of QbD
It offers a higher level of assurance regarding the quality of the medication product	Implementing it can be costly, as it requires additional resources, such as trained personnel, specialized software, and equipment
It gives the pharmaceutical business cost savings and efficiency	QBD is a detailed and time consuming process that involves identifying key factors that affect quality, verifying that the design meets the standards, and monitoring and controlling the quality of the final product or process

It creates transparency, reason, and predictability in the scale up, validation, and commercialization processes	It is a structured and systematic approach, which can limit flexibility and creativity in product development. This can be a disadvantage when dealing with new or innovative products.
It makes the pharmaceutical manufacturing process more efficient and lowers production costs and product rejects	It is not suitable for every product or process. It is mainly applied to products or processes that are relatively stable, consistent, and well-understood
It also gets rid of batch failures	It requires a lot of data collection and analysis to assess the impact of changes. This can be difficult when dealing with complex processes or systems.
It lowers the CMC supplement and encourages continual improvement	It relies heavily on data to make decisions and identify areas for improvement. If the data is inaccurate or incomplete, it can lead to incorrect conclusions and ineffective solutions
It improves chances for approval during the first cycle	It requires a lot of documentation, which can be time-consuming and difficult to maintain. This can lead to delays and errors
Prevent issues with regulatory compliance	

Elements of quality by design

The key elements of QbD are summarized in Figure 1 below.

Figure 1. Flowchart showing the key elements of QbD and how they relate.



Quality Target Product Profile (QTPP)

The definition of the Quality Target Product Profile (QTPP) is a prospective summary of the quality features of a drug product that should be attained to assure the intended quality, taking into account the drug product's safety and efficacy. Defining the quality characteristics of the drug product that will ideally be achieved to ensure the desired quality, while taking the drug product's safety and efficacy into account. The qualities are based on customer voice (pharmacists, physicians, and patients) and take into account the pharmaceutical equivalent and bio equivalent. The drug's quality target product profile is in accordance with the QTPP template provided by the USFDA guidance document on quality target product profile for fixed dose combination tablets. Table 3 shows the format of selection of quality target product profile [15].

Table 3. Format of selection of QTPP.

QTPP element	Target	Justification
Dosage form, route of administration, pharmacokinetics, strength, drug product quality attribute and container closure system.	Product specific	Pharmaceutical equivalent requirement or specific

Identification of Critical Quality Attributes (CQAs) and defining its criticality

Identification of CQAs is done through risk assessment as per the ICH guidance Q9. CQAs are generally associated

with the drug substance, excipients, intermediates (in process materials) and finished drug product, identified on the basis of quality, safety, efficacy and multidisciplinary. CQAs are summarized on the basis of quality attributes identified as a target along with the justification for being CQA. Table 4 shows a format of CQA identification [16].

Table 4. Format of CQA identification.

Quality attribute of drug product	Target	Is it CQA	Justification
It should include product and process specific quality attributes	Desired quality	Based on impact of attribute on QTPP	Statement should clearly justify the CQA criticality level scientifically as well as technically

Drug product CQAs normally studied includes physical attribute, assay, content uniformity, drug release/dissolution, degradation products, redispersibility, microbiological limits, isotonicity, impurities etc.

Identification of Critical Material Attributes (CMAs)

The critical material attributes of drug substance is identified as;
Physical characterization of drug substance: Physical appearance, PSD, pH solubility, hygroscopicity, polymorphism, flow, solid state form
Chemical characterization of drug substance: pH, pKa, FDS, stability
Biological characterization of drug substance: Partition coefficient, BCS, etc.
Among the things used are raw materials, starting materials, reagents, solvents, processing aids, intermediates, packaging, and labelling materials [17].
The evaluation of the relationship between drug substances and drug product is required for the identification of CQAs of drug products. The majority of excipient functionality must function in order to comprehend material properties. Critical quality features are also influenced by the choice of salt, solid forms, particle size, and morphology. In most circumstances, material qualities can be quantified and fixed, but they can also change throughout processing. Examples include impurity profile, porosity, specific volume, and sterility [18].

Critical Process Parameter (CPPs)

To ensure that the process yields the desired quality, it should be monitored or managed. In order to produce a product of the desired quality, a pharmaceutical manufacturing process frequently involves a number of unit activities (such as mixing, milling, granulation, drying, and so on). The selection of CPPs, which are responsible for ensuring CQAs, is done through a list of potential CPPs that has been made based on risk analysis [19].

