FORMULATION AND PROCESS OPTIMISATION OF ETHIONAMIDE 250 MG TABLETS USING QUALITY BY DESIGN PRINCIPLES

NASREEN ISAACS

2015

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Submitted in fulfilment of the requirements for the degree of

MAGISTER SCIENTIAE

in the

FACULTY OF HEALTH SCIENCES

at the

NELSON MANDELA METROPOLITAN UNIVERSITY

December 2015

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DECLARATION

I hereby declare that the work on which the dissertation is based is original (except where acknowledgments have been made) and that neither the whole work nor any part thereof has been, is being or is to be submitted for another degree at this or any other university.

_____

Miss N Isaacs

Signed on _____ day of _____ at the Nelson Mandela Metropolitan University.

DEDICATION

This study is dedicated to my parents, Zaid and Shanaaz Isaacs. Thank you for all the unconditional love, guidance and support that you have always given to me.

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ACKNOWLEDGEMENTS

All Praises to the Almighty, the Most Gracious the Most Beneficent

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

- My supervisors, Prof Gareth Kilian, Dr Wai Ling Au and Dr Mbali Keele for their support and assistance during my post graduate studies.
- Dr Matthew Worthington, Mr Nelesh Jaganath, Mr Eric Watkins, Mr Daya Moodaley, Miss Diane Moodley, Miss Tarynlee Maxwell and Miss Mathie Postma-Botha for their guidance and encouragement.
- Mr Chris Ncoyo, Mr Fillis Martins, Mr Lundi Hlulani, Mr Michael Williams, Miss Chantel Marais, Mrs Amor Marx and the other staff members working in the pilot plant division for all their help and welcoming support.
- The Pharmacy Department at the Nelson Mandela Metropolitan University.
- Aspen Pharmacare and the NMMU Post Graduate Scholarship for their funding of the research project.
- My parents, Zaid and Shanaaz Isaacs for their unconditional love, support and encouragement.
- My family and friends for their support.
- My fellow post graduate friends for their encouragement to ‘cross the finish line’.
- Although my name alone appears on the title page, many other people have given me support and advice and has been part of my journey of reaching my goals, thank you.

LIST OF ABBREVIATIONS

ANDA:	Abbreviated New Drug Application
ANOVA:	Analysis of Variance
API:	Active Pharmaceutical Ingredient
AUC:	Area under the curve
BBD:	Box-Behnken Design
BCS:	Biopharmaceutics Classification System
CAPA:	Corrective Action Preventative Action
CCD:	Central Composite Design
CCRD:	Central Composite Rotatable Design
CI:	Confidence Interval
cGMP:	current Good Manufacturing Practice
cMAs:	Critical Material Attributes
C_{max}:	Maximum Plasma Concentration
cQAs:	Critical Quality Attributes
cPPs:	Critical Process Parameters
DoE:	Design of Experiments
FDA:	Food and Drug Administration
FMEA:	Failure Mode Effects Analysis
FMECA:	Failure Mode Effects and Criticality Analysis
FTA:	Fault Tree Analysis
GI:	Gastro-intestinal
GMP:	Good Manufacturing Practice
HACCP:	Hazard Analysis and Critical Control Points
HIV:	Human Immunodeficiency Virus
HMI:	Human Machine Interface
ICH:	International Conference on Harmonisation
IPI:	Inactive pharmaceutical ingredient
LOD:	Loss on Drying
MCC:	Microcystalline Cellulose
MDR:	Multiple Drug Resistant
MDR-TB:	Multiple Drug Resistant Tuberculosis
ml:	millilitres
N/A:	Not Applicable
NLT:	Not Less Than

NMT:	Not More Than
OFAT:	One Factor at a Time
OGD:	Office of Generic Drugs
PAT:	Process Analytical Technology
PI:	Prediction Interval
PLM:	Product Life-cycle Management
PQRI:	Product Quality Research Institute
PSD:	Particle Size Distribution
QbD:	Quality by Design
QbT:	Quality by Testing
QMS:	Quality Management System
QRM:	Quality Risk Management
q.s:	quantity supplied
QTPP:	Quality Target Product Profile
Qty:	Quantity
RLD:	Reference Listed Drug
rpm:	rotations per minute
RPN:	Risk Priority Number
RSD:	Relative Standard Deviation
RSM:	Response Surface Methodology
SD:	Standard Deviation
SOP:	Standard Operating Procedure
SSG:	Sodium Starch Glycolate
T_{max}:	Time for achieving maximum plasma concentration
TAMC:	Total aerobic microbial count
TB:	Tuberculosis
TBE:	To be established
TLC:	Thin Layer Chromatography
TPP:	Target Product Profile
TYMC:	Total combined yeasts and mould count
$t_{½}$:	half life
UOC:	Uniformity of Content
UOM:	Uniformity of Mass
USP:	United States Pharmacopoeia
WHO:	World Health Organisation
XDR-TB:	Extensively Drug Resistant Tuberculosis

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SUMMARY

Purpose: The traditional approach of Quality by Testing (QbT) limits the assurance of product quality to in-process and post-production testing. To overcome these limitations, a more proactive and systematic means to product development and optimisation is required. Quality by Design (QbD) is an example of such an approach which focuses on understanding the product and its manufacturing process and emphasises that quality should be built into the product and not merely tested. The study aims to optimise ethionamide tablets, an immediate release oral solid dosage form using QbD.

Methodology: A dynamic summary of the product characteristics was established to ensure the desired quality is achieved. The critical quality attributes (cQAs) of the product were identified. The risk assessment was first performed by using qualitative descriptors followed by the failure mode effects analysis (FMEA) method to identify the risk factors that may affect the product cQAs. Design of Experiments (DoE) were performed and analysed using Minitab® statistical software version 16.0 (Minitab Inc., United Kingdom). An initial screening of the risk factors was completed using a 2^{6-3} fractional factorial design to identify the significant factors affecting the cQA. Response surface methodology (RSM), by means of a central composite rotatable design (CCRD) was used to investigate the effects of the significant factors on the response and to create the design space. All experimental runs were randomised to avoid any subjective decisions.

Results: The risk assessment identified six factors that had the highest risk of affecting dissolution (cQA). These include, the active pharmaceutical ingredient (API) particle size, the quantity of povidone binder, impeller speed during dosing, massing time, impeller speed during wet mix and the moisture content after drying the wet granule. Pareto ranking and analysis of variance (ANOVA) indicated that the impeller speed during dosing and the moisture content after drying the wet granule were the significant factors affecting the cQA. Optimisation with the CCRD further clarified the relationship between the significant factors and the cQA and the design space was established based on the constraints set on the response. The optimised manufacturing process was chosen using the desirability factor and identified the optimal setting for impeller speed during dosing at 115 rpm and the moisture content at 2.5% m/m. The optimised product was prepared and results showed that the batch corresponded reasonably well with those predicted for the desired quality attribute. The control strategy was developed to better mitigate the risks and the updated risk assessment showed that all the potential failure modes were lowered.

Conclusion: DoE and risk assessment tools provided an effective and efficient means to build quality into the manufacture of ethionamide tablets. Therefore, the study ascertains the concept of QbD for an immediate release tablet that was first introduced onto the market in the 1960s.

Keywords: Ethionamide, Quality by Design (QbD), risk assessment; failure mode effects analysis (FMEA); Design of Experiments (DoE); fractional factorial designs; response surface methodology (RSM); design space; control strategy

CHAPTER 1 – INTRODUCTION

1.1 Background

Quality is measured by its degree of excellence. Quality assured products are safe, effective and fit for their intended purposes. However, if the quality of pharmaceutical products is measured by its fitness for purpose, then safety and efficacy are not separate from quality, but form part of it. In instances when a pharmaceutical product is classified as unsafe, or not efficacious, then it is not fit for its intended purpose. Accordingly, quality must be taken to include safety and efficacy (Sharp, 2000). Quality is a comprehensive system, involving personnel, equipment and resources providing assurance that those products will be consistently fit and appropriate for their intended use (Soulebot *et al.*, 1997; World Health Organisation, 2007). Continuous quality improvement is a critical step for the pharmaceutical industry to maintain a competitive advantage in the market place. Therefore, the aim of pharmaceutical development is to produce a product of an acceptable quality (International Conference on Harmonisation, 2009a).

Under the traditional approach of Quality by Testing (QbT), a product specification is set by observing data from a small number of batches believed to be an acceptable quality and then setting acceptance criteria that require future batches to be the same. Specifications are tight because it is used to assure consistency of the manufacturing process. Testing of products can only be performed on a small sample, simply because the majority of the tests are destructive in nature and if the entire batch were tested to assure its quality, there would be no product. Since a few tablets out of a batch of several million are tested, industries are usually expected to conduct extensive in-process tests and post-production tests to ensure the outcome meets the predefined specifications, if not, batches are reworked or discarded. The combination of stringent manufacturing steps and excessive testing is what assures quality under the traditional approach (Karanokov *et al.*, 2011; Sharp, 2000; Travedi, 2012; Yu, 2008). In addition, the traditional one-factor-at-a-time (OFAT) approach to experimentation has a lot of constraints as it does not determine interactions among the factors considered for experimentation, it requires more experimental runs and requires a lot more resources (Tanco *et al.*, 2007). This limits the opportunities for statistical and basic problem analysis. Therefore, product testing is retrospective, and is based on detection rather than prevention (Yu, 2008).

Pharmaceutical manufacturing is a highly regulated industry compared to the food or automotive industry and the cost of current good manufacturing practice (cGMP) compliance is high. In this era of competition, quality has prime magnitude, and failure to meet such quality-allied goals produces challenges for industry (Woodcock, 2010). The Food and Drug Administration (FDA) acknowledges that more controls are required for pharmaceutical manufacturers and better regulatory decision-making. The FDA therefore adopted a more methodical approach to product development emphasising on product and process understanding which improves interaction with regulatory authorities at a scientific level instead of a process level (Varu & Khanna, 2010).

Quality by Design (QbD) is an example of such an approach. The core objective of QbD is to develop a robust formulation and manufacturing process that facilitates any adjustment of potential variables within a design space (International Conference on Harmonisation, 2009a). Critical quality attributes (cQAs) are characteristics that need to be controlled within an appropriate range to ensure product quality. An attribute is critical when it falls outside the acceptable range and has the potential to cause harm to the patient (Food and Drug Administration, 2012). The risk assessment is a science-based process used to identify the material attributes and process parameters that potentially have an effect on the product's cQAs. Subsequently optimisation of these factors, using Design of Experiments (DoE) should be used to determine the relationship among the factors that can influence the product's cQAs. Therefore, QbD provides a holistic approach to product development and optimisation (International Conference on Harmonisation, 2006, 2009a; Roy, 2012; Tanco *et al.*, 2007; Wahid & Nadir, 2013).

As the science of pharmaceutical manufacturing evolves, the application of QbD improves the efficacy and the effectiveness of risk management; decision-making, and creates a regulatory framework that can accommodate process change and improvement. The advantages of this approach are reduced batch failures and an increase in manufacturing flexibility, therefore, patient safety and product efficacy become the focus (Eon-Duval *et al.*, 2012; Nasr, 2007).

The concept of QbD was first outlined in the 1960s and then pioneered by Toyota to improve their early automobiles. Since then, industries like technology, telecommunications, aeronautics and companies manufacturing medical devices began incorporating QbD into their products, which significantly improved their product efficacy (Avellant, 2008). The concept of QbD being adopted by the FDA only occurred at the beginning of the early 2000's. Ethionamide, an immediate release tablet was introduced to the market at about the

same time as QbD, thus creating the opportunity of taking a long existing product i.e. a legacy product, and optimising and reengineering it using the QbD approach.

In order to optimise the formulation and manufacturing process of an immediate release tablet, QbD will be applied. The model drug selected for this study is ethionamide, a second-line drug used in the treatment of multiple drug resistant tuberculosis (MDR-TB) (Gibbon, 2013). At present, there is only one South African pharmaceutical company manufacturing ethionamide 250 mg tablets (Gibbon, 2013). With the growing number of MDR-TB cases in South Africa, the need to fulfil the demand requires the manufacture of the drug on a wider scale. Hence, the need to implement QbD in the manufacture of ethionamide to ensure market demands are satisfied without compromising product quality, effectiveness and cost. Furthermore, QbD provides faster regulatory approval, improves interaction between pharmaceutical industry and regulatory authorities at a scientific level and provides a better overall business model.

1.2 Problem Statement

Traditional pharmaceutical development involves an empirical approach that uses trial and error with selective or limited process optimisation. The development process limits the assurance of quality to in-process and end product testing, requiring regulatory approval when changes to the manufacturing process are made. Batch release is also dependent on the results of these tests. Products formulated using robust QbD principles are void of these limitations. Implementing QbD will aid in designing a robust manufacturing process for ethionamide tablets.

1.3 Aim and objectives

1.3.1 Aim of the study

The aim of this study was to optimise the formulation and manufacturing process of an immediate release oral solid dosage form of an antimycobacterial drug i.e. ethionamide 250 mg tablets, using a systemic approach of applying the principles of QbD.

1.3.2 Objectives

The objectives derived from the aim are therefore to:

1. Establish a Quality Target Product Profile (QTPP) for ethionamide
2. Identify the critical quality attributes (cQAs) of the product
3. Identify the material attributes and process parameters that will impact the product cQAs
4. Apply design of experiments (DoE) to assess the influence of the selected formulation and manufacturing process variables on the product cQAs as follows:

4.1 Create a design space using the outcome of the DoE analysis

4.2 Identify optimal settings of the selected input variables within the design space

5. Propose a formulation and manufacturing process that meets specifications
6. Establish a control strategy after evaluating and optimising the product

CHAPTER 2 – LITERATURE REVIEW

2.1 Introduction

Tablets are the most widely used dosage form due to its convenience in terms of its self-administration, compactness and ease of manufacturing and since oral solid dosage forms do not require sterile conditions they are less expensive to manufacture. Immediate release tablets are designed to disintegrate and release their medicament and are widely used for their better therapeutic availability (Nyol & Gupta, 2013; Reddy *et al.*, 2010). The leading technique of forming tablets is by powder compression that relies on acceptable powder flow into die cavities during compression and in order to improve powder flow, powders are usually granulated. Wet granulation is considered to be the most effective in terms of production time and cost to prepare good granules (Alderborn, 2013). Tablet design is not always a simple and straightforward process and it should meet the needs of the pharmaceutical industry, regulatory bodies and patients. Tablet product design embraces the QbD initiative because this systematic approach incorporates the most current regulatory science thinking (Al-Achi *et al.*, 2013). The criteria in QbD represent a logical progression of activities encompassing the optimisation of pharmaceutical products.

