OPTIMISATION OF A LEGACY PRODUCT WITH A HISTORY OF TABLET FRIABILITY FAILURES UTILISING QUALITY BY DESIGN

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2018

OPTIMISATION OF A LEGACY PRODUCT WITH A HISTORY OF TABLET FRIABILITY FAILURES UTILISING QUALITY BY DESIGN

By

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Submitted in partial fulfilment of the requirements for the degree of

Master of Pharmacy (Industrial) to be awarded at the Nelson Mandela University

April 2018

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DECLARATION

I, Eric Watkins, hereby declare that the treatise for Master in Pharmacy (Industrial) to be awarded is my own work and that it has not previously been submitted for assessment or completion of any postgraduate qualification to another University or for another qualification.

_____

Mr. E. Watkins

Signed on 29 day of March 2018 at the Nelson Mandela University.

TABLE OF CONTENTS

AKNOWLEDGEMENTS VIII

LIST OF KEY ABBREVIATIONS IX

LIST OF FIGURES X

LIST OF TABLES XI

SUMMARY XII

CHAPTER 1 1

INTRODUCTION TO THE STUDY 1

1.1 Introduction to Quality by Design 1

1.2 Motivation for the study 2

1.3 Problem Statement 4

1.4 Aim of the study 4

1.5 Objectives 4

CHAPTER 2 5

QUALITY BY DESIGN AS A TOOL FOR THE OPTIMISATION OF A LEGACY PRODUCT 5

2.1 Introduction 5

2.2 Application of QbD in the pharmaceutical industry 6

2.3 Advantages of QbD 8

2.4 Elements of Quality by Design 8

2.4.1 Identifying the Quality Target Product Profile 10

2.4.2 Identification of Critical Quality Attributes 11

2.4.3 Critical Material Attributes and Critical Processing Parameters 12

2.4.4 Quality Risk Management 12

2.5 Design space development 16

2.6 Control strategy 19

2.7 Product lifecycle management 19

2.8 Friability as a test of tablet mechanical strength 20

CHAPTER 3 22

METHODOLOGY ..... ERROR! BOOKMARK NOT DEFINED.

3.1 Introduction 22

3.2 Implementation of Quality by Design 22

3.2.1 Identify and define QTPP's 24

3.2.2 Identify the cQA's 24

3.2.3 Initial Risk Assessment 25

3.2.4 Execution of the DoE 26

3.2.4.1 Experimental Design 26

3.2.4.2 Statistical methods used in the analysis of data 28

3.2.5 Establishment of design space 29

3.2.6 Risk control: implementing a control strategy 29

3.3 Manufacturing process 30

3.3.1 Evaluation of granule and tablets 31

3.3.1.1 Loss on drying 31

3.3.1.2 Friability and Wearability 31

3.3.1.3 In-Vitro Disintegration Test 33

3.3.1.4 Hardness 33

3.4. Ethical consideration 34

CHAPTER 4 35

RESULTS AND DISCUSSION ..... ERROR! BOOKMARK NOT DEFINED.

4.1 Introduction 35

4.2 Quality Target Product Profile of Product X 35

4.3 Critical Quality Attributes identification 37

4.4 Quality Risk Assessment 40

4.5 Execution of DoE 41

4.6 Response surface methodology results 42

4.6.1 Effect on Defect rate 43

4.6.2 Effect on Friability 47

4.6.3 Effect on Wearability 51

4.7 Design space establishment 55

4.8 Manufacture of confirmatory batch 57

4.9 Risk control 57

CHAPTER 5 601

CONCLUSIONS AND RECOMMENDATIONS 60

REFERENCES 63

AKNOWLEDGEMENTS

I extend my sincere appreciation and thanks to the following people and institutions:

- My wife Althea, thank you for supporting me and my dreams, and never trying to hold me back from what I want in life.
- My supervisors, Prof Gareth Kilian and Miss Nasreen Isaacs
- My colleagues and friends Dr. M. Worthington, Dr. W.L. Au and Mr. N. Jaganath for their guidance and support.
- Aspen Pharmacare for the funding of the research project.
- The Nelson Mandela University for the opportunity to fulfil a lifelong ambition.

LIST OF KEY ABBREVIATIONS

ANOVA:	Analysis of Variance
BCS:	Biopharmaceutics Classification System
CCD:	Central Composite Design
CI:	Confidence Interval
cQA's:	Critical Quality Attributes
CMA's:	Critical Material Attributes
CPP's:	Critical Process Parameters
DoE:	Design of Experiments
FDA:	Food and Drug Administration
ICH:	International Council on Harmonisation
LOD:	Loss on Drying
NLT:	Not Less Than
NMT:	Not More Than
OFAT:	One Factor at a Time
PLM:	Product lifecycle management
QC:	Quality Control
QbD:	Quality by Design
QbT:	Quality by Testing
QTPP:	Quality Target Product Profile
R&D:	Research and Development
RSM:	Response Surface Methodology
S-value:	Standard error of the regression
R^2-value:	Coefficient of determination
USP:	United States Pharmacopoeia
w.r.t.:	with reference to

LIST OF FIGURES

Figure 2.1: Typical elements of QbD (Source: Kan *et al.*, 2014). 10

Figure 3.1: A flow diagram illustrating the QbD steps to optimise the manufacturing process of Product X (Adapted from: Kan *et al.*, 2014). 23

Figure 4.1: Main effects plot for Defect rate (%). 45
Figure 4.2: Residual plots for Defect rate (%). 45
Figure 4.3: Bevelled tooling - Contour plot of Defect rate (%) vs moisture, hardness. 46
Figure 4.4: Non-bevelled tooling - Contour plot of Defect rate (%) vs moisture, hardness. 46
Figure 4.5: Main effects plot for Friability after 4 min (% m/m). 49
Figure 4.6: Residual plots for Friability after 4 min (% m/m). 49
Figure 4.7: Bevelled tooling: Contour plot of Friability (% m/m) vs moisture, hardness 50
Figure 4.8: Non-bevelled tooling: Contour plot of Friability (% m/m) vs moisture, hardness. 50
Figure 4.9: Main effects plot for Wearablity after 20 min (% m/m). 53
Figure 4.10: Residual plot for Wearability after 20 min (% m/m). 53
Figure 4.11: Bevelled tooling: Contour plot of Wearability after 20 min (% m/m) vs moisture, hardness. 54
Figure 4.12: Bevelled tooling: Contour plot of Wearability after 20 min (% m/m) vs moisture, hardness. 54
Figure 4.13: Response optimiser plot of the input factors: hardness, moisture, and tooling. 55
Figure 4.14: Contour plot showing Product X's design space. 56

LIST OF TABLES

Table 2.1: Empirical vs Systematic development (Source: Berridge, 2006). 8
Table 2.2: Example of a qualitative risk assessment ranking system used by the FDA (Food and Drug Administration, 2012) 15
Table 2.3: An example of an initial risk assessment of the formulation variables (Source: Food and Drug Administration, 2012). 16

Table 3.1: Elements of a QTPP. 24
Table 3.2: Elements of cQA. 25
Table 3.3: Pivotal batch study design. 27

Table 4.1 (a): Quality Target Product Profile for Product X tablets. 35
Table 4.2 (a): Critical and non-critical quality attributes of Product X. 37
Table 4.3: Manufacturing process risk assessment. 40
Table 4.4 (a): Risk assessment justification. 40
Table 4.5: Overview of DoE study. 42
Table 4.6: ANOVA analysis of the Response surface regression: Defect rate versus Hardness, Moisture, and Tooling. 43
Table 4.7: ANOVA analysis of the Response surface regression data: Friability versus Hardness, Moisture, and Tooling. 47
Table 4.8: ANOVA analysis for response surface regression: Wearability versus Hardness, Moisture, and Tooling. 51
Table 4.9: Summary of design space at various moisture and hardness values 57
Table 4.10: Summary of the 95 % CI of the confirmatory batch of Product X 57
Table 4.11: Manufacturing process risk assessment 58
Table 4.12 (a): Risk assessment justification 59

SUMMARY

Purpose: The concept of Quality by Design (QbD) was introduced as a method of building quality into the product during the initial stages of manufacturing. This study explores the suitability of utilising QbD to optimise a legacy product. With the aid of QbD, a higher level of quality assurance and product knowledge was achieved. Sound scientific and risk-based decisions allowed for a robust manufacturing process with inherent operational quality and flexibility.

Methodology: By the establishment a quality target product profile (QTPP) and determining the influence of the critical processing parameters (CPP's) on the product's critical quality attributes (cQA's) the process understanding of Product X can be more accurately defined. The relationships between several explanatory variables will be explored by using a sequence of Design of Experiments (DoE) to obtain an optimal response. The DoE were performed and analysed using Minitab® statistical software version 17.0 (Minitab Inc., United Kingdom). A Response Surface Methodology (RSM) using a central composite experimental design (CCD) was utilised to capture the data.

Results: The data was analysed using the collection of statistical models (ANOVA) to analyse the differences between the means and their associated procedures. Input variables investigated were: compression machine tooling shape, hardness, and loss on drying LOD (post drying). The significant value (α) of 0.05 helped to determine if the null hypothesis would be accepted or rejected. The DoE identified the factors that had the highest risk of affecting the output variables and helped to establish the design space. Post completion of the DoE, a confirmatory batch was made which served as a diagnostic tool for evaluating the effectiveness of the generated model. The establishment of a strategy to control the variables and responses is of critical importance in order to appropriately use the flexibility given to products developed or optimised using QbD principles.

Conclusion: This study show that the structured approach used in Quality by Design methodology can be successfully applied to optimise a commercialised legacy product.

Keywords: central composite design (CCD); Design of Experiments (DoE); design space; Quality by Design (QbD), response surface methodology (RSM)

CHAPTER 1
INTRODUCTION TO THE STUDY

1.1 Introduction to Quality by Design

The concept of Quality by Design (QbD) was introduced by Joseph Juran in the early 1990s. He extensively documented the concept of building quality into products (Juran, 1992). The main goal of his initiative was “planning for quality”; that is, building quality into the product(s) during the initial stages of manufacturing. He believed that product quality at the initial stages of manufacturing is just as important as ensuring quality at the end of the manufacturing stages.

QbD was included in a pharmaceutical regulatory guideline for the first time in the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Q8 (R2)) guideline. The ICH Committee was formed in 1990, to discuss the scientific and technical aspects of product registration. According to the ICH guidelines, QbD is defined as a systematic approach to develop pharmaceutical products that begin with predefined objectives. It emphasises product and process understanding and process control based on sound science and quality risk management (International Council for Harmonisation, 2009).

Before QbD was introduced to the pharmaceutical industry at the beginning of the 21st Century by Joseph Juran, the quality inspection practice commonly used in the pharmaceutical industry had been the Quality by Testing (QbT) approach. The main problem with the QbT method of ensuring quality assurance and compliance is that it is based on the inspection of the final outcome of the manufactured product, by which time the defective products have already been produced. The QbT approach is an expensive, inaccurate, and non-informative activity that does not explain why the error occurred or how it can be corrected (Korakianiti & Rekkas, 2011).

Conversely, the advantages of using QbD include: a better understanding of the manufacturing process, fewer batch failures or recalls, more efficient and effective control of change, and an enhanced approach to pharmaceutical development. This

could provide opportunities for a more flexible regulatory and manufacturing approach. The QbD approach is more scientific, risk-based, holistic, and proactive. It contrasts strongly with the QbT principle, which is characterised by a manufacturing process that is not flexible or robust (Kan *et al.*, 2014).

1.2 Motivation for the study

It has been determined that an oral solid dosage form, Product X (so named to avoid disclosing proprietary information of the company where this study will be conducted), lacks process manufacturing robustness. Therefore, Product X will be used as the focus of the research.

With the aid of QbD methodology the research will aim to build quality into the manufacturing process of Product X, starting at the first step of the manufacturing process. Product X was developed without any QbD methodology and is currently manufactured at a South African generic medicines manufacturer. Product X is classed as a legacy product by the company, which means that it is a product which was developed prior to the year 2001, but is currently being commercialised by the company (Falce *et al.*, 2015). A commercialised product is manufactured, distributed, and marketed within a specified market place. The activities during the manufacturing of a legacy product at this stage of the product lifecycle should ensure that the product quality routinely meets the desired process performance.

The Technical Report (Aspen Pharmacare (PTY) LTD, 2016b) gave more background about the current problems experienced during Product X batch manufacture. Analytically, batches passed quality control (QC) and technical laboratory testing. However, every batch manufactured failed the acceptable quantitative limits inspection test after coating. The following interventions were implemented by the manufacturing site to try and improve the batch manufacturing process:

- The in-process loss on drying (LOD) limits has been revised to reduce markings on tablet cores.
- The product was compressed in a dehumidified cubicle to reduce marking.

- Tableting tooling was polished frequently during tableting.
- An average hardness closer to the upper limit of the specification was targeted during tableting to minimise marking and chipping.
- The tableting machine was run at minimum speed to increase dwell time and reduce chipping.
- The de-duster was run at minimum speed as it was suspected that some of the tablet chipping was caused by the de-duster.

The Technical Report has shown that increasing tablet compression force to achieve the maximum registered hardness does not improve the failing friability results or the chip marks observed on the bevelled edge of the tablet. The granule gains moisture rapidly after drying and therefore it has been decided that the product must be compressed in a dehumidified tableting cubicle.

The punch shape, die-wall friction, and the tableting speed influence the thermo-mechanical behaviour of tablets, and it has been shown that the maximum temperature and temperature distribution of the compressed powder changes dramatically when different shaped punches are used. Temperature will not be investigated in this study, but literature does indicate that punch shape could potentially influence the mechanics of a tablet (Krok *et al.*, 2016).

The interventions above have led to an improvement in tablet appearance, but have not completely removed the rejections, and acceptable quantitative limit failures are still experienced. At present, the pharmaceutical company does not have a viable product to supply to the market, and additional interventions will require further investigation to improve the tablet core robustness. Although the purpose of this study is not to examine the financial implications of Product X, there is a financial loss to the pharmaceutical company when products are manufactured and not marketed and sold because the pharmacopoeial standards have not been met.

It has been decided that more work is needed to optimise the product and that QbD implementation will be best suited to optimise Product X. With the help of QbD methodology, it could be proven that it is possible to build quality into the product

and create a design space that will enable the successful completion and marketing of batches.

1.3 Problem Statement

The case for a more efficient approach to the optimisation of a legacy product utilising QbD principles is investigated. By implementing this approach, the possibility exists that a higher level of quality assurance and product knowledge could be achieved. With the aid of sound scientific and risk-based decisions, a robust manufacturing process with inherent operational flexibility could potentially be achieved.

1.4 Aim of the study

The aim of the study is to utilise a QbD approach to minimise tablet friability failures and the occurrence of chipped tablets during tableting utilising a Design of Experiments study to define and optimise the critical parameters of Product X with the use of mathematical modelling.

1.5 Objectives

The objectives as derived from the aim are as follows:

1. Determine the Quality Target Product Profile (QTPP) for Product X.
2. Define the critical quality attributes (cQA's) of Product X.
3. Determine the critical material attributes (CMA) and critical process parameters (CPP) of Product X.
4. Define a design space for Product X through the Design of Experiments study.
5. Determine and verify these optimal settings of the selected input variables within the design space.
6. Propose a manufacturing process that would minimise tablet friability failures and the occurrence of chipped tablets.
7. Design a control strategy for Product X after the optimisation of the identified CPP's and CMA's has been completed.

CHAPTER 2
QUALITY BY DESIGN AS A TOOL FOR THE OPTIMISATION OF A LEGACY PRODUCT

2.1 Introduction

Regulatory bodies in the pharmaceutical industry have highlighted the importance of an elevated level of quality in pharmaceutical products. This elevated level of quality expected from pharmaceutical tablets could lead to potential problems being experienced during the manufacturing process. If Product X subsequently fails to meet this elevated level of quality standards, the entire batch of tablets may need to be rejected.

The current focus on quality comes after the United States Food and Drug Administration (FDA) acknowledged in 2002 that the quality of drug products at the time was below the level of standards as set out by the FDA. To enable better regulatory decision making, attention to other aspects of manufacturing, such as product development, was necessary. The Pharmaceutical cGMP for the 21st Century document, published by the FDA in the same year, highlighted the importance of increasing the quality of drug product applications. In 2007, the FDA noted that a large number of supplemental information was received for every change in the manufacturing process of the product (Sangshetti *et al.*, 2014). This is indicative of the traditional one-factor-at-a-time (OFAT) approach to drug development that was widespread practice at the time. The OFAT approach did not allow for estimation of interaction between relevant CPP's or CMA's and only a trial-and-error sequence of development allowed scientists to estimate possible interactions. The urgency with which the FDA pursued the implementation of QbD in drug development highlighted the possible lack of quality that is associated with the OFAT approach (Czitrom, 1999).