There are three parameters

Unclassified parameters: Unclassified parameters are factors or variables that have not been thoroughly evaluated in terms of their impact on product or process quality. They are not yet classified as critical or non-critical parameters. Process conditions, raw materials, equipment, and other factors that have yet to be fully evaluated in terms of their impact on product quality are examples of these parameter. More research or data are required to determine whether an unclassified parameter is critical or non-critical. Manufacturers may use tools such as Design of Experiment (DOE) or Process Analytical Technology (PAT) to investigate the impact of unclassified parameters on product quality and determine if they need to be controlled or monitored. Unclassified data are crucial because they may eventually be found to be critical or non-critical [20].
Critical parameters: Critical parameters are factors or variables that have a significant impact on the quality of the product or process. These parameters are considered as important because they directly influence the Critical Quality Attributes (CQAs) of the final product. Examples of critical parameters can include things such as temperature, pressure, pH, humidity, mixing time, stirring speed, and composition. These parameters can directly affect the quality of the final product, such as its purity, potency, and stability.
A manufacturer can establish a design space, which is the range of operating conditions under which the process or product is expected to perform as intended, by understanding the relationship between critical parameters and critical quality attributes. Manufacturers can monitor and control critical parameters in real-time using Process Analytical Technology (PAT) and other tools to ensure that the process is operating within the design space and that the product meets the required quality standards [21].
Non-critical parameters: Non-critical parameters are those that have no significant impact on the quality of the product or process. When compared to critical parameters, which have a significant impact on product quality, these parameters are less important. Non-critical parameters can include equipment settings or environmental conditions that have no direct impact on product quality but must be controlled for other reasons such as safety, regulatory compliance, or process efficiency.
The temperature in the manufacturing room is an example of a non-critical parameter; it can affect the process, but as long as it is controlled within a certain range, it will not have a significant impact on the final product. Non-critical parameters are important to consider in QbD because they can still affect the process and may require control, but

they are not as important as critical parameters. A manufacturer can ensure that the process is consistent and efficient without affecting the final product quality by identifying and controlling non-critical parameters [22].

Design space

The term "design space" refers to the set of operating conditions under which a process or product is expected to perform as intended and meet the required quality standards in the field of Quality by Design (QbD). It is defined by the set of variable inputs and their levels. For example, temperature, pressure, and composition that have been shown to produce consistent product quality.

Design space is created by combining process understanding, experimentation, and risk assessment. Key Process Parameters (KPPs) and Critical Quality Attributes (CQAs) can be identified by understanding the underlying processes and their interactions, as well as through experimentation and risk assessment. The relationship between KPPs and CQAs can then be used to define the design space, which is the set of operating conditions under which the process or product is expected to function as intended [23].

Design space is an important concept in QbD because it allows for systematic exploration of the design space, which can then be used to optimize the design of the process or product, resulting in higher quality and lower variability. Furthermore, by comprehending the design space, appropriate process controls can be implemented to ensure that the process or product operates within the design space and meets the required quality standards.

Control strategy

The CMA of the input materials and intermediates, control of the process parameters, final drug product quality, and final packaging all fall under the purview of the control strategy, which is based on a thorough understanding of the process and the product. All of these components of the control strategy are included in Process Analytical Technology (PAT).

This system includes testing for raw materials, in-process materials, and finished products. The manufacturing process for drug products is carried out as specified in a set batch record. It is necessary to control a factor that has been designated as risky. The design space should contain the control space, which establishes upper and lower limits for a raw material (or) a process where parameters and material are routinely managed and ensures the quality of the final product. There is currently a control plan for each process [24].

The following components of a control strategy include:

- Materials input characteristics (e.g., drug substances, excipients)
- The state of the equipment
- In-process checks.
- The final product's specifications

Steps for pharmaceutical QbD implementation

The following steps can typically be used to describe how QbD is practically used in the process of developing new pharmaceutical products.

- Specify the product's desired performance goals and the QTPPs;
- Determining the CQAs;
- Determining potential CMAs and CPPs;
- Setup and execution of DoE to link CMAs and CPPs to CQAs and get enough information of how these parameters impact QTPP. Thereafter, a process Design Space should be defined, leading to an end product with desired QTPP;
- Recognize and eliminate the sources of variability in the production process and the raw materials;
- Constantly assess and enhance the manufacturing procedure to ensure consistent product quality.

Tools of QbD

There are several tools and techniques used in QBD to ensure that the final product or process meets the desired quality standards. Some of the most commonly used tools include:

Design of Experiments (DOE): This tool is used to determine the critical elements that influence a process's or product's quality. It enables the systematic varying of various inputs to ascertain their influence on the output. The Design of Experiments (DOE) method involves methodically organizing, carrying out, analyzing, and deriving conclusions from controlled tests to assess the variables that affect the value of a parameter or set of parameters. In the area of Quality by Design (QbD), DOE is a potent tool because it enables systematic exploration of the design space, which is the collection of all feasible combinations of input variables and their levels, to find the elements that have the biggest influence on product quality.

