Review Article

Comprehensive review on quality by design in fast dissolving tablets

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Abstract

Fast-disintegrating tablets (FDT), also known as orally disintegrating tablets (ODT), are innovative oral dosage forms designed to quickly disintegrate in the mouth without the need for water, providing an effective solution for patients with swallowing difficulties, including pediatricians, geriatricians, and patients with dysphagia. It is preferred over traditional tablets due to its rapid disintegration, improved taste, and increased patient compliance. However, due to their fragile structure, high porosity, and sensitivity to humidity, FDTs require precise design strategies to ensure optimal performance, safety, and stability. Quality by Design (QbD), as described in the ICH guidelines, provides a systematic and scientific approach to developing reliable FDT formulations. QbD includes defining a quality target product profile (QTPP), defining critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs), and creating a design space to ensure consistent product quality. Through risk assessment and design of experiments (DoE), manufacturers can optimize formulation parameters such as superdisintegrants, binders, porosity, and compressive strength to achieve the desired balance between rapid disintegration and mechanical strength. Control strategies that include raw material evaluation, in-process monitoring, humidity control, and final product testing further improve product reliability. Case studies show that the QbD approach significantly improves the solubility, stability, and bioavailability of FDT. Overall, QbD enables efficient and cost-effective development of high-quality FDTs, ensuring compliance with regulatory requirements and improving patient outcomes.

Keywords: Fast dissolving tablet, Quality by Design, quality target product profile, critical quality attributes, critical material attributes, critical process parameters.

Introduction

Fast DISSOLVING tablet are the type of tablets which melts easily and quickly in the mouth without using much water .it helps the children to take the medicine as well as also helpful for older people and anyone who faces the trouble while swallowing the normal tablets for making the tablet works properly the manufacturing companies use an special method called (QBD) QUALITY BY DESIGN METHOD .This method helps them in designing the tablet in a smart and planned manner so that the final product is always safe ,strong , effective .The oral route of delivery is thought to be superior due of ease of consumption, pain avoidance, simplicity in production, and significant acceptability of patients. The main disadvantage of solid unit dose forms such as tablets and capsules are uncomfortable to swallow (dysphagia). which causes patients to be unacceptable, particularly in pediatric elderly individuals. Oral Disintegrating Tablets (ODTs) were characterized by the USFDA as "A solid dose form that contains an active agent or therapeutic substance which breaks down quickly, typically in a few seconds when positioned on the tongue. [1,2] Another name for these dose types is quick mouth-dissolving, oro-dispersible, and disintegrating tablets, tablets that dissolve quickly as well as tablets that dissolve quickly. The United States Pharmacopoeia (USP) certified these terms as ODTs. Pharmaceutical companies are concentrating their efforts on creating novel dosage models for already-available medications that combine protection and effectiveness while lowering dosing frequency and enabling the cost-effective manufacture of these dosage units because the cost of creating a new medication entity is relatively high. Up to 50–60% of all measurement systems are covered in oral substance organization classes.[3] Easy organization, effective dosage, self-medication, pain avoidance, and, most importantly, patient continuity are all benefits of good dosage systems. For certain people, swallowing pain is a significant drawback of this dosage form. In cases of motion sickness, people have trouble swallowing traditional treatments, such as tablets, when water is unavailable. Unexpected bouts of coughing during the common cold, respiratory illness and bronchitis [2]. The swallowing difficulties are a common occurrence in elderly people as a result of anxiety in Young people's dysphasia, hand tremors, and shock because of undeveloped sensory and strong systems, and individuals with schizophrenia increasing the adherence to unfortunate patients. Geriatrics and pediatrics struggled with poor adherence to oral tablet swallowing therapy, resulting in the decreased overall efficacy of therapy [3, 4] For this reason, tablets that could easily break down in the oral cavity have received a lot of attention. Fast-dissolving tablets (FDTs) are defined by the US Food and Drug Administration (USFDA) as "a solid dosage type containing a medicinal substance or active ingredient that normally disintegrates easily within seconds when put on the tongue." A fast-dissolving medication delivery system was initially created in the late 1970s as a substitute for conventional dose formulations for elderly and pediatric patients. These tablets are typically made to dissolve in saliva in less than 60 seconds [4].Oral disintegrating tablets, also known as fast-dissolving tablets or oral dissolving tablets, are new oral dosage forms created by pharmaceutical goods technicians that dissolve rapidly in saliva—typically in a