When the document "Pharmaceutical cGMP's for the 21st century: A Risk-Based Approach" was published in September 2004, it showed for the first time that the FDA knew how inappropriate QbT testing was at the time, and was starting to realise the importance of a more scientific approach to product development through QbD

methodology. The published document highlighted the importance of designing efficient manufacturing processes based on a scientific understanding of how these parameters influence product performance and quality. Should the QbD methodology be followed it could allow regulatory policies to be flexible enough to allow changes to the manufacturing processes without obtaining approval from the regulatory authorities (Sangshetti *et al.*, 2014).

By utilising a QbD approach to optimise Product X, and by identifying the critical process parameters during manufacturing, improvements could build product robustness and quality into the manufacturing process of Product X and reducing the friability problems associated with Product X.

2.2 Application of QbD in the pharmaceutical industry

Data reviewed (Aspen Pharmacare (PTY) LTD, 2016a, 2016b) indicated that the development of Product X at the pharmaceutical company was based upon the traditional OFAT approach to product development. These systems were in place at the time of development at the company and hence will not be scrutinised for this study. During development, little attention was given to the impact of processing variables on product performance and quality, and therefore the manufacturing process understanding was restricted. The quality of Product X was tested and identified using the traditional QbT method at the time of development.

The QbT method is the traditional method of testing quality of a product by ensuring that, at the end of the manufacturing process, the product meets a set of criteria or specification approved by a regulatory body. This method applied to Product X, was highly labour intensive and extremely expensive. The QbT method left no room for post-approval changes to the manufacturing process, or, if there were changes, they would be subjected to regulatory approval. Failure of Product X to comply with this set of specifications would result in complete batch rejection (Charoo *et al.*, 2012).

The systematic approach utilised in the QbD methodology helps to optimise the manufacturing process of Product X, starting at the first step of manufacturing. Improved control over the production process will consistently yield a product that

has built in quality, and the desired characteristics required for successful batch manufacture (Visser *et al.*, 2015). The use of QbD methodology will allow for flexibility of the manufacturing process the detection of quality problems during the early phases of the product manufacturing lifecycle. If quality is designed into the manufacture of Product X using the QbD method, the manufacturing process could benefit by product manufacture flexibility and an early error detection capability. This in turn will lead to action to remedy problems without compromise in cost or end quality of the product (Sangshetti *et al.*, 2014).

Because quality by design allows for early problem detection it can be useful in drug discovery, drug manufacture, and drug delivery. The QbD methodology allows for quality to be implemented and confirmed in every step of the manufacturing process. It aims to reduce defects to the lowest possible level and move away from the current pharmaceutical practice of quality by testing to one where quality is built into the product from the first step of the manufacturing process.

Pharmaceutical QbD was introduced after an agreement was reached between the regulatory bodies of Europe, Japan, and the United States of America, as well as experts from pharmaceutical industries in 2005. The FDA published the elements of this pharmaceutical QbD philosophy and these are highlighted in the ICH guidelines. The three guidelines that are central to the pharmaceutical QbD concept are:

1. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use: Pharmaceutical development Q8 (R2) (International Council for Harmonisation, 2009).

2. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use: Quality risk management (Q9) (International Council on Harmonisation, 2006).

3. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use: Pharmaceutical Quality System (Q10) (International Council on Harmonisation, 2009).

2.3 Advantages of QbD

If the principles of QbD are implemented during product development and large-scale manufacturing, the quality of the product has a better likelihood to be compliant when measured against regulatory standards as specified by the pharmaceutical company. The ICH Q8 (R2) guideline highlights the change in thought processes should QbD methodology be implemented and these changes are highlighted in Table 2.1 below.

Table 2.1: Empirical vs Systematic development (Source: Berridge, 2006).

Empirical development		**Systematic development**
Data Driven		Knowledge driven
Retrospective		Prospective
"Test to document quality"	ICH Q8	Science and Risk-based assurance of Quality
Acceptance criteria based on batch data		Acceptance criteria based on patient needs
Variability not understood and avoided		Variability explored and understood (Design Space)

2.4 Elements of Quality by Design

The ICH Q8 (R2) guideline seeks to enable the use of an expanded model during product development through the implementation of a design space. The design space necessitates ranges of CMA's and CPP's to be established through complex mathematical relationships. A combination of manufacture processing variables will lead to the development of a design space that will result in the product meeting the defined quality. The QbD approach to development is based on statistically designed

experiments that include primary process variables and response surface models (Kayrak-Talay *et al.*, 2013).

The process of obtaining a design space for Product X manufacture is explained in the ICH Q8 (R2), ICH Q9, and ICH Q10 guidelines, published by the International Council of Harmonisation. These guidelines all contribute and combine to form part of the various elements that comprise QbD. Figure 2.1 below provides a pictorial representation of the typical steps to be followed when implementing QbD methodology to optimise product manufacturing. The steps in the QbD methodology are discussed under the following headings:

1. Quality Target Product Profile
2. Identification of quality attributes
3. Risk assessment to identify process risk
4. Design space development
5. Control strategy
6. Life cycle management.

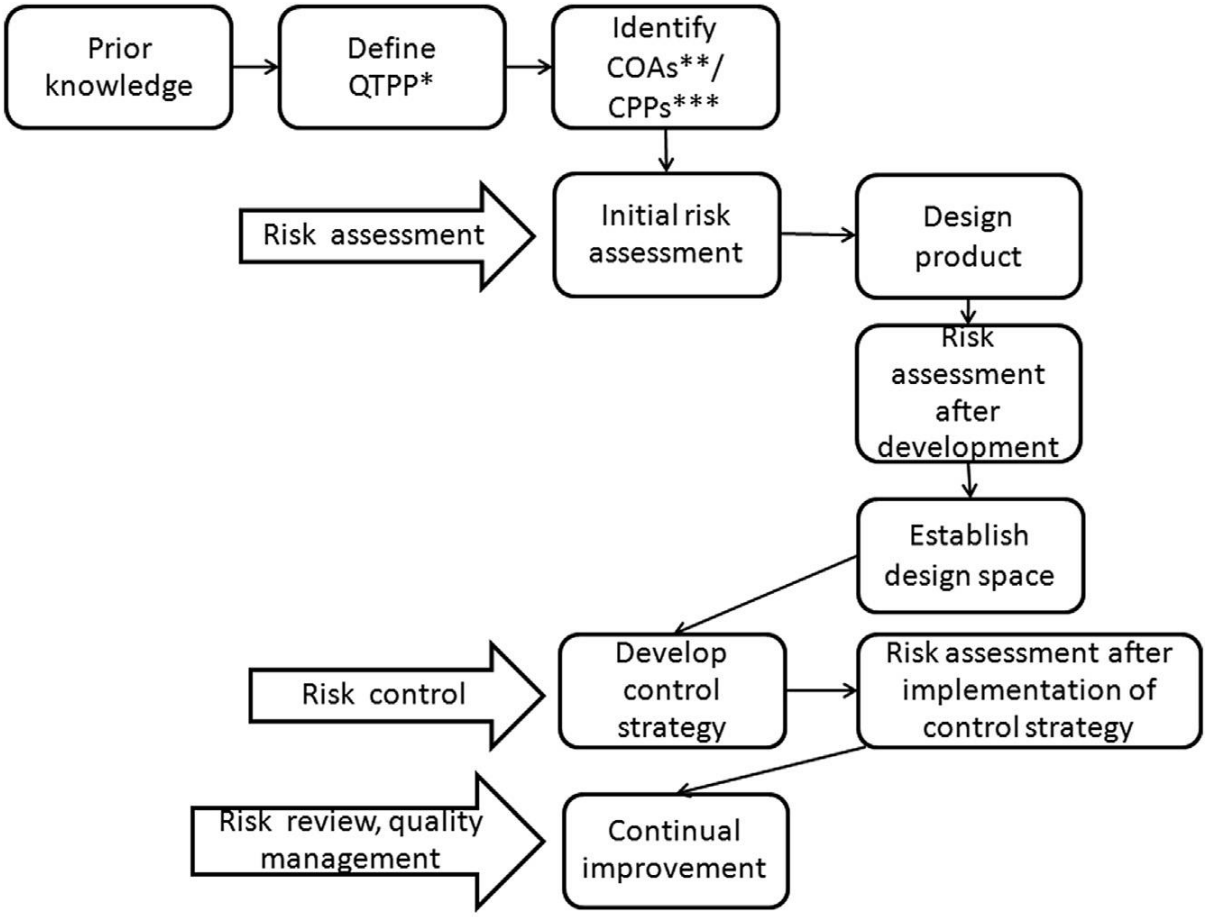

Figure 2.1: Typical elements of QbD (Source: Kan *et al.*, 2014).

2.4.1 Identifying the Quality Target Product Profile

The Quality Target Product Profile (QTPP) is a quantitative surrogate to measure aspects of dosage form safety and efficacy in the design or optimisation of a manufacturing process. Quantitative targets need to be set out to meet product specific performance requirements to ensure safety and efficacy. The QTPP is not regarded as a regulatory specification as it is necessary to include tests, such as stability, which do not form part of product release testing but are related to patient relevant product performance. The ideal QTPP is based on performance and not on mechanisms to achieve desired performance (Lionberger *et al.*, 2008).

The ICH Q8 (R2) guideline plays a leading role in the entire drug design and development, as well as the optimisation of the pharmaceutical drug product. The QTPP is defined in the ICH Q8 (R2) guideline as a summary of the quality characteristics or attributes that will ensure the safety and efficacy of a drug product. The QTPP describes the design criteria for the product and should therefore form the basis for development of the cQA's, CPP's, and the control strategy. The QTPP can be updated or revised at any time during the various stages of development as new information about the product is generated (International Council for Harmonisation, 2009).

Possible attributes to be included in the QTPP includes:

- Route of administration, dosage form, and delivery systems
- Dosage strength and container closure system
- Therapeutic release or delivery and attributes affecting dissolution
- Shelf-life, pharmacokinetic profile, potency.

Identifying critical attributes will help to build quality into the optimisation of Product X from the first step of manufacturing (Sangshetti *et al.*, 2014).

2.4.2 Identification of Critical Quality Attributes

A cQA is defined by the ICH Q8 (R2) guideline as a tool to ensure that the desired quality of a product is met. The desired quality is determined by analysing the physical, chemical, biological, or microbiological properties or characteristics of the product. This allows for the establishment of an appropriate limit, range, or distribution to guarantee that the product quality is met (International Council for Harmonisation, 2009). Critical quality attributes are essential aspects in the manufacturing control strategy of the product, and the goal is to identify these cQA's based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet those quality attributes (Food and Drug Administration, 2012).

The drug substance and excipients are required to be linked to the product through the identified cQA's. Typically, these form part of the product purity, strength, drug release, and stability. The list of cQA's under investigation is comprehensive and includes additional properties like hardness, friability and wearability. The cQA's can

be used to describe product performance and determinants of product performance. Critical quality attributes are derived from previous knowledge and are evaluated in a risk assessment. The inclusion or exclusion of potential cQA's can be executed as further knowledge or better process understanding is gained. It is critical that the team performing the optimisation has access to real-time data in order to update and change the cQA's (Sangshetti *et al.*, 2014). Generally, cQA's are part of the attributes of the final product and this procedure will also be used in the evaluation of Product X.

2.4.3 Critical Material Attributes and Critical Processing Parameters

The true value of following QbD methodology to optimise a manufacturing process lies in the fact that it enables scientists to base decisions on scientific knowledge which will build quality into the manufacturing process of a product automatically. The keys to gaining scientific knowledge lie in the identification of the CMA's and CPP's. The CMA of the drug substance, excipients and in process materials are only taken into account if it does affect the cQA's of the drug product. (Charoo *et al.*, 2012).

The ICH Q8 (R2) guideline defines a CPP as an in-process parameter that could impact on an identified critical quality attribute due to variability associated with this process parameter. Therefore, a CPP and CMA should be controlled to ensure that the process produces a product that meets the required quality consistently (International Council for Harmonisation, 2009). The manufacturing history of Product X will be used to identify and determine if there are any CMA's or CPP's that need to be investigated in this study. The accuracy of the scientific knowledge gained around the CMA's and CPP's will enable the process to reach and maintain the desired state of quality approved by the regulatory body.

2.4.4 Quality Risk Management

A valuable tool in the QbD process is risk management and analysis. Risk analysis is a tool that can be used to identify risks, and rank them in order of priority, thus enabling scientists to assign priority to the risks with the highest ranking and manage

these risks using scientific data. The ICH Q8 (R2) guideline defines quality risk management as a systematic approach for the assessment, control, communication, and review of the drug product across the product lifecycle in order to identify and review risks to the quality of the drug product (International Council on Harmonisation, 2006).

Risk is defined as the probability of occurrence of harm and the severity of that harm. Product risk assessment consists of an objective evaluation of risk in which assumptions and uncertainties are clearly considered and presented. Key to this process of quality risk management is the identification of risks in the product manufacturing process, where the analysis and evaluation of risks play a vital part in building quality into the product. Once risks have been identified, a mitigation strategy needs to be developed and implemented to accept and control the identified risk. The effectiveness of this mitigation strategy after implementation needs to be reviewed. The three components to risk assessment are risk identification, risk analysis, and risk evaluation.

- Risk identification: this is the use of information to identify potential risks to safety and efficacy of the product.
- Risk analysis: the estimated risk associated with the identified hazards.
- Risk evaluation: the significance of the risk is determined using a quantitative or qualitative risk criteria scale.

These components of quality risk assessment aim to provide answers to the following set of questions: what can go wrong, what is the probability of something going wrong, and what are the consequences if something does go wrong (Zhang & Mao, 2017).

A key objective of risk assessment in pharmaceutical development is to identify which material attributes and process parameters affect the drug product cQA's. The aim is to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the cQA's comply to the desired requirements (Anuj & Fuloria, 2012). The identification of the CPP's and CMA's is an on-going process throughout the manufacturing life cycle of the product in the pharmaceutical company. During the initial phases of

development, prior knowledge or experience of scientists serves as the primary basis for the product's designation as there is not sufficient process or product understanding with regards to the product under development (Anuj & Fuloria, 2012).

In order to minimise the risk at the initial stages of the manufacturing process, the QbD process utilises risk assessment. An effective quality system requires that an in depth and thorough risk assessment is incorporated into the QbD process. Achieving the correct application of risk management between the different stakeholders is difficult, as each may perceive different potential harms and assign a different probability of each harm occurring. Additionally, they may attribute different severities to each harm (International Council on Harmonisation, 2006). These different perceptions will be strongly based on the working experience gained by the individual team member who forms part of the risk assessment team or the department in which the individual is employed, i.e. engineers may place a different emphasis on probability associated with a risk than a pharmacist.

The FDA defines quality risk management as a systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product lifecycle. The goal of quality risk management is therefore to identify risks within a process or event, analysing the significance of these risks, and then to take appropriate measures to mitigate such risks if deemed unacceptable. The primary principles of quality risk management as identified in the ICH Q9 are that the evaluation of the risk to quality should be based on scientific knowledge, and must ultimately be linked to the protection of the patient. Further, the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk (International Council on Harmonisation, 2006).

Risk analysis is a diverse process that includes quantitative and qualitative methods. Quantitative risk analyses assign fixed numerical values (within a margin of error) to both the probability and utility (severity and occurrence) of an outcome, while a qualitative risk analysis is the opposite of this. The qualitative risk analysis represents both the probability and value of an outcome using an interval scale, where each interval is typically represented by a non-numerical label. Quantitative

methods are associated with objectivity and qualitative methods with subjectivity (Bendale *et al.*, 2015).

The risk analysis utilised during this study, which aims to optimise processing parameters, will employ a qualitative risk analysis method. The qualitative risk analysis is a process of the assessment of the impact of the identified risk factors. The qualitative model is characterised by the use of subjective indices, such as ordinal hierarchy: low, medium, high. The relative risk that each attribute presents is ranked as high, medium or low. The high-risk attributes warrant further investigation whereas the low risk attributes require no further investigation. The medium risk is considered acceptable based on current knowledge, although further investigation for medium risk may be needed to reduce the risk. A relative risk ranking system that could be used throughout pharmaceutical development is summarised in Table 2.2. (Food and Drug Administration, 2012).

Table 2.2: Example of a qualitative risk assessment ranking system used by the FDA (Food and Drug Administration, 2012)

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is acceptable. Further investigation may be needed to reduce the risk.
High	Risk is unacceptable. Further investigation is needed to reduce the risk.

The best presentation of benefit-risk considerations involves focusing on the individual benefits and risks, as well as their frequency, and weighing them appropriately. The FDA determined that this can be accomplished by a qualitative descriptive approach for structuring the benefit-risk assessment that satisfies the principles outlined by the FDA, whilst acknowledging that quantification of certain components of the benefit-risk assessment is an important part of the process to support decision-making (Food and Drug Administration, 2012).

Alexander Gaffney, the Regulatory Focus news editor, referred to the FDA report: “Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making” and suggested the report gave more information as to why a quantitative

only approach would not be sufficient to product development. According to him, a quantitative report would fall short because it could potentially reduce complex decisions into binary decisions, reducing the information taken into account when the decision is made, and thus reducing the accuracy of the decision (Gaffney, 2013).