Prior Knowledge (PK): Prior knowledge is an important tool in the field of Quality by Design (QbD) because it allows for the incorporation of existing knowledge about the process or product into the design process. This can include

information about the materials, equipment, and manufacturing processes used, as well as data from previous studies or experiments.

QbD practitioners can find potential sources of variability and create controls to reduce them by utilizing prior knowledge. The design space a set of operating circumstances under which the process or product is expected to function as intended can also be established using prior knowledge.

Prior knowledge is important for risk management as well. To identify and evaluate any potential risks related to the product and the process, a QbD approach uses information about the patient, the process, and the product. In order to guarantee that the product meets the necessary quality standards, suitable risk mitigation strategies can be implemented once the risks have been identified.

Risk Assessment (RA): In the area of Quality by Design (QbD), risk assessment is a crucial tool because it enables the systematic identification and assessment of potential risks related to a given product or procedure. Making sure the product satisfies the necessary quality requirements and is secure for its intended use is the aim of risk assessment. Risk characterization and hazard identification are typically the two main parts of risk assessment in QbD. Identifying potential risks associated with the product or process, such as chemical or physical risks, is known as hazard identification. Risk characterization entails assessing the likelihood and seriousness of these hazards as well as figuring out the overall risk connected to the process or product.

Risk assessment helps to ensure that appropriate risk mitigation strategies are implemented, such as process or product design changes, testing, or monitoring. Additionally, risk assessment can be used to establish design space, which is the set of operating conditions under which the product is expected to perform as intended.

Mechanistic Models (RM): A mathematical representation of a process or system that details the underlying physical and chemical processes that control its behavior is known as a mechanistic model. In the field of Quality by Design (QbD), mechanistic models can be used as a tool to enhance our comprehension of the underlying processes and to forecast how a product or process will behave under various operating conditions. Mechanistic models can be used to identify important process parameters and their relationships, as well as to simulate the behavior of a product or process. The design of the process or product can then be optimized using this information, resulting in higher quality and less variability. Mechanistic models can also be used to forecast a product's behavior.

Process Analytical Technology (PAT): Process Analytical Technology (PAT) is a collection of tools and techniques for understanding, controlling, and optimizing manufacturing processes in real time. PAT is an important tool in the field of Quality by Design (QbD) because it enables continuous monitoring and control of the manufacturing process, which can be used to ensure that the product meets the required quality standards and is safe for its intended use.

Analytical techniques such as spectroscopy, chromatography, and mass spectrometry, as well as process control techniques such as multivariate data analysis and modeling, are examples of PAT tools. These tools enable real-time monitoring of Critical Quality Attributes (CQAs) such as composition, purity, and particle size, as well as the detection and correction of process deviations.

PAT also enables the identification of Key Process Parameters (KPPs) and their relationships, which can then be used to optimize the design of the process or product, resulting in higher quality and lower variability. PAT can also be used to define design space, which is the set of operating conditions under which a process or product is expected to perform as intended.

Classification of dosage forms

The dosage form is how a drug substance is presented to the market. This also implies the means or the condition by which drug molecules are delivered to sites of action within the body. The need to convert a drug to dosage form includes;

- Accurate dose.
- Protection, e.g., coated tablets and sealed ampules.
- Protection from gastric juice.
- Masking taste and odour.
- Placement of drugs within body tissues.
- Sustained release medication.
- Controlled release medication.
- Optimal drug action.
- Insertion of drugs into body cavities (rectal, vaginal)
- Use of the desired vehicle for insoluble drugs.

Different dose forms of the same drug are required. It is critical to have various dosage forms of the same medication. This will help to reduce discomfort, provide immediate relief, and promote patient compliance.

A dosage form should have the following desirable characteristics:

- Convenient to handle, use and store.
- Stable during storage and use.
- Withstand mechanical shock during transport.

- Flexibility in different drug strength.
- Provide expected therapeutic effect.
- Extent, drug release, onset, intensity, duration of action.
- Predictable.
- Economical and elegant.

The dosage form can be classified based on the physical form, site of application, route of application and uses. Figure 2 shows general classification of dosage forms, Figure 3 classification of dosage based on physical form, Figure 4 shows classification of dosage based on route of administration, Table 5 illustrates classification of dosage based on site of Application and Figure 5 shows classification of dosage based on uses

Figure 2. Classification of dosage forms.