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matter of seconds—without the need for water. More than half of patients in the population choose FDT over other dose kinds, according to recent industry surveys. Two ways are often used to produce mouth-dissolving tablets. The first method uses super disintegrates like sodium croscarmellose, sodium starch glycolate, and crospovidone. Optimizing tablet pore structure for vacuum and freeze drying is an additional strategy. In all cases, direct compression is favored since it is simple, quick, and economical. QbD (Quality by Design): ICH Based on excellent science and quality risk management (ICH), QbD is an organized approach to manufacturing that begins with predetermined goals and focuses on knowledge of commodities, methods, and process regulation.[5]

What is (QBD)

Quality by design means building quality into the product in an right form from the starting of manufacturing the tablet and it's focus on :-

- Understanding the formulation
- Identifying all factors that affect the final tablet quality
- Understanding the manufacturing process
- Controlling these factors scientifically[6]

QbD components include the Quality Target Product Profile (QTPP): It is defined as "a prospective description of the quality attributes of a drug product that is preferably accomplished to achieve the desired quality, taking into consideration the safety and effectiveness of the drug substance."The physical, chemical, biological, and microbiological properties of the input material are referred to as:-

Critical Material Attributes (CMA): To guarantee the intended consistency of the medication product, excipient, or process product, CMA must be within the permissible limit spectrum of delivery.

Critical Quality Attributes (CQA): Physical, chemical, biological, or microbiological characteristics that, in order to preserve the substance's ideal consistency, should fall outside of acceptable bounds, spectrum, or delivery. For instance, dissolution.

Critical Process Parameter (CPP): Variables monitored prior to or throughout the process have a significant impact on the final product's appearance, impurity, and output.

Design Space: A multi-layered combination and association of processing parameters and input factors (such as material qualities) that have been demonstrated to offer quality assurance.

Design of Experiments (DoE): An organized investigation in which inputs are changed and the outcome variance is computed to ascertain the degree of each input's or combination of inputs' influence

Risk assessment is a team that determines the overall method or approach for identifying the danger and risk variable that may cause harm (risk assessment), as well as for studying and assessing the impact of the risk (risk identification and risk assessment).

Quick-Dissolving Tablet Dosage Forms Using QbD Method: A tablet is a solid unit dosage form or prescription oral dosage form of a drug or other medicinal substance that has enough excipients. It is made up of a mix of pharmaceutical products and super disintegrates, typically in the form of a fine powder that is compressed or squeezed into a solid dosage.[7,8]

Why QbD is important for fast-dissolving tablets:

FDTs have sensitive properties like good mouth feel, fast disintegration and mechanical strength so these features can easily change with small variation in formulation or processing:

Performance Requirements for FDTs are extremely sensitive without water, FDTs must dissolve in the mouth in a matter of seconds. Small changes can have a big impact on:

- Time of disintegration
- Hardness/friability
- Mouthfeel
- Masking of taste

QbD aids in locating and managing sources of variability.

Sturdiness and Diminished Batch Errors: FDTs are weak mechanically and susceptible to moisture.

QbD decreases rejection of batches, differences between batches & Manufacturers can get more consistent quality by comprehending material features and processes.

Reduced Development Cost and Faster Approval

QbD reduces trial-and-error formulation and improves scale-up efficiency, which is critical for complex dosage forms like FDTs.[9]

Regulatory Expectation for Modern Formulation Development

Regulatory agencies encourage the use of QbD as it:

- Provides scientific justification
- Reduces post-approval changes
- Ensures product understanding

Improved Patient Compliance and Safety

FDTs target patients who have difficulty swallowing (pediatric, geriatric, psychiatric).