The risks associated with Product X lies in the fact that manufactured batches are currently made without a granulation time design space, but with prior knowledge the scientists possess about the manufacturing history. Therefore the risk of over/under granulation can be assigned as having a high/medium/low risk value. This will alert the Research and Development (R&D) team as to which specific parameters should be prioritised during the optimisation process. A control strategy can also be put in place, in example, to perform release dissolution and/or dissolution according to the Biopharmaceutics Classification System (BCS). Table 2.3 is a typical example of a risk assessment tool that could be used in QbD laboratory scale batches during process development or optimisation to prioritise parameters or attributes with higher risk. Table 2.3 is an example of qualitative in risk assessment (Food and Drug Administration, 2012).

Table 2.3: An example of an initial risk assessment of the formulation variables (Source: Food and Drug Administration, 2012).

Drug Product CQA	Formulation Variables				
	Drug Substance PSD	MCC/Lactose Ratio	CCS Level	Talc Level	Magnesium Stearate Level
Assay	Medium	Medium	Low	Low	Low
Content Uniformity	High	High	Low	Low	Low
Dissolution	High	Medium	High	Low	High
Degradation Products	Low	Low	Low	Low	Medium

2.5 Design space development

Sir Ronald Fisher at the Rothamsted Agricultural Field Research Station in London, England, developed DoE in the early 1920's. He established that various input factors influenced the response factors. A developed DoE model will make deliberate changes to input process variables (factors) to observe the corresponding processing changes in the process output when applied. It is possible to create a design that is insensitive to all sources of variation, and the information gained by

analysing the experiment could be used to improve functional performance of the product (Antony, 2014).

The choices made during the design of the DoE model are dependent on the information obtained from the completed risk assessment. The DoE model is built by defining the relationship between factors affecting manufacturing processes and the output of these manufacturing processes. It could enable scientists to manipulate factors or input variables according to a pre-designed model. The DoE model of the development of Product X will aim to produce a science-based knowledge model of the manufacturing process that meets the quality criteria and leads to better product and process understanding. Building a design space should allow manufacture of Product X to happen within this design space, and this in turn will ensure the product will meet all quality specifications as set out by the regulatory authority. DoE is effective in the design and development of different dosage forms, and this study will try and prove that it has a functional use in the optimisation of a legacy product.

The objective in creating a design space for Product X can be achieved by analysing experimental results regarding mathematical modelling from the results of the DoE experiments. The combinations of factors and their influence on the final product quality can be evaluated during experimental batches. The aim of the design space is to define the ranges of each CPP or CMA by taking into account their various interactions, whilst complying with the defined product cQA's (International Council for Harmonisation, 2009; Lourenço *et al.*, 2012).

One aspect of a DoE model is the use of fractional factorial screening trial designs to help and build the DoE model. Fractional factorial screening designs only investigate two levels, and this provides an effective way to reduce the expense and resources needed by considering many process parameters in a minimum number of experimental runs or trials. Factors that demand further investigation are highlighted by the screening trials. Screening trials generally do not investigate the nature of interactions between these trials. These trials helps to establish which input factors are most likely to be important when setting up the DoE study (Antony, 2014). Product X has a well-known and documented product history and having this product knowledge at hand allows for the omission of screening trials for legacy products.

Experimentation where the effects of more than one response of the factor are investigated is known as a full factorial experiment. The advantage of using a full factorial experiment is that the effects of individual parameters as well as their relative importance in a given process are obtained, and that the interactional effects of two or more variables can also be known (Regti *et al.*, 2017).

The construction and execution of an experiment has a direct impact on the validity of an experiment and therefore attention to experimental design is important and is it possible to use a central composite design (CCD) to define how the experiments will perform in the experimental region being studied. The CCD is an experimental design used in statistics and can be used in a response surface methodology (RSM) (Bezerra *et al.*, 2008). In a CCD experimental design a multi-level factorial or fractional factorial is chosen to allow the estimation of all factors and first order interaction terms, augmented with further points, which allow polynomial effects to be estimated (Dashtianeh *et al.*, 2013).

Response surface methodology (RSM) allows for the accurate collection of mathematical and statistical data and techniques. This makes RSM useful in the optimisation of a process. This optimisation is based on the fit of a polynomial equation to the experimental data. The objective of making statistical provisions with the use of the experimental data obtained can only be interpreted from the data generated through the experimental process. The benefit in the application of a RSM is that it can determine the influence of several input variables on the quality of the product. Simultaneous optimisation can be achieved if the levels of these variables that attain the best system performance can be identified (Bezerra *et al.*, 2008).

Response surface methodology (RSM) can be used to generate a model that will be able to predict and determine the optimal conditions for Product X (Zhang *et al.*, 2012). By utilising the RSM model based on CCD, the manufacture of Product X can be optimised to achieve maximum efficiency and predictability by using the effect of the influential parameters. In order to prove the value of the RSM, an experiment is proposed at the conclusion of the study that is referred to as the confirmatory batch or experiment. This experiment aims to confirm that the identified optimum design space that was established during the experiments is valid.

2.6 Control strategy

The ICH Q10 guideline defines a control strategy as a tool to assess process performance and product quality by utilising a planned set of controls derived from the current product and process understanding as defined in the generated quality risk assessment of the product (International Council on Harmonisation, 2009). The correct quality risk management tool selection enhances the understanding of risks in a process that would then support the control strategy. These controls are based on process and formulation understanding and can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (International Council for Harmonisation, 2009).

2.7 Product lifecycle management

The implementation of the product lifecycle management (PLM) allow the implementation of quality systems into the manufacturing lifecycle of the product. Once the design space has been established, and sufficient mitigating factors have been implemented to reduce the risks identified, the knowledge generated will help to optimise the manufacturing process. In order to maintain adequate controls and feedback to assure the quality of Product X, tools used in the maintenance of the product quality are change controls, validation, trend analysis, management review, quality risk management, and operator training. If the correct quality systems in the manufacture of Product X are implemented, it will help to improve the quality of the manufacturing process, facilitate continuous improvement, demonstrate state of control, and manage process parameters movement within the design space.

With the implementation of the DoE model the opportunity exists for the company to implement DoE and use the QbD approach to improve quality and provide a method to ensure consistency in the manufacture of Product X with the advantage to ensure that there is consistency in quality. During the manufacture of routine batches, more experience and knowledge is gained, and this will contribute to the PLM. The design space established should not be changed unless there are good justifiable reasons,

and periodic maintenance to the manufacturing process can be performed using the internal quality systems. With the QbD approach to development, the continuous improvement through the product lifecycle is possible. In contrast to this, the conventional method of manufacturing was a frozen and unchangeable manufacturing process (Sangshetti *et al.*, 2014).

According to ICH Q8 (R2) guideline, the process performance of the product can be monitored to ensure that it is working as expected to deliver product quality attributes as predicted by the design space established (using the DoE study) during product development (International Council for Harmonisation, 2009).

2.8 Friability as a test of tablet mechanical strength

The acceptability of the mechanical strength of Product X's tablets is assessed based on the friability test described in the USP (United States Pharmacopeial 39 - NF 34, 2016). Tablet component particles lost due to abrasion, mechanical shock, and friction can be referred to as tablet friability. Loss of product in subsequent manufacturing processing stages is caused by tablets with a high friability. Poor tablet appearance due to high friability could potentially create doubts in the minds of patients regarding tablet quality. This means that tablet performance and quality is assessed with tablet friability. Generally a weight loss of less than 1% is acceptable for compressed and uncoated tablet products (Osei-Yeboah & Sun, 2015). This friability % value has been shown to be influenced by the moisture content present in granules. The moisture content has to be opitmised as the amount of moisture influences the compaction properties of tablets. Granules with moisture that has been optimised has been shown to produce tablets with a lower friability % value (Afrasiabi *et al.*, 2001).

Product X has a history of friability problems as can be seen in the Technical Report that has been written (Aspen Pharmacare (PTY) LTD, 2016b). Chipped tablets have been a common occurrence during the tableting phase of manufacturing, and to optimise the product's manufacturing process, a QbD study will be utilised. A Trial Batch Advice report generated for a total of four production batches recommended that the entire batch had to be destroyed due to chipped tablets present in the bulk.

Investigations performed during batch manufacture at the company showed that a significant improvement was noticed by changing the tooling size and shape. The investigation showed that LOD, tablet hardness, and tooling shape and size impact tablet friability and the chipping observed on the tablets (Aspen Pharmacare (PTY) LTD, 2016b).

The implementation of a DoE model in the optimisation of Product X will make it possible to scientifically determine the optimum parameters to apply during product lifecycle management.

CHAPTER 3
METHODOLOGY

3.1 Introduction

The ICH Q8 (R2) guideline was constructed specifically for the development of products, but the guideline shows that the accumulation of scientific data will help scientists make better decisions during development. This is in line with the goal pursued in a legacy product optimisation, which in this case is Product X. The optimisation of Product X with the help of QbD methodology has helped to build quality into the product by collecting science-based information. The optimisation of the manufacturing process of Product X was an important method in achieving high quality at low cost. When using the QbD methodology, sources of variability were investigated and mitigated with the help of the creation of a design space, and this design space allowed for a robust and flexible manufacturing method for the manufacture of Product X.

3.2 Implementation of Quality by Design

To build quality into the manufacturing process of Product X, steps are followed to allow process understanding linked to manufacture controls; thus leading to the desired performance of Product X within a design space. This means that the finished product quality control was moved upstream to the critical processing steps and CPP's rather than relying on the traditional end-product quality by testing procedures. QbD helped to define the scientific understanding of the influence the manufacturing process had on product cQA's and this study presents a roadmap for the optimisation of a legacy product using QbD principles. Figure 3.1 illustrates the steps followed for the optimisation of the manufacturing process of Product X. The individual steps are discussed in the following sections:

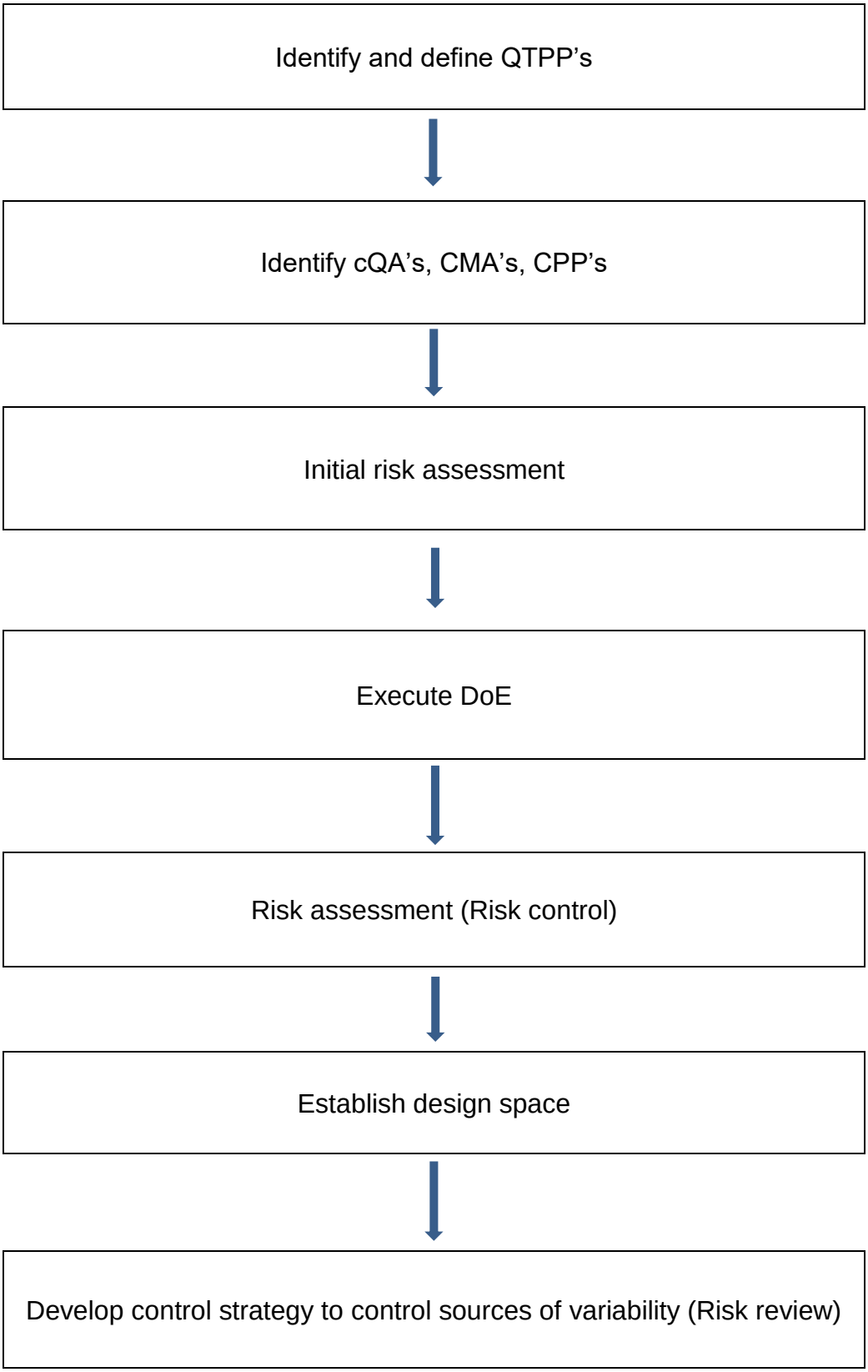

Figure 3.1: A flow diagram illustrating the QbD steps to optimise the manufacturing process of Product X (Adapted from: Kan *et al.*, 2014).

3.2.1 Identify and define QTPP's

By establishing a QTPP and identifying the product critical quality attributes from the QTPP, the process understanding of Product X was more accurately defined. The QTPP represent a summary of specific elements of Product X that can impact on safety and efficacy. The successful optimisation of Product X was approached by keeping the quality of the end product in mind. The first step in the optimisation process of Product X was the identification of the QTPP, and the typical elements of a QTPP are listed in Table 3.1 below:

Table 3.1: Elements of a QTPP.

Elements of QTPP that potentially can impact on safety and efficacy of Product X	Dosage form
	Route of administration
	Dosage strength
	Pharmacokinetics
	Stability
	Drug product quality attributes
	Container closure system
	Administration
	Alternative methods of administration

3.2.2 Identify the cQA's

The elements of the defined QTPP that will have an influence on the manufacturing process are named cQA's. Any physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired quality of Product X can be defined as a cQA (Berridge, 2006). The cQA's are derived from the QTPP and are chosen based on product knowledge. Table 3.2 gives an indication of the potential cQA's that could be derived from the QTPP.

Table 3.2: Elements of cQA.

Attributes of the Drug Product	
Physical Attributes	Appearance
	Odour
	Size
	Score configuration
	Mass
	Hardness
	Friability
	Disintegration
Identification	
Assay	
Content uniformity	
Dissolution	
Degradation products	
Water content	
Microbial limits	

3.2.3 Initial Risk Assessment

The process of quality risk management can be based on the ability to evaluate the risk to quality based on scientific knowledge and linking this to the protection of the patient. The level of risk dictates the level of effort and formality of the study (International Council on Harmonisation, 2006). A systematic approach to the assessment, control, communication, and review of risks to the quality of Product X across the product lifecycle was critical in gaining scientific knowledge into the manufacturing processing problems of Product X. The three key elements in the quality risk management process investigated in this product optimisation study were Risk Assessment, Risk Control, and Risk Review.

The initial risk assessment performed was based upon current product knowledge as per the Technical report of Product X (Aspen Pharmacare (PTY) LTD, 2016b). This

identification process helps to understand and predict sources of variability in the manufacturing process of Product X, and implement an appropriate control strategy to ensure that the cQA's comply with the desired requirements. The qualitative risk assessment method executed in this study used qualitative indicators such as high, medium and low. The formulation of Product X cannot be changed as changes could lead to a costly regulatory strategy to be implemented and due to this reason, the optimisation of the manufacturing process focussed on the processing stages of the wet granulation process as discussed above in Section 1.2. Critical processing parameters that can influence Product X's cQA's were identified as a risk and ranked as high, medium or low. Should a "high risk" be identified based on current product knowledge the risk will be analysed, and evaluated quantitatively to lower the probability of product quality variation through optimisation by DoE. Risks categorised as medium or low will not be investigated and will be deemed acceptable for this study..

3.2.4 Execution of the DoE

Design of Experiments is a systematic series of experiments in which deliberate changes are made according to a pre-approved model to input factors identified in the initial risk assessment. This was done to help identify the cause of the significant changes in the output responses of the product. The DoE helped to determine if there were meaningful relationships between factors and responses and to evaluate all the potential factors simultaneously, speedily, and systematically.

3.2.4.1 Experimental Design

The methodology selected was a RSM model with an experimental design that was based on the central composite design (CCD) model. This was used to generate scientific data for interpretation. This model design allowed relationships between several explanatory variables to be explored, as specified by the DoE model, to obtain an optimal response and allow for estimation of the curvature once all the results are obtained. The experimental design was randomised to avoid any bias during the capturing of data.