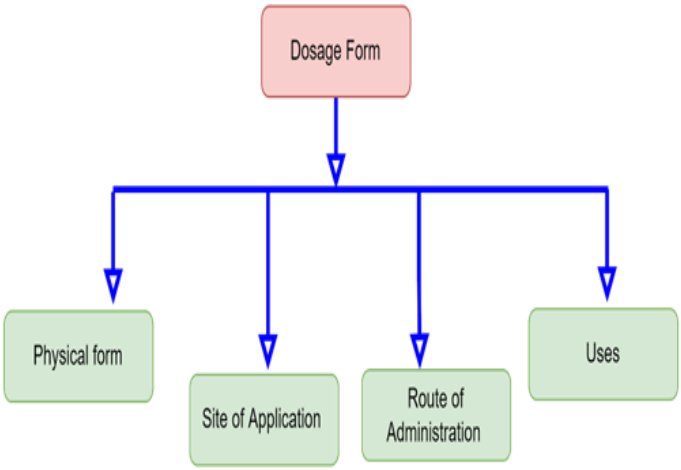


Figure 3. Classification of dosage based on physical form.

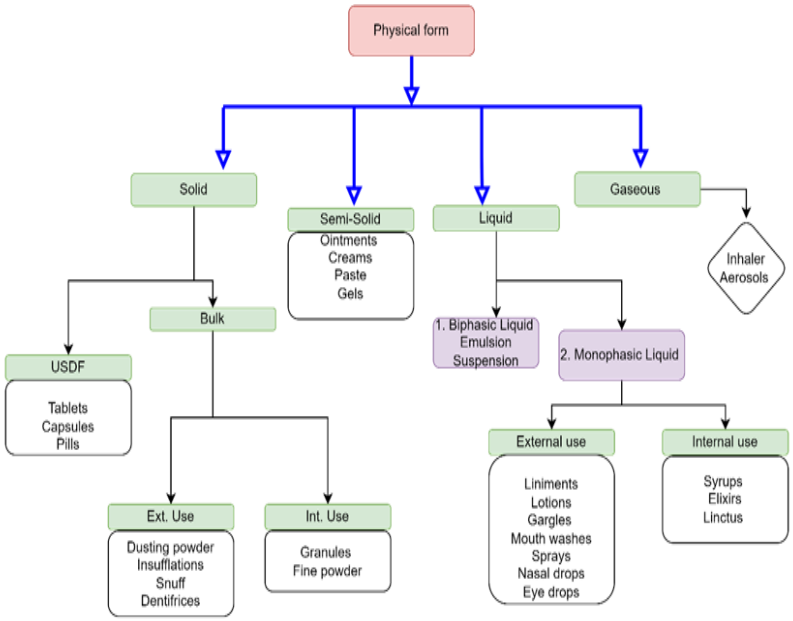


Figure 4. Classification of dosage based on route of administration.

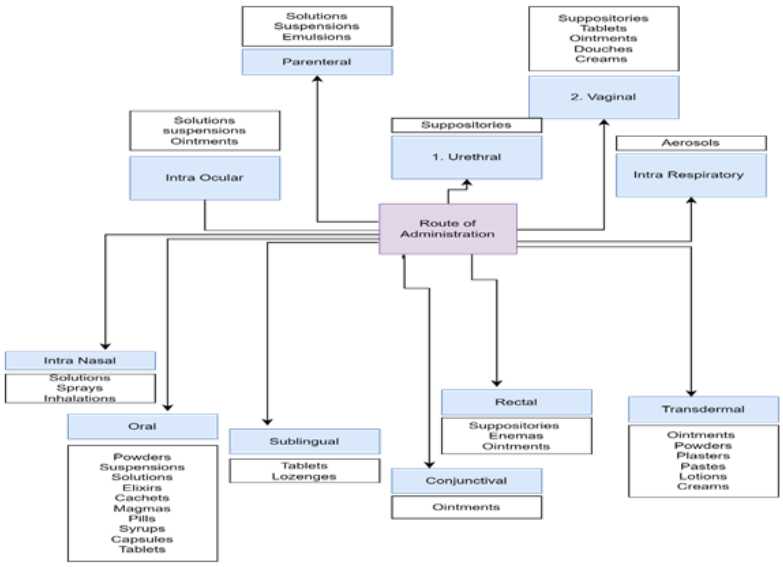
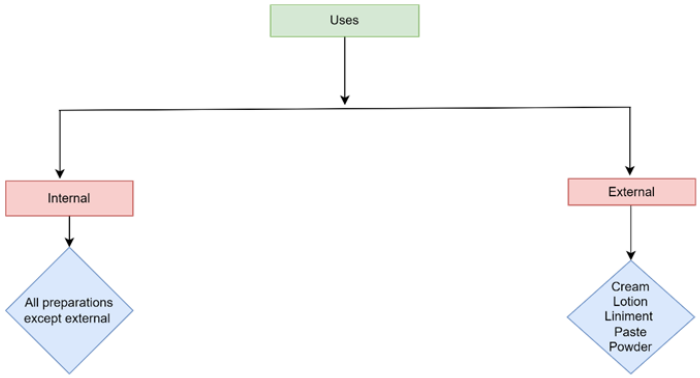


Table 5. Classification of dosage based on site of application.