QbD ensures:

- Reliable disintegration
- Proper dose delivery
- Better taste and mouthfeel
- Thus, improving therapeutic safety.[10]

Target Product Profile (TPP) –

The expected characteristics of the finished pharmaceutical product are summarized in the Target Product Profile (TPP). The TPP is developed at an early stage of the product development process and primarily focuses on the intended clinical use of the product. According to FDA/ICH guidelines, the TPP defines key elements such as the therapeutic indication, route of administration, strength and dosage form, safety and efficacy goals, pharmacokinetic (PK) specifications, and the target patient population. [11]

Quality Target Product Profile (QTPP)

A subset of the TPP, the QTPP concentrates on the quality attributes that guarantee patient acceptability, safety and efficacy. ICH Q8 (R2) states that QTPP is a "prospective summary of the quality characteristics of a drug product that should be achieved to ensure the desired quality." It outlines the qualities that the product needs to have before production may start.[12]

Establishing the QTPP for Fast Dissolving Tablets (FDTs)

Fast-dissolving tablets are challenging dosage forms as they must disintegrate rapidly in the oral cavity while maintaining acceptable taste and adequate mechanical strength to prevent breakage during handling. The tablet should dissolve quickly to ensure rapid onset of therapeutic action, yet possess sufficient hardness for stability.

In defining the QTPP for FDTs, the developer considers the following factors:

i. **Intended use:** Rapid onset of action and ease of swallowing.
ii. **Target patient population:** Dysphagic patients, elderly, and pediatric populations.
iii. **Route of administration:** Oral; tablet dissolves on the tongue without the need for water.
iv. **Critical quality requirement:** Fast oral disintegration and dissolution of the dosage form.
v. **Performance objectives:** Rapid disintegration, pleasant taste, and adequate mechanical strength.
vi. **Regulatory expectations:** Compliance with FDA guidance on orally disintegrating tablets (ODTs) and ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System). [13]

Table 1: Showing QTPP for FDTs [14]

QTPP Element	Target Requirement for FDT	Justification
Dosage form	Fast-dissolving / Orally disintegrating tablet	Must disintegrate rapidly in the mouth without the need for water
Route of administration	Oral (oral cavity/buccal)	Suitable for patients who have difficulty swallowing conventional tablets
Strength	Appropriate dose strength (e.g., 5 mg, 10 mg, etc.)	Based on therapeutic requirement, dose accuracy, patient acceptability, and product quality
Appearance	Smooth, uniform, crack-free tablet	Enhances patient acceptability and reflects good manufacturing quality
Dosage uniformity	Uniform weight and content (within pharmacopeial limits)	Weight variation directly affects dose uniformity
Porosity	High and controlled porosity (typically 20–40%)	Ensures rapid saliva penetration and quick disintegration
Taste masking	Pleasant, non-bitter, palatable taste	Critical for pediatric and geriatric patient compliance
Disintegration time	< 30 seconds (USP ODT requirement); ideal 5–15 seconds	Ensures rapid breakdown in the oral cavity
Hardness	2–4 kg/cm² or sufficient to maintain integrity	FDTs are fragile; balance between mechanical strength and rapid disintegration is essential
Friability	< 1%	Ensures adequate mechanical stability during handling and transport
Dissolution	≥ 85% drug release within 15 minutes	Guarantees rapid onset of therapeutic action
Moisture protection	Low moisture sensitivity; appropriate protective packaging	FDTs are prone to degradation and softening due to moisture
Stability	Compliance with ICH stability guidelines	Ensures acceptable shelf life and product quality throughout storage

Detailed Description of Specific QTPP Elements

A. Weight (WT) in QTPP>>Why weight matters in FDTs:
Tablet weight is directly related to dosage consistency and significantly influences disintegration time, hardness, and friability. Very low-weight tablets (100–250 mg) are particularly prone to variability, increasing the risk of non-uniform performance.

Target requirements (as per pharmacopeial limits):
• Tablets weighing ≤ 250 mg: permissible weight variation of ±10%
• Tablets weighing > 250 mg: permissible weight variation of ±5%

Effect on product performance:
Lower tablet weight necessitates higher porosity and careful selection of superdisintegrants to ensure rapid disintegration. Weight variation also affects mouthfeel and the speed of tablet breakdown in the oral cavity.

QbD justification:
Since tablet weight influences multiple dependent quality attributes—such as porosity, hardness, friability, and content uniformity—it is considered a **Critical Quality Attribute (CQA)** in the development of fast-dissolving tablets. [14,15]

B. Taste Masking in QTPP>

Taste masking is exceptionally critical for fast-dissolving tablets (FDTs) because the drug dissolves directly in saliva and comes into immediate contact with the taste buds. Inadequate taste masking can lead to bitterness, unpleasant mouthfeel, and poor patient compliance, especially in pediatric and geriatric populations.