The manufacturing problems associated with Product X are well known to the manufacturing facility, and are clearly identified in the Technical and Pharmaceutics development report of Product X (Aspen Pharmacare (PTY) LTD, 2016a, 2016b). The input factors identified in the documents that formed part of the optimisation process of Product X were tooling, hardness, and LOD (moisture after drying of granules). The parameters used to establish the DoE design are based on the documented history of Product X, and the product history allowed the screening trial batches to be excluded from the DoE design. The DoE design therefore only included pivotal batches which had been generated by the statistical software, Minitab® 17 (Minitab Inc., United Kingdom), and the design is set out in Table 3.3 below:

Table 3.3: Pivotal batch study design.

Standard Order	Run Order	Pt Type	Blocks	Hardness (N)	LOD (% m/m)	Tooling Diameter: 12.7 mm Shallow Concave
18	1	-1	1	47	1.50	Non-bevelled
11	2	0	1	90	1.50	Bevelled
23	3	0	1	90	1.50	Non-bevelled
26	4	0	1	90	1.50	Non-bevelled
20	5	-1	1	90	0.79	Non-bevelled
10	6	0	1	90	1.50	Bevelled
3	7	1	1	60	2.00	Bevelled
1	8	1	1	60	1.00	Bevelled
8	9	-1	1	90	2.20	Bevelled
24	10	0	1	90	1.50	Non-bevelled
6	11	-1	1	132	1.50	Bevelled
16	12	1	1	60	2.00	Non-bevelled
9	13	0	1	90	1.50	Bevelled
22	14	0	1	90	1.50	Non-bevelled
19	15	-1	1	132	1.50	Non-bevelled
2	16	1	1	120	1.00	Bevelled
12	17	0	1	90	1.50	Bevelled
4	18	1	1	120	2.00	Bevelled
7	19	-1	1	90	0.79	Bevelled
21	20	-1	1	90	2.20	Non-bevelled
25	21	0	1	90	1.50	Non-bevelled
14	22	1	1	60	1.00	Non-bevelled
5	23	-1	1	47	1.50	Bevelled
17	24	1	1	120	2.00	Non-bevelled
13	25	0	1	90	1.50	Bevelled
15	26	1	1	120	1.00	Non-bevelled

3.2.4.2 Statistical methods used in the analysis of data

The statistical designs and analysis were carried out using the statistical software package Minitab® version 17.0. The data was analysed by using the Analysis of Variance (ANOVA) statistical method, which compares the means of several samples. By analysing the variation between the means, it was possible to differentiate between statistically significant differences at different factor levels. This allowed for the accumulation of scientific data in the interpretation of the experimental outcome and helped to establish whether some factors influence other processing parameters (Ostertagov¨¢ & Ostertag, 2013).

The statistical software program calculated the probability (p-value), and the interpretation of the p-value allowed for the acceptance or rejection of the null hypothesis. The significance level (α) was set at 0.05, and this value was used as the benchmark for determining statistically significant differences for the effect of factors on the response and lack-of-fit. Hence, the null hypotheses criterion was applied to the following:

- Factors: there is no correlation between the variables and the response.
- Interactions: No interactions exist between factors in their effect on the response.
- Lack-of-fit: the model correctly predicts the relationship between the response and the factors.

The p-value helped to establish if there was a difference between the means of the factors investigated, and measured the appropriate fit of the model. Additionally, the model's goodness-of-fit will be assessed and verified using the Standard error of the regression (S) and Coefficient of determination (R^2) values.

The s-value was interpreted as the distance observed between values and their fall from the regression line, and the smaller the values, the closer the observations were to the fitted line (Frost, 2014). The R^2-value was used to measure the distance the data generated are to the fitted regression line and will have a value between 0% and 100%. If the value obtained is 0%, it will mean the model generated explains none of the variability of the response data around its mean, and if the value

generated is 100% it means the model explains all the variability of the response data around its mean (Frost, 2013).

The manufacture of pivotal batches was randomised to avoid subjectivity. Manufacturing of a single confirmatory batch using the optimised parameters as determined by the DoE will serve as a diagnostic tool to evaluate the effectiveness of the model. The confirmatory batch was to be considered successful if the results of the batch fell within the 95% confidence intervals of the DoE and lower tablet friability values were observed when compared to the production batches.

3.2.5 Establishment of design space

The design space was established based on the results obtained from the experiments. The design space establishment was achieved by the implementation of the control strategy. The update to the initial risk assessment based on the scientific data accumulated ensured that the selected risk factors identified in the initial risk assessment were maintained within the design space. The risk control strategy implemented was a multidimensional combination and interaction of CMA's and CPP's that have been demonstrated to provide assurance of quality. The advantage of having an established design space was that changes made to the process, but that still fall within the design space, were not considered as a change by the regulators.

3.2.6 Risk control: implementing a control strategy

The risk ranking tool used to establish a control strategy in the study was a qualitative risk ranking tool as discussed in Section 2.4.4 and the results obtained from the experiments performed based on the DoE model gave much-needed information as to what kind of risks there may be in the manufacturing procedure and how to document and control these risks. Should these risks be adequately controlled and defined, it will allow for the manufacture of Product X to be flexible and in compliant with the high level of quality as stipulated by the regulatory authorities.

3.3 Manufacturing process

Separate granules for each batch were wet granulated in a 10 litre High Shear Mixer Granulator (RMG 10 LTR, India), using purified water as granulating medium. Every batch (all with the same formulation) was granulated using identical granulation parameters, manufacturing equipment size, -make, and -model; thus reducing inter-batch variability.

The excipients were dry mixed with an impeller speed set at 200 rpm and a chopper speed set at 2500 rpm for 180 seconds. The granulating medium was dosed into the granulator over a period of 120 seconds with the impeller speed set at 100 rpm and chopper speed set at 1000 rpm. After dosing, the granule was granulated for 60 seconds with the impeller speed set at 200 rpm and the chopper speed set at 2500 rpm. The granules were wet milled through a 10.0 mm screen with the speed set at 300 rpm using a Quadro Co-mill Model number 197 (Quadro Co-Mill; Ontario; Canada). The granules were dried in a Retsch fluid bed dryer, Model number: TG100 (Retsch Fluid Bed Dryer; Haan; Germany), with the inlet temperature set at 60 ^{o}C.

The granule was dried until a specified moisture content (loss on drying) was attained as set out in the experimental design plan. Once the LOD was attained, the granules were milled through a 1.5 mm round hole screen. The granule was blended for 10 minutes at 10 rpm, after which the lubricants were screened through a 850 µm screen into the intermediate bulk container and blended for 5 minutes using a IMA Pharm Canguro Turbula Bin Blender model number J50 (IMA Pharma Canguro Turbula Bin Blender; Bologna Italy).

The final blend was compressed on a Korsch XL 100 machine, Model number: K1510247 (Korsch AG; Berlin, Germany). The tooling and hardness were changed according to the experimental design. Eliza tools (Parle Elizabeth Tools Pvt. Ltd; Thane; India) had manufactured the tooling used in this study.

3.3.1 Evaluation of granule and tablets

Product history has shown that, without changing the formulation, a passing and failing friability result could be obtained with the exact same granule using different compression tooling (Aspen Pharmacare (PTY) LTD, 2016a). This indicated that the formulation lacks robustness, which in turn impacted tablet friability and tablet chipping, as observed during the tableting phase of manufacturing. Testing carried out on the granule of the trial batches included: Loss on drying, Friability and Wearability, In-Vitro Disintegration Test, and Hardness.

3.3.1.1 Loss on drying

The LOD test was performed using a Moisture Analyser machine (Mettler Toledo LJ16, Switzerland). The test was performed by sample a single sample of the granule from each batch after fluid bed drying with the weight of the sample fixed at approximately 2 grams. The sample granule was placed in a moisture balance set at 105^{o}C. Moisture balances determined the remaining dry granule after a drying process of the original 2-gram granule sample was completed. The percentage loss of mass was then calculated and used as the LOD result. The granule was dried until a LOD result was obtained that met the parameters as set out by the design of the study.

$$\text{Moisture content } (\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ x } 100 \qquad \textbf{[Equation 3.1]}$$

3.3.1.2 Friability and Wearability

Once tablet cores have been compressed, performing a friability and wearability test helped to assess the tendency of the tablets to break, crumble, or chip during the next processing phase of tablet manufacturing that could be coating or packing. Friability failures can be caused by several factors including (but not limited to) poor tablet design, low moisture content, insufficient binder, and low hardness. The aim is to compress tablets that are hard enough that they do not break or chip in any of the

processing phases of tablet manufacturing, but are friable enough that they disintegrate in the gastrointestinal tract.

Friability: The friability tester has become the accepted standard throughout the pharmaceutical industry for determining the resistance of uncoated tablets to the abrasion and shock experienced in coating, packing, and shipping operations. The friabilator machine: PTF3 (Pharma Test, Hainburg, Germany) was used to carry out the friability tests. This machine consists of a single baffle attached to a rotating wheel. The Friabilator will repeatedly drop one sample consisting of 10 random tablets sampled per batch over a fixed time and height for a period of 4 minutes and at a rotation speed of 25 rpm. The tablets were visually inspected for broken tablets, and the percentage of tablet mass loss due to broken or chipped tablets was calculated (United States Pharmacopeial 39 - NF 34, 2016). The higher the percentage of tablet mass loss due to chipping or breaking, the more likely it is that breakage and chipping of tablets will occur in the subsequent phases of tablet manufacturing. The percentage friability of tablets was measured as per the following formula and the calculated value indicated the ability to withstand tablets breaking or chipping (Sharma *et al.*, 2014):

$$\text{Percentage friability } (\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ x } 100 \qquad \textbf{[Equation 3.2]}$$

Wearability: The testing involves repeatedly dropping one random collected sample per batch with a total weight equal to at least 50 grams of the tablets over a fixed time in a Friabilator: PTF3 (PharmaTest, Hainburg, Germany), using a rotating wheel set at a speed of 25 rpm for a duration of 20 minutes. The rotating wheel is made in the form of a plexiglass abrasion-type drum that has an approximate diameter of 20 cm and has 12 to 13 lamellae.

Just as the case with friability testing, the higher the percentage of tablet mass loss due to chipping or breaking, the more likely breakage and chipping of tablets will occur in the subsequent phases of tablet manufacturing. The percentage wearability of tablets was measured as per the following formula and the calculated value indicated the ability to withstand tablets breaking or chipping:

$$\text{Percentage wearability (\%)} = \frac{\text{Initial weight – Final weight}}{\text{Initial weight}} \text{ x } 100 \qquad \textbf{[Equation 3.3]}$$

3.3.1.3 In-Vitro Disintegration Test

The disintegration test was performed with an Erweka Model ZT304 tablet disintegration tester (Erweka, Heusenstamm, Germany) to determine the time it takes for a solid oral dosage form such as a tablet to completely disintegrate. The time of disintegration is regarded as a measure of the tablet quality. One sample consisting of six random tablets sampled per batch and was placed in a basket-rack assembly and the basket-rack was lowered into the disintegration media set at a temperature of 37 ± 2 °C (water) at a constant frequency rate (United States Pharmacopeial 40 - NF 35, 2017a). The time in seconds taken for disintegration with no meaningful mass remaining in the apparatus was measured and documented (Sharma *et al.*, 2014).

3.3.1.4 Hardness

The mechanical strength of tablets is routinely measured and is of importance to process optimisation to make certain that the mechanical strength of Product X's tablets has good structural integrity during the conditions of storage, transportation, and handling. One commonly used test recommended by the United States Pharmacopeial (USP) is to ascertain the mechanical integrity of tablets by measuring and documenting the tablet's breaking force, also known as tablet hardness (United States Pharmacopeial 40 - NF 35, 2017b). The equipment used for this purpose of evaluation was an Erweka hardness tester Model Number: TBH320TD (Erweka, Heusenstamm, Germany). Ten tablets were sampled at random and tested, after which the average hardness reading and mean standard deviation (SD) were calculated (Sharma *et al.*, 2014).

3.4. Ethical consideration

There are no ethical considerations for this study as it excludes the use of animals and humans as subjects. The formulation and other proprietary information will be excluded from this treatise and it will not result in a conflict of interest between Aspen Pharmacare (PTY) LTD. and Nelson Mandela University.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 Introduction

The DoE performed in this study on Product X helped to identify and create a design space for the manufacturing process of Product X. The benefit of the design space is that it allows for changes to the parameters of the manufacturing process if the parameters to be changed fall within the design space (Sangshetti *et al.*, 2014). The DoE study has proven that the quality of Product X is within the specified quality ranges in this developed design space. The DoE that forms part of the QbD methodology helped to identify the manufacturing processes that could possibly lead to failure of quality and to form a control strategy to reduce the risks. Quality by Design plays a vital role in identifying the manufacturing process parameters that may lead to a high possibility of product quality failures.

4.2 Quality Target Product Profile of Product X

The quality characteristics that could influence the safety and efficacy of Product X are captured in a QTPP. The QTPP tries to establish and capture the importance of the desired end product quality of Product X. Table 4.1 below represents the QTPP of Product X. Quality attributes that do not relate to tablet appearance, friability, wearability, and compression tooling were not assessed for this study.

Table 4.1 (a): Quality Target Product Profile for Product X tablets.

QTTP Element	Target	Justification
Dosage form	Tablet.	Pharmaceutical equivalence requirement: same dosage form.
Dosage design	Immediate release tablet.	Immediate release design required to meet label claims.
Route of administration	Oral.	Pharmaceutical equivalence: same administration route.

Table 4.1 (b): Quality Target Product Profile for Product X tablets (continued).

QTTP Element		Target	Justification
Dosage strength		500 mg.	Pharmaceutical equivalence requirement: same dosage strength.
Container closure system		Container closure system qualified as suitable for this drug product.	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping.
Drug product quality attributes	Physical attributes	Round, white, shallow concave, bevelled edged tablet.	Pharmaceutical equivalence requirement: must meet the same compendial or other applicable (quality) standards for the various drug product quality attributes.
	Identification	Targets for product identification are set according to pharmacopoeial standards.	
	Assay	Release: 500.0 mg (475.0 – 525.0 mg) 95 – 105% LC.	
	Content uniformity	Conforms to USP <905> Uniformity of Dosage Units for active X.	
	Degradation products	Compendial method used.	
	Dissolution	Compendial method used.	
	Moisture	LOD: 1 – 2% after drying.	
Stability		At least a 24 month shelf-life at room temperature.	Pharmaceutical equivalence requirement: equivalent or better than shelf-life requirement.
Administration / concurrence with labelling		The optimised product must have a similar effect to the registered reference product.	Labelling states that the product can be administered with or without food.

4.3 Critical Quality Attributes identification

Product X is a well-known product at the manufacturing site with a well-known documented history (Aspen Pharmacare (PTY) LTD, 2016b). Therefore, the study relied on the product history to identify the quality attributes that had an impact on the desired in-process and end-state quality of Product X. Table 4.2 indicates which of the quality attributes were classified as being cQA's of the drug product with justification for the choices.

Table 4.2 (a): Critical and non-critical quality attributes of Product X.

Attributes of the Drug Product		Target	Is it a cQA?	Justification
Physical Attributes	Appearance / Defect rate	A round white to off-white tablet. Colour and shape acceptable to the patient, no visual tablet defects observed.	Yes	Appearance not directly linked to safety and efficacy, but if tablets are broken and chipped accurate dosage taken by patient cannot be determined. The target is set to ensure patient acceptability. Product currently uses non-bevelled tooling for compression of tablets.
	Odour	No unpleasant odour.	No	In general, a noticeable odour is not directly linked to safety and efficacy, but can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odour. No organic solvents will be used in the drug product manufacturing process.
	Size	Similar to currently registered drug product.	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the currently registered drug product.

Table 4.2 (b): Critical and non-critical quality attributes of Product X (continued).

Attributes of the Drug Product		Target	Is it a cQA?	Justification
Physical Attributes	Score configuration	No score-line present.	No	This is a fixed dose tablet; half dose is not applicable. Currently the registered product is also un-scored.
	Mass	600 mg (570 – 630 mg).	No	Mass is a routine test per compendial requirements for tablets which can influence assay and uniformity of content. The target ensures a low impact on patient safety and efficacy.
	Hardness	90 N (60 – 120 N).	Yes	Hardness is a routine test per compendial requirements for tablets which can influence tablet defect rate, wearablity and friability. The possibility exists that hardness influences appearance, friability, and wearability.
	Friability	Not more than 1.0% m/m loss after 4 minutes.	Yes	Friability is a routine test per compendial requirements for tablets. Friability failures will result in a product that will not pass the appearance quality criteria.
	Wearability	Not more than 1.0% m/m loss after 20 minutes.	Yes	Wearablity failures will result in a product that will not pass the appearance quality criteria.
	Moisture	LOD: 1 – 2% after drying.	Yes	Limit is set in order to ensure granule meets batch release criteria but product history has shown that moisture influence appearance, friability, and wearability.
	Disintegration	Not more than 15 minutes.	No	Disintegration is a routine test per compendial requirements for tablets. The target ensures a low impact on dissolution and hence bioavailability.

Table 4.2 (c): Critical and non-critical quality attributes of Product X (continued).