Site	Dose form
Skin	Ointment, cream, lotions, liniment
Tooth	Tooth powder, toothpaste
Eye	Solution, ointment, cream
Hand	Hand cream, lotion, hand wash
Foot	Cream, ointment, dusting powder
Hair	Hair cream, hair lotion, shampoo
Nasal	Solution, spray, inhalation

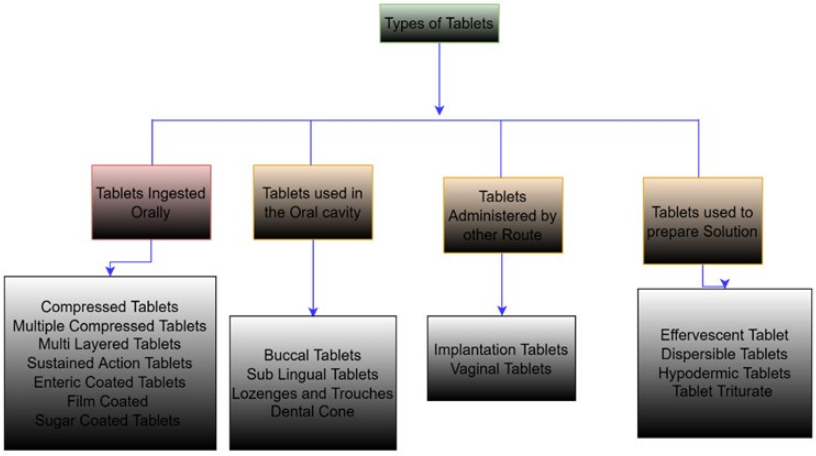
Figure 5. Classification of dosage based on uses.



Tablets and their types

Tablets are solid oral dosage forms often manufactured using acceptable pharmaceutical excipients. Depending on their intended use and manufacturing method, they may differ in size, shape, weight, hardness, thickness, disintegration, dissolution properties, and other factors. Tablets constitute approximately 90% of all dosage forms. Tablets are simple and easy to use. They deliver a correct dose of the active ingredient in handy portable packaging and can be engineered to safeguard dangerous drugs or mask unpalatable ingredients. However, one limitation is its slow onset of action compared to parenteral, liquid orals and capsules. Figure 6 illustrate various types of tablets.

Figure 6. Types of tablets.



Fixed Dose Combinations (FDCs)

The food and drug administration, USA defines a combination product as a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product. Fixed Dose Combinations (FDCs) combine two or more active ingredients within a single pharmaceutical administration form. They are also known as single pill combinations.

Types of fixed dose combinations

- Based on the number of constituents drugs present in the production as shown in Table 6.

FDCs can be grouped into three (3) types based on the number of drugs present in the product.

Table 6. Types of FDC drugs based on number of constituent drugs present.

Type of FDC drugs	Examples
Two dose combination	Augmentin=Amoxicillin (250 mg)+Clavulanic acid (125 mg)
	Co-trimoxazole=Sulphamethoxazole (800 mg)+Trimethoprim (160 mg)
Three dose combination	Rinizide=Isoniazed (100 mg)+Pyrazinamide (375 mg)+Rifampicin (150 mg)
Four dose combination	Sinarest=Paracetamol (500 mg)+Phenylephrine hydrochloride (10 mg)+Chlorpheniramine maleate (2 mg)+Caffeine (30 mg)

- Based on therapeutic effect as shown in Table 7.

Based on their therapeutic effect, FDC drugs can be classified into four categories.

Table 7. Classification of FDC drugs based on therapeutic effect.

Classification	Explanation
Rational	Two or more drugs combined in a fixed dose formulation (Tablet, capsule, syrup powder, injection) must have their plasma half-life, peak plasma concentration, and volume of distribution to be approximately the same.
Irrational	If the combination of the drugs is illogical in terms of plasma half-life and pharmacokinetics of the drug
Absurd	If there is no rationale or justification for combination, there is no increase in efficacy compared to individual drugs.