Objectives of taste masking:
• Avoid bitterness and aversive taste
• Improve mouthfeel and palatability
• Ensure overall patient acceptability and compliance

Common taste-masking techniques used in FDTs include:

i. **Use of sweeteners and flavoring agents** to improve palatability
ii. **Drug particle coating** using pH-dependent polymers (e.g., *Eudragit® E-100*)
iii. **Complexation techniques**, such as inclusion complexes with β-cyclodextrin
iv. **Ion-exchange resins**, including Indion® and Tulsion®
v. **Microencapsulation** of drug particles to prevent immediate drug–taste bud interaction[16]

Critical of critical quality attributes

Critical Quality Attributes (CQAs) are defined as the physical, chemical, biological, or microbiological properties or characteristics of a pharmaceutical product that must be controlled within appropriate limits, ranges, or distributions to ensure the desired product quality, safety, and efficacy. Identification and control of CQAs form the cornerstone of the Quality by Design (QbD) paradigm and are essential for both conventional tablets and fast-dissolving tablets (FDTs).The determination of CQAs for tablet dosage forms is a systematic process that integrates the Target Product Profile (TPP) and the Quality Target Product Profile (QTPP) with the physicochemical properties of the active pharmaceutical ingredient (API), formulation variables, and process parameters. Additionally, formal risk assessment tools such as Failure Mode and Effects Analysis (FMEA) and Ishikawa (fishbone) diagrams are widely employed to evaluate the potential impact of material attributes and process variables on final product quality. Through this risk-based approach, several tablet characteristics are consistently identified as critical, including hardness, friability, disintegration time, drug release or dissolution, content uniformity, and moisture content.

Tablet hardness, also referred to as crushing strength, is a key CQA as it determines the mechanical integrity of the dosage form and directly influences disintegration and dissolution behavior. In the case of FDTs, hardness requires careful optimization, as both excessively high and low values can lead to product failure. High hardness may result in delayed wetting and prolonged disintegration, whereas low hardness produces fragile tablets prone to breakage during handling. Hardness is affected by multiple factors, including compression force, binder concentration, moisture content, and excipient particle size. Typically, FDTs require a lower hardness range (2–4 kg/cm²) compared to conventional tablets (4–10 kg/cm²) to balance rapid disintegration with sufficient mechanical strength.

Friability is another critical attribute that reflects the tablet's ability to withstand mechanical stress during manufacturing, packaging, transportation, and handling. Excessive friability compromises dose integrity, packaging efficiency, and patient acceptability. Friability is influenced by compression force, lubricant level, porosity, hardness, and moisture content. Pharmacopeial standards such as the United States Pharmacopeia (USP) and European Pharmacopoeia (Ph. Eur.) specify an

acceptable friability limit of less than 1%, which is particularly challenging to achieve for FDTs due to their porous structure.

Drug release or dissolution is a fundamental CQA as it governs the rate and extent of drug availability for absorption, thereby directly affecting bioavailability, onset of action, and batch-to-batch consistency. Dissolution behavior is influenced by API solubility, particle size, tablet porosity, type and concentration of superdisintegrants, binder and lubricant selection, and tablet hardness. Conventional immediate-release tablets typically require 80–85% drug release within 15–30 minutes, whereas FDTs often exhibit faster dissolution profiles owing to their rapid disintegration in the oral cavity.Overall, the identification and control of CQAs through a QbD-based, risk-driven framework enable the development of robust tablet formulations with consistent performance. In fast-dissolving tablets, where patient-centric attributes such as rapid disintegration and palatability are critical, precise optimization of CQAs becomes even more essential to ensure product quality and therapeutic effectiveness. [17]

Development of designing space -Design space, as defined by ICH Q8, is the multidimensional combination and interaction of material attributes and process parameters that ensures product quality. In practical terms, it represents the safe operating range within which changes do not adversely affect the Critical Quality Attributes (CQAs).For fast-dissolving tablets (FDTs), establishing a design space is particularly important due to their sensitivity to minor formulation and process variations. Key formulation variables include porosity, binder concentration, and superdisintegrant level, while critical process variables involve mixing time, compression force, and drying conditions. Since FDTs require rapid disintegration, adequate mechanical strength, high porosity, and acceptable taste, small deviations can markedly impact hardness, friability, drug release, and disintegration time. A well-defined design space therefore ensures consistent and reproducible product quality.