Attributes of the Drug Product	Target	Is it a cQA?	Justification
Identification	Positive for Active X.	No	Critical for safety and efficacy, but can be controlled by the company Quality Management System and will be monitored at drug product release. Formulation and processing variables do not impact identity; therefore this cQA will not be discussed during formulation and process development.
Assay	Release: 500.0 mg (475.0 – 525.0 mg) 95 – 105% LC.	No	Assay variability will affect safety and efficacy. Process variables changed in the study will not influence assay.
Content uniformity	Conforms to USP <905> Uniformity of Dosage Units for Active X.	No	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables will not impact content uniformity during this study.
Dissolution	Compendial method used.	No	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables will not affect the dissolution profile during this study.
Degradation products	N/A (as per validated in-house requirement).	No	Can affect safety; can be controlled based on compendial requirements or currently registered drug product characterisation to limit patient exposure. Formulation and process variables will not impact degradation products during this study.

4.4 Quality Risk Assessment

A risk assessment for the overall drug product manufacturing process is presented in Table 4.3 and identifies the high risks that may affect cQA's of the final drug product. Table 4.4 describes the CPP's which affects the cQA's identified for the various stages of Product X's of the manufacturing process.

Table 4.3: Manufacturing process risk assessment.

cQA	Dry mix	Dosing	Wet mix	Wet milling	Drying	Dry milling	Blending	Compression
Appearance / Defect rate	Low	Low	Low	Low	Low	Low	Low	High
Hardness	Low	Low	Low	Low	Low	Low	Low	High
Friability	Low	Low	Low	Low	High	Low	Low	High
Wearability	Low	Low	Low	Low	High	Low	Low	High
Moisture	Low	Low	Low	Low	High	Low	Low	Low

Table 4.4 (a): Risk assessment justification.

Formulation attributes	Drug Product cQA's	Justification
Dry mix	Appearance / Defect rate	The dry mix phase of the manufacturing process has no influence on any of the cQA's and for the purposes of this optimisation study is not investigated. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Dosing	Appearance / Defect rate	The dosing phase of the manufacturing process has no influence on any of the cQA's and for the purposes of this optimisation study is not investigated. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Wet mix	Appearance / Defect rate	The wet mix phase of the manufacturing process is not investigated for the purposes of this optimisation study and therefore has no influence on any of the cQA's. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Wet milling	Appearance / Defect rate	The wet milling phase of the manufacturing process is not investigated for the purposes of this optimisation study and therefore has not influence on any of the cQA's. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	

Table 4.4 (b): Risk assessment justification (continued).

Formulation attributes	Drug Product cQA's	Justification
Drying	Appearance / Defect rate	The wet granules are suspended and agitated in a warm air stream in a constant state of motion. The LOD limit is specified in the batch document and this specification needs to be achieved in order to comply with regulatory requirements. The risk is low.
	Hardness	Product history has shown that the drying of the granule does not influence the tablet compression characteristics. The risk is low.
	Friability	Batch history has shown that a LOD value obtained with a value closer to the lower end of the product specification resulted in higher friability/wearability results during the compression phase. The risk is high.
	Wearability	
	Moisture	
Dry milling	Appearance / Defect rate	The dry milling phase of the manufacturing process is not investigated for the purposes of this optimisation study and therefore has no influence on any of the cQA's. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Blending	Appearance / Defect rate	The blending phase of the manufacturing process is not investigated for the purposes of this optimisation study and therefore has no influence on any of the cQA's. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Compression	Appearance / Defect rate	Tooling changes (from bevelled to non-bevelled tooling) made to the product indicated that it could affect the defect rate, friability, and wearability of Product X. The risk is high.
	Friability	
	Wearability	
	Hardness	Product history has shown that hardness changes made during compression influence tablet integrity. The risk is high.
	Moisture	The moisture of the granule is controlled with the reading obtained after drying. The risk is low.

4.5 Execution of DoE

The function of the DoE study was to address the problems identified in the report generated by Aspen (Aspen Pharmacare (PTY) LTD, 2016b). The DoE batches were manufactured at the Aspen Port Elizabeth (PTY) Ltd. Formulation and Development Laboratory. A CCD which forms part of a RSM statistical method was used to analyse the data to find the optimal processing parameters during the pivotal study. The relationships between several explanatory variables were explored using a sequence of DoE batches to obtain an optimal response and allow estimating the curvature once all the results are obtained. The experimental design required a total of 26 batches to be manufactured in a randomised manner in order to avoid any biased capturing of data. Input variables investigated were: compression machine

tooling size and shape, hardness, and LOD (post drying). Table 4.5 below provides an overview of the DoE study design.

Table 4.5: Overview of DoE study.

Run Order	Hardness (N)	Moisture (% m/m)	Tooling: 12.7 mm
1	47	1.50	Non-bevelled
2	90	1.50	Bevelled
3	90	1.50	Non-bevelled
4	90	1.50	Non-bevelled
5	90	0.79	Non-bevelled
6	90	1.50	Bevelled
7	60	2.00	Bevelled
8	60	1.00	Bevelled
9	90	2.20	Bevelled
10	90	1.50	Non-bevelled
11	132	1.50	Bevelled
12	60	2.00	Non-bevelled
13	90	1.50	Bevelled
14	90	1.50	Non-bevelled
15	132	1.50	Non-bevelled
16	120	1.00	Bevelled
17	90	1.50	Bevelled
18	120	2.00	Bevelled
19	90	0.79	Bevelled
20	90	2.20	Non-bevelled
21	90	1.50	Non-bevelled
22	60	1.00	Non-bevelled
23	47	1.50	Bevelled
24	120	2.00	Non-bevelled
25	90	1.50	Bevelled
26	120	1.00	Non-bevelled

4.6 Response surface methodology results

The deliberate changes made to the manufacturing method as stipulated in the DoE design aided in the identification of the significant changes in the output responses of the product. The data was analysed using the collection of statistical models (ANOVA) to analyse the differences between the means and their associated

procedures. The significant value (α) of 0.05 helped to determine if the null hypothesis would be accepted or rejected. The null hypothesis criterion had been applied to the factors, interactions, and lack of fit model. The model's goodness of fit had also been assessed and verified using the S and R^2-values. The results are discussed in the section below.

4.6.1 Effect on Defect rate

Table 4.6 below summarises the influence of the input variables on the response and defect rate.

Table 4.6: ANOVA analysis of the Response surface regression: Defect rate versus Hardness, Moisture, and Tooling.

Source		p-value	Comment
Model	Linear	< 0.001	Significant
Terms	Hardness	< 0.001	Significant
	Moisture	< 0.001	Significant
	Tooling	< 0.017	Significant
Model	Square	0.114	Non-significant
Terms	Hardness*Hardness	0.055	Non-significant
	Moisture*Moisture	0.577	Non-significant
Model	2-Way Interaction	0.035	Non-significant
Terms	Hardness*Moisture	0.049	Significant
	Hardness*Tooling	0.656	Non-significant
	Moisture*Tooling	0.025	Significant
Lack of Fit		0.106	Non-significant

Model Summary	
S -value	2.66257
R^2-value	84.42 %

The model describing the defect rate (%) using bevelled or non-bevelled tooling is as follows:

Bevelled = 62.8 - 0.640 Hardness - 17.9 Moisture
+ 0.001632 Hardness*Hardness - 1.62 Moisture*Moisture
+ 0.1333 Hardness*Moisture

Non-bevelled = 48.3 - 0.620 Hardness - 11.3 Moisture
+ 0.001632 Hardness*Hardness -1.62 Moisture*Moisture
+ 0.1333 Hardness*Moisture

According to the linear model, all three variables had a p-value less than 0.05, which rejects the null hypothesis. Thus, each variable had a statistically significant role on the percentage defect rate of the product. The squared model failed to reject the null hypothesis as the p-values of the variables were all greater than 0.05. Hence, the variables did not impact on the responses for a squared model. The 2-way interaction model indicated that hardness*moisture did have a significant influence on the percentage defect rate of Product X.

The p-value for lack of fit is larger than the significance level (α) and therefore the data generated fails to reject the null hypothesis, i.e. there is not enough evidence to conclude that there is lack of fit in the simple linear regression model. The S-value of 2.7 indicates that most of the results generated during the experiments are very close to the average of the experiments. The R-squared value indicates that the model explains 84.42% of the variability of the response data around its means, which shows that there is a reasonable fit of the model on all the data points.

Tablets that contain lower moisture requires compression forces that are higher to allow the compression of tablets at a specific hardness to pass the appearance criteria during the compression phase of manufacturing (Gordon, 1994). A harder tablet will reduce the tablet defect (%), as can be seen in the main effects plot for defect rate (Figure 4.1 below). The figure also shows that higher moisture after drying produces a lower tablet defect rate, and that bevelled tooling also produces tablets with a lower defect rate percentage. The residual plot (Figure 4.2) show that the sample mean of the observed data is a good estimate of the population mean and it serves as an observable estimate of the unobservable statistical error. The contour plots (Figures 4.3 and 4.4) of the defect rate percentage versus moisture

and hardness of the non-bevelled and bevelled tooling indicate that higher hardness and higher moisture produce tablets with the lowest percentage of defective tablets.

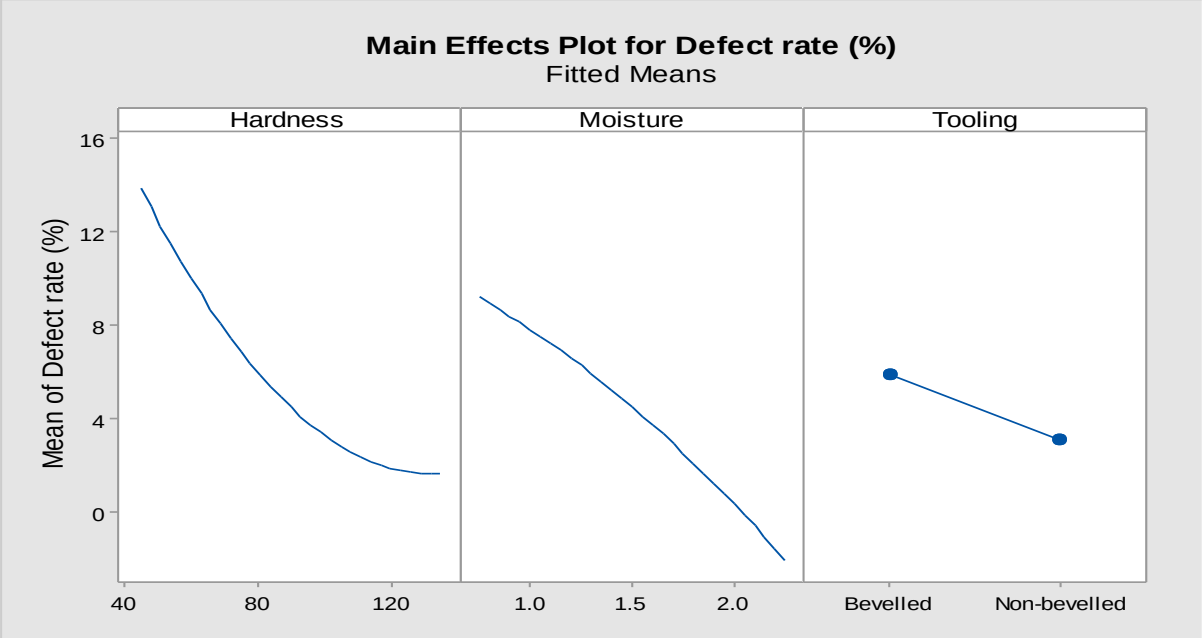

Figure 4.1: Main effects plot for Defect rate (%).

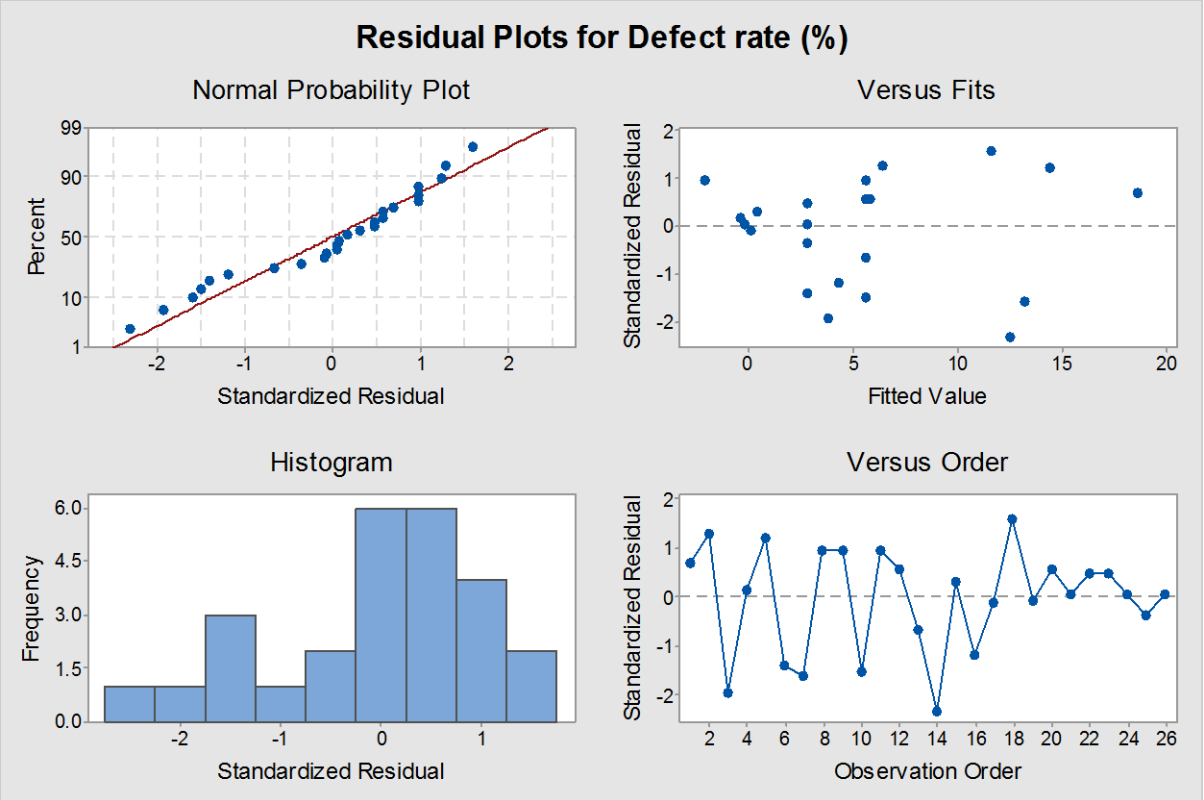

Figure 4.2: Residual plots for Defect rate (%).

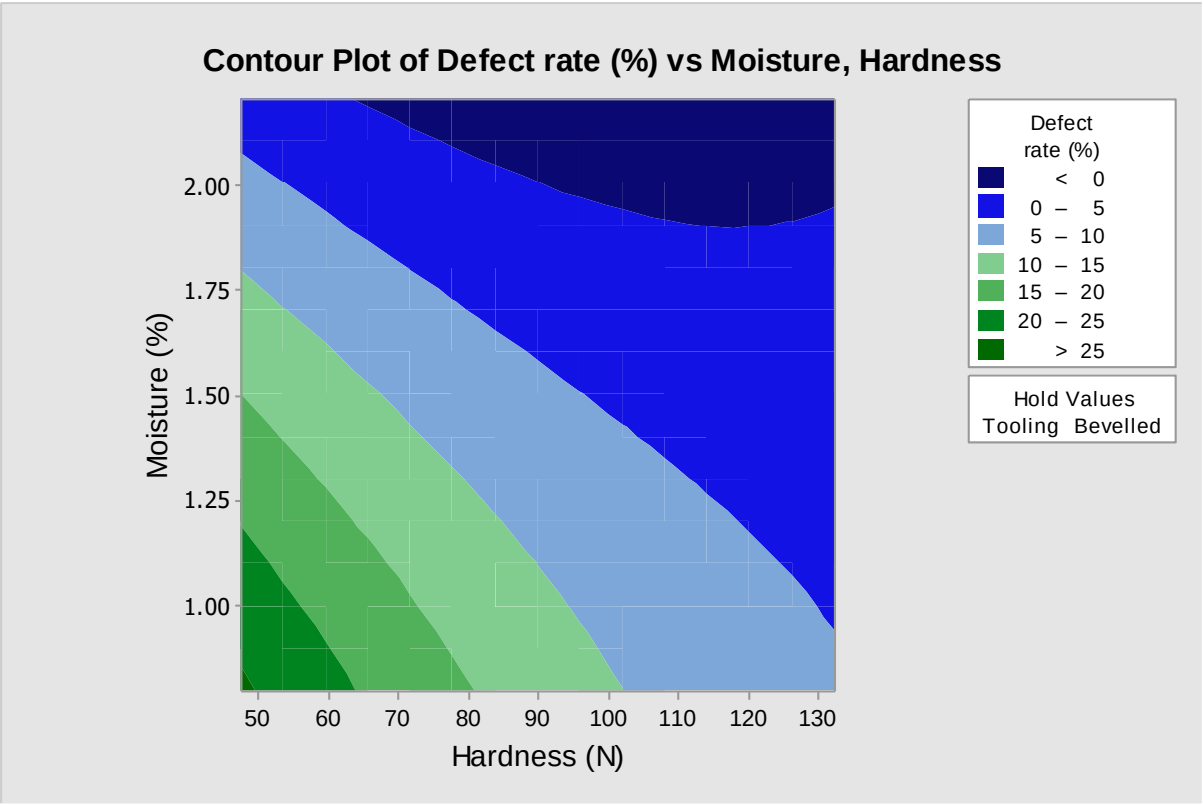

Figure 4.3: Bevelled tooling - Contour plot of Defect rate (%) vs moisture, hardness.