Characteristics of rational FDCs according to WHO guidelines

- Active Pharmacological Ingredients (API) with a complementary mechanism of action.
- Decrease the occurrence of resistance to antimicrobial agents.
- Increase the efficacy of combinations.
- Decrease the incidence of ADR or toxicity.
- Increase the compliance of drug therapy with decreased pill burden.
- Decrease the total cost of therapy.

- Dose of each API should be appropriate for defining a more extensive group of the population.

Table 8 give some examples of rational drugs.

Table 8. Examples of rational FDC drugs.

Generic combination	Category	Dosage form
Amoxicillin+Clavulanic acid	Antibiotic	Tablet
Artemether+Lumefantrine	Antimalarial	Tablet
Ethinylestradiol+Levonorgestrel	Anti-fertility	Tablet
Lidocaine+Epinephrine	Local Anesthetic	Injection
Benzoic acid+Salicylic acid	Antiseptic	Ointment, Cream
Neomycin+Bacitracin	Antibiotic	Ointment
Rifampicin+Isoniazid+Pyrimethamine	Antituberculor	Tablet

Advantages and disadvantages of FDCs

When it comes to treating numerous illnesses like cardiology, HIV/AIDS, malaria, and tuberculosis, where polypharmacy is the norm, FDC medications that include two or more Active Pharmaceutical Ingredients (APIs) in a single oral dose form are crucial. However, there are both therapeutic and non-therapeutic benefits and drawbacks to the FDC drugs.

Therapeutic advantages of FDC product

The FDC products offer the chance to mix many medications with various pharmacological mechanisms into a single dosage unit. In some therapeutic areas, such as the treatment of hypertension, viruses, diabetes, and cholesterol, this has significantly improved clinical outcomes. FDC has several clinical advantages, although they are not limited to:

- The therapeutic actions of two molecules working in concert. This was found for Aggrenox®, a combination of the oral antiplatelet medication dipyridamole and aspirin, which demonstrated superior efficacy to the co-administration of both medications.
- Because potassium clavulanate is an inhibitor of lactamases, shielding amoxicillin from breakdown by lactamases produced by many microbiological species, the FDC of amoxicillin and potassium clavulanate enhances the effectiveness of amoxicillin. Amoxicillin's range of antibacterial activity is significantly increased by this combination.
- Drugs are occasionally combined to reduce the risk of drug abuse, such as in Suboxone® (buprenorphine plus naloxone) and Lomotil® (diphenoxylate and atropine). Suboxone® contains both buprenorphine and naloxone to prevent opioid addicts from injecting the drug to experience the partial opioid agonist effects of buprenorphine. If Suboxone® is administered intravenously, Naloxone, an opioid antagonist, will cause withdrawal symptoms. The anticholinergic actions of atropine are used in combination with diphenoxylate to counteract the opioid like effects of diphenoxylate at high doses.
- The pairing of short acting pseudoephedrine and long-acting loratidine for prolonged coverage in allergy medications like Claritin-D.
- In order to reduce drug addiction and drug resistant bacteria, particularly for antiviral and antitubercular medications, the drugs are occasionally combined. Atripla®, a single tablet, contains efavirenz, emtricitabine, and tenofovir for the treatment of HIV. FDC products with rifampicin, isoniazid, pyrazinamide, and ethambutol are available for the treatment of tuberculosis.
- Drug combinations are occasionally used to enhance safety and tolerance. For instance, the Arthrotec® tablet combines the Non-Steroidal Anti-Inflammatory medication Diclofenac with the prostaglandin analogue misoprostol (NSAID). The gastro protective properties of misoprostol help to lessen the GI irritation and ulceration that diclofenac causes.
- The FDC medicines increase patient compliance by lightening the load on dosing units. For instance, the well-known cocktail medicines for HIV/AIDS patients include a number of active substances to prevent HIV replication from occurring more than once and to lessen the risk of developing drug resistance. In order to prevent the emergence of drug resistance, patient compliance is crucial.

Non therapeutic advantages of the FDC product

- The emerging FDC for anti-retroviral medications considerably increases HIV patient compliance, especially in third world countries. This is due to both the decreased burden of dosing as well as the fact that FDC products are frequently less expensive than several individual products.

- Compared to the expenses of producing separate items, the FDC products have lower manufacturing costs. The distribution logistics are made simpler by the FDC goods at the same time.
- The FDC products give pharmaceutical companies a chance to maintain their product pipeline when the market for blockbuster medications slows. This was demonstrated by the fact that a sizable portion of recently approved pharmaceutical medicines are FDCs.