Regulatory acceptance of Design Space-Although not mandatory, design space is strongly encouraged by regulatory authorities as part of the Quality by Design (QbD) approach. Regulatory agencies, including the FDA, accept design space submissions within the Pharmaceutical Development section of CTD Module 3. Operations conducted within an approved design space are not considered post-approval changes and do not require regulatory variation.

The implementation of design space provides manufacturing flexibility, supports scale-up, reduces batch failures, and minimizes regulatory burden. By maintaining predictable control over key CQAs, design space enhances robustness and ensures consistent quality and performance of fast-dissolving tablets throughout the product lifecycle.

Impact of Design Space on Product Flexibility-The establishment of a design space provides significant flexibility to pharmaceutical manufacturers. During routine production, it allows adjustments in critical parameters such as mixing time and compression force without the need for regulatory approval, thereby compensating for variability in raw materials and improving batch-to-batch consistency. Design space also facilitates scale-up from laboratory to pilot and commercial manufacturing by accommodating necessary process adjustments and reducing the risk of scale-up failures.

Furthermore, operation within the approved design space contributes to faster production and lower manufacturing costs by minimizing batch failures, reducing end-product testing, decreasing regulatory submissions, and enabling rapid troubleshooting. Most importantly, design space enhances product robustness and quality by ensuring predictable control over critical attributes such as disintegration time, friability, taste masking, mechanical strength, and drug release. Consequently, fast-dissolving tablets become more resilient to variations in equipment and environmental conditions. [18,19,20]

Control Strategy:

A control strategy for Fast Dissolving Tablets (FDTs) is the methodical regulation of material characteristics, processing parameters, in-process testing, and final product specifications to guarantee quick disintegration, palatable flavor, mechanical strength, stability, and consistency from batch to batch.

a. Control of Raw Materials in the Fast Dissolving Tablet (FDT)

Raw Material Control in a QbD-based control approach is the methodical assessment, testing, and monitoring of all input materials (API + excipients) to make sure they fulfill predetermined requirements so that the final FDT product consistently satisfies its Critical Quality Attributes (CQAs). Because FDTs necessitate: Very quick disintegration Elevated porosity Excellent mouthfeel Delicious flavor Sufficient mechanical power The formulation's raw materials must have strictly regulated functional, chemical, and physical characteristics.

Why raw material control is critical in FDTs The Significance of Raw Material Control in FDTs Because of this, FDTs are extremely sensitive to changes in excipient quality. The item is brittle. dissolves in a matter of seconds requires superior taste masking. Low-weight pills require appropriate flow. requires certain wetting behavior and porosity. Hardness, friability, and disintegration time are examples of CQAs that can be significantly changed by even little adjustments to source materials.

b. Control Strategy in In-Process Control for Fast Dissolving Tablets (FDTs)

The tests and inspections carried out throughout manufacturing to make sure the process is functioning within the designated Design Space and that Critical Quality Attributes (CQAs) will be satisfied are known as in-process controls, or IPCs. ICH Q10 (Pharmaceutical Quality System) defines an in-process control strategy as: > A collection of controls used throughout the production process to keep an eye on things and make necessary adjustments to guarantee constant product quality. IPCs are particularly crucial for Fast Dissolving Tablets since FDTs are: Minimal weight, Extremely delicate & Extremely susceptible to compressive force and moisture depending on superdisintegrant activity and porosity.

c. Finished Product Testing in the Control Strategy of Fast Dissolving Tablets (FDTs)

The last stage of the control plan (ICH Q8/Q9/Q10) is finished product testing, which guarantees that the Fast Dissolving Tablet satisfies all Critical Quality Attributes (CQAs) prior to batch release. Due to the fragility, moisture sensitivity, and need for quick disintegration of FDTs, final product testing must verify: Quick disintegration (less than 30 seconds), Appropriate masking of taste, Sufficient mechanical power, Adequate friability, Quick release of drugs & Stability in the presence of moisture. Thus, finished product testing confirms that a final tablet that complies with all previous raw material controls, in-process controls, and CPPs was produced.

d. Moisture control in FDTs

Fast-dissolving tablets (FDTs) are highly sensitive to moisture due to their intentionally high porosity, which facilitates rapid disintegration, and the frequent use of hygroscopic excipients such as crospovidone and mannitol. In addition, FDTs are generally lightweight and mechanically fragile. Excessive moisture uptake can lead to tablet softening, capping, increased friability, delayed disintegration, and reduced shelf life as a result of chemical degradation or microbial growth. Conversely, inadequate moisture control may compromise mechanical integrity, resulting in brittle tablets. Therefore, effective moisture control is a critical aspect of

the formulation, processing, and packaging strategy for fast-dissolving tablets.

Controlling Moisture When Handling Raw Materials Techniques:

1. Using excipients with low moisture content Superdisintegrants with specific moisture content, mannitol, and microcrystalline cellulose.
2. Raw material moisture specification (CMA) For instance, API: less than 1% moisture Crospovidone: less than 5% moisture
3. Appropriate raw material storage Containers that are airtight and have controlled humidity (RH < 50%) Prevent exposure of hygroscopic materials to the environment.
4. Hygroscopic excipient pre-drying (if necessary) prevents aggregation and guarantees consistent blending. [22,23]

1. Case studies of QBD applied to fast dissolving tablets

a. Flurbiprofen Fast-Dissolving Tablet

Study: QbD approach to develop fast-dissolving tablets using melt-dispersion paired with surface-adsorption

What they did: PEG-6000 (carrier) and lactose (adsorbent) concentrations were optimized using a central composite design (CCD). Solubility, flow (angle of repose, Carr's index), and percentage drug release were among the responses they measured. Key Results: Compared to a regular tablet, which released approximately 60 minutes of flurbiprofen, the optimized tablet released almost 99% of the drug in 15 minutes. Rats' in-vivo pharmacokinetics revealed 1.39× increased bioavailability and 1.38× higher C_{max} compared to the traditional tablet. Learning Points: The dissolution rate and flow characteristics were enhanced by combining surface adsorption with melt dispersion (to produce amorphous solid dispersion). Finding the best carrier/adsorbent combinations that balance flow and release was made possible by QbD (DoE). Understanding the process made it easier to convert in vitro advancements into actual increases in bioavailability.

Points of Learning: The dissolution rate and flow characteristics were enhanced by combining surface adsorption with melt dispersion (to produce amorphous solid dispersion). The identification of ideal carrier/adsorbent combinations that balance flow and release was made possible by QbD (DoE). Understanding the mechanism made it easier to convert in vitro enhancements into actual increases in bioavailability. [24,25]

b. **Aspirin Fast-Dissolving Tablet Study**: Design-based formulation and assessment of aspirin FDT quality. What they did: Povidone (binder) and crospovidone (superdisintegrant) were used in a Box-Behnken design (3^2). Disintegration time, hardness, dissolution, etc. were among the responses. Key Outcomes: A "best" batch (F7) with good disintegration, dissolution, and physical stability was found. For ninety days, the optimized formulation held steady at both 25°C/60% RH and 40°C/70% RH.

Points of Learning: To achieve the two objectives of mechanical strength and quick disintegration, DoE assists in methodically balancing binder and disintegrant. Design space concepts combined with risk assessment lower variability and promote stable manufacturing. Because QbD was aware of the factor ranges that guaranteed acceptable performance, stability testing became more logical.[27]

c. Functionality of Disintegrants in Rapid Disintegration Tablets

Study: Using a QbD approach, the functionality of disintegrants and their mixtures to enable quick tablet disintegration. What they did: They investigated the effects of various disintegrants, their combinations, and compression pressure on disintegration time and hardness using DOE (design of experiments) and response-surface methodology (RSM). Important Results: For each disintegrant (or their combinations), they determined the ideal ranges (acceptance space) that produce quick disintegration without sacrificing hardness. demonstrated that a combination of disintegrants can outperform a single disintegrant.

Points of Learning: It is essential to comprehend how excipients work, particularly disintegrants. For disintegrant levels, QbD aids in defining "safe zones," or acceptable spaces. The formulation is robust because it is possible to tolerate acceptable process variation within the design space. Disintegrant concentration and compression pressure have a high interaction, thus they should be tuned together rather than separately.[28]

Advantage and challenges of QBD in FDT formulation

Advantages of QbD in FDT Formulation

1.Higher-quality products Understanding Critical Quality Attributes (CQAs) such as disintegration time, hardness, friability, and dissolution are emphasized by QbD. guarantees that FDTs operate consistently even when raw materials or processing circumstances vary

2. Sturdy Formulation Design determines Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs). reduces batch failures by assisting in the design of a formulation and procedure that can withstand variability.

3. Risk Mitigation & Regulatory Compliance makes regulatory filings (such as those to the FDA and EMA) easier because QbD exhibits knowledge-driven development. helps make risk-based decisions about scale-up, process parameters, and excipients.

4. Effective Development Trial-and-error experiments can be minimized through systematic design with Design of Experiments (DoE). enables the improvement of FDT properties such as mechanical strength, mouthfeel, and quick disintegration.[30]

Challenges of QbD in FDT Formulation

. Problems with Formulation Fast disintegration and mechanical strength must be carefully balanced for FDTs. For novel excipients, QbD necessitates a thorough understanding of material properties, which might be challenging. Mapping compatibility problems between superdisintegrants and APIs is crucial.

Cost Difficulties QbD calls for: advanced analytical instruments (such as particle size analyzers, HPLC, and NIR). extensive testing (DoE studies for process optimization/formulation). Compared to conventional empirical methodologies, the initial investment is high. Staff training on QbD principles incurs additional costs.

Time Obstacles labor-intensive first work: Risk analyses (FMEA/FMECA) Design and implementation of experiments Analyzing data to determine design space QbD has a longer development timeline up front, but it might lessen failures afterward.

Difficulties in Technical Expertise needs qualified workers with expertise in: DoE and statistical evaluation Analytical process technology (PAT) Excipients' material science Rules and regulations (ICH Q8-Q11). Poor design space definition or incorrect data interpretation can result from a lack of experience. [31]

Future Perspectives of FDTs

Integration with PAT & Continuous Manufacturing

Prospects and Benefits: Real-time Quality Monitoring: During the tablet manufacturing process, PAT tools (such as NIR, Raman spectroscopy, and terahertz sensing) can keep an eye on critical quality attributes (CQAs) like porosity, content uniformity, and disintegration. Terahertz frequency-domain sensing, for example, has been investigated for quick and non-destructive tablet porosity measurement, which is connected to disintegration behavior. Enhanced Control & Robustness: By combining PAT with continuous manufacturing, it is simpler to keep strict control over material attributes (CMAs) and process parameters (CPPs), guaranteeing constant FDT quality. This is consistent with QbD principles (i.e., comprehending and managing design space). Speed & Efficiency: When compared to batch processing, continuous manufacturing (CM) greatly reduces production cycles. PAT reduces waste and batch failures by instantly detecting and correcting undesirable deviations.[31,32]

Challenges / Risks:

High Initial Investment: It costs a lot of money to set up continuous manufacturing lines that are integrated with PAT (spectrometers, sensors, control systems). Complex Process Development: For FDTs, which frequently have competing CQAs (e.g., rapid disintegration vs. mechanical strength), defining the design space and creating consistent management strategies are difficult tasks. Regulatory and Validation: Continuous processes must show equivalency (or superiority) to traditional procedures, and regulators may demand strong validation of PAT techniques. Technical expertise: To develop, analyze, and respond to real-time data, teams of highly qualified individuals (process engineers, PAT specialists, data scientists) are needed.[33]

Personalized FDTs (Using QbD + 3D Printing)

1. Prospects and Benefits: Tailored Dosing: 3D printing allows for dose customisation, particularly with methods like semisolid extrusion and fused deposition modeling (FDM).
2. To guarantee that every customized FDT satisfies quality standards, a QbD-guided approach can assist in optimizing formulations, printer parameters, and design.
3. In one study, for instance, QbD was utilized to create 3D-printed immediate-release tablets with a changeable API dose by varying the tablet's size or layer height. On-demand, Point-of-Care Manufacturing: Customized FDTs are produced locally using 3D printers at points of care, such as pharmacies and hospitals. Some research has even created printers that have PAT and controls built in.
4. New Dosage Forms: Creative designs are feasible, such as a 3D-printed "tablet-in-syringe" FDT for patients with dysphagia (difficulty swallowing). This has significant benefits for the patient.
5. Risk-based Design: Using QbD, one may methodically identify important factors (design, material, and process) and create a design space for 3D-printed FDTs such that quality is guaranteed even with customized designs.
6. Regulatory Alignment: Designing a 3D printer and process with risk assessments and control measures lowers risk and facilitates regulatory filings; QbD helps align with regulatory requirements.

Difficulties and Dangers:

Printability & Mechanical Properties: Ensuring that 3D-printed FDTs have appropriate mechanical strength, low friability, and still disintegrate swiftly is hard. For example, the optimized 3D-printed formulation for "tablet-in-syringe" FDTs exhibited minimal hardness, which aids in disintegration but may provide handling and packaging issues.

Content Uniformity: It is more difficult to achieve uniform medication distribution in small, customized units, particularly when the drug loadings are high or the doses are very small.

Content may be impacted by variations in extrusion, layer height, or ink flow. Scale & Throughput: Although 3D printing is great for personalization, it is still difficult to scale it to high throughput (for high-volume use). Additionally, printing is typically slower than tableting.Quality assurance and regulations pertaining to 3D-printed point-of-care tablets are still being developed. It is difficult to guarantee batch-to-batch (or print-to-print) uniformity, clean and sterilize printers, and validate PAT at the point of care. Cost and Accessibility: Investment, training, and quality procedures are needed to set up 3D printers (with PAT) in dispersed locations (like pharmacies or hospitals).

Combining All: QbD + PAT + Continuous Manufacturing + 3D Printing for FDTs

Imagine a future model that is hybrid:

1. Digital & Predictive Development: Create FDT formulations suited for 3D printing (or continuous tablets) using in-silico modeling, DoE, and QbD; define a "design space" around print parameters, ink/material properties, disintegration, dose, etc.

2. Automated, Self-Driving Production: Consider a "self-driving" data factory (or tableting factory) where formulations are loaded automatically, tablets are produced continuously or through 3D printing, PAT keeps an eye on quality in real-time, and feedback loops modify parameters to maintain target CQAs.Work on comparable platforms is being done for tablet development.[33]

Conclusion

Using the QbD approach for the development of the current study of Montelukast sodium orally disintegrating tablets involved many stages. One of the major stages was to perform an initial risk assessment for the purpose of linking the impact of CMAs to drug product CQAs. The formulation variables identified as high and medium risk on the drug CQAs for the product were lowered to low risk. Microcrystalline cellulose (MCC) displayed medium risk and high risk to content uniformity (CU). to breakdown and disintegration. CCS, or croscarmellose sodium, exhibits Magnesium stearate and has a significant danger of disintegration and dissolution. demonstrated a considerable risk of dissolving due to the low concentration applied. Optimization has been done using DOE v. 13.2, and the hazards were reduced to a low risk.

F5 was deemed optimal among the formulations due to its maximal drug release and short disintegration time. A rigorous QbD analysis was used in the development and optimization of Montelukast oral disintegrating tablets.In the formulation of fast dissolving tablets (FDTs),

The Quality by Design: (QbD) approach is a methodical, scientific, and risk-based approach that guarantees a strong product with consistent quality, improved performance (rapid disintegration and dissolution), and dependable bioavailability while also offering regulatory flexibility and process efficiency. Important findings and advantages include:

Ensured Product Quality: By moving the emphasis from "quality by testing" to "quality built-in by design," QbD increases the degree of assurance that the finished product continuously satisfies its predetermined quality target product profile (QTPP).Improved Bioavailability and Onset of Action: The QbD approach's improved and reliable rates of dissolution and disintegration frequently result in improved drug bioavailability, particularly for poorly soluble drugs, and a quicker onset of therapeutic action, which is a key objective for FDTs. Process Control and Understanding: Determining the design space offers a comprehensive grasp of how various factors impact the quality of the finished product. Manufacturers can operate within a broad range of parameters thanks to this information, which reduces manufacturing unpredictability and batch failures.

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