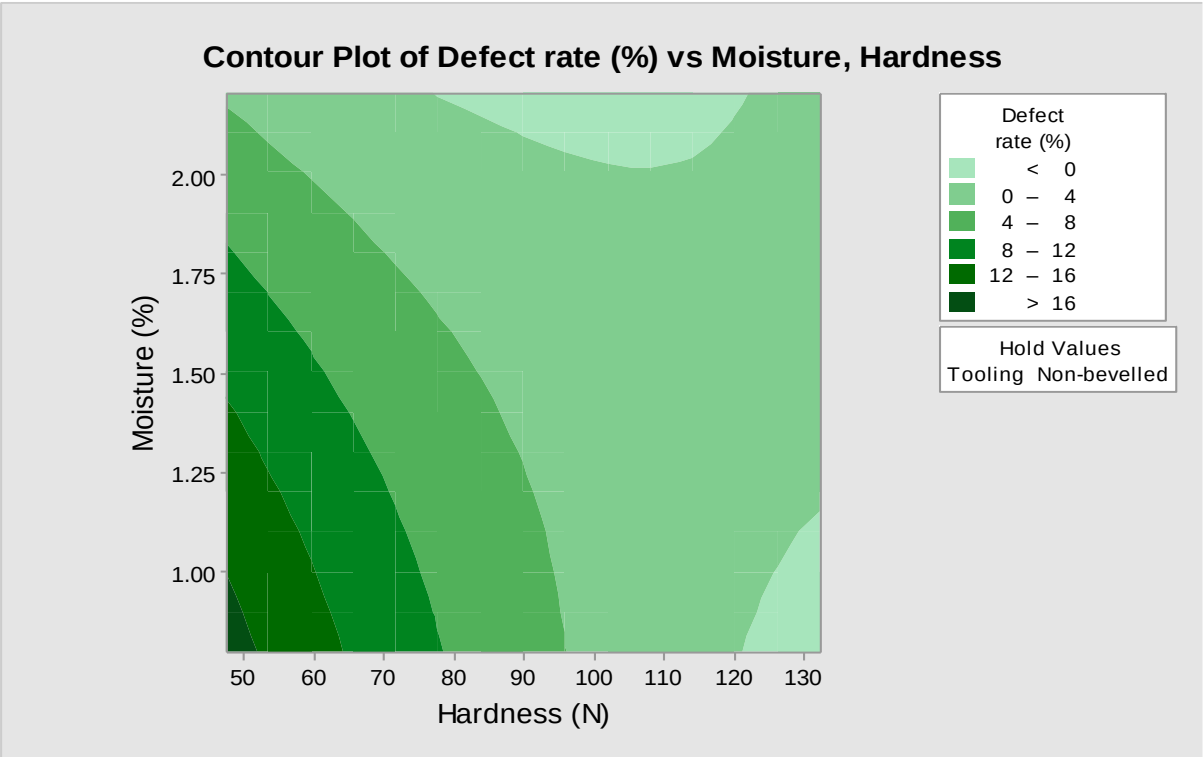

Figure 4.4: Non-bevelled tooling - Contour plot of Defect rate (%) vs moisture, hardness.

4.6.2 Effect on Friability

Table 4.7 below summarises the influence of the input variables on the response: tablet friability.

Table 4.7: ANOVA analysis of the Response surface regression data: Friability versus Hardness, Moisture, and Tooling.

Source		p-value	Comment
Model	Linear	< 0.001	Significant
Terms	Hardness	< 0.001	Significant
	Moisture	0.1	Non-significant
	Tooling	< 0.001	Significant
Model	Square	0.001	Significant
Terms	Hardness*Hardness	< 0.001	Significant
	Moisture*Moisture	0.819	Non-significant
Model	2-Way Interaction	0.403	Non-significant
Terms	Hardness*Moisture	0.197	Non-significant
	Hardness*Tooling	0.425	Non-significant
	Moisture*Tooling	0.439	Non-significant
Lack of Fit		0.112	Non-significant

Model Summary	
S -value	0.0113207
R^2-value	89.95 %

The model describing the effect on friability (% m/m) using bevelled or non-bevelled tooling is as follows:

Bevelled: Friability after 4 min (%) = 2.596 - 0.04201 Hardness - 0.291 Moisture
+ 0.000159 Hardness*Hardness
- 0.028 Moisture*Moisture
+ 0.00358 Hardness*Moisture

Non-bevelled: Friability after 4 min (%) = 3.132 - 0.04355 Hardness - 0.381 Moisture
+ 0.000159 Hardness*Hardness
- 0.028 Moisture*Moisture
+ 0.00358 Hardness*Moisture

According to the linear model, the hardness and tooling variables had a p-value less than 0.05, which rejects the null hypothesis. Therefore, each variable had a statistically significant role on the percentage friability (% m/m) of the product. The squared model indicated that hardness*hardness did have a significant influence on the friability (% m/m) of Product X and that the moisture*moisture had no significant effect on the friability. The 2-Way Interaction model failed to reject the null hypothesis as the p-values of the variables were all greater than 0.05. Hence, the interaction of the variables did not impact on the friability of the tablets.

The p-value for lack of fit is larger than the significance level (α) and therefore the data generated fails to reject the null hypothesis. There is not enough evidence to conclude that there is lack of fit for the regression models. The S-value of <0.02 indicates that most of the results generated during the experiments are very close to the average of the experiments. The R-squared value indicates that the model explains 89.95 % of the variability of the response data around its means.

Research has shown that tablets that contain lower moisture leads to tablets compressed with lower tensile strength, as well as reduced tablet porosity (Gabbott *et al.*, 2016; Sebhatu *et al.*, 1997). The main effects plot show that bevelled tooling gives a lower friability percentage result in Figure 4.5. The main effects plot also shows that higher moisture gives a tablet with a lower friability percentage, and tablets with a higher hardness produced, tablets with a lower friability percentage value. The residual plots (Figure 4.6) show that the sample mean of the observed data is a good estimate of the population mean and it serves as an observable estimate of the unobservable statistical error. The contour plots (Figures 4.7 and 4.8) of the friability percentage versus moisture and hardness of the non-bevelled and bevelled tooling indicate that higher hardness and higher moisture produce tablets with the lowest friability percentage.

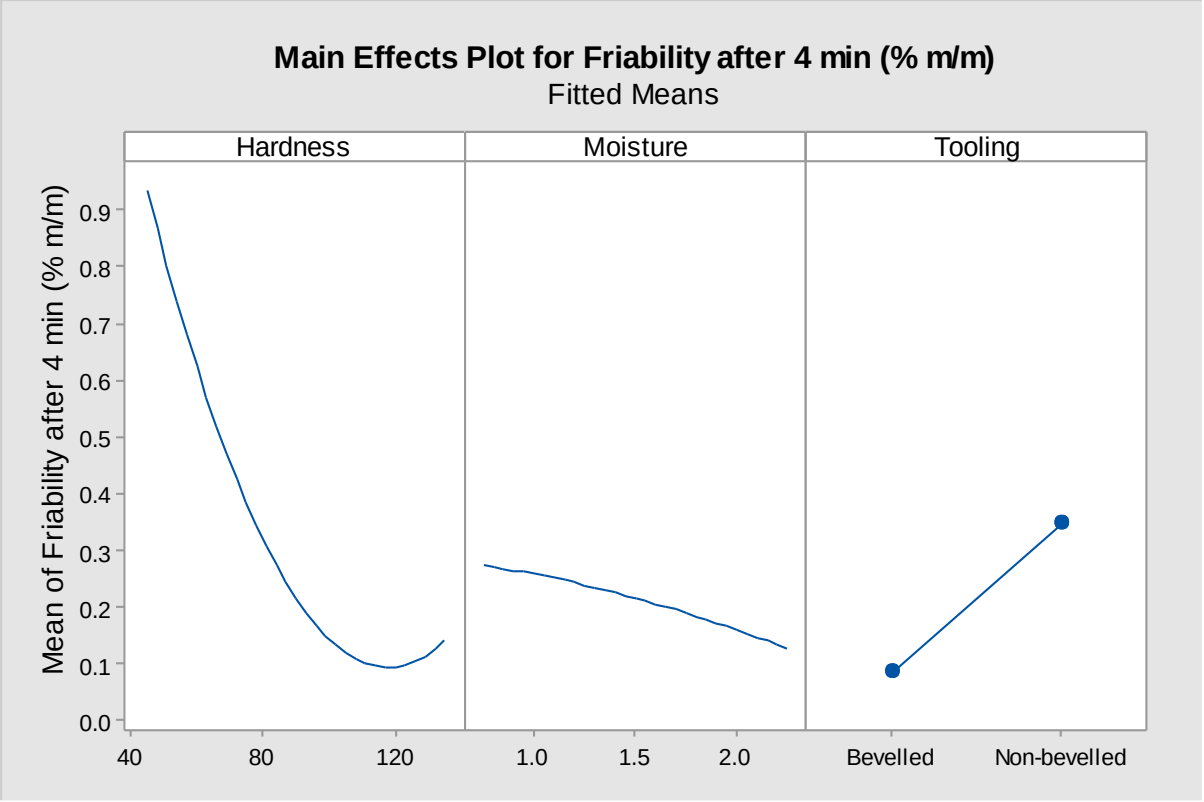

Figure 4.5: Main effects plot for Friability after 4 min (% m/m).

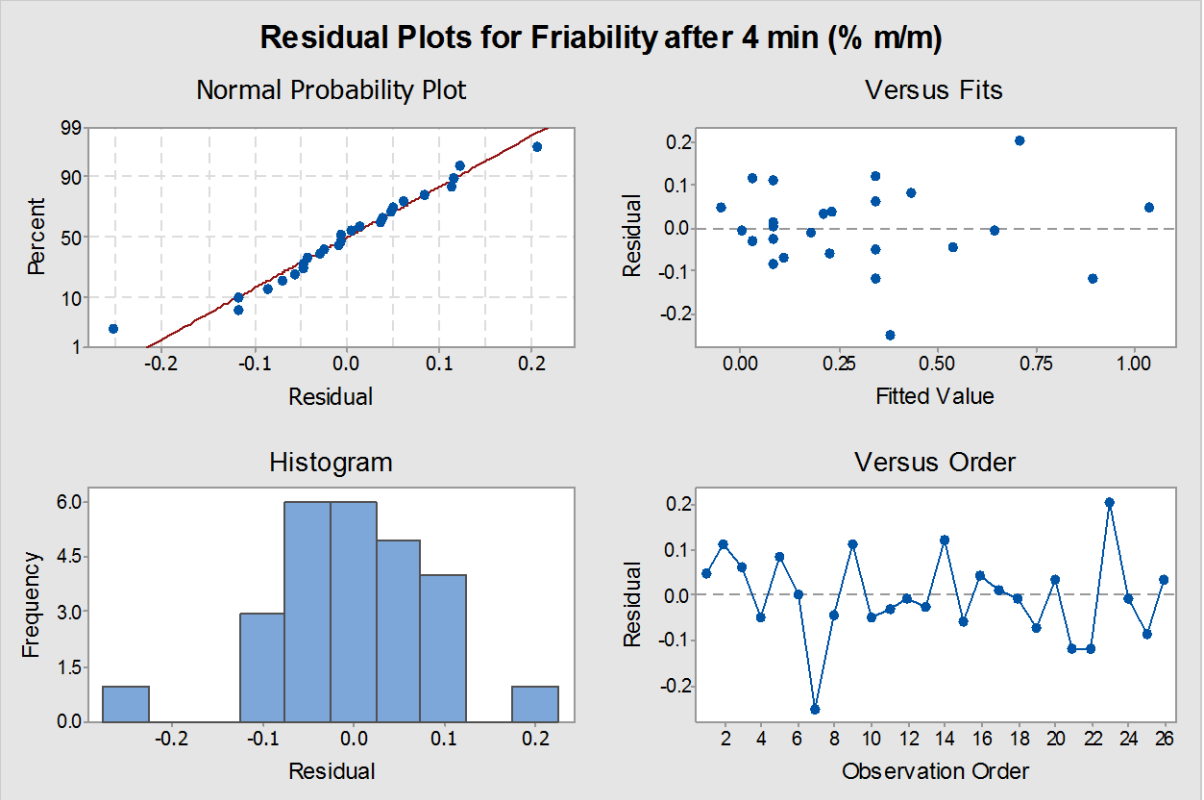

Figure 4.6: Residual plots for Friability after 4 min (% m/m).

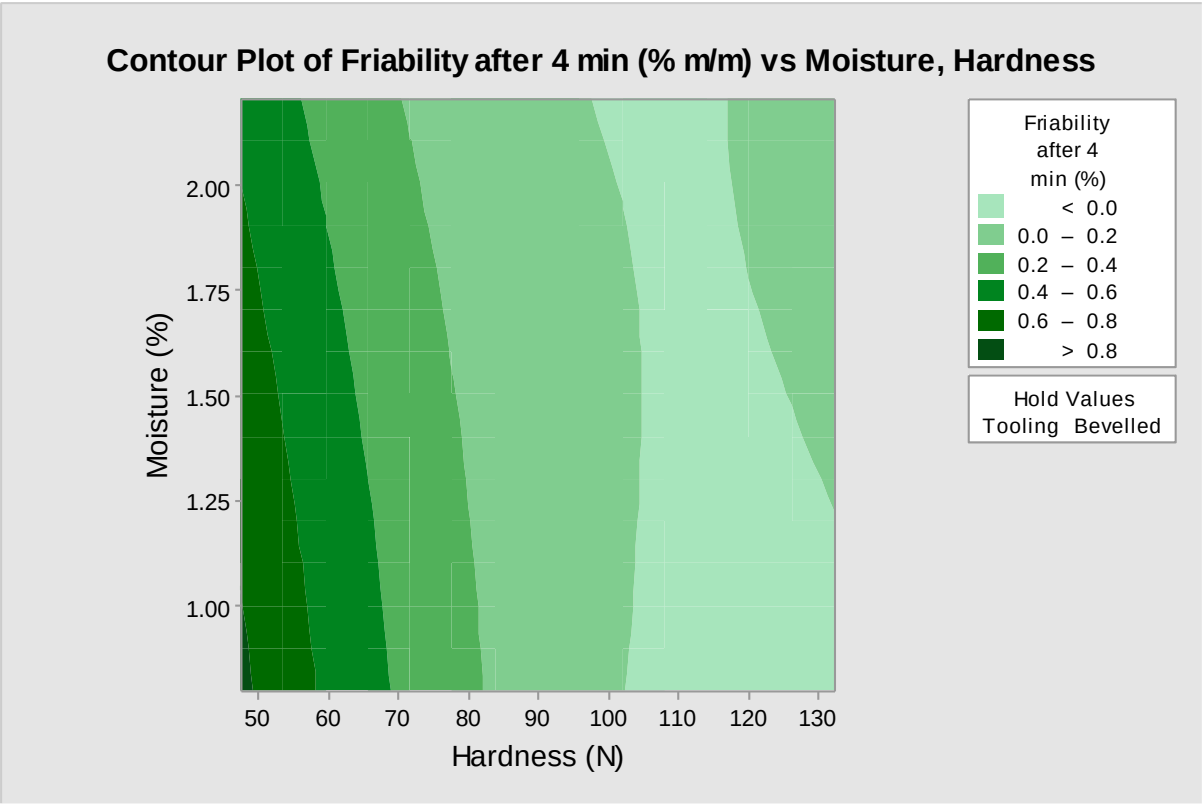

Figure 4.7: Bevelled tooling: Contour plot of Friability (% m/m) vs moisture, hardness

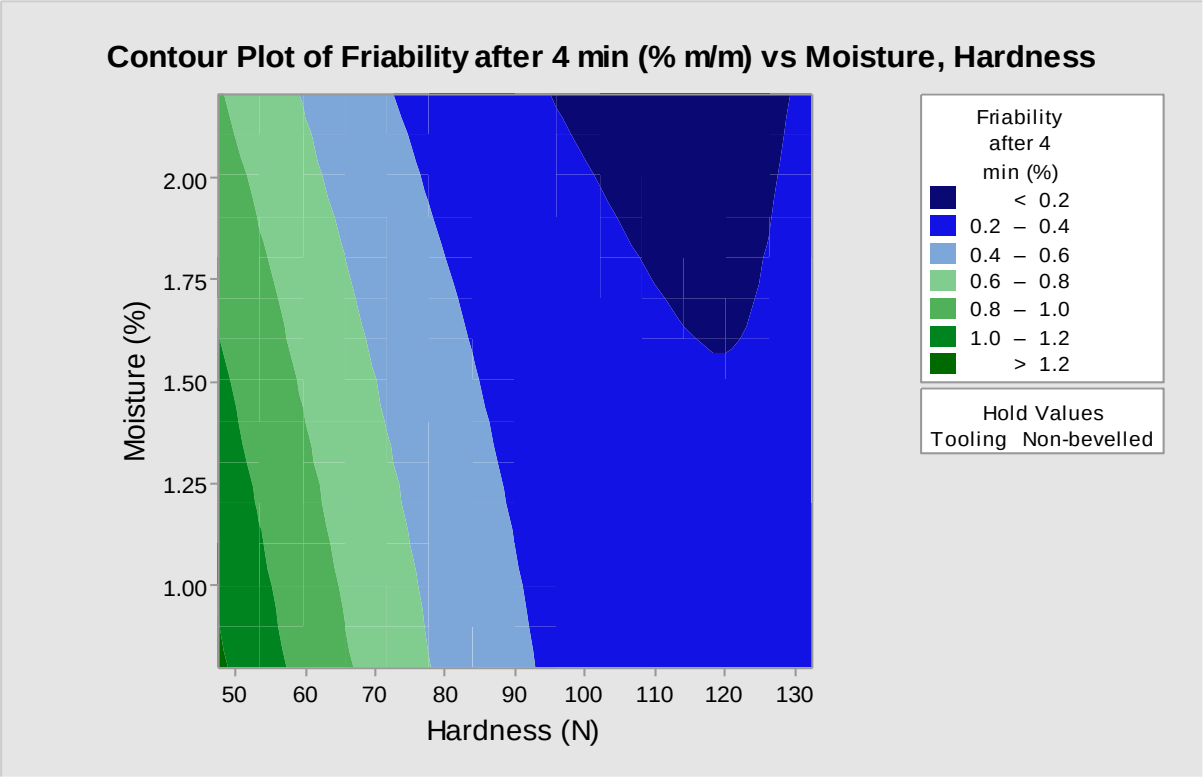

Figure 4.8: Non-bevelled tooling: Contour plot of Friability (% m/m) vs moisture, hardness.