Tuberculosis (TB) remains a major global health problem. According to the World Health Organisation (WHO) (2013), globally 3.6% (95% CI: 2.1 – 5.1%) of new TB cases and 20.2% (95% CI: 13.3 – 27.2%) of previously treated cases are estimated to have MDR-TB. In South Africa, the percentage of new TB cases with MDR-TB is 1.8% (95% CI: 1.4 – 2.3%) and an estimated number of retreatment TB cases with MDR-TB is 6.7% (95% CI: 5.4 – 8.2%). These estimates are unchanged since 2011 (World Health Organisation, 2013a). Development of TB drug resistance caused by the successful adaptation of the pathogen to the first line anti-TB drugs are mainly associated with inadequate therapy, poor patient compliance, interrupted drug supply and inappropriate drug regimens. This has necessitated the selection of second-line drugs to replace the ineffective first line drugs (Brossier *et al.*, 2010; Ongaya *et al.*, 2012; Seyoum *et al.*, 2014).

Ethionamide, a second-line antimycobacterial drug is a structural thionamide analogue of isoniazid, the cornerstone of first line TB treatment. Ethionamide is considered to be the most active anti-TB drug after aminoglycosides and fluoroquinolones and is a component of most of the drug regimens used for treating MDR-TB or suspected MDR-TB (Brossier *et al.*, 2010). Ethionamide is used in combination with other anti-TB drugs and is never and should

not be used alone and is used as part of South Africa's standard regimen to treat MDR-TB and extensively drug resistant TB (XDR-TB) (Gibbon, 2013). Ethionamide is efficacious, relatively non-toxic and has been used since the 1960s (Ongaya *et al.*, 2012). By nature, a large historical database of the API, excipients and process data exists for legacy products. This data can be used to improve product and process understanding and that this information can be used to reengineer and optimise pharmaceutical products (Yacoub *et al.*, 2011).

2.2 Quality by design in the pharmaceutical industry

In 2002, the FDA identified a succession of continuing issues in the pharmaceutical industry that the traditional approach to pharmaceutical development had not solved. These problems include among others, the lack of mitigation of potential risks, and the lack of process understanding. The FDA acknowledged that more control for drug manufacturing processes and better regulatory decision-making are required. As a result, the FDA initiated a course of action that encouraged risk mitigation through predicting potential problems early enough for both manufacturers and regulatory authorities (Rathore & Winkle, 2009; Sangshetti *et al.*, 2014; Woodcock, 2010).

In order to improve the competence and modernise the pharmaceutical industry, in 2004, the FDA initiated a significant initiative titled, "Pharmaceutical cGMPs for the 21st century: A risk-based approach". An important part of this initiative was to shift the focus of the pharmaceutical industry away from the empirical approach of QbT to a more systematic and holistic approach of product development, which is QbD (Ahmed *et al.*, 2014). QbD is a concept first outlined by quality expert Joseph Moses Juran who stated that quality could be planned and that most quality crises and problems relate to the way quality is initially planned. Although QbD has been used before in various industries like the food and automotive industry to enhance and sustain the quality of their products, it is only at the start of the 21st century that the FDA has adopted it (Ahmed *et al.*, 2014; Kale & Bajaj, 2014).

In the past few years, the FDA has made significant progress in implementing the concept of QbD. The FDA's Office of Generic Drugs (OGD) has published reports and presented at public industry forums, focusing and defining QbD specifically for generic companies. The OGD has issued specific product development examples for immediate release and modified release dosage forms, summarising the elements of QbD for implementation. Pharmaceutical manufacturers can implement QbD at the early product development stages,

the pilot scale and at later stages of the commercial scale (Food and Drug Administration, 2011, 2012; Rodriguez-Perez, 2012; Sangshetti *et al.*, 2014).

The International Conference on Harmonisation (ICH) guidelines, Q8: Pharmaceutical Development, ICH Q9: Quality Risk Management and ICH Q10: Pharmaceutical Quality System provides the roadmap on how QbD affects, ensures, maintains and optimises product quality. Implementation of QbD is an innovative challenge for generic companies. The FDA OGD has assigned QbD for generic industry with opportunities for robust processes, cost reduction, lower rate of batch failure and faster science-based regulatory assessment and approval (International Conference on Harmonisation, 2006, 2009a, 2009b; Karanokov *et al.*, 2011; Varu *et al.*, 2010). The concept of building quality into a product is emphasised by the ICH Q8 guideline, which states that "quality cannot be tested into products, i.e., quality should be built in by design" (International Conference on Harmonisation, 2009a).

QbD is the successor to the traditional approach of QbT that the FDA agency has employed until the late 1900s and early 2000s. QbD focuses on building quality into the product through proper planning and highlights that the mere analysis of the final product, post-production, will not suffice. This is achieved by understanding the product and its manufacturing process, the risks involved in product manufacturing and the best method to mitigate those risks. Understanding the product and its process aids in detecting quality-associated problems early enough to permit actions without compromise to cost, available resources or product quality (Ahmed *et al.*, 2014; Rodriguez-Perez, 2012; Sangshetti *et al.*, 2014).

Previous experience is a valuable tool to the accumulation of institutional knowledge. Researchers and formulation teams can learn from the mistakes and successes of historical production data (Roy, 2012). The FDA has stated that QbD is an amalgamation of quality risk management, prior knowledge and experience, and DoE, with emphasis on a control strategy to achieve robustness (Nasr, 2007; Woodcock, 2010). Implementing the principles of QbD does not eliminate product and process variability, however, it allows the formulator and the team to develop and optimise a product that can accommodate the range of variability (Roy, 2012). Hence, the emphasis is on preventing quality problems and not on just correcting them.

According to the FDA's risk-based approach to pharmaceutical development, the goal of the regulatory system is to ensure that patients should not feel hesitant about the quality of their

medicines. In the current state, uncertainty during the review process delays approval of certain drug delivery systems (Food and Drug Administration, 2004). This challenge is expected to increase and is likely to result in multiple review cycles of new drug product applications and delaying the approval of generic drug products in a timely manner. Furthermore, FDA resources spent debating issues relating to acceptable variability, need for additional testing control and determining how specification acceptance limits are established. These debates are avoidable if the application included a more science-based approach, such as QbD. The FDA believes that the ICH guidelines will encourage industry and regulators to increase the use of risk management tools to ensure drug quality and address current pressures felt by both regulatory authorities and the pharmaceutical industry with respect to post approval changes. For the regulatory authority, there is a need to reduce the burden of supplement review and provide review oversight to only certain changes using risk assessment (Food and Drug Administration, 2004; Sangshetti *et al.*, 2014).

Although there is a specification for drug products under both the QbT and QbD, the roles of the specification are completely different. Under QbT, each batch has to be tested against the specification to ensure its quality and manufacturing consistency. Under the QbD approach, specifications are solely used for the confirmation of product quality not manufacturing consistency and process control. (Fraser & Kerboul, 2012; Roy, 2012; Yu, 2008).

There are parallel opportunities of applying QbD to analytical methods as that of manufacturing process. Though it is not adopted by all pharmaceutical industries, it has future perspective because it may become mandatory by regulatory bodies. However, QbD approach by pharmaceutical companies starting 1st January 2013 is recommended. The interim phase of FDA adoption and legal implementation of QbD has given industries opportunities to familiarise and apply QbD principles to current methods (Sangshetti *et al.*, 2014).

South Africa is a member of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) and follows the PIC/S guidelines, as well as the guidelines issued by the South African Medicine Control Council (PIC/S, 2014). 'The Guide to Manufacturing Practice in South Africa*'* by the South African Medicines Control Council is a commonly used guideline by pharmaceutical manufacturers, which has been adapted for South Africa from the PIC/S guideline. It provides a guidance to facilitate compliance to cGMP and encompasses the proactive approach of Quality Risk Management (QRM) and pharmaceutical quality systems discussed in the ICH Q9 and Q10

guidelines, respectively. The GMP Annex 20 corresponds to ICH Q9 guideline on QRM. It provides guidance on the systematic approach to QRM facilitating compliance with GMP and other quality requirements. It includes principles to be used and options for processes, methods and tools which may be used when applying formal risk management approaches. In addition, the GMP guideline highlights QRM as part of development, a concept discussed in the ICH Q8 guideline (Medicines Control Council, 2010). In addition, implementing QbD has several opportunities for the pharmaceutical industry which includes,

- opportunities for facilitating continuous improvement throughout the product life-cycle,
- contributes a better understanding of scientific and risk-based regulatory assessment and approval,
- reduced batch failure rates,
- lower operating costs from fewer failures and deviation investigations, and
- increased predictability of manufacturing output and quality robust processes which gives industry opportunities for robust processes (Varu *et al.*, 2010).

The comparison between the traditional approach of QbT and the modern approach of QbD is summarised in Table 2.1.

Table 2.1 Comparison between the traditional state and the desired QbD state (Adapted: McCurdy, 2011)

Aspect	Traditional state	Desired QbD state
Pharmaceutical development	Empirical	Systematic
Manufacturing process	Secluded: validation on three batches	Adjustable within design space; continuous verification within a design space; focus on control strategy
Process control	In-process testing; offline analysis; end product testing	Process Analytical Technology (PAT); real time release testing
Product specifications	Primary means of quality control; based on batch data	Part of overall quality control strategy; based on product performance

Aspect	Traditional state	Desired QbD state
Control strategy	Mainly by intermediate and end product testing	Risk-based; control shifted upstream
Life-cycle management	Reactive to problems and out of specifications; post approval changes needed	Proactive approach; Continual improvement enabled within design space

The ability of building quality into the product aids in identifying product characteristics that are critical to quality from the perspective of the patient and translates them into the attributes that the drug product should have (Patil & Pethe, 2013). QbD confirms product quality and not just the manufacturing consistency and process control. The initiative challenges the pharmaceutical industry to look beyond end product testing for ensuring product quality and performance (Roy, 2012; Yu, 2008). The product and process design and development can however not be separated because a formulation cannot become a product without a process i.e. a formulation without a process is, for all intents and purposes, a pile of powder (Yu, 2008). The various constituents of QbD are discussed under the following headings and are summarised in Figure 2.1:

- Quality Target Product Profile
- Critical Quality Attributes
- Quality Risk Management
- Design of Experiments
- Design Space
- Control Strategy
- Product Life-cycle Management

Figure 2.1 A flowchart illustrating the process of applying the principles of QbD (Adapted: Travedi, 2012)

2.2.1 Quality target product profile

In terms of the prescribing information goals, the Target Product Profile (TPP) summarises the drug development program. The TPP presents all relevant medical and scientific information in relation to the drug's labelling such as its indication, contraindications, description and clinical pharmacology. The TPP is a tool for setting the strategic foundation for drug development which emphasis the statement 'planning with the end in mind' (Yu, 2008). Addressing these concerns in the early stages of the drug development process reduces failure at the later stages of development. However, the TPP changes as knowledge

of the drug increases. Therefore, updating the TPP is required during the drug development program to reflect new information or any changes in the clinical development program which should include the new safety and efficacy data (Food and Drug Administration, 2007; Sangshetti *et al.*, 2014).

The QTPP is a natural extension of the TPP for product quality. The QTPP is a summary of the quality characteristics of a drug product to ensure that the desired quality of the product is achieved (Food and Drug Administration, 2007). In order to reproducibly deliver the therapeutic benefit promised on the label, the QTPP ensures that the formulation strategies are well established and keeps the formulation effort focused and efficient (Fahmy *et al.*, 2012; Roy, 2012; Sangshetti *et al.*, 2014; Yu, 2008). QTPP may include targets such as impurities and stability, release profiles and other product specific performance requirements (Lionberger *et al.*, 2008).

Generic drugs are similar or bioequivalent to the innovator counterpart with respect to the pharmacokinetics and pharmacodynamic properties. Furthermore, an approved generic drug is considered identical in dosage form, strength, route of administration and intended use (Varu *et al.*, 2010). For the reason that a generic drug product must contain the same active pharmaceutical ingredients (API) as the original formulation, the QTPP can readily be determined from the reference product, scientific literature and pharmacopoeial monographs. The predefined quality product specifications make the product and process design and development more objective and efficient (Charoo *et al.*, 2012; Sangshetti *et al.*, 2014; Varu *et al.*, 2010; Yu, 2008). The FDA recommends that tablets to be swallowed intact should be of a similar size and shape to their reference counterpart for comparable ease of swallowing as well as patient acceptance and compliance with the treatment regimens. This should also be considered when establishing the QTPP (Food and Drug Administration, 2013).

2.2.2 Critical quality attributes

A cQA is a physical, chemical and microbiological characteristic that must be controlled directly or indirectly to ensure the quality of the product (International Conference on Harmonisation, 2009a; Kharad *et al.*, 2011; Yu, 2008). According to the ICH Q8 guideline (2009), cQAs are an essential part of pharmaceutical product development and should be within an appropriate limit, range or distribution. The identification of a cQA from the QTPP is based on the severity of the risk to a patient should the attribute fall outside the appropriate

range (Food and Drug Administration, 2012). The cQAs include aspects that may affect product purity, strength and drug release for oral solid dosage forms. For raw materials, the attributes that may affect the drug product cQAs include those properties such as particle size distribution (PSD) and bulk density (Sangshetti *et al.*, 2014; Yu, 2008). All quality attributes are identified through a risk management system and it is imperative to investigate the subset of cQAs that also have a high potential to influence the formulation and process variables.

