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DEVELOPMENT OF ORAL FAST DISINTEGRATING FILMS IN QUALITY BY DESIGN FRAMEWORK: A REVIEW

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ABSTRACT

The goal of pharmaceutical expansion is to produce a high-quality product and manufacturing process that consistently delivers the product's intended performance. During the design and development of a product in QbD, a company must define its desired product profile, identify the critical quality attributes, understand the impact of raw materials on the CQAs, and identify the control source of variability. Oral fast disintegrating films were developed in the QbD framework to understand and control the product and process with quality-based risk management, Fast dissolving oral thin films are useful in patients who have struggled to swallow tablets or hard gelatine capsules, such as children, the elderly, and the bedridden or developmentally disabled. Due to their advantages over other oral dosage forms, oral fast dissolving films are the most advanced form of the dosage form. This type of technology provides a convenient method of dosing medication not only for special population groups such as pediatric geriatric, bedridden, and mentally ill patients but also for general populations. The current review delivers an account of oral fast disintegrating films' formulation and product development through the implementation of QbD aspects such as QTPP, CMAs, CQAs risk assessment, and risk estimation matrix.

Keywords: Quality by design, pharmaceutical development, QTPP, CQAs, risk estimation matrix, Ishikawa diagram

INTRODUCTION

Quality by design is one of the most unique approaches that have been used in drug development, in the new product and marketed product manufacturing QbD can be used in predetermining the risk in the various operations, and providing highly accurate with suitable control strategies. QbD was defined as "A systematic method for the development which starts by predefining objectives and emphasizing on understanding and controlling the product and processes based of sound science and quality-based risk management". The QbD concept is profiled under the international council of harmonization (ICH) Q8 R2 guidelines **[1]**.

The intention of creating a consistent and better quality into a product and its manufacturing stages is completely dependent on pharmaceutical development. The studies which are performed under the development stages and other critical parameters tend to pave the way to obtaining better scientific knowledge. Thus, these will help in creating a design pattern with better control and specifications. It is worthy to mention that quality should be made from the design stages, rather than checking product quality for process succession **[2]**.

Quality-by-design (QbD) can help in the early analysis of hazards and quality-related issues during the formulation stages of products and also guarantees that any control procedures can be instigated at stages of development. As QbD relies on science-based methods, hence can be used in producing optimized and advanced manufacturing procedures with no regulatory inspections and inquiry necessities **[3]**.

Various researchers have worked on creating unique and creative development strategies for novel delivery systems using QbD strategies. Some of the tools utilized in the QbD method include:

1. Quality Target Product Profile (QTPP)
2. Critical Quality Attributes (CQAs),
3. Critical Process Parameters (CPPs),
4. Critical Material Attributes (CMAs) **[4]**.

Implementation of QbD in the formulation of OFDFs

The QbD approaches for the formulation development of OFDFs were established according to ICH Q8 (R2) guidelines. The various steps in the QbD approach are the Identification of QTPP, and the selection of CQAs, and CPPs. Achieving the design space through the design of experiments. The road map for the implementation of QbD approaches has depicted in **(Figure 1)**.