4.6.3 Effect on Wearability

Table 4.8 below summarises the influence of the input variables on the response: tablet wearability.

Table 4.8: ANOVA analysis for response surface regression: Wearability versus Hardness, Moisture, and Tooling.

Source		p-value	Comment
Model	Linear	< 0.001	Significant
Terms	Hardness	< 0.001	Significant
	Moisture	0.080	Non-significant
	Tooling	0.531	Non-significant
Model	Square	0.069	Non-significant
Terms	Hardness*Hardness	< 0.037	Significant
	Moisture*Moisture	0.446	Non-significant
Model	2-Way Interaction	0.111	Non-significant
Terms	Hardness*Moisture	0.047	Significant
	Hardness*Tooling	0.338	Non-significant
	Moisture*Tooling	0.245	Non-significant
Lack of Fit		0.132	Non-significant

Model Summary	
S -value	0.269621
R^2-value	74.65 %

The model describing the effect on wearability (% m/m) using bevelled or non-bevelled tooling is as follows:

Bevelled: Wearability after 20 min (%) = 5.06 - 0.0682 Hardness - 0.96 Moisture
+ 0.000182 Hardness*Hardness
- 0.226 Moisture*Moisture
+ 0.01358 Hardness*Moisture

Non-bevelled: Wearability after 20 min (%) = 4.25 - 0.0638 Hardness - 0.63 Moisture
+ 0.000182 Hardness*Hardness
- 0.226 Moisture*Moisture
+ 0.01358 Hardness*Moisture

According to the linear model, only the hardness variable had a p-value less than 0.05, which rejects the null hypothesis; thus it had a statistically significant role on the percentage wearablity of the product. The squared model indicated that hardness*hardness did have a significant influence on the wearability (% m/m) of Product X and that moisture*moisture had no significant effect on the model. The 2-Way Interaction model indicated that hardness*moisture did, have a significant influence on the wearablity (% m/m) of Product X. The hardness*tooling and moisture*tooling had no significant impact on the wearability (% m/m) of Product X.

The p-value for lack of fit is larger than the significance level (α) and therefore the data generated fails to reject the null hypothesis. There is not enough evidence to conclude that there is lack of fit in the regression models. The S-value of 0.27 indicates that most of the results generated during the experiments are very close to the average of the experiments. The R-squared value indicates that the model explains 74.65 % of the variability of the response data around its means.

The influence on tablet wearability by moisture, hardness, bevelled and non-bevelled tooling is shown in the main effects and contour plots below. Tablets that contain lower moisture requires compression forces that are higher to manufacture tablets at a specific hardness during the compression phase of manufacturing (Gordon, 1994). The main effects plot (Figure 4.9) show that tablet hardness plays a practically significant effect on tablet wearability. The trend indicates that a harder tablet will reduce the tablet wearability (% m/m). The residual plot (Figure 4.10) show that the sample mean of the observed data is a good estimate of the population mean and it serves as an observable estimate of the unobservable statistical error. The contour plots (Figures 4.11 and 4.12) of the wearability percentage vs moisture and hardness of the non-bevelled and bevelled tooling indicate that higher hardness and higher moisture produces tablets with the lowest wearablity percentage.

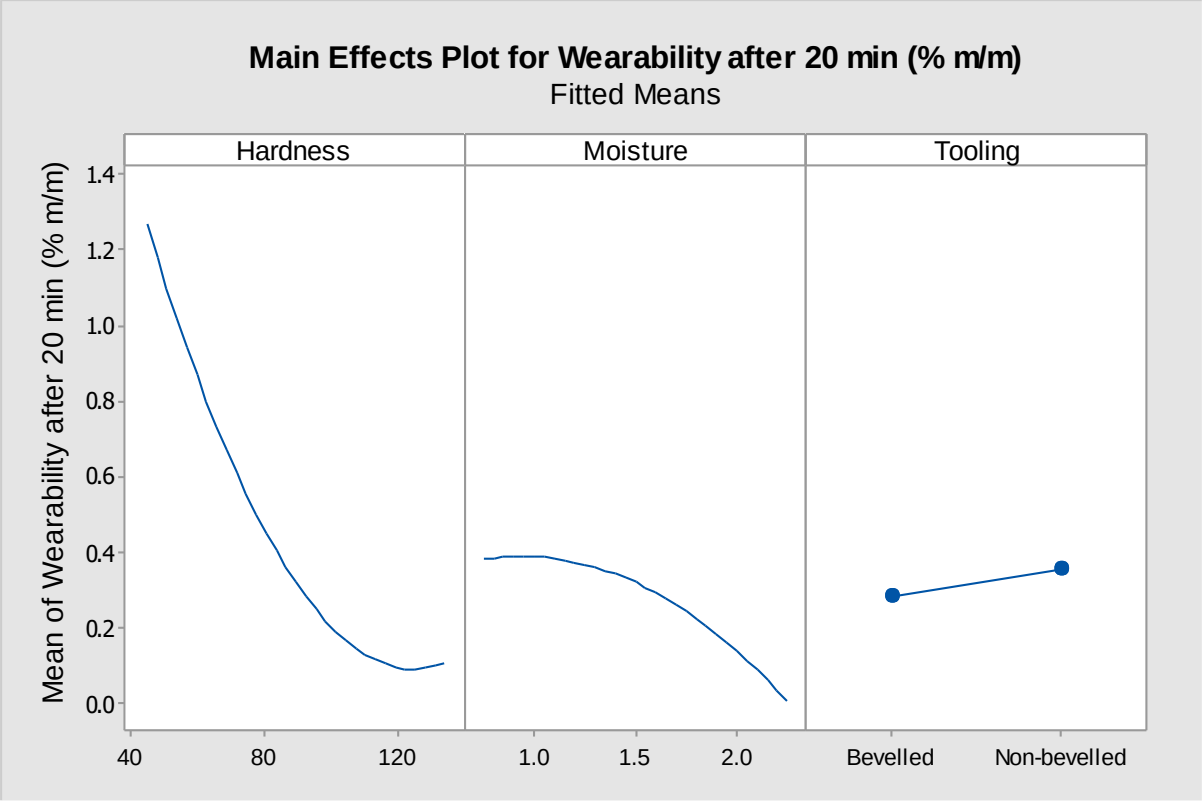

Figure 4.9: Main effects plot for Wearablity after 20 min (% m/m).

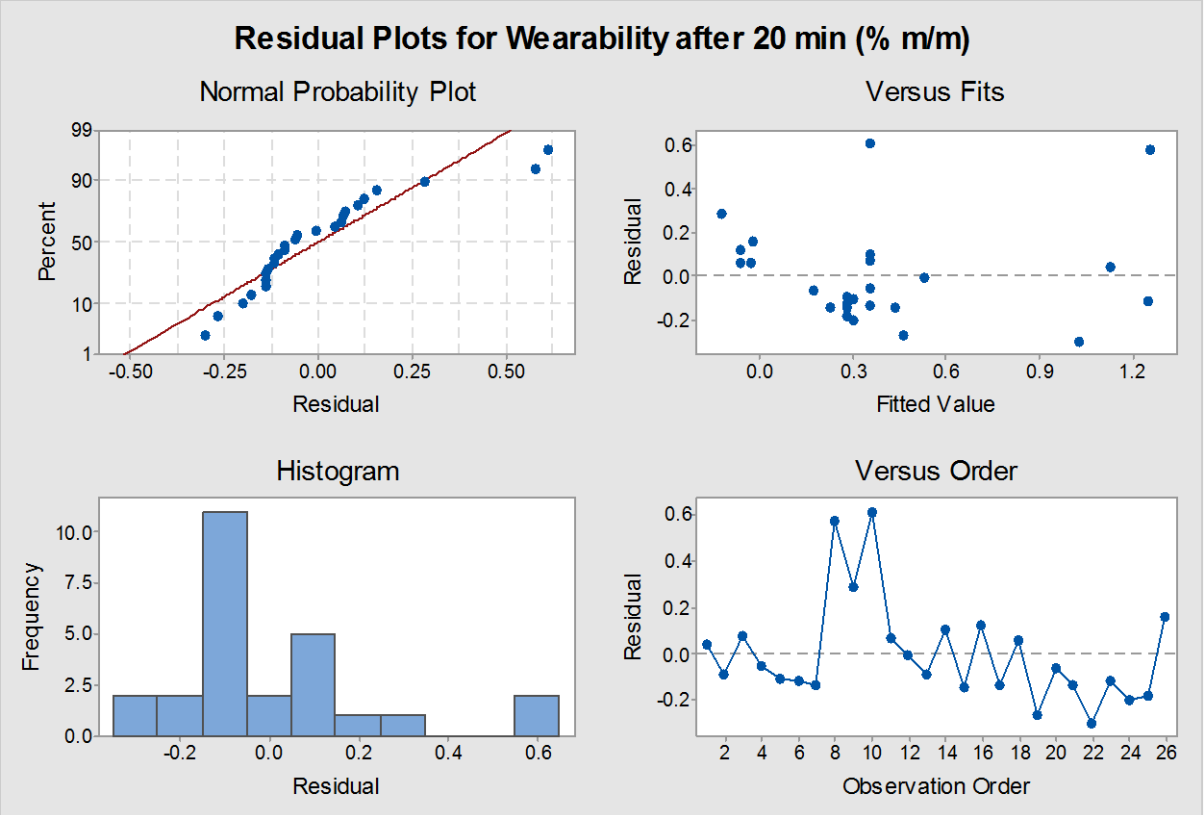

Figure 4.10: Residual plot for Wearability after 20 min (% m/m).

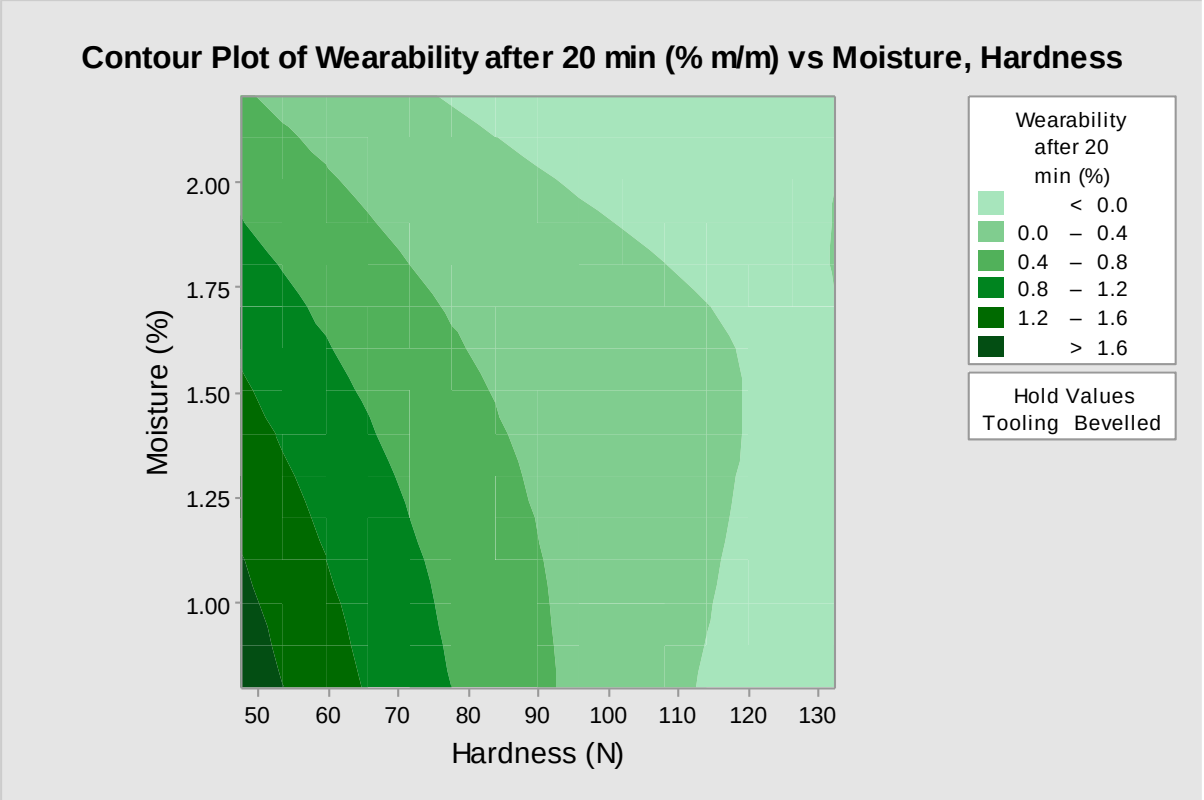

Figure 4.11: Bevelled tooling: Contour plot of Wearability after 20 min (% m/m) vs moisture, hardness.

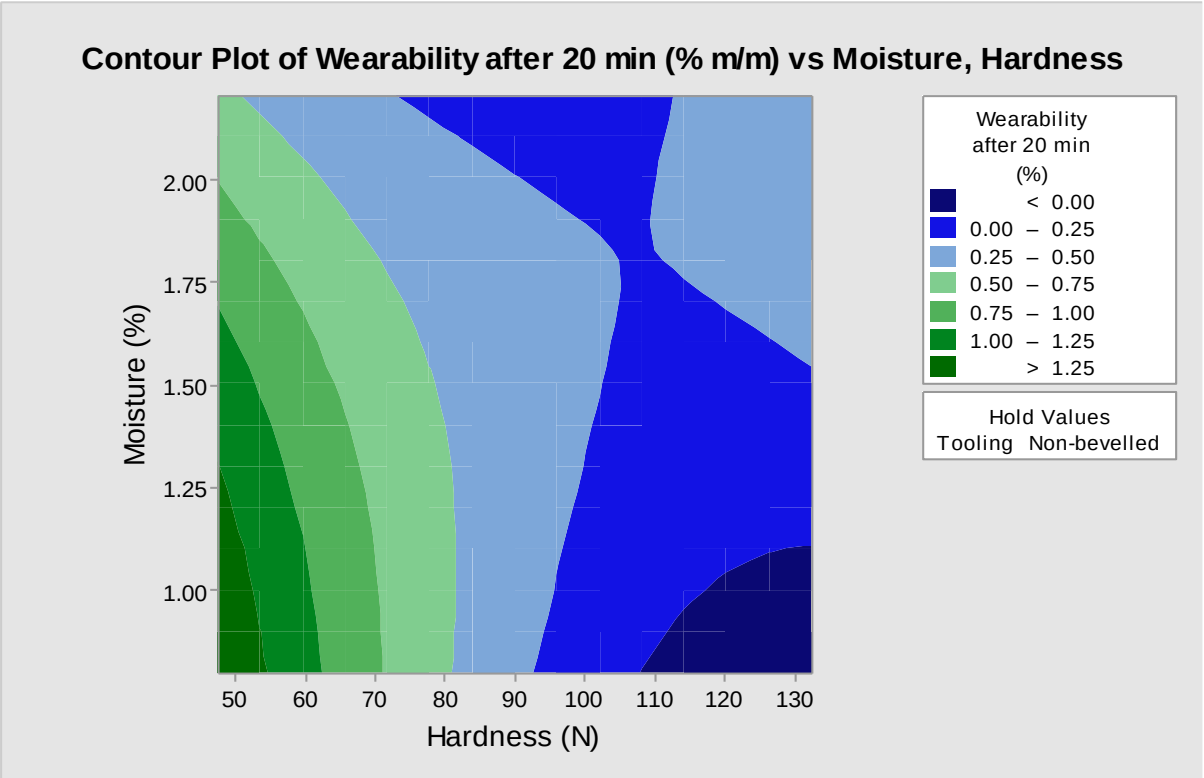

Figure 4.12: Bevelled tooling: Contour plot of Wearability after 20 min (% m/m) vs moisture, hardness.