2.2.2.1 Critical material attributes and process parameters

Manufacturing processes consist of a succession of unit operations to produce the desired drug product. These discrete activities involve physical changes, such a milling, mixing, granulation or drying. Critical process parameters (cPPs) and critical material attributes (cMAs) are potential variables that may negatively influence product quality if there are any changes in that attribute. In order for processes to reach and maintain its desired quality, potential cPPs and cMAs are controlled. Process parameters include the type of equipment and equipment settings, batch size, operating and environmental conditions. The quality, physicochemical characteristics and quantity of the API, excipients and intermediate bulk material are examples of material attributes (International Conference on Harmonisation, 2009a; Kharad *et al.*, 2011; Yu, 2008). Ideally, data used to identify cPPs should be derived from commercial scale processes to avoid any potential impact of scale-up. However, in reality these studies are often conducted on laboratory or pilot scale batches (Yu, 2008).

2.2.3 Quality risk management

During the development stages, where the formulation and processes have not been established and finalised, there are numerous sources of variability. This is a matter of concern, since statistical methodologies suffer from a limitation in that each variable added to the study, additional experiments need to be completed. This may not always be feasible, as studying too many variables, increase experimental costs (Fahmy *et al.*, 2012). QRM is a key enabler for the application of QbD as it serves as a tool to prioritise the potential cQAs for subsequent evaluation and focuses resources on the perceived critical areas (International Conference on Harmonisation, 2009a).

A hazard is a situation that poses a level of threat. Generally most hazards are dormant with only a theoretical risk of causing harm to people, product, processes or the environment and is an ever-present property (Sandle, 2012). A risk is the combination of the probability of occurrence of harm and the severity of that harm (International Conference on Harmonisation, 2006).

QRM is a systematic means of identifying, scientifically evaluating, and controlling potential risks to product quality throughout its life-cycle (International Conference on Harmonisation, 2006; Rodriguez-Perez, 2012). An iterative process of QRM and formal experimental designs identifies the significant cMAs and cPPs. Predicting the manner in which the sources of variation of the identified cMAs and cPPs will impact on the product cQAs and the ability to control these variables is the primary goal of process understanding (International Conference on Harmonisation, 2006; McCurdy, 2011; World Health Organisation, 2010).

The challenge for pharmaceutical teams is identifying the selected formulation and manufacturing input variables that potentially have the greatest impact on the product cQAs. The approach of risk assessment centres on identifying a risk, assessing the severity of harm and calculating the probability of the risk occurring. Attempts are made to mitigate the risks by eliminating the hazard, reducing the potential for harm and/or monitoring it. Therefore, the above constituents a proactive method to risk assessment (Sandle, 2012). Information used for risk identification and analysis can include historical data, theoretical analysis, informed opinions and the concerns of those impacted by the decisions (International Conference on Harmonisation, 2006).

The ICH Q9 guideline (2006) highlights the various risk management tools that pharmaceutical industries and regulators may use to access and manage risks. Examples include, flow charts, Ishikawa (fish bone) diagrams, Fault Tree Analysis (FTA), Failure Mode Effects and Criticality Analysis (FMECA), Hazard Analysis and Critical Control Points (HACCP) and Failure Mode Effects Analysis (FMEA) (International Conference on Harmonisation, 2006). Each QRM tool has its distinct characteristics and not one tool or set of tools is acceptable to every situation of QRM. The QRM tools selected should be compatible with the data and should be capable of delivering and communicating a cohesive risk control plan. Successful QRM tool selection begins with an awareness of the interrelationship between understanding the risks and the choice of the risk management tool. Risk understanding influences QRM tool selection and similarly, QRM tool selection enhances risk understanding. However, this interrelationship may seem illogical as it is premature to select a QRM tool before knowing the nature of the risk to be assessed. To

overcome this challenge, the multidisciplinary team involved in the risk assessment should define the scope and boundaries of the risk assessment and identify available data to support the assessment. QRM tools can be selected by an informal means such as an unstructured discussion, therefore, QRM leverages lessons from previous experience of a multidisciplinary team (Murray & Reich, 2011).

QRM tool selection is rarely an objective process and each QRM has its unique attributes. QRM tools are designed to translate data into knowledge that enhances the overall quality decisions and risk controls (Murray *et al.*, 2011). There is a spectrum of methods available for assessment, ranging from quantitative to qualitative. Qualitative exposure assessments are descriptive or categorical, whereas quantitative assessments are mathematical analysis of numerical data. Quantitative approaches can be ranked or measured against another and compared to a predetermined scale. A qualitative assessment may be undertaken as part of the first evaluation to determine if the risks are significant enough to warrant a more detailed analysis. At minimum the evaluation criteria should address the probability and severity of risk (Sandle, 2012). Table 2.2 shows the risk matrix with evaluation levels for probability and severity to potential failures (Frank *et al.*, 2008).

Table 2.2 Two level risk matrix with evaluation for probability and severity (Source: Frank *et el.,* 2008)

	Probability		
Severity	**Low**	**Medium**	**High**
High potential to impact product quality	Medium	High	High
Medium potential to impact product quality	Medium	Medium	High
Low potential to impact product quality	Low	Low	Medium

*This table has been amended and sourced from the Product Quality Research Institute (PQRI), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, United States of America; website: http://www.pqri.org/index.asp

The risk assessment of the API, excipients and manufacturing process evaluates the impact of each material attribute and process parameter on the product cQAs. According to ICH Q9 guideline (2006), three fundamental questions are often helpful to define the risks:

- What is the risk?
- What is the likelihood of the risk occurring?
- What is the severity of the risk should it happen?

The relative risk that each attribute presents is ranked using the qualitative descriptors 'low', 'medium' or 'high'. The 'low' risk attributes do not require any further analysis, whereas the 'high' risk attributes are unacceptable and require further analysis. In general, 'medium' risks are also considered acceptable; however investigations may be conducted in order to reduce such risks (International Conference on Harmonisation, 2006). Table 2.3 explains the relative risk ranking system.

Table 2.3 Overview of the relative risk ranking system (Adapted: Food and Drug Administration, 2012)

Risk Ranking	Acceptable? (Y/N)	Further investigation? (Y/N)	Justification
Low	Y	N	Generally acceptable risk attributes
Medium	Y	Y	Further investigation may be needed in order to reduce risk.
High	N	Y	Risk attributes are unacceptable and will require further analysis

Some of the simpler QRM tools are flow charts and Ishikawa (fish bone) diagrams. The flow chart method shows how actions are interrelated and is able to integrate interfaces into the flow providing a simple visual representation of the steps involved. Therefore, this method facilitates understanding, explaining and systematically analysing complex processes and associated risks. The advantage of the Ishikawa diagram is systematically displaying all the influencing variables on one page. Fish bone diagrams are more effective for analysing a

single step rather than complex systems, which is a disadvantage when using this risk assessment tool (Sandle, 2012).

FTA is a logical diagram that shows the relation between system failure as well as failures of the components of the system and is widely used in the engineering industry. Thus, FTA provides a graphical depiction of all chains of failure of a system and results in a fault tree with a varying number of branches and sub-branches, depending on its complexity. At each level in the tree, combinations of the fault modes are described. However, the challenge to using this QRM tool is, if the wrong cause is selected, the sub-branches may fail to detect the actual issue. Furthermore, FTA is a better retrospective analytical tool rather than a preventative measure (Sandle, 2012).

FMEA is a method whereby each potential failure mode in a system is analysed to determine its effects on the system. The power of FMEA lies in its ability to prioritise risks based on the risk severity, probability, and ability to detect the risks and is a popular and well-accepted QRM tool in the pharmaceutical industry (Murray *et al.*, 2011). The risks are rated on a scale of 1 to 5 or on a scale of 1 to 10 for each of the causes i.e. severity, probability and detection. Based on this scaling system, a high severity event would be given a high score, whereas a low severity event would be given a score of 1. With probability, if something were quite certain to happen, then a higher score would be given, whereas if something were very unlikely to happen, then a score of 1 would be given. With detection, if there is a good detection system in place, a score of 1 is given, whereas a non-existent detection system would be given a higher score. These three factors are multiplied together to give a risk priority number (RPN). The RPN is generated for all risk factors and the factors with the highest RPN follows greater priority and are evaluated first. With the calculated RPN, a cut-off value is often used, whereby each failure mode above this value must be addressed as a potential major risk. Whereas failure mode with a RPN below this value are a lower risk and do not require immediate action (Sandle, 2012). A more detailed numerical scoring for prioritising risks may be completed according to ICH Q9 Guideline “Quality Risk Management ICH Q9 Annex I: Methods and Tools” (2006).

When the FMEA is extended by a criticality analysis, the technique is then called FMECA. In order for FMECA to be performed, the product or process specification should be established. FMECA can identify places where additional preventative actions might be appropriate to minimise potential risks (International Conference on Harmonisation, 2006).

HACCP is a management system, developed by the food industry. Product or process safety can be addressed through the analysis and control of biological, chemical and physical hazards from raw material production to manufacturing, distribution and use of the finished product. HACCP focuses more on prevention and can be used to reduce the reliance upon in-process monitoring or end product testing. HACCP systems are generally useful for examining changes, such as advances in equipment design, processing procedures, or technological developments. The advantages of the HACCP approach includes a systematic overview of the process for the evaluation of each processing step, allows each step to examine the possible risks, and allows for the specification of the measures required for controlling each risk. Unlike the FMEA, HACCP cannot be used to rank or prioritise risks and is also less effective for focusing on an aspect for the process, as the objective of the HACCP is to map out an entire process (Sandle, 2012).

QRM does not take precedence over industry's obligation to comply with regulatory requirements. However, effective QRM facilitates better and more informed decisions, provide regulators with greater assurance of a company's ability to deal with potential risks and potentially affects the extent and level of direct regulatory oversight. In addition, QRM may facilitate better use of resources by manufactures and regulators (Rodriguez-Perez, 2012).

While an effective risk management system is essential in ensuring that a process yields products of acceptable quality, these systems are not able to ensure that the process being managed is optimal. This requires that the process itself is designed in a way that ensures quality products are produced reproducibly. This type of process design can be facilitated more effectively using DoE along with a host of analytical and statistical tools that will be discussed in the following sections.

2.3.4 Design of Experiments

Optimisation refers to the science of allocating available resources to the best possible effect. The development and optimisation of a pharmaceutical product are important techniques whereby the cMAs and cPPs are analysed in order to achieve the desired product quality (Sharma & Pancholi, 2011).

Formulation of pharmaceutical products was previously performed mainly on the basis of the experience of the formulator and often in combination with the univariate method. The

traditional method of OFAT is less dependable and more time consuming. The drawback with the traditional approach is that to keep the number of experiments on an adequate level, only a few variables can be used at the cost of omitting valuable information. It is challenging to evolve an ideal formulation using this classical technique since the combined effects of the independent variables are not considered (El-Say *et al.*, 2011; Mahdavi *et al.*, 2013; Wahid *et al.*, 2013).

DoE is a structured and organised method to determine the relationship among factors that influence the response variables. The applications of DoE are often sequential in nature. A well designed DoE provides valuable information and can result in identification of cause and effect relationship between variables, therefore, these systematic techniques are preferable. In today's competitive market, DoE in product development and optimisation are becoming increasingly necessary because they are quick and cost-effective (Ahmed *et al.*, 2014). Analysis of data from designed experiments enables formulation scientists to create a mathematical model and contour plots that represent the cMAs and cPPs affecting the product cQAs (Myers & Montgomery, 1995; Sharma *et al.*, 2011; Wahid *et al.*, 2013).

The overall approach towards process characterisation involves three key steps (International Conference on Harmonisation, 2006; Myers *et al.*, 1995; Yu, 2008).

1. Phase zero: Screening experiments
2. Phase one: Pivotal trial experiments
3. Phase two: Identifying the optimal setting of the selected input variables

Attention to the experimental design is important as the validity of an experiment is affected by its construction and execution. An experimental design involves selecting the combination of factors (input variables) and the levels of each factor to be tested. The formulation scientist may choose a number of experimental designs such as a full factorial, fractional factorial, orthogonal composite or central composite design to name a few (Myers *et al.*, 1995).

Factorial designs are widely used in experiments involving several factors on the response variables. A special case of the factorial design where each factor of the *k* factors of interest has only 2 levels are named 2^k factorial designs. These are often used to fit a first order response surface model and are basic building blocks used to create other response surface designs. However, two level factorial designs are inherently constrained to identify a first

order linear model between factors and the response variable; and it will be inadequate to fully characterise data if the relationship between the response variable and one or more factors is non-linear (Ledolter & Swersey, 2007; Myers *et al.*, 1995; Reddy, 2011).

As the number of factors in a 2^k factorial design increases, the number of runs required increases exponentially. Attempting to study all the possible contributing factors becomes unfeasible because as the number of factors in a 2^k factorial design increases the number of experimental runs required increases. As a result, this may exceed the resources of most experimenters. Fractional factorial designs may be used in these circumstances to depict value information from fewer runs and is among the most widely used experimental designs in industrial organisations. A major use of fractional factorials is in screening experiments (Dashtianeh *et al.*, 2013; Myers *et al.*, 1995).

Screening experiments are designed to investigate the factors with the intention of reducing the list of candidate factors to a significant few so that the subsequent experiments will be more efficient. Screening adds value in developing a design with a minimal number of experiments yet capturing the target formulation and processing conditions. The pivotal experiments determine if the levels of the significant factors from the screening experiments will produce a response that is near the optimum or in a region that is in close proximity to the optimum. Phase two of DoE begins with designing a model that will accurately approximate the true response function. The predictive model may be analysed to determine the optimum settings (Myers *et al.*, 1995).

Response surface methodology (RSM) is an efficient mathematical approach that is widely applied in product optimisation. RSM explores the relationship between several input variables and one or more response variables. A central composite design (CCD) is an experimental design useful in RSM in which a multi-level factorial design, augmented with axial points and central points allows estimation of polynomial effects and permits the design to be rotatable. A Box-Behnken design (BBD) is an efficient option to CCD. The BBD is a proficient 3-level design for second order responses and is comparable in a number of design points to the CCD, when there is three or four input variables ($k=3$, $k=4$). There are however, no BBD when the experimental plan involves two input variables ($k=2$) (Myers *et al.*, 1995). The use of RSM in the pharmaceutical industry aids in mapping the response surface over a particular region of interest, thus predicting, in advance, the changes in response that will result if there are any adjustments to the input variable. When the mathematical relationship between the factors and the response needs to be fully

characterised, these multi-level designs are more appropriate, as they are flexible and can take a wider variety of functional forms (Dashtianeh *et al.*, 2013; Myers *et al.*, 1995).
Full factorial designs and CCD models perform equally well and both experimental designs lead to the same conclusions regarding the optimum setting of the selected input variables. However, the CCD tends to be more conservative than the factorial design. Theoretical consideration and the fact that the CCD requires fewer experimental units, the range of experimental data is wide enough to detect a statistically significant variation; thus justifying the recommended use of CCD. In general, all required information should be obtained from as few experiments as possible while not compromising the desired goals (El-Say *et al.*, 2011; Myers *et al.*, 1995; Panneton *et al.*, 1999).