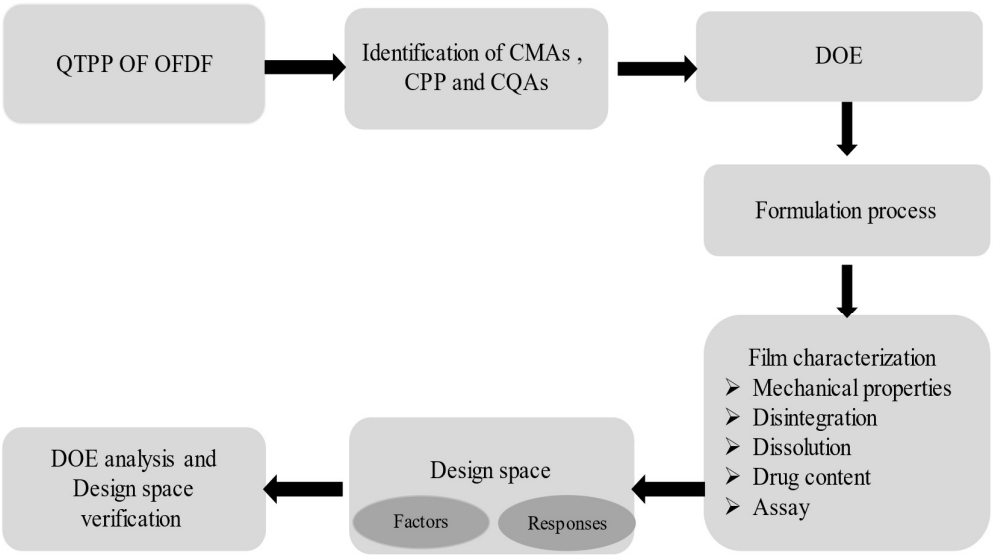

Figure 1: Roadmap for the implementation of QbD in the formulation of oral fast disintegrating films

QTPP for oral fast disintegrating film

It is defined as "A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." Quality Target Product Profile is established considering the existing product information, standards, scientific literature, etc. The data obtained can be introduced during the design of formulation/products as variables along with drug properties and uptake characteristics throughout the formulation development **[5]**. The QTPP and its target with the justification given in **(Table 1).**

Table 1: Quality Target Product Profile for oral fast disintegration film

Attributes for quality drug product	Target	Justification
Physical Appearance	The patient approves of the color and shape, and there are no visual film flaws.	Colour, shape, and appearance are set to ensure patient acceptance.
Odour	No disagreeable odour	Odour can have an impact on patient acceptance.
Size	2x2 cm	Because it is simpler to administer in the oral cavity
Flavour and sense of taste	No bitter taste	The bitter taste can have an impact on patient acceptance.
Time of disintegration	< 30s	The disintegration time of the film has a direct impact on the film's quick onset of action and efficacy.
Drug Assay	Label claim of 100%	Safety and efficacy will be impacted by assay variability. Process variables might have an impact on the drug product's assay. Therefore, the assay will be verified throughout the development of the product and process.
Content uniformity	According to pharmacopeial specification	Safety and effectiveness will be impacted by content uniformity variations.
Drug Dissolution	According to pharmacopeial specification	Bioavailability is impacted when the dissolution specification is not met. The dissolution profile is influenced by both formulation and process variables. Throughout the development of products and processes, this CQA is examined.
Container and closure system	Protect during dispensing and transportation	Stability will be impacted by containers and closures

Critical material attributes

The critical material attributes (CMA's) are an element of QbD that has a direct impact on product quality as well as pharmaceutical production which includes raw material, reagents, solvents, APIs, intermediates packaging, and labelling materials. An appropriate range is to be set to obtain favorable quality outputs during drug, excipient, or in-process material utilization **[6]**.

The materials that mainly affect the critical quality attributes of oral fast dissolving film are polymers, plasticizers, and surfactants **(Table 2)**.

Table 2: Effects of Critical Material Attributes on oral fast disintegration film

Critical material attributes	CQAs on OFDF with justification
API ➢ Solubility ➢ Impurities ➢ Melting point ➢ Crystallization	Affects the product quality, safety, stability, and formulation of OFDF
Excipients ➢ Polymers	Affects mechanical properties, the thickness of the oral film, and mainly the disintegration of OFDF
➢ Plasticizer	Affects the mechanical strength and elongation and folding endurance of the OFDF
➢ Surfactant	Affects the dispersibility and solubilization of OFDF
➢ Sweeteners	Affects the patient's compliance

Critical process parameters

A process parameter whose impact and variability on the critical quality attributes, A formulation that involves many unit operations that may include many processes, and those which mainly affect the quality of the product with the small changes in the parameters of the process that can be stated as a critical process parameter (CPP). Many criteria can fall under CQAs from this perspective like pH, temperature, pressure, humidity, etc **[7]**. the critical process parameter's impact on CQAs is given in **(Table 3)**.

Table 3: Critical Process Parameter on oral fast disintegrating film

OPERATION	CPP	Impact on CQAs
Mixing	Temperature RPM Order of addition Duration of stirring	Drug content Appearance Thickness
Drying	Temperature Airflow Solvent used	Drug content Mechanical strength Thickness
Casting	The surface of the Petri plate Pouring speed	Content uniformity Thickness
Cutting	Size Shape	Drug content Tensile strength Elongation

Critical quality attributes

CQAs can be defined as "A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality,". This process is a continuation step after QTPP and can affect the variables

obtained from both the process and formulation stages. Some elements like dosage strength and dosage form fall under the quality attributes of drug products which are covered under QTPP but not in CQA. CQAs include variables like content uniformity, assay, and permeation flux range as they are variable at any point **[8]**. critical quality attributes of OFDF with justification given in **(Table 4)**.