Disadvantages of the FDC products

- Products made with FDC limit dosing flexibility. Multiple strength combinations are created to cover standard doses for each drug component of the FDC product in order to make up for the decreased dosing flexibility. However, the FDC medicines are not very helpful when patients or some disease therapies call for frequent dose modifications.
- Due to the fact that multiple medications are given in a single dose unit, it is more challenging to identify what is causing the adverse drug reactions of FDC products.
- Pharmacists may find it difficult to track their patients medication therapy when using FDC products. For instance, when the blood creatinine is 1.5 mg/dL in men and 1.4 mg/dL in women, metformin is not recommended. It is possible to overlook this need for FDC products that contain metformin.
- The maximum amount of a particular medicine in FDCs is often overlooked by pharmacists and doctors. For instance, the maximum daily intake of acetaminophen is 4 g/day. When a patient takes more than one FDC of acetaminophen along with codeine, oxycodone, or hydrocodone in addition to acetaminophen for pain relief, the upper limit may be exceeded.
- Occasionally, paediatric and elderly patients may find the FDC's tablet size difficult to swallow due to the FDC's ability to combine many medications into one tablet. For instance, metformin, which is administered in doses ranging from 500 mg to 2000 mg, is the cornerstone of therapy for type 2 diabetes. The pill size may be too large to swallow easily when metformin is coupled with any other antidiabetic medications.

DISCUSSION

Quality attribute test of tablets

Tablet appearance: Tablet appearance refers to the visual characteristics of a tablet, including size, shape, color, and markings. The look of a tablet can influence a patient's perception of the product and willingness to take it. It is also crucial in terms of regulatory compliance and safety concerns. Some of the key aspects of tablet appearance include:
Size and shape: Tablets can come in various sizes and shapes, such as round, oval, rectangular, and others. The size and shape of a tablet can affect its ease of swallowing and the way it looks to the patient.
Color: Tablets can have various colors, such as white, yellow, pink, brown, and others. The color of a tablet can be used to differentiate it from other tablets and to make it more visually appealing to the patient.
Markings: Tablets can have various markings, such as numbers, letters, logos, and others. Markings can be used to identify the tablet and to provide information about the dosage or the manufacturer.
Surface features: Tablets can have various surface features, such as smoothness, roughness, porosity, and others. Surface features can affect the tablet's ease of swallowing, the way it looks to the patient, and its stability.
Transparency: Tablets can have various transparency, such as opaque, semi-transparent, transparent, and others. Transparency can affect the way the tablet looks to the patient and the ability to see the inner ingredients.
Consistency: Tablets should be consistent in their appearance and size, it is important that the tablets have a uniform appearance, size and shape, with minimal variations between individual tablets.
Breakability: Tablets should have the appropriate strength and be able to withstand normal handling and storage conditions without breaking or crumbling easily.

Content uniformity

Content uniformity is a measure of the uniformity of the active ingredient(s) within a batch of tablets or capsules. It is an important aspect of pharmaceutical quality control, as variations in the active ingredient content can affect the safety and efficacy of the product.
The FDA and other regulatory bodies have established guidelines for content uniformity, which typically require that:

- The active ingredient content of individual tablets or capsules must be within a specified range, typically between 90% and 110% of the labeled amount.
- The standard deviation of the active ingredient content among the individual tablets or capsules must be within a specified limit, typically less than or equal to 7%.
- The number of tablets or capsules that fall outside of the specified range should be minimized, usually less than or equal to 2%.

To ensure content uniformity, various analytical techniques are used for testing, such as:

- High Performance Liquid Chromatography (HPLC)

- Ultraviolet-Visible spectrophotometry (UV-Vis)
- Fourier Transform Infrared Spectroscopy (FTIR)
- X-ray Powder Diffraction (XRPD)
- Near Infrared Spectroscopy (NIR)

The appropriate analytical technique is selected based on the characteristics of the active ingredient and the excipients of the formulation.
It is important to note that, content uniformity is just one aspect of product quality, and it should be considered in conjunction with other Critical Quality Attributes (CQAs) such as dissolution, disintegration, and stability.

Weight uniformity test

Weight uniformity refers to the consistency of weight among a group of items. This is an important aspect of quality control in manufacturing and packaging, as it ensures that products are consistent in size and weight, which is important for consumer satisfaction and safety. In the pharmaceutical industry, weight uniformity is critical for ensuring that medication doses are consistent and accurate.