There has been a significant increase amongst industrial organisations in the United States of America and in Europe using DoE in quality improvement. Many industries like the automotive, biotechnology, pharmaceutical, medical devices and chemical industries where design methodology has been implemented, has shown an improvement in their ease of manufacture, higher reliability and enhanced field performance (Ahmed *et al.*, 2014; Dashtianeh *et al.*, 2013). Although the concepts of QbD, RSM and QRM are not new concepts to quality improvement, however the culmination of these concepts is unique to the QbD paradigm in the pharmaceutical industry as adopted by the FDA. Figure 2.2 illustrates the juxtapose relationship between quality risk assessment and DoE.

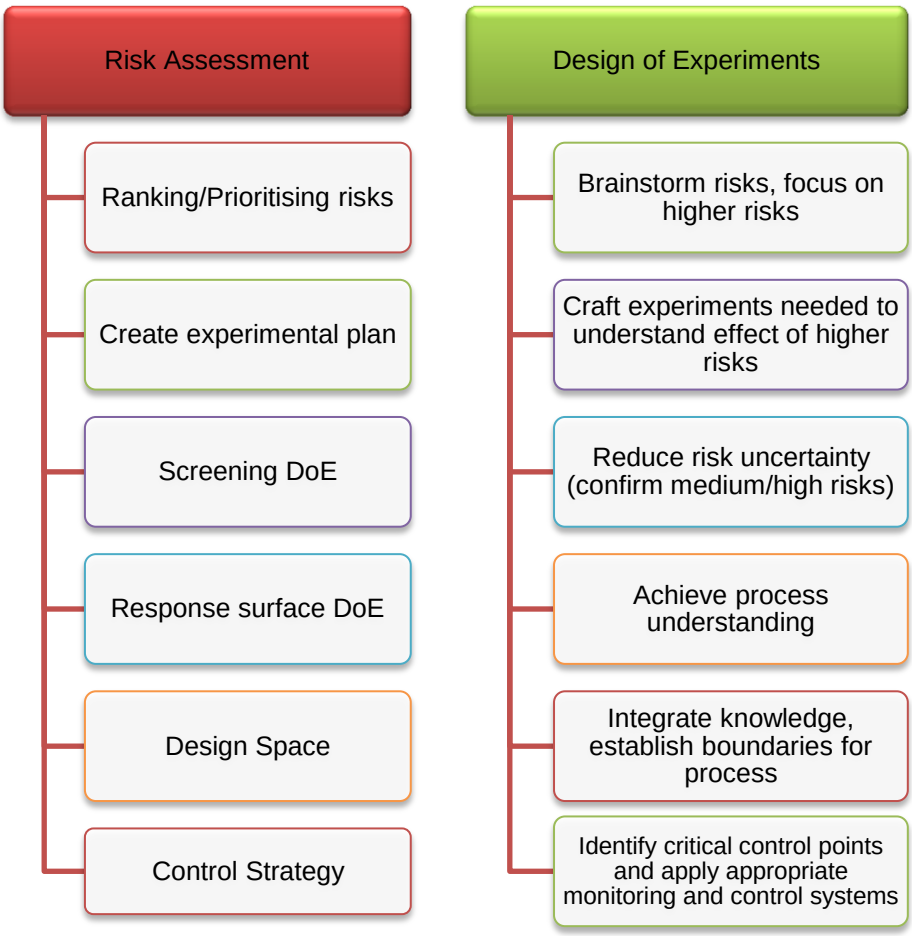


Figure 2.2 Representation of the relationship between risk assessment and DoE (Adapted: McCurdy, 2011)

2.3.4.1 Creating a design space

A combination of proven acceptable ranges does not constitute a design space. However, a proven acceptable range based on univariate experimentation provides useful information about the process and is useful during the initial risk assessment (International Conference on Harmonisation, 2009a). The risk assessment and DoE leads to an understanding of the linkage and effects of cPPs and cMAs on product cQAs. The QbD approach has encouraged formulation scientist to reach the desired state of drug manufacturing. The emphasis has changed from the need to demonstrate that the products will consistently meet tight specifications to a new situation of being able to demonstrate that the product quality is controlled within a broader design space (International Conference on Harmonisation, 2009a; Karanokov *et al.*, 2011).

A design space is a multidimensional combination and interaction of material attributes and process parameters that have proven to provide quality assurance. The ranges of the cMAs and cPPs and their impact on the response outcome defines the design space. In addition, a design space can be described through mathematical relationships i.e. prediction algorithm, which is a mathematical representation of the design space. Regardless of how a design space is established, it spans the entire process, providing more operational flexibility. The result is that production processes are adaptable and scale up of pharmaceutical batches should be straightforward (International Conference on Harmonisation, 2009a; Karanokov *et al.*, 2011). However, design space may be potentially scale and equipment dependent as the design space determined at small scale may not be relevant to the process at commercial scale. It may be necessary to provide additional information to demonstrate that the design space is scale independent, if possible in terms of dimensionless numbers (Kayrak-Talay *et al.*, 2013; Mukharya *et al.*, 2012; Travedi, 2012).

The design space is subjected to regulatory approval once the design space has been established. Movement within the design space is not considered a change (from a regulatory filing perspective). In certain instances, the parameters that positioned at the perimeter of the design space are termed the edge of failure. It can be helpful to determine the edge of failure for cPPs and cMAs, beyond which the relevant quality attributes, cannot be met. Movement outside the design space is the proposed area for cMAs and cPPs not meeting identified product cQAs and would generally require a regulatory change post approval. Changes made in the formulation and manufacturing process during development and life-cycle management should be considered as opportunities to gain additional knowledge and further support the establishment of the design space (Dashtianeh *et al.*, 2013; International Conference on Harmonisation, 2009a; Kharad *et al.*, 2011; Roy, 2012).

2.3.4.2 Control Strategy

It is essential to determine the edge of failure. In these situations, it is necessary to set boundaries at acceptable tolerance intervals around the edges of failure to better mitigate the risks near such edges. The control strategy is a planned set of controls that assures that the manufacturing process will remain in control within the normal variation in material attributes and process operating ranges (International Conference on Harmonisation, 2009a; McCurdy, 2011). Using risk assessment in creating the control strategy is unique to the QbD paradigm. The control strategy justifies that the culmination of in-process controls, input material specifications, container closure systems and post-production product testing will

produce a quality drug product. The investigation of QRM and DoE collates an appropriate control strategy (Avellant, 2008; McCurdy, 2011; Roy, 2012; Yu, 2008).

2.3.4.3 Life-cycle Management

Although QbD may seem like a predominantly statistical-focused approach, this concept is much broader (Fraser *et al.*, 2012). QbD is a product and process life-cycle approach founded on continuous improvement as illustrated in Figure 2.3.

Figure 2.3 Illustration demonstrating the continuous improvement of product and process performance using QbD and Product Life-cycle Management (Source: Fraser & Kerboul, 2012)

QbD is a cycle in which product and process design and performance create a close loop of knowledge and continuous improvement. Even in a vast complex pharmaceutical environment, product life-cycle management (PLM) makes production more efficient. The

PLM platform brings together all relevant elements and delivers a structured process by which all disciplines can work together to proactively improve product quality. The ability to build knowledge, from every aspect of the process contributes to the success of PLM. Using structured approaches reduces product and process variation, reduces risks and allows flexibility for continuous improvement within a design space. In the pharmaceutical industry, this reduces regulatory oversight ensuring that the natural outcome of QbD and PLM are safe and efficacious products (Fraser *et al.*, 2012; International Conference on Harmonisation, 2009a, 2009b).

The ICH Q10 guideline of pharmaceutical quality system, provides tools to facilitate continual improvement of drug products such as change management systems, corrective action and preventative action (CAPA) systems, quality monitoring systems, and management review systems (International Conference on Harmonisation, 2009b). PLM has proven to be an effective tool, not only in the pharmaceutical industry, but also in industries with human safety issues, aerospace regulations and the automotive industry. Companies implementing PLM are reaping the benefits of fewer problems, lower cost, higher yields, employees equipped to make worthy decisions and are more confident during the audit process (Fraser *et al.*, 2012; Nasr, 2011). Continuous improvement is an essential element in a modern quality system with an aim to improve efficacy by optimising a process and reducing waste in production. Executing these methods in a structured manner focuses on reducing variability in processes and product quality characteristics. Therefore, the fundamental design of a manufacturing process does not change. The pharmaceutical manufacturing for the 21st century provides a systems review of the current system and describes the desired state and explains how the combined work products of the cGMP initiative are positioned to provide a comprehensive set of regulatory tools to facilitate the journey to the desired state i.e. the design space (Food and Drug Administration, 2004).

2.3 Tablet Manufacturing Process

The most convenient method and preferred method of drug administration for the vast majority of patients is via the oral route. The ease of delivery, combined with a relatively rapid onset of action, along with lower cost per dose, makes this route an ideal way of augmenting the therapeutic effects. Amongst the oral dosage forms, tablets are the most widely used due to its convenience in terms of compactness and self-administration by patients (Pathak *et al.*, 2011).

The purpose of tablet design is to create a drug delivery system that meets specific functional and performance criteria. However, tablet design is not always simple and straightforward. The optimum performance of the tablet depends on a number of criteria that often have competing objectives, which results in complex and significant interaction effects that cannot be easily predicted or managed (Al-Achi *et al.*, 2013; Pathak *et al.*, 2011). For example, the hardness influences the compaction of substances inside the tablets; the higher the hardness, the higher the compaction of the tablets. The higher compaction may cause a decrease in the porosity of the tablet matrix. Hence, the tablets with high compaction have a high ability to retard the water penetration into the core, resulting in a slower drug release, and vice versa (Nanjwade *et al.*, 2010; Saeio *et al.*, 2007). Therefore tablets must have an acceptable degree of hardness and friability to prevent breakage prior to use, in addition the tablets should disintegrate in the required time period and the API should be released in order to exhibit its therapeutic effect.

Commonly, tablets are formed by powder compression. An applicable method of improving the powder flow is granulation (Alderborn, 2013). Wet granulation is a common unit operation in the pharmaceutical industry, a complex process with many parameters which may affect product quality (Kayrak-Talay *et al.*, 2013). Wet granulation is a process in which fine particles are bound together by forming agglomerates by agitation of the powder by convection in the presence of a liquid, followed by drying. High shear mixers are often equipped with an impeller turning at moderate to high speeds which facilitates the contact between the mass of the fine particles and the binder mass and an additional smaller chopper blade turning at high speeds cutting down large agglomerates that can form in the process. Wetted powder particles are mixed, densified and agglomerated under the action of shear and compaction forces imposed by the impeller (Chitu *et al.*, 2011b; Kayrak-Talay *et al.*, 2013).

Granulation improves mixing homogeneity, improves tablet compression by adding a solution binder, increases bulk density, improves the flow characteristics of formulations consisting of cohesive powders, reduces dust problems and reduces segregation. Wet granulation is an effective means in terms of production time and cost to produce granules of an acceptable quality. Of the various equipment used for wet granulation, high shear mixer granulators and fluidised bed granulators are most common (Alderborn, 2013; Kayrak-Talay *et al.*, 2013).

The function and characteristics of excipients are critical to tablet formulation, as this may affect the product proficiency. Any incompatibilities with the excipients may hinder the

excipients to perform their specific function; therefore information on excipient performance can be used to justify the use of those excipients. The successful formulation of a stable and effective solid dosage form depends on the careful selection of excipients (Rus *et al.*, 2012). The goal of product design is to gain timely regulatory approval that meets the needs of patients, health care providers and manufacturing industries. In order to meet and sustain this goal, product design must incorporate the most current regulatory science thinking which is often provided in the FDA and ICH guidance documents. Therefore, product design embraces the QbD initiative (Al-Achi *et al.*, 2013).

In order for effective formulation and product design to take place, not only should a thorough knowledge of the manufacturing process be obtained but also the API. A review of ethionamide, the model drug, with reference to its pharmacological and physicochemical properties will be discussed and forms part of understanding the product as a whole.

2.4 Review of ethionamide

2.4.1 Pharmacological profile of ethionamide

2.4.1.1 Mechanism of action

Ethionamide is a prodrug that needs to be activated by mycobacterial enzymes to exert its antimycobacterial effect. The gene responsible for this activation step is *EthA*, which encodes a NADPH-specific FAD-containing monooxygenase that oxidises ethionamide to form an s-oxide metabolite (ETA-SO, in Figure 2.4). The oxidised form adducts with NAD+ which binds and inhibits the enzyme, *InhA,* which is an NADH-dependent enoyl-acyl carrier protein reductase of the fatty acid biosynthesis II system required for mycolic acid synthesis which is involved in the cell wall synthesis of *Mycobacterium tuberculosis*. Inhibition of *InhA* leads to cell wall defects that rapidly kill *Mycobacterium tuberculosis,* as shown in Figure 2.5 (Brossier *et al.*, 2010; Frenois *et al.*, 2004; Gray, 2013; Vale *et al.*, 2012; Wolff & Nguyen, 2012).