Table 4: Critical Quality Attributes of oral fast disintegrating film

CQAs of OFDF	Limits	Justification
➢ Assay	90-100%	If any evaluation deviates, the CQAs will have an impact on the drug's safety, efficacy, and quality.
➢ Content uniformity	85-115%	
➢ Drug release	85-100%	
➢ Folding endurance	150-250	
➢ Disintegration	30-60(sec)	

Risk assessment

The risk assessment helps to improve product and process design, understanding, controlling, and contributes to process capability improvement, a decrease in product variability, and a reduction in defect rates. Enhanced capacity for post-approval change management and root cause analysis. **(Figure 2)** shows the process impact and controls on the quality of a product by QbD.

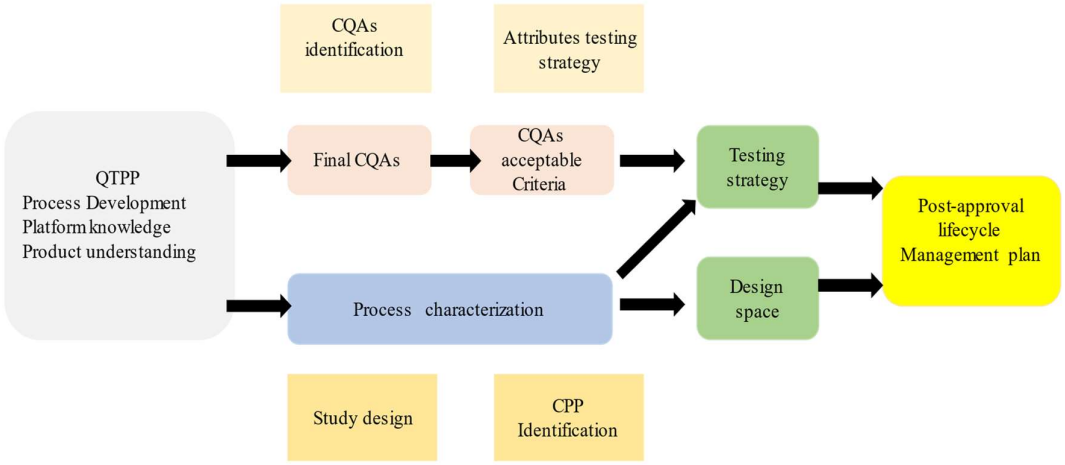

Figure 2: Risk Assessment with process impact and controls on the quality of a product by QbD

The risk assessment could be done using various risk assessment tools according to the ICH Q9 guideline. The risk assessment tools mainly used in the formulation are

- Cause and effect analysis
- The five WHYs
- Fault tree analysis
- Failure mode effect analysis
- Risk ranking
- Risk estimation matrix

This valuation is useful for different aspects related to procedure as well as materials included that can lead to low-quality products and also can affect product quality

deficiency. Thus, risk assessment can be used to focus on the developmental side to implement control tactics which can highly impact the quality aspect of the products **[9]**.

Preliminary risk assessment

Cause-and-effect diagrams are one of the risk assessment tools, that is used to identification of risk with the construction of the OFDFs considering the past formulation and product quality aspects. This provides a possible range of cause-effect dependencies for each level of parameters present in a process. The cause-and-effect diagram for the development of OFDF has represented in **(Figure 3) [10]**.

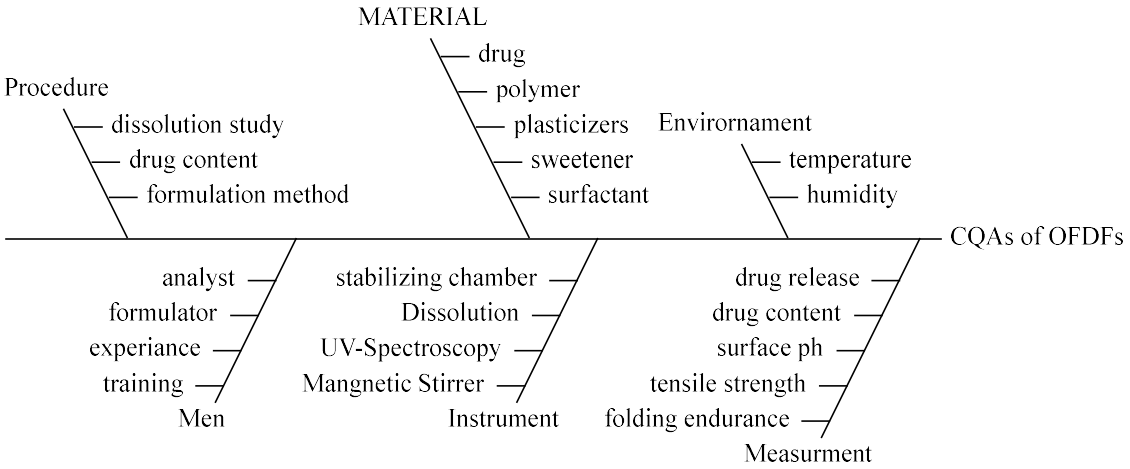

Figure 3: Cause and Effect diagram on CQAs of oral fast disintegrating film

Risk Estimation Matrix

REM (risk estimation matrix) is a system implemented to link the CMAs to the CQAs, risk was coded as a high medium, and low. The process of selection of CMAs was carried out using this risk estimation matrix strategy considering the possible risk potential involved in every factor available **[11]**. **(Table 5)** shows the risk estimation matrix for OFDF in that the red colour represents a high risk on the CQAs, the yellow colour represents the medium risk on the CQAs and the green colour represents a low risk on the CQAs.

Table 5: Risk Estimation Matrix for oral fast disintegrating oral films

CQA CMA/CPP	Content Uniformity	Disintegration time	Dissolution	Weight Variation	Thickness	Folding endurance
Drug	High	Low	Medium	Low	Low	Low
Polymers	Medium	High	High	High	High	Medium
Gums	Low	High	High	Medium	Medium	Low
Surfactant	Low	Low	Low	Low	Low	Low
Flavouring agent	Low	Low	Low	Low	Low	Low
Sweetening agent	Low	Low	Low	Low	Low	Low

Design of Experiment

The design of experiments is the foundation of QbD; designing or building quality into products is essential in the manufacturing of pharmaceutical products **[12]**. The use of DOE principles allows for a better understanding of the various method parameters and variables that influence CMAs **[13]**. Design of Experiment is a structured organized method for defining the relationship between factors affecting a process. In other words, the latter is a method of achieving knowledge by establishing a mathematical relationship between process inputs and outputs. The types of design and their uses in the design of experiments are given in **(Table 6)**.

Table 6: Types of design used in Design of Experiment

Types of design	Screening	Optimization
Full Factorial design	Yes	No
Fractional factorial design	Yes	No
Placket Burman design	Yes	No
Central composite design	No	Yes
Box-Behnken design	No	Yes
D-optimal design	Yes	Yes
Axial(mixture) design	Yes	No

Design Space

The development of the quality Target Product Profile, which describes the expected performance attributes of the product, is the first step in creating a Design Space. For the initial inquiry into the significance of quality characteristics and process parameters, experiments to be carried out can be identified using prior information and a preliminary risk assessment.

The demonstrated acceptable ranges for CPPs as well as the approved values for the CPPs' associated CQAs are both included in the Design Space. The organization's Pharmaceutical Quality System regulates normal operating ranges, which are a part of the Design Space. The Design Space contains operating ranges for process parameters classified in the intermediate criticality category mentioned before. The amount of process knowledge required to develop the Design Space will determine whether or not extra data, such as the manufacturing design parameters, is provided **[14]**. **(Figure 4)** indicates the structural representation of the design space.

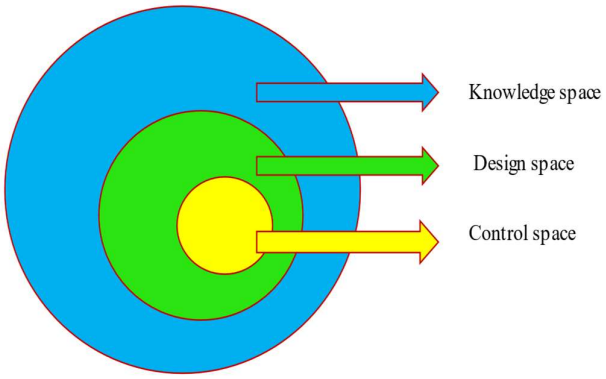

Figure 4: Structural representation of design space

Control strategy

The CQAs and CPPs that are part of the Design Space and hence need to be included in the Control Strategy are identified by the risk assessment's findings. The Control Strategy may include, for instance, requirements for the purchase of raw materials, API characteristics, operating parameters for processes, in-process controls, and the corresponding acceptance criteria, release testing, and drug product requirements and their corresponding acceptance criteria **[15]**. **(Table 7)** shows the continuous monitoring of the inputs and the parameters by the control strategy.

Table 7: Continuous monitoring of CMAs or system suitability parameters can be used to achieve this.

Inputs	Elements
➢ Criticality of quality attributes ➢ process and analytical methods capability	In process control testing Raw material controls Specification Product characterization Stability studies Process validation

Components for OFDFs

The components used for the formulation of OFDF include polymers, surfactants, and plasticizers. sweetening agents and flavouring agents **[16]**. The percentage concentration of various ingredients has shown in **(Table 8)**.

Table 8: Amount of ingredients for oral fast disintegrating films

Drug	1-25%
Water-soluble polymer	40-50%
Gelling and thickening agent	1-25%
Plasticizer	1-25%
Sweetening agent	1-25%
Surfactant	0-25%
Colour	0-10%
Flavour	0-10%

POLYMER

Polymer is one of the important ingredients in oral films, robustness depends on the amount of polymer added in the formulation and they use to provide the thickness properties also disintegrate

quickly in the oral cavity as they come to contact with saliva and provide quicker onset of release **[17]**.

Plasticizer

This ingredient is an important component to bring about better tensile and elongation strength to the formulation. These mechanical properties directly correspond to film strength and provide proofing against cracks, peeling as well as the abrupt release of drug constituents. The flexibility is required to decrease film breakability which is improved with the use of plasticizers. Also, plasticizers should be volatile and inert with polymers and solvents used to help improve film strength to hold film contents **[18]**.

A few of the examples of plasticizers used in formulating oral films are propylene glycol (PG), Polyethene glycol (PEG), Glycerol, and Phthalate derivatives like diethyl, dimethyl, and dibutyl phthalates, etc, citrate derivatives like triethyl, tributyl, acetyl citrate, etc, triacetin, castor oil.

Sweetening Agent

The use of sweeteners is directly to provide better palatability of the formulations as films are directly in contact with the oral cavity and may also directly contribute to patent compliance. **[19]**.

Surfactants

Surfactants provide dispersibility and wetting which directly corresponds to better solubilization of films and allow the drug to release quickly. One of the most used surfactants is poloxamer 407. Examples of some of the surfactants used in film formulations include SLS (sodium lauryl sulfate), Tween, benzalkonium chloride, etc **[20]**.

Flavour

These are incorporated into the formulation to induce flavour into the formulation making it useful for patients to select their choice of flavour and improving compliance. Flavours help mask the bitterness from the incorporated drug or excipients and prevent nauseating feelings in patients. Flavours alongside sweeteners help produce saliva and increase film disintegration and dissolvability. The USFDA-approved flavours for oral films are liquorice, mint, sucralose, etc. **[21]**.

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Conflicts of Interest:

There is no conflict of interest.

CONCLUSION

QbD is a tool for fostering process understanding, which is critical for ensuring product quality and performance. Fast dissolving oral films have recently gained popularity as a dosage form because they are the most acceptable and accurate oral dosage form that bypasses the hepatic

system and produces a greater therapeutic response. Fast dissolving oral films also have higher patient compliance and are more cost-effective. In comparison to traditional formulation development like (OFAT) one factor at a time, QbD is a more cost-effective and time-efficient strategy in the design and manufacturing of pharmaceutical products by implementing risk assessment, DoE, and design space. QbD was affordable and practicable in the pharmaceutical field with a better understanding of the materials and processes. Hence, the product failures could be strayed during the formulation development and have a great impact on the scale-up potential of the formulation.

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