4.7 Design space establishment

The response optimiser was used to jointly optimise the responses by identifying the most optimal settings of the three input factors: hardness, moisture, and tooling. The Minitab® 17 software calculated the composite desirability of the input parameters of hardness, moisture and tooling as 1.00, which predicts that at those variable settings the responses achieved will be close to the target requirements. In addition to the composite, the desirability was also calculated for the individual responses, namely wearability, defect rate, and friability. Figure 4.13 shows the value obtained for all three responses were 1.00, which again indicated the predicted response achieved will be close to the chosen target requirements. Figure 4.13 shows that bevelled tooling is more advantageous to use than non-bevelled tooling and, as a result, only bevelled tooling (which is currently registered with the Medicine Control Council of South Africa) was used to generate the design space.

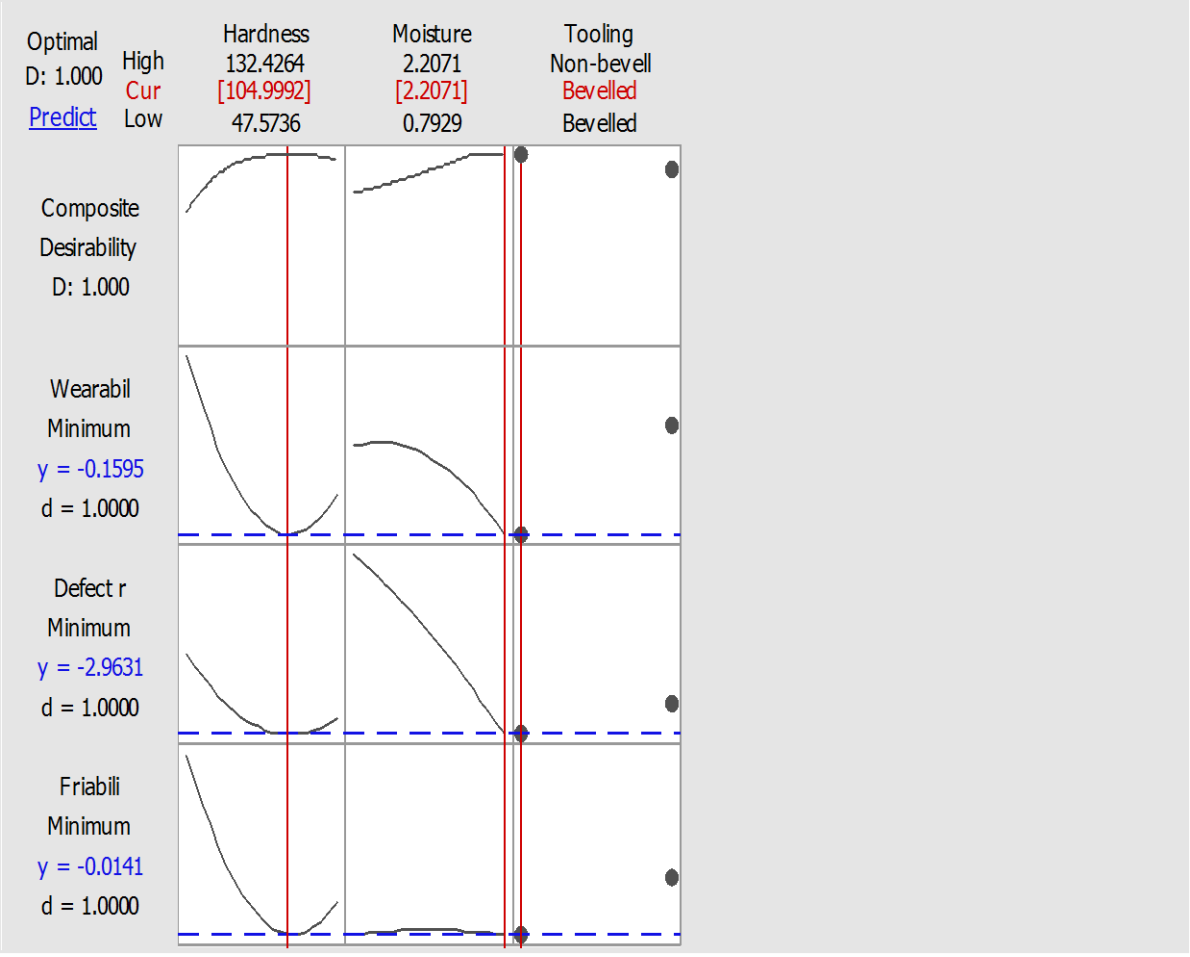

Figure 4.13: Response optimiser plot of the input factors: hardness, moisture, and tooling.

Hardness and moisture were identified as having significant effects on the defect rate, friability, and wearability and therefore the design space was created around these parameters as shown Figure 4.14 below. The objective of the design space is to minimise tablet defects, friability, and wearability failures. The design space allows for flexibility during the processing manufacturing stages and ensures that the quality of Product X meets the required criteria.

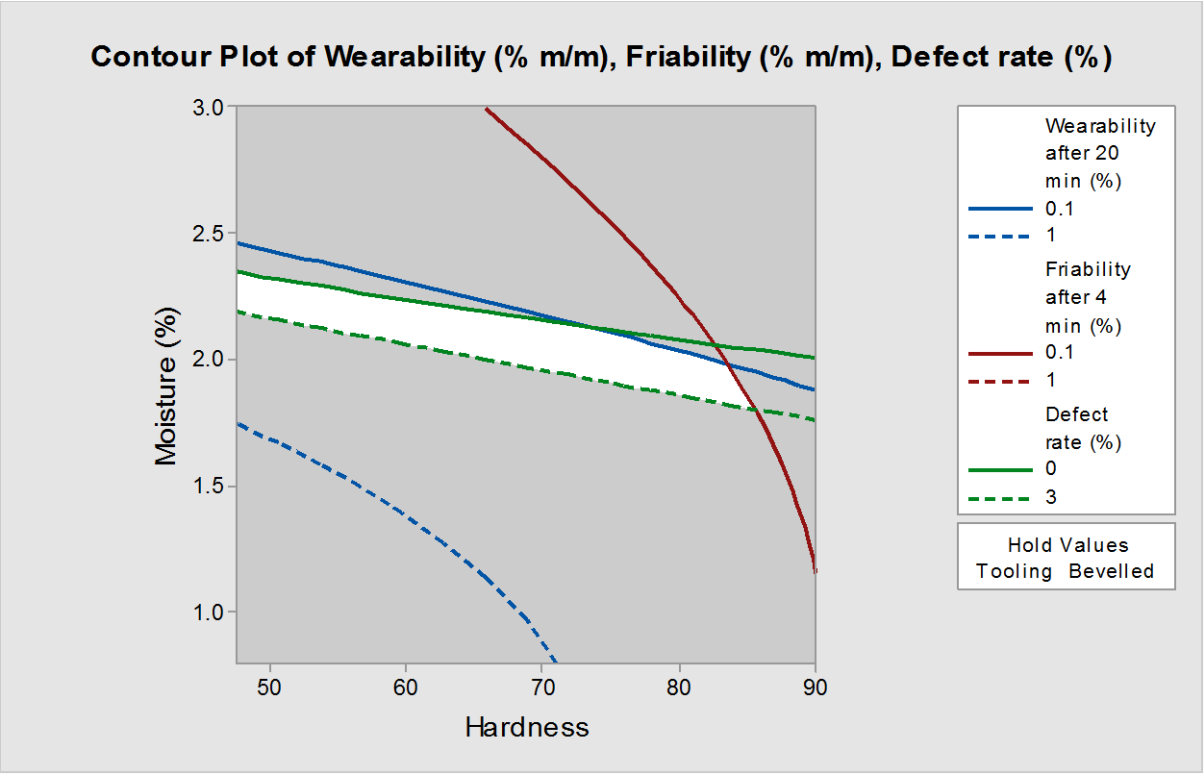

Figure 4.14: Contour plot showing Product X's design space.

The design space (Figure 4.14) created by Minitab software also highlights potential input parameters (CPP's) that would fall within the area of acceptable quality, which is indicated in Table 4.9 below. The current registered specification for moisture is 1.0 - 2.0% and 60 N - 120 N for hardness, which is within the design space. Considering the regulatory impact of changing the already registered specification, the confirmatory batch was made and tested at the registered Product X's specification for moisture and hardness. Therefore, it was decided against changing the input parameters to the optimum parameters as indicated in Figure 4.13 and parameters that fell within the registered Product X specification and design space was chosen.

Table 4.9: Summary of design space at various moisture and hardness values

Hardness (N)	85	80	70	60	50
Moisture (%m/m)	1.9	1.9	2.0	2.1	2.3
Tooling	Bevelled	Bevelled	Bevelled	Bevelled	Bevelled

4.8 Manufacture of confirmatory batch

Post completion of the DoE, a confirmatory batch was made which served as a diagnostic tool for evaluating the effectiveness of the generated model. The batch was to be considered successful if the results of the batch fell within the 95% confidence intervals (CI) of the DoE. The confirmatory batch was manufactured with a target hardness of 85 N and target LOD of 1.9%. The confirmatory batch of Product X was analysed and the results are shown in Table 4.10 below.

Table 4.10: Summary of the 95 % CI of the confirmatory batch of Product X

Response	**Units**	**Predicted mean**	**Actual mean**	**95% CI low**	**95% CI high**
Defect rate	**%**	-2.46	0	-6.286	1.363
Friability	% m/m	0.033	0.03	- 0.129	0.196
Wearability	% m/m	-0.112	0.19	- 0.049	0.274

The actual means of the responses from the confirmatory batch falls within the 95% CI for all responses; thus the model generated with the help of DoE trials is able to describe the relationship of the input variables (at the studied ranges) with the responses. The successful manufacture of the confirmatory batch shows the design space generated can be used during future batch manufacture of Product X.

4.9 Risk control

The results obtained from the DoE were used to update the risk associated with the input variables and responses. The risk assessment performed initially was updated with the knowledge gained from the DOE experiments. The establishment of a strategy to control the variables and responses is of critical importance in order to appropriately use the flexibility given to products developed or optimised using QbD principles. The control strategy is defined as a set of controls derived from the

process, in this case the DoE study, that ensures the product's performance and quality are consistent, and that they meet the required regulatory specifications (International Council for Harmonisation, 2009). These changes were made once the results of the DoE has been reviewed and assessed. The updated risk assessment and justification falls within the proposed design space and, essentially, the updated risk assessment and justification will allow regulatory flexibility within the manufacturing processing steps of Product X.

The DoE study provided the evidence needed to prove to the regulatory authority that quality was built into the manufacturing process. Table 4.11 provides an overview of the changes made to the manufacturing process risk assessment, and Table 4.12 provides an overview of the updated process parameters and input material attributes which affect the various stages of the manufacturing process of Product X. The updated risk assessment will allow justification for the flexible manufacturing of Product X, as long as the parameters used will fall within the design space.

Table 4.11: Manufacturing process risk assessment

Drug Product cQA	Dry mix	Dosing	Wet mix	Wet milling	Drying	Dry milling	Blending	Compression
Appearance / Defect rate	Low	Low	Low	Low	Low	Low	Low	Low
Hardness	Low	Low	Low	Low	Low	Low	Low	Medium
Friability	Low	Low	Low	Low	Low	Low	Low	Low
Wearability	Low	Low	Low	Low	Low	Low	Low	Low
Moisture	Low	Low	Low	Low	Medium	Low	Low	Low

Table 4.12 (a): Risk assessment justification

Formulation attributes	Drug Product cQA's	Justification
Dry mix	Appearance / Defect rate	The dry mix phase of the manufacturing process has no influence on any of the cQA's and is for the purposes of this optimisation study not investigated. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Dosing	Appearance / Defect rate	The dosing phase of the manufacturing process has no influence on any of the cQA's and is for the purposes of this optimisation study not investigated. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Wet mix	Appearance / Defect rate	The wet mix phase of the manufacturing process is not investigated for the purposes of this optimisation study and therefore has not influenced any of the cQA's. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Wet milling	Appearance / Defect rate	The wet milling phase of the manufacturing process is not investigated for the purposes of this optimisation study and therefore has not influenced any of the cQA's. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Drying	Appearance / Defect rate	The wet granules are suspended and agitated in a warm air stream in a constant state of motion. The LOD limits set out in the batch document needs to be achieved in order to comply with regulatory requirements. The risk is low.
	Hardness	Product history has shown that the drying of the granule does not influence the tablet compression characteristics. The risk is low.
	Friability	The DoE showed that drying has no influence on friability or wearablity. The risk is low.
	Wearability	
	Moisture	Moisture after drying (LOD) plays an important role in minimising the wearablity, friability, and defect rate of Product X. The LOD range will be set to the optimal setting obtained from the design space and will be controlled via the batch manufacturing record. The current quality management system in place at the pharmaceutical company will ensure compliance. The risk is medium.
Dry milling	Appearance / Defect rate	The dry milling phase of the manufacturing process is not investigated for the purposes of this optimisation study and therefore has not influenced any of the cQA's. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	

Table 4.12 (b): Risk assessment justification

Formulation attributes	Drug Product cQA's	Justification
Blending	Appearance / Defect rate	The blending phase of the manufacturing process is not investigated for the purposes of this optimisation study and therefore has not influenced any of the cQA's. The risk is low.
	Hardness	
	Friability	
	Wearability	
	Moisture	
Compression	Appearance / Defect rate	The DoE indicated that tooling has the ability to influence the defect rate of Product X, therefore a specific set of tooling is to be specified in the batch manufacturing record. This will be controlled with the help of the quality management system currently in place at the pharmaceutical company. The risk is low.
	Friability	The DoE study proved that the compression phase of manufacturing influence tablet friability and wearability. The risk is low.
	Wearability	
	Hardness	Product history has shown that hardness changes made during compression influences tablet integrity. The DoE established an optimum hardness range that, if it is deviated from, will influence tablet integrity negatively. The hardness range will be set to the optimal setting obtained from the design space and will be controlled via the batch manufacturing record. The current quality management system in place at the pharmaceutical company will ensure compliance. The risk is medium.
	Moisture	The moisture of the granule is controlled with the reading obtained after drying. The risk is low.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

The decision to utilise QbD to optimise a legacy product was based on the fact that all batches of Product X manufactured at the pharmaceutical company, failed the acceptable quantitative limits inspection test after coating. The manufactured batches were rejected because of this inspection failure. Interventions performed before the implementation of QbD at the pharmaceutical company proved to be unsuccessful and costly. This study was designed to find a feasible and alternative method of optimising Product X.

The scientific grounds for the application of QbD to the development of a New Drug Application is well established and set out in the ICH Q8 (R2) guidance. This study showed that the structured approach associated with QbD can be utilised in mitigating problems during the manufacturing phase of a legacy product and could help to ensure that a higher level of quality assurance is obtained.

The DoE helped to optimise and build a design space for the manufacturing process of Product X, and in doing so showed how the identified CPP's, namely moisture and hardness, were found to have the most significant effect on the identified cQA's, namely tablet friability, wearability, and defect rate failures. The study showed that tooling shape played a lesser role in the quality of the final product.

The design space was identified with the aid of mathematical modelling, and the optimal settings of the input variables within the design space were determined. The confirmatory batch showed that the design space created is of relevance and accurate, and that the product met all quality requirements could be successfully manufactured. Product manufacture within the proposed design space minimised tablet friability failures and the occurrence of chipped tablets for future batches.

This study shows that acceptable quality can be built into the manufacturing process of Product X using QbD. When implementing QbD to optimise a commercialised legacy product, the scientific knowledge generated w.r.t. the product's process

controls are invaluable. The implementation of QbD could help correct many of the potential errors of the commercialised legacy product and ensure that the product routinely meets the desired process performance and quality.

The objectives of the study were met and it was possible to determine the QTPP, cQA's, CMA's, and CPP's of Product X. Scientific risk-based decisions made in the planning and preparation of a DoE study helped to establish a robust manufacturing process for Product X. The QbD methodology aided in the establishment of an adequate risk control strategy that could be successfully implemented in the manufacturing life cycle of Product X. Further studies on this topic could explore the financial benefits that possibly exists by implementing a QbD study into the process lifecycle of a legacy product.

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