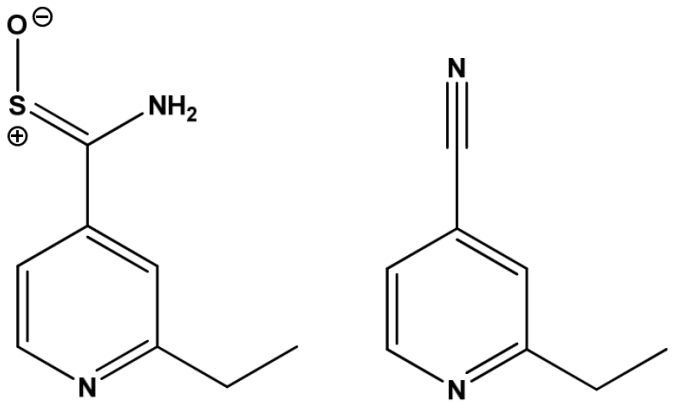


Figure 2.4 Chemical structure of ethionamide (left) and its s-oxide metabolite (right) (Source: Vale *et al*., 2012)

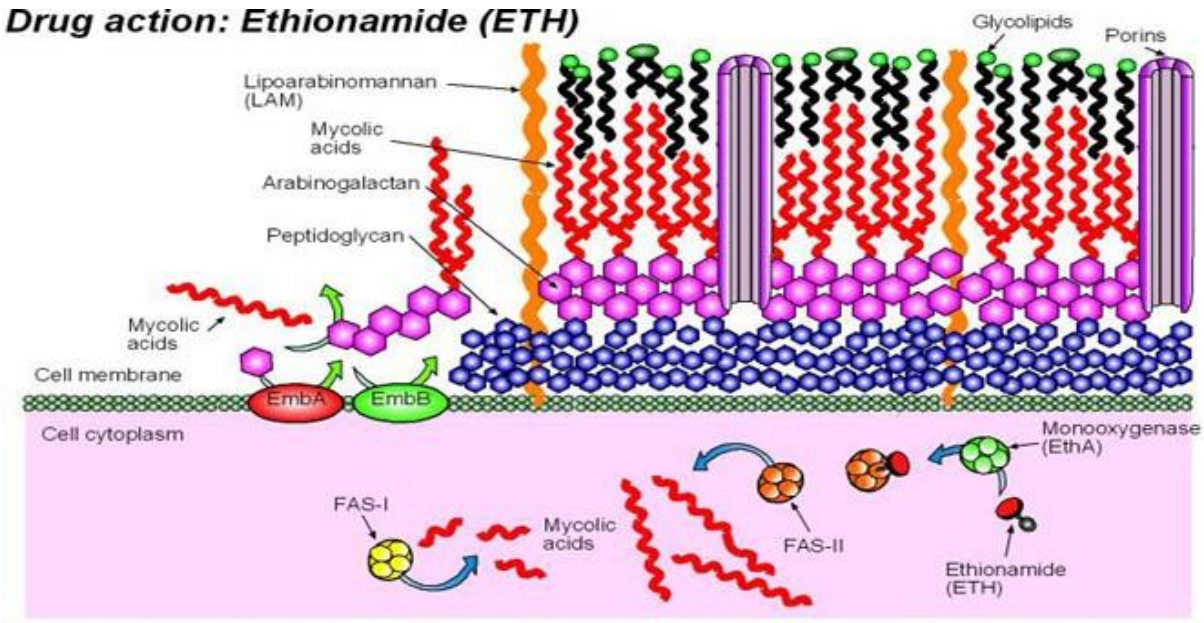


Figure 2.5 Graphical illustration of the mechanism of action of ethionamide (Source: Gray *et al*., 2013)

2.4.1.2 Side Effects

The most common side effects include, gastrointestinal (GI) effects, nervous system effects and hepatic effects. The poor GI tolerance causes nausea, vomiting, diarrhoea, abdominal pain, metallic taste and excessive salavation. Side effects of the central nervous system

include psychotic disturbances, mental depression, restlessness, drowsiness and dizziness. Ethionamide is hepatotoxic and is generally reversible on discontinuation of treatment. The rare side effects include hypoglycaemia, gynecomastia, alopecia, impotence, menorrhagia and hypersensitivity reactions including rash and photosensitivity (Antituberculosis Agents, 2001; Deck & Winston, 2012; Dipiro *et al.*, 2011; Gibbon, 2013; Sweetman, 2011).

2.4.1.3 Pharmacokinetics

An estimated 80% of an oral dose of ethionamide is absorbed from the GI tract and its absorption is unaffected by food. It is also widely distributed into bodily tissues and fluids, reaching concentrations in the cerebrospinal fluid equal to those in the plasma with 30% of the drug bound to plasma proteins. Ethionamide is extensively metabolised in the liver to the active and inactive metabolites, with 1.0% unchanged drug eliminated renally. Plasma T_{max} is reached at 2 hours with a C_{max} of 2 µg/ml. The plasma half-life (t½) of ethionamide is 2 to 3 hours (Antituberculosis Agents, 2001; Gibbon, 2013; Thee *et al.*, 2011).

2.4.2 Physicochemical properties of ethionamide

The chemical names for ethionamide include, 2-ethylpyridine-4-carbothioamide; 2-ethyl-4-thiopyridylamide; ethionamide; 2-ethylisonicotine thioamide; 2-ethyl-thioisonicotinamide; 2-ethylisonicotinthioamide; 2-ethylthioisonicotinamide (Pubmed Compound Database, 2014).

Ethionamide contains not less than 98.5% and not more than the equivalent of 101.0% of 2-ethylpyridine-4-carbothioamide, calculated with reference to the dried substance (British Pharmacopoeia Commision, 2014).

Ethionamide is composed of small yellow crystals or a yellow crystalline powder (Ph. Eur.6.8) that has a slight sulphide-like odour. Ethionamide is soluble in methyl alcohol; sparingly soluble in alcohol; practically insoluble in water and is achiral and non-hygroscopic (Sweetman, 2011; World Health Organisation, 2005). It has a partition coefficient (octanol/water) Log P value of 0.3966 and a dissociation constant (pyridyl nitrogen) pKa value of 4.49 (Pubmed Compound Database, 2014). The chemical structure of ethionamide is shown in Figure 2.6 below.

Figure 2.6 Chemical structure of ethionamide [2-ethylpyridine-4-carbothioamide] (Source: Sweetman, 2011)

The molecular weight and chemical formula of ethionamide is $C_8H_{10}N_2S$ = 166.24 g/mol (Sweetman, 2011). Ethionamide has a melting point of ~ 163 °C ("Ethionamide," 2008) and the pH of a 1% slurry in water is between pH 6.0 to 7.0 (Sweetman, 2011). Based on the revised WHO criteria for Biopharmaceutics Classification System (BCS), ethionamide is classified as a Class III drug (high solubility, low permeability) (World Health Organisation, 2005).

2.4.4 Marketed products

The international markets of oral formulations containing 250 mg ethionamide are listed in Table 2.4. To date, there is only one formulation available in South Africa.

Table 2.4 International commercially available ethionamide 250 mg tablets

Brand names	Pharmaceutical manufacturers	Country
Ethatyl	Sanofi-Aventis	South Africa
Ethide	Lupin	India
Ethiokox	Radicura	India

Brand names	Pharmaceutical manufacturers	Country
Ethionamide Medopharm	Medopharm	Thailand
Ethomid	Vesalius Pharma	Colombia
Etionamida	AC Farma	Peru
Etomid	Macleods	Georgia
Eton	Umeda	Thailand
Etyomid	Koçak	Turkey
Myobid	Panacea	India
Trecator	Wyeth	United States of America
Tubermin	Meiji Seika Kaisha	Japan

2.4.5 Challenges to previous formulations

In 2005, Wyeth pharmaceuticals in the United States released notification that Trecator – SC sugar coated tablets have been reformulated to a film coated tablet and renamed to Trecator. The new formulation was designed to improve dissolution and stability (Tucker, 2005). To compare the bioavailability of film-coated and sugar-coated formulations of ethionamide, 40 healthy individuals were assigned to receive either of the formulations, in randomised order. Seven subjects reported a total of 10 adverse events (5 with each formulation), all of which were mild and considered possibly related to drug treatment. None of the events resulted in discontinuation from the study. Comparing the area under the curve (AUC) values, the formulations were bioequivalent. The mean standard deviation (SD) pharmacokinetic properties observed with the film- and sugar-coated tablets, respectively, where C_{max} was 2160 (614) and 1484 (636) ng/ml and T_{max} was 1.0 (0.5) and 1.5 (0.9) hours (Korth-Bradley *et al.*, 2014).

The implication of these differences in pharmacokinetics may potentially lead to patient intolerance when the film coated formulation is introduced at the same initial dose as the

sugar coated formulation. It was advisable that health care professionals monitor patients and have their dosages re-titrated when switching to the film coated formulation (Tucker, 2005).

CHAPTER 3 – METHODOLOGY

3.1 Introduction

Tablets are a common and widely used pharmaceutical dosage form in which the drug substance is in its prescribed amount, so it is more stable, compact and easier to administer. Patient compliance, high precision dosing and manufacturing efficiency makes tablets the dosage form of choice (Harbir, 2012; Nyol *et al.*, 2013; Pathak *et al.*, 2011). The manufacturing process should be controlled to ensure tablets are aesthetically appealing and have the physical stability to maintain their physical attributes, meet the predetermined specifications and yield their therapeutic efficacy.

Designing a product and its manufacturing process to consistently deliver the intended performance of the product is the focus of pharmaceutical development. QbD are void of the limitations of the traditional approach to pharmaceutical development and optimisation and focus on building quality into the product. Previous experience and knowledge provide the scientific understanding to support the establishment of the design space, specifications and manufacturing controls (International Conference on Harmonisation, 2009a). Final properties of tablets depend on the choice of the excipients and the process parameters of both the granulation process and tablet equipment. This chapter will discuss the application of QbD to the optimisation of ethionamide tablets, its manufacturing process and quality testing.

3.2 Application of quality by design

Institutional knowledge is key to the application of QbD (Roy, 2012). A panel discussion was arranged with subject matter experts to discuss the various sectors of the QbD paradigm. The panel consisted of at least eight personnel who had pharmaceutical experience in either technical support, production or regulatory affairs. The experience of the team of formulation scientists ranged from 3 to 40 years in the industry.The team provided insight and expertise based on their knowledge and experience in the pharmaceutical industry, about this product and other products that may assist with understanding the product. The discussions were structured and carried out according to the ICH Q8 and Q9 guidelines and the template examples as shown in the FDA document, “Abbreviated New Drug Application (ANDA): immediate release dosage forms” (Food and Drug Administration, 2012; International Conference on Harmonisation, 2006, 2009a). Meetings were scheduled for 1 to 2 hours and

were held at Aspen Pharmacare, Port Elizabeth. The number of meetings required were subject to covering all components of the QbD process. The templates were subject to alteration to be more specific to the study; such alterations were based on the outcome of the discussion and results. The design involved, establishing a QTPP, identifying the product cQAs, performing a risk assessment, performing DoE and establishing a control strategy. Figure 3.1 illustrates the plan of work for optimising ethionamide tablets and details of each step will be discussed in the following sections.

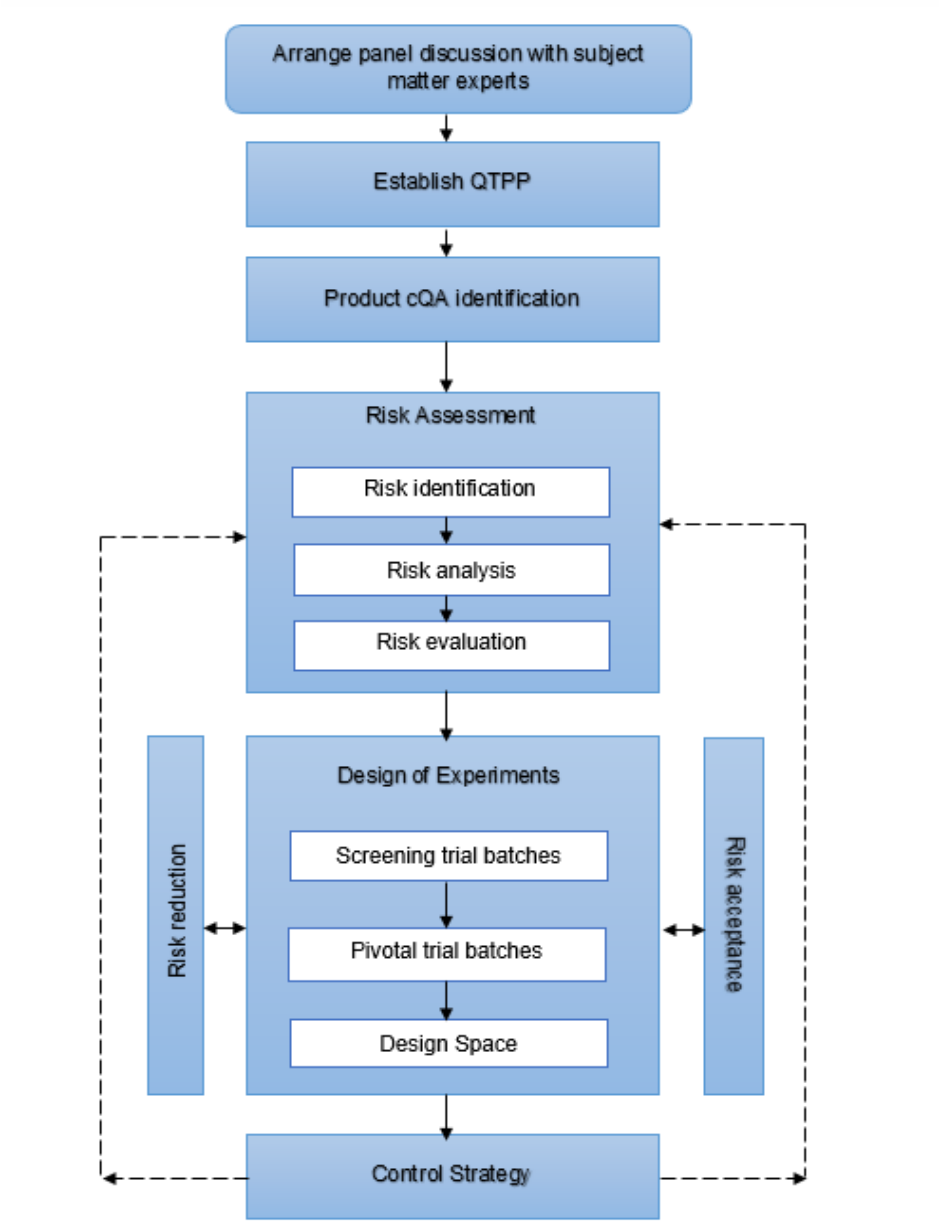


Figure 3.1 A flow diagram illustrating the plan of work for optimising ethionamide tablets

3.2.1 Establishing a quality target product profile

The purpose of this exercise was to identify the quality characteristics that ethionamide should possess in order to deliver the desired therapeutic effect as assured on the product label. The QTPP will present all the relevant medical and scientific information to ensure that the desired quality, and thus efficacy and safety of ethionamide tablets are achieved. The elements of the QTPP are listed in Figure 3.2 below.

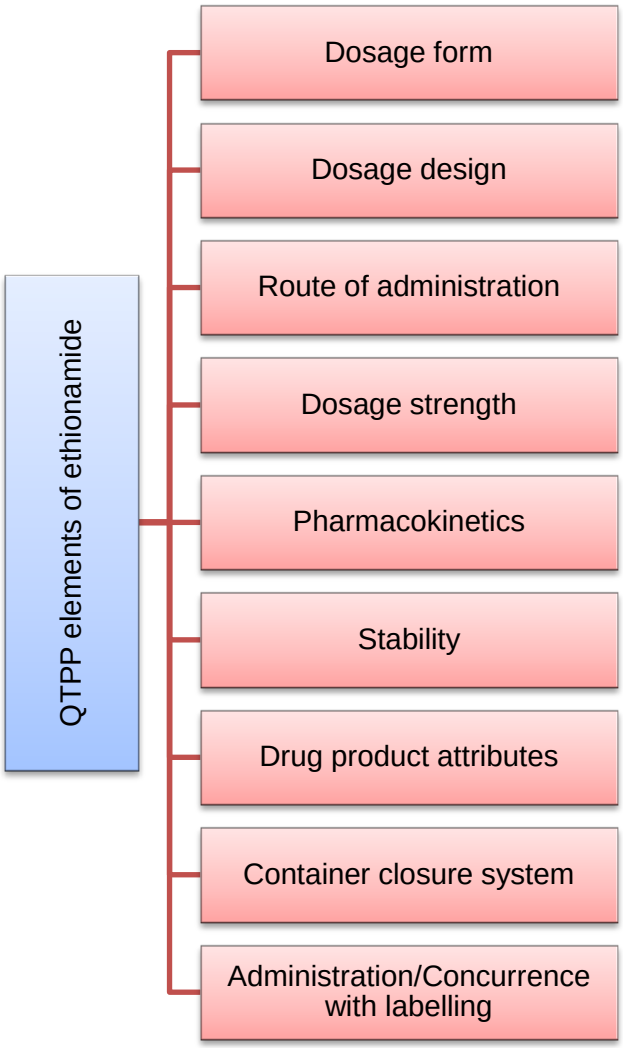


Figure 3.2 Graphical representation of the QTPP for ethionamide 250 mg tablets

3.2.2 Identifying the product critical quality attributes

Once the QTPP for ethionamide was defined and translated into the relevant targets, the cQA was determined. The identification of a cQA from the QTPP is based on the severity of

harm to a patient should the drug product fall outside the acceptable range for that attribute (Food and Drug Administration, 2012). The list of potential cQAs are shown in Figure 3.3 below. Subsequently, the subset of cQAs that have a higher potential to be impacted by the input variables will be further investigated.

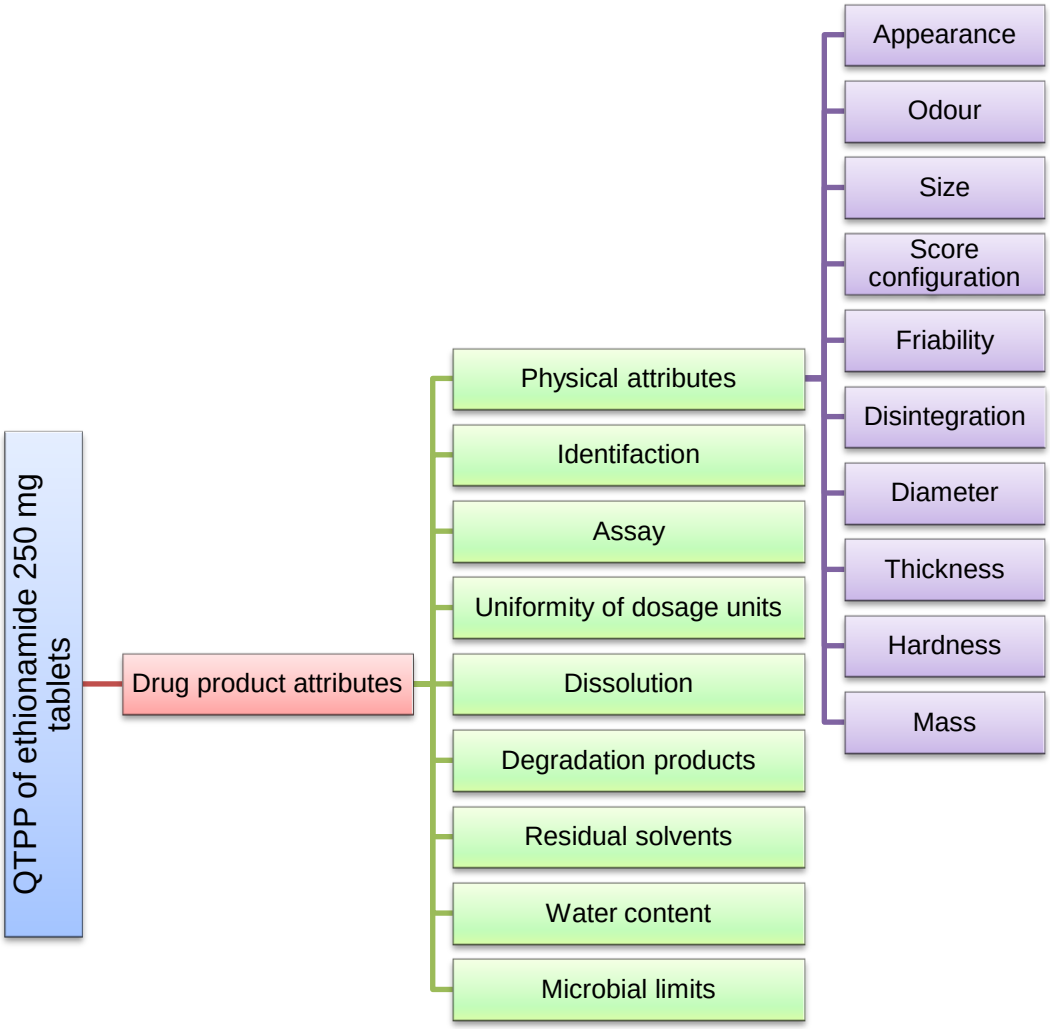


Figure 3.3 Illustration of the process of identifying the potential cQAs of ethionamide 250 mg tablets

3.2.3 Quality risk management

The process of developing a pharmaceutical drug product can be thought of as a funnel, whose top represents the many unknowns that are present at the start of the development process. As the process continues to move towards the narrow opening of the funnel, the number of unknowns are reduced. As a result, the variables that have a significant influence

on the response variables are identified (Al-Achi *et al.*, 2013). QRM forms the foundation of this process. Risk identification and risk analyses are the two basic components of risk assessment as outlined in the ICH Q9 guideline. The goal of these two assessments is to obtain the variables posing the highest risk to the cQAs. The output of the risk assessment is both a quantitative estimate of the risk and a qualitative description of a range of risk (Al-Achi *et al.*, 2013; International Conference on Harmonisation, 2006).

3.2.3.1 Quality Risk Assessment

A qualitative risk assessment was used as part of the first evaluation to determine if the risks are significant enough to warrant a more detailed analysis. At minimum, the evaluation criteria addressed the probability and severity of the risks as discussed in Section 2.2.3. The risk assessment of the API, excipients and manufacturing process were performed to evaluate the impact each material attribute and process parameter has on the product cQAs (Figure 3.4). Risks were categorised using qualitative descriptors such as 'low', 'medium' and 'high', as described in Table 2.2 and Table 2.3 in Chapter 2 above.

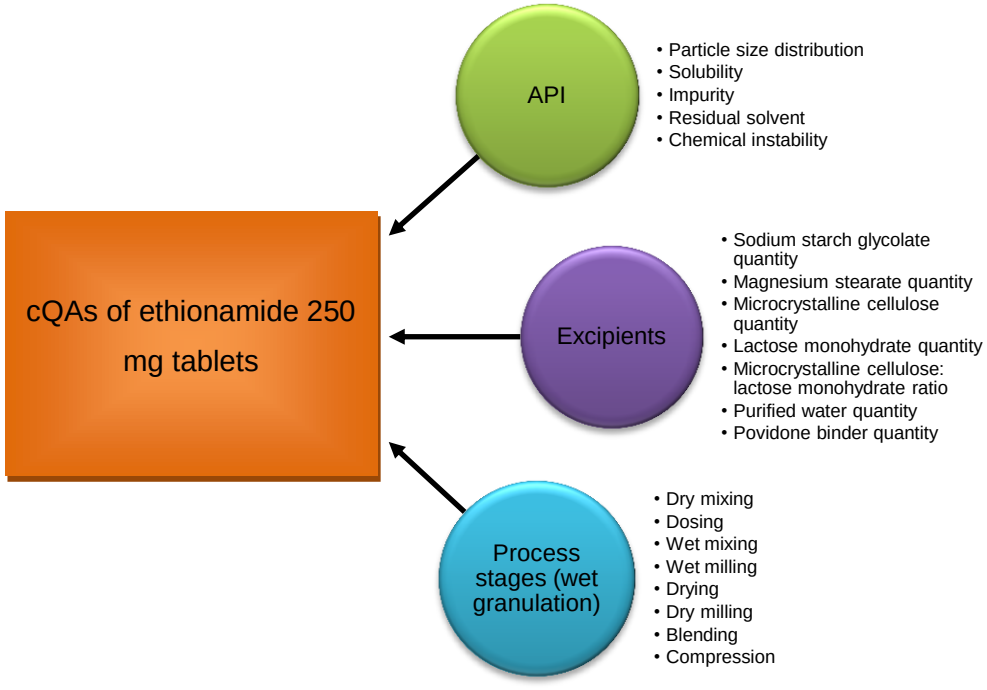


Figure 3.4 Illustration of the material attributes and process parameters that may influence the product cQA

After the ‘medium’ and ‘high’ risks were identified, these were further examined using a quantitative risk assessment. FMEA was used to prioritise the risk factors that may have the greatest potential of not meeting the QTPP. The failure modes were categorised into those from the API, excipients and the manufacturing process. The manufacturing process failure modes were further categorised by unit operations. Table 3.1 summarises the steps involved in creating the FMEA.

Table 3.1 Summary of the steps used in creating the FMEA (Adapted: International Conference on Harmonisation Q9 Guideline, 2006)

Completing the FMEA	
1.	List the potential failure modes for each process step
2.	List the effects of the failure mode
3.	Rate the severity of the effect
4.	Identify the causes of the failure mode/effects
5.	Identify the controls in place to detect the failure modes and rank its effectiveness
6.	Multiply the severity, occurrence and detection numbers to determine the RPN
7.	Sort by RPN and identify the most critical issues. The higher the RPN, the higher the potential risk
8.	Develop an action plan and assign specific action
9.	Once actions have been completed, severity, occurrence and detection are rescored

The risks were rated on a scale of 1 to 10 for each of the causes i.e. severity (S), probability of occurrence (O) and detection (D). Based on this scaling system, a high severity event would be given a 10, whereas a low severity event would be given a score of one. With probability, if something were quite certain to happen, then a 10 would be given, whereas if something were very unlikely to happen, a score of one would be allocated. For detection, if there is a good detection system in place, a score of one is given, whereas a non-existent detection system would be given 10. A review of the FMEA scoring system is shown in Table 3.2. These severity, occurrence and detection numbers were multiplied together to give a risk priority number (RPN). The RPN was generated for all risk factors and the factors with the highest RPN were the main priority and were evaluated. The cMAs and cPPs with a RPN $\geq$ 50 were further examined in the subsequent DoE.

Table 3.2 A review of the FMEA scoring system (Adapted: International Conference on Harmonisation Q9 Guideline, 2006)

Severity		
10	Dangerously high	Failure could lead to death or permanent injury to the patient. Severe impact to quality. Product recall
9	Extremely high	Failure could lead to injury to the patient. Failure would create noncompliance with registered specifications. May lead to recall
8	Very high	Failure could lead to adverse reactions for patient. Failure would create noncompliance with GMP regulations. May cause stop in production flow
7	High	Failure leads to patient perception of safety issue. Failure renders individual units unusable. Failure causes high degree of customer dissatisfaction. May cause significant impact to quality
6	Moderate	Failure causes a high degree of customer dissatisfaction and numerous complaints. Failure unlikely to lead to recall
5	Low	Failure likely to cause isolated customer complaints
4	Very Low	Failure relates to non-dosage form issues and can easily overcome by the patient
3	Minor	Failure could be noticed by the customer but is unlikely to be received as significant to warrant a complaint. Failure to meet specification may cause minor impact on quality
2	Very minor	Failure not readily apparent to the patient
1	None	Failure would not be noticeable to the patient. Quality within specification. May result in a deviation
Occurrence		
10	Very high: failure is almost inevitable	More than once occurrence per day or a probability of more than 3 occurrences in 10 units
9		One occurrence every 3 to 4 days or a probability of 3 occurrences in 10 units
8	High: repeated failures	One occurrence per week or a probability of 5 occurrences in 100 units
7		One occurrence every month or 1 occurrence in 100 units
6	Moderate: Occasional failures	One occurrence every 3 months or a probability of 3 occurrences in 100 units
5		One occurrence every 6 months to 1 year or one occurrence in 10000 units
4		One occurrence per year or 6 occurrences in 100 000 units
3	Low relatively few failures	One occurrence every 1 to 3 years or six occurrences in 10 000 000 units
2	Occasional failures: Infrequently	One occurrence every 3 to 5 years or 2 occurrences in 1 000 000 000 units
1	Remote: Failure is unlikely	One occurrence in greater than 5 years or less than 2 occurrences in 1000 000 000 units
Detection		
10	Absolute uncertainty	The product is not inspected or the defect caused by the failure is not detectable (virtually impossible to detect)
9	Very remote	Product is sampled, inspected and released based on acceptable quality level
8	Remote	Product is accepted based on no defects in a sample. Failure will only be detected at finished product testing
7	Very low	Product is 100% manually inspected in the process
6	Low	Product is 100% manually inspected using go/no-go or other mistake proofing gauges
5	Moderate	Some statistical process control is used in the process and product is final inspected off-line
4	Moderately high	Statistical process control is used and there is an immediate reaction to out-of-control conditions
3	High	An effective statistical process control is in place with process capabilities greater than 1.33
2	Very high	All product is 100% automatically inspected
1	Almost certain	The defect is obvious and there is 100% automatic inspection with regular calibration and preventative maintenance of the inspection equipment. Failure will definitely be detected.

3.2.4 Experimental design

The focus of the DoE was to identify the significant factors affecting the product cQA, i.e. dissolution and to determine the optimal level settings for the manufacturing process. Therefore, obtaining a manufacturing process that produces tablets with a low friability, acceptable crushing strength, low disintegration time and an acceptable dissolution profile.

Two experimental designs were developed in order to optimise the formulation and manufacturing process of ethionamide tablets. The first screening study was developed in order to determine the factors to be used in the optimisation phase. Secondly, the pivotal experiments will determine if the levels of the significant factors from the screening experiments will produce a response that is in close proximity to the optimum and select the optimum settings of the selected variables. Statistical designs and analysis were carried out using the software package Minitab® statistical software version 16.0 (Minitab Inc., United Kingdom). Experimental runs for the screening trial batches and the pivotal trial batches were randomised to avoid any subjective decisions.

In order to evaluate the effect of the high risk factors on the considered responses, Analysis of Variance (ANOVA) was applied. ANOVA has the ability to identify main and interaction effects of independent factors on the response. ANOVA uses a calculated probability value (p-value) to determine if the main effects of the independent variables on the response were statistically significant. A p-value less than or equal to 0.05 ($p \leq 0.05$) is considered significant for statistical analysis at a 95% confidence interval (CI). ANOVA does not only help to determine the main effects of independent variables on the responses but also evaluates the interactions amongst these factors. Occasionally a statistically significant value would indicate that the effect of one factor on the response is not statistically significant ($p > 0.05$) but may indicate an interaction with another factor where the interaction is significant ($p \leq 0.05$).

3.2.4.1 Screening trial batches

As the number of possible combinations in a complete factorial design increase, the number of experimental runs increases; thus it may be necessary to reduce the size of such problems in order to undertake practical work in the field. Reduced design refers to any design approach that involves experimental manipulations of all the independent variables,

but includes fewer experimental conditions than a complete factorial design with the same number of variables. Reduced designs are often necessary to make simultaneous investigation of multiple independent variables feasible. However, any removal of experimental conditions to form a reduced design involves some loss of statistical information which may have substantial scientific effects. Generally a design is selected to achieve a particular aliasing structure while considering the cost (Louviere *et al.*, 2000).

Fractional factorial designs merit serious consideration because of the economy and its versatility. Fractional factorial designs involve selection of a particular subset of the complete factorials, so that particular effects of interest can be established as efficiently as possible. That is, all fractions require assumptions about non-significance of higher-order effects i.e. interactions between two or more attributes (Louviere *et al.*, 2000).

The screening trial batches were completed with the purpose of identifying those factors from the risk assessment to have a significant effect. The preliminary screening trial was conducted using a 2^{6-3} fractional factorial design. A 2^{6-3} fractional factorial design is a 2^{-3} = ⅛ fraction of the complete factorial. This model contained no interactions because these cannot be estimated in a resolution III design. A fractional factorial design minimises experimentation during the screening phase of the study as the aim was simply to determine which of the high risk factors chosen would impact the product cQA and would then be further examined during the optimisation phase (pivotal study). The selected formulation and manufacturing input variables selected for the screening trial batches include: API particle size, povidone binder quantity, impeller speed during dosing, massing time, impeller speed during wet mix and moisture content after drying the wet granule. Two levels for each factor were set at either low (-) or high (+) according to results of preliminary investigations, the outcome of the panel discussion with the subject matter experts and literature are summarised in Table 3.3. The range of each factor is wide enough to detect a significant variation but not so wide that the edge of failure is exceeded. Experimental runs for the screening trial batches are shown in Table 3.4.

Table 3.3 Formulation and process factors and their levels for the screening trial batches using a 2^{6-3} fractional factorial design

Independent variables (factors)		Levels		
		Units	Low (-1)	High (+1)
1	API particle size	D_{50} (µm)	95.18	267.00
2	Povidone binder quantity	% m/m	3	5
3	Impeller speed during dosing	rpm	100	200
4	Massing time	s	120	360
5	Impeller speed during wet mix	rpm	100	200
6	Moisture content	% m/m	1	3

Table 3.4 Experimental plan for the screening trial batches using a 2^{6-3} fractional factorial design

Standard Order	Run Order (Formulation)	Critical material attributes and process parameters					
		API particle size	Binder quantity (povidone)	Impeller speed during dosing	Massing time	Impeller speed during wet mix	Moisture content
Units		D_{50} (µm)	% m/m	rpm	s	rpm	% m/m
1	1	267.00	3	100	360	200	3
5	2	267.00	3	200	360	100	1
8	3	95.18	5	200	360	200	3
7	4	267.00	5	200	120	100	3
6	5	267.00	3	200	120	200	1
4	6	95.18	5	100	360	100	1
3	7	267.18	5	100	120	200	1
2	8	95.18	3	100	120	100	3

The data generated by the experiments indicated only the levels used for the risk factors. The composition and parameters were computed based on the experimental plan. The 2^{6-3} fractional factorial design is a resolution III design, subsequently only the main effects of the factors were considered. The software was used to determine model fit and was defined as a p-value, derived from the ANOVA analysis, of less than 0.05. Pareto ranking analysis was used to select the significant factors for further studies and the p-value calculated using an F-test was less than 0.05 (Myers *et al.*, 1995).

3.2.4.2 Response surface methodology

Based on the results of the screening trial, three significant factors were identified, which included povidone binder quantity, impeller speed during dosing and moisture content. Povidone binder can be controlled at the recommended 4% m/m quantity; thus complies with pharmaceutical formulation requirements (Rowe *et al.*, 2006). Therefore pivotal trial batches focused primarily on process optimisation. The factors selected to be included in the pivotal trial batches (optimisation phase) were impeller speed during dosing and moisture content.

In order to optimise the manufacturing process, RSM was employed as the statistical tool for design and analysis. RSM, using a central composite rotatable design (CCRD) was selected. A graphical representation of the CCRD model is shown in Figure 3.5, illustrating the factorial, axial and centre points (Myers *et al.*, 1995, p. 299).

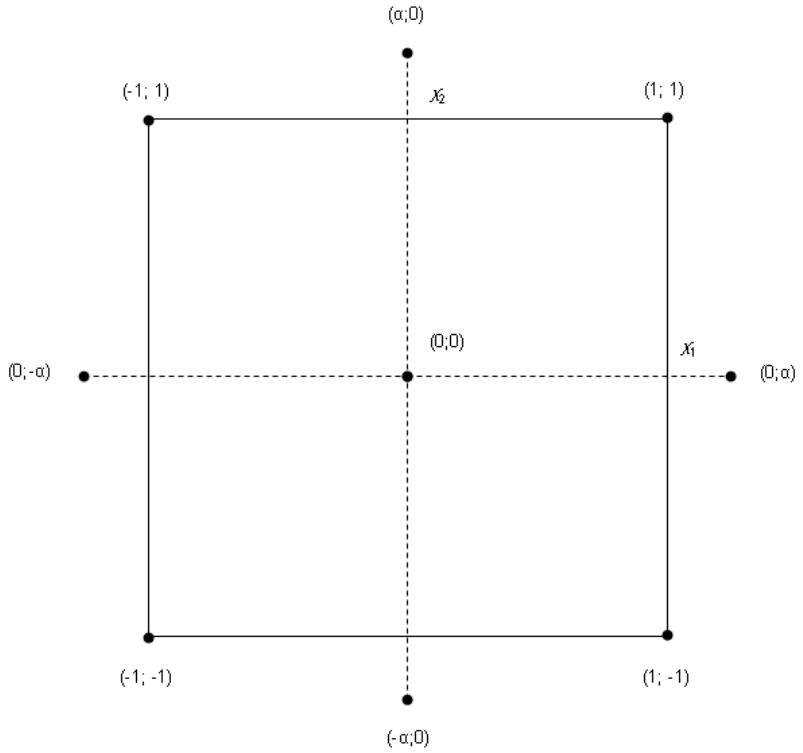


Figure 3.5 Schematic representation of the CCRD model where k=2 (Adapted: Myers *et al*., 1995)

An alpha value (α-value) was chosen so that all the points outside the origin are of the same distance from the centre, in order to achieve a spherical or rotatable design. The α-value was calculated using Equation 3.1, where n = number of factors.

$$\propto \text{value} = 2^{n/4} \qquad \textbf{[Equation 3.1]}$$

The α-value of 1.414 was used to define the axial points (Minitab® statistical software). A summary of the factors and levels are shown in Table 3.5.

Table 3.5 Factors and their levels for the CCRD

Factors		Units	Factor Level				
			-α	**-1**	**0**	**+1**	**+α**
Impeller speed during dosing	X_1	rpm	89.64	100.00	125.00	150.00	160.36
Moisture content	X_2	% m/m	2.40	2.50	2.75	3.00	3.10

Levels of these risk factors were set at either low (-1), centre point (0) and high (+1) for the optimisation phase (pivotal trial batches).The experimental plan for the CCRD capitulated 13 experimental runs, containing four cubes points, five centre points in cube, four axial points and zero centre points in axial. A single replicate (unreplicated) was employed for the design. As a result, there is no estimate of error. An approach to the analysis of an unreplicated factorial design is to assume that certain high order interactions are negligible and combine their mean squares to estimate the error. Daniel (1959) in Myers & Montgomery (1995) suggests plotting the estimates of the effects on the normal probability graph and the effects that are negligible are normally distributed (Myers *et al.*, 1995). Table 3.6 illustrates the experimental plan for the pivotal trial batches.

Table 3.6 Experimental plan of the CCRD for the pivotal trial batches

Run Order (Formulation)	Standard Order	Point Type	Blocks	Risk Factors	
				Impeller speed during dosing	Moisture content
1	10	0	1	125.00	2.75
2	6	-1	1	160.36	2.75
3	1	1	1	100.00	2.50
4	5	-1	1	89.64	2.75
5	7	-1	1	125.00	2.40
6	11	0	1	125.00	2.75
7	4	1	1	150.00	3.00
8	9	0	1	125.00	2.75
9	13	0	1	125.00	2.75
10	12	0	1	125.00	2.75
11	3	1	1	100.00	3.00
12	8	-1	1	125.00	3.10
13	2	1	1	150.00	2.50

ANOVA analysis was used to determine the most appropriate model to fit each response and product cQA; and lack of fit and R^2 statistics calculated for each model were used to aid in choice of the model. Once data was fitted to an appropriate model, a design space was created by the overlay of the contour plots and optimisation of the manufacturing process was calculated based on the product cQA. Criteria for the product were set such that an optimum manufacturing process would be obtained. Criteria for the design are shown in

Table 3.7. The optimised manufacturing process was determined using the desirability function (D-function) using the response optimiser in Minitab® statistical software.

Table 3.7 Criteria used for the optimisation of factors in the RSM design

Product cQA	Criteria	Importance	Weight	Minimum	Maximum
Dissolution	Maximise	High	1	90	105

3.2.4 Establishing a control strategy

The control strategy in the QbD paradigm is established via the risk assessment that takes into account the criticality of the selected input variables. Based on the outcome of the DoE, the initial risk assessment would be updated according to the severity of the risk, probability of occurrence and the ability to detect these potential risk factors. The planned set of controls would ensure that the previously selected risk factors are maintained within the design space to ensure product quality is maintained.

3.3 Materials and Methods

3.3.1 Materials

The function and characteristics of excipients are critical to tablet formulation, as this may affect the product proficiency. Excipient compatibility is an important part of understanding the role of inactive pharmaceutical ingredients (IPI) in the product. These drug-excipient studies were performed as part of the pre-formulation studies to confirm the drug-excipient interaction and have shown that there were no incompatibilities between the API and the proposed excipients.

The following raw materials were utilised in this study: ethionamide (Liaoning Beiqi Pharmaceutical Co. Ltd, China); microcrystalline cellulose (Flocel® 101) (Gujurat Microwax, India); lactose monohydrate (Pharmatose 200M) (DMV – Fonterra Exc, New Zealand);

sodium starch glycolate (Amishi Drugs and Chemicals, India); Povidone K25 (Kollidon K25) (BASF SE, Germany); magnesium stearate VEG EP 05 (Faci Asia Pacific PTE Ltd, Singapore). All raw materials were kindly donated by Aspen Pharmacare, Port Elizabeth.

3.3.2 Preparation of ethionamide tablets

The proposed method of manufacture is by wet granulation. Wet granulation is the oldest and most accustomed method of tablet manufacturing (Agrawal & Naveen, 2011). In wet granulation, the addition of a liquid binder is generally adequate to aid in the bonding of the raw materials. For each DoE batch, the raw materials were weighed (Mettler Toledo balance SR 32001; Switzerland) in accordance with the experimental plan. The DoE batches were manufactured at a 10 litre scale using Granulator Rapid Mixer and Wet Granulator (RMG 10 LTR, India).

Granulating medium was prepared by mixing Povidone K25 and purified water (Heidolph Electrical Stirrer; Model Number: 50115; Germany). Ethionamide, lactose monohydrate, sodium starch glycolate (SSG) and microcrystalline cellulose (MCC) were dry mixed with the impeller speed set at 200 rpm and chopper speed set at 2500 rpm for 240 seconds (Rapid Mixer & Wet Granulator; Model Number: RMG 10 LTR; India). The granulating medium was added to the bowl over a 90 second period (dosing time) at a chopper speed of 1500 rpm and the impeller speed set according to the experimental plan. The granules were wet milled through a 6.0 mm screen at 300 rpm (Quadro Co-Mill; Model Number 197; Canada) and dried in a 40 °C pre-heated fluid bed dryer (Retsch Fluid Bed Dryer: Model Number TG100; Germany) until a specified percentage moisture content (loss on drying) was reached. After being dry milled through a 1.5 mm screen, SSG was sieved through a size 40-mesh screen, added to the bulk material and blended (IMA Pharma Canguro Turbula Bin; Model Number: J50; Italy) for 10 minutes at 11 rpm. The lubricant, magnesium stearate, was screened through a size 40-mesh, added to the granules and blended for 5 minutes at 11 rpm. The final blend was subsequently compressed into tablets using a Karnavati Mini Press (Karnavati Mini Press II; Model Number: UNIK – PC 20 MT; India). Machine parameters were kept constant. The tooling used to compress tablets was 11.10 mm round shape, shallow concave, embossed and scored punches (Eliza-Tool, India). The manufacturing processing is presented graphically in Figure 3.6.

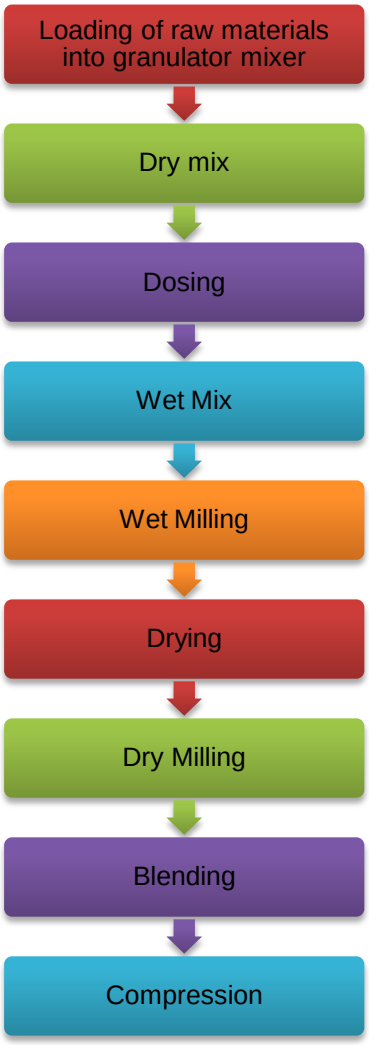


Figure 3.6 A flow diagram illustrating the process involved in the manufacturing of ethionamide 250 mg tablets

3.3.3 Evaluation of granule moisture content

The moisture content after drying the wet granule was measured using a Moisture Analyser (Mettler Toledo LJ16, Switzerland). The granule sample (2 g – 5 g) was placed in a heating pan, weighed and heated at a temperature of 105 °C and a drying time set to the automatic switch-off criterion (2 mg/30 seconds) The percent reduction in the weight due to moisture loss i.e. loss on drying (LOD) was determined.

$$Moisture\ content\ (\%) = \frac{(initial\ weight - final\ weight)}{initial\ weight} \times 100$$

[Equation 3.2]

3.3.4 Evaluation of tablets

The quantitative assessments of tablets are important in the design of tablets and to monitor the product quality. Evaluating these properties, assures that the tablets do not vary from one formulation batch to another; consequently controlling the quality attributes. Tablets were evaluated according to the product cQA. For this product, dissolution is the identified cQA that have the potential to be impacted by the formulation and process variables. Conversely, physical attributes such as tablet friability, hardness, and disintegration time were not identified as a potential cQA for ethionamide tablets, these are still considered important elements of the QTPP. Tablet friability is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in handling. The resistance of tablets to capping or breaking before usage depends on its hardness. However, if tablets are too hard, it may not disintegrate in the required time period under test conditions. The disintegration test does not offer any guarantee that the resultant particles will release the drug substance in solution at the correct rate. These physical attributes will be monitored. All the response variables and their specifications are listed in Table 3.8 below.

Table 3.8 Summary of the specifications for the in-process control tests of each response variable

Response variables (dependent)	**Specification**
Tablet friability	Not more than 1% m/m loss after 4 minutes, rotating at 25 rpm
Disintegration time	Not more than 15 minutes (900 seconds)
Dissolution profile	Not less than 80% of active is released per dosage unit within 45 minutes

3.3.4.1 Dissolution

Although the disintegration time is a useful tool for production control, it does not necessarily imply that the drug has dissolved in its entirety. A tablet may have a rapid disintegration time yet it may be biologically unavailable. An imperative means for characterising the biopharmaceutical quality of a product is to perform *in vitro* dissolution testing. Therefore, the dissolution rate is a more indicative of the availability of the drug than the disintegration test; thus is an essential factor in drug absorption (Hanson, 1982).

Dissolution testing is a regular quality control procedure in cGMP. The standard dissolution test is a simple and inexpensive indicator of the product's physical consistency. Specifying dissolution limits ensures batch-to-batch consistency within a specific range. Meeting these specifications assures an acceptable *in vivo* biopharmaceutical performance. If one batch differs extensively from others in its dissolution characteristics, or if the dissolution times of the production batches show consistent trend upwards or downwards, it serves as a warning that either the raw material, formulation or process may not be in control (Hanson, 1982; Huang *et al.*, 2011).

Dissolution studies were performed in-house according to validated standard operating procedures (SOP) using a United States Pharmacopoeia (USP) I dissolution apparatus (Hanson SR II 6-flask Dissolution Test Station; Model Number 64-705-045, United States of America), equipped with six vessels. Nine hundred millilitres (ml) of 0.1 M hydrochloric acid (HCl), as the dissolution medium was added to each of 6 vessels sited in the water bath at a temperature of 37 °C ± 0.5 °C. Baskets were set to rotate at 100 rpm. One tablet was transferred to each of the six baskets and at time zero, the baskets were immersed in the dissolution medium. Ten ml aliquots were withdrawn at 10, 15, 20, 30 and 45 minute intervals from each vessel into separate test tubes. Two ml of the filtered sample was transferred into a 50 ml volumetric flask and made up to volume with the 0.1 M HCl. The solution was filtered through a 0.45 µm Pall AcrodiscGxF/GHP filter.

The dissolution medium was prepared by transferring 8.5 ml of HCl (32% v/v) (Merck KGaA, Germany) into 10 litres of purified water (Riggtek DissoPrep X8, Germany). The standard solution was prepared by weighing and transferring approximately 55 mg of ethionamide working standard into a 100 ml volumetric flask, adding 60 ml of the dissolution medium and sonicating until dissolved (Branson Ultasonic 8510, United States of America). The solution was allowed to cool to room temperature and the solution was made to volume with

dissolution medium. Two ml of this solution was transferred into a 100 ml volumetric flask and made up to volume with the dissolution medium. The solution was filtered through a 0.45 µm Pall Acrodisc PSF GxF/GHP filter, discarding the first 5 ml of the filtrate.

The dissolution of ethionamide from tablets was measured using a UV-VIS Spectrophotometer (UV-Pharmaspec 1700 UV-visible spectrophotometer, Japan). Ethionamide concentration of each sample (n=6) at each time interval and the absorbance of the standard (five replicates) was spectrophotometrically determined at 274 nm with a 1 cm cell and the dissolution medium as the blank. Data acquisition was performed using UV Probe® 2.43 software. Microsoft Excel® was used to calculate the percentage drug released using Equation 3.3. The parameters used in the formula for the dissolution test are summarised in Table 3.9.

$$\%\ ethionamide\ released\ per\ tablet = \frac{Asam\ \times mass\ of\ standard\ \times 2\ \times 900\ \times 50 \times C\ \times 100}{Astd\ \times 100\ \times 100\ \times label\ claim\ \times 2 \times 100}$$

[Equation 3.3]

Table 3.9 Parameters used in the formula for the dissolution test

A_{sam}	Absorbance of ethionamide in the sample solution
A_{std}	Average absorbance of ethionamide in the standard solution
Mass of standard	Mass of ethionamide working standard taken to prepare the standard solution (55 mg)
C	Potency of the ethionamide working standard, expressed in percentage (100.6%)
Label Claim	Amount of ethionamide present in each tablet i.e. dosage unit, expressed in mg (250 mg)
Requirement: Not less than 80% of active is release per dosage unit within 45 minutes	

*Note: The values in the brackets represent the mass weighed, volume of the standard solution, volume of the dissolution medium, label claim and the potency of ethionamide.

3.3.4.2 Tablet Hardness

Tablets are manufactured by compressing a powder formulation in a die between rigid punches. Following the compression process, the tablets are subjected to bulk handling and other post-compaction operations; thus bioavailability behaviour and mechanical integrity should be maintained until administration. Tablet compression is an important unit operation because the shape, strength and tablet weight are determined. A practical method to ensure the strength is the compression test also known as the tablet hardness test (Sinka *et al.*, 2009). Tablet hardness is an essential evaluation tool during manufacturing as it may influence parameters such as disintegration and dissolution properties (Huang *et al.*, 2011).

Ten tablets were randomly selected from each formulation batch and tablet breaking strength i.e. hardness, was measured using a hardness tester (Erweka Hardness tester; Model Number: TBH 320TD; Germany). The average hardness and mean standard deviation (SD) of the 10 tablets from each batch was calculated. In addition to the hardness testing, the tablet thickness (including ± SD) was simultaneously calculated.

3.3.4.3 Friability

Friability is a measure of the tablets ability to withstand shock and abrasion without crumbling during handling of manufacturing, packing, shipping and consumer use. Twenty tablets were randomly taken from each formulation batch. Tablet samples were weighed accurately (Mettler Toledo AG204; Switzerland) and placed in a friabilator (PharmaTest Friabilator PTF 3; Germany). Tablets were rotated at 25 rpm for 4 minutes, totalling 100 revolutions. Finally tablets were removed from the friabilator, de-dusted and weighed. The weight difference between the initial and final weight was recorded. The loss in tablet weight indicates the ability of the tablets to withstand abrasion in handling. The percent friability was determined by using Equation 3.4 below.

$$\%\, friability = \frac{(initial\ weight - final\ weight)}{initial\ weight}\ x\ 100$$

[Equation 3.4]

3.3.4.4 Disintegration time

Active absorption of oral dosage forms depend on adequate releases of the API from the product. Disintegration is evaluated to ensure that the API is completely accessible for dissolution and absorption from the gastrointestinal tract (Bushra *et al.*, 2008).

Tablet disintegration was tested using Erweka Tablet Disintegration Test Unit (Model Number: ZT 304; Germany). Six tablets were randomly selected from each batch (n=6) for the disintegration test. One tablet was introduced on each of the cylindrical (glass) tubes. Water was used as the disintegration medium at 37 °C ± 0.5 °C, with the apparatus suspended so that when it was in the highest position the wire mesh was at least 15 mm below the surface of the medium and 25 mm above the bottom of the beaker when suspended in the lowest position. The upper open ends of the tubes remained above the surface of the water. The time it took for each tablet to disintegrate such that all particles had passed through the mesh screen was recorded as the disintegration time and presented in seconds.

3.4 Statistical analysis

3.4.1 General descriptive statistics

Replicate measurements were represented as a means ± standard deviation (SD) and tabulated using Microsoft Excel® 2013.

3.4.2 Multifactorial analysis

Statistical design and analysis were carried out mainly using the software package Minitab® statistical software version 16.0 (Minitab Inc., United Kingdom). The software was used to determine model fit regression coefficient (R^2), adjusted R^2 (R^2 adj) and predicted R^2 (R^2 pred). Appropriate fit was defined as a p-value of 0.05 or less. The 2^{6-3} fractional factorial design is a resolution III design and only the main effects were considered. Main effects for the variables chosen were analysed using Pareto ranking analysis where the length of the horizontal bar represented the impact of the input variable on the response. ANOVA analysis was used to select the significant factors for further studies where the p-value calculated

using an F-test was 0.05 or less (where the confidence interval was 95%). For the RSM design, ANOVA analysis was used to determine the most appropriate model to fit each response and lack of fit were calculated. The lack of fit estimates the error variance independently of the model. A significant lack of fit ($p>0.05$) indicates that the model accurately fits the model. Once data was fitted to an appropriate model, optimisation of the manufacturing process was calculated within the design space.

3.5 Ethical consideration

Ethical clearance was not required, as the research did not involve any human and/or animal subjects. Data gathered for the purpose of the study were focused on optimising a pharmaceutical product.

CHAPTER 4 – RESULTS AND DISCUSSION

4.1 Introduction

QbD builds quality into pharmaceutical products by identifying characteristics that are critical to quality from the patient's perspective and translates those characteristics into attributes that the product should have (Lionberger *et al.*, 2008; Patel *et al.*, 2013). Establishing the QTPP of ethionamide tablets forms a roadmap for the optimisation process and it supports the notion of 'planning with the end in mind' (Roy, 2012; Yu, 2008). Identifying the cQA from the QTPP is based on the severity of harm to the patient should the attribute fall outside its acceptable range (Food and Drug Administration, 2012). The quality risk assessment tools categorises the critical material attributes and process parameters according to the potential risk this may have on the cQA. Furthermore, the identified high risk factors are examined in the subsequent DoE study. While the risk assessment is essential for identifying the high risk factors, this tool can be facilitated more effectively using DoE.

The objective of the DoE study was to identify the significant factors from the risk assessment that may influence the product cQA as DoE has proven to be an effective tool in formulation and process development. The major advantage of using DoE for product optimisation is that it facilitates the screening process which allows a systematic evaluation of a large number of variables simultaneously with a limited number of experiments. Once these significant factors are identified and evaluated, the final formulation and manufacturing process can be defined by optimising the levels of the cMAs and cPPs within a design space. Risk mitigation and the implementation of a control strategy will ascertain the quality of the product based on the product knowledge. This chapter presents the outcome of applying a systematic approach to optimising an immediate release ethionamide 250 mg tablet using QbD.

4.2 Quality Target Product Profile (QTPP) of ethionamide

The purpose of this exercise was to identify the quality characteristics that ethionamide should possess in order to deliver the desired therapeutic effect as assured on the product label. Based on the clinical, pharmacokinetic and physicochemical characteristics of ethionamide, the QTPP was established, thus ensuring that the desired quality would be achieved consequently the desired quality of ethionamide 250 mg tablets is achieved. Table 4.1 represents the QTPP of ethionamide.

Table 4.