Disintegration time test

Disintegration time test is a method used to evaluate the ability of a tablet or capsule to disintegrate or break apart in a liquid medium. This test is used to ensure that the product is able to release its active ingredients in a timely and consistent manner, which is important for optimal bioavailability and effectiveness.
The test is typically conducted using a disintegration test apparatus, which simulates the conditions of the human gastrointestinal tract. The tablet or capsule is placed in a basket or tube and submerged in a liquid medium, usually water or simulated gastric juice, at a specific temperature and agitation. The time it takes for the tablet or capsule to fully disintegrate is recorded and compared to the manufacturer's specifications.
Disintegration time test is an important quality control measure for oral dosage forms and is regulated by various pharmacopeias such as USP, BP and EP. It is also used to evaluate the performance of new formulations and to detect any changes in the formulation that may affect disintegration time.

Dissolution test

A dissolution test is a method used to evaluate the rate and extent of a drug substance that releases from a dosage form (such as a tablet or capsule) into a liquid medium. The test is used to measure the bioavailability of the drug and ensure that it is released from the dosage form in a consistent and timely manner, which is important for optimal efficacy and safety.
The test is typically conducted using a dissolution test apparatus, which simulates the conditions of the human gastrointestinal tract. The dosage form is placed in a basket or paddle and submerged in a liquid medium, usually water or simulated gastric juice, at a specific temperature and agitation. The amount of drug substance released into the liquid medium is measured at specific intervals and compared to the manufacturer's specifications.
Dissolution test is an important quality control measure for oral dosage forms and is regulated by various pharmacopeias such as USP, BP and EP. It is also used to evaluate the performance of new formulations and to detect any changes in the formulation that may affect dissolution. Additionally, the dissolution test is used to compare different brands of a drug and to evaluate the effect of different factors such as pH, temperature, and agitation on the dissolution of the drug.

Tablet hardness test

Pharmaceutical tablet hardness testing (or more correctly known as diametric/diametrical crushing strength) is a way of measuring the quality of tablets. Tablet hardness testing can be used to calculate the tensile strength of tablets to assess the manufacturability and compactibility of formulations.
Tablet hardness can serve as a guide for product development and as a quality-control specification. The tablets should not be too hard or too soft, as a hard tablet could prevent the dissolution of the tablet, which is needed for an accurate dosage. However, if the tablet is too soft it could lead to quick disintegration, and it can easily chip or break during packaging and transport.
Factors that could affect the hardness of tablets are:

- The speed of compression.
- The flow and air entrapment.
- Formulation variable.
- Process parameters.

Tablet thickness test

The tablet thickness test is used to determine how thick a tablet is. It provides an information of tablet variation. Tablets are manufactured using various shapes of tooling, and controlling the thickness of all individual tablets using

a specific shape of tooling is a significant challenge.
A vernier caliper, thickness gauge, or automated equipment is used to measure tablet thickness (Automatic weight, hardness, thickness, and tablet diameter test instrument). Depending on the size of the tablet, the thickness of the tablet should be controlled within 5% of a standard value.

Friability test

Friability testing is used to assess the durability of tablets during the packaging and transport processes. Using a rotating drum with a baffle, a sample of tablets is dropped repeatedly over a fixed time period. The outcome is examined for broken tablets and the percentage of tablet mass lost due to chipping. A friabilator is used to measure it.
The Friability test is commonly used in pharmaceutical industries and research to determine the durability of tablets during packing and transit. It improves product consistency and reproducibility in batch to batch production. It is responsible for determining the quality of pharmaceutical products. As a regulatory perspective, it is used in research and development in accordance with pharmacopoeia standards such as USP, BP, and IP.

Challenges of the QbD approach

- The primary and main barrier to QbD implementation is a lack of knowledge about the pharmaceutical process. The end result has typically been of greater importance to pharmaceutical firms than the scientific understanding of the process involved.
- Reaching agreement on how to address QbD through collaboration and cooperation between field inspectors and the FDA review and compliance sectors continues to be a difficulty.
- The vast majority of pharmaceutical companies believe that more concrete instructions on how to really adopt QbD are necessary. Companies requested clarification from FDA on QbD terminology, approved procedures, criteria to select and deselect important quality attributes, standards by which to appraise the sufficiency of controls, and criteria for analytical method substitution.
- For the effective application of QbD, there is a need for more collaboration across numerous disciplines inside the organization, including process development, production, and quality control.

CONCLUSION

Pharmaceutical companies believe that QbD may prolong the time it takes to submit an application for approval or may give the regulatory body unneeded information that could pose a barrier to the approval process. This study demonstrated that the integrated approach of QbD, statistical analysis, and PAT offers a robust control strategy for the ultimate goal of the QbD paradigm, *i.e.,* the production of drug products of consistent quality by implementing RTRT based on a deep understanding of the product and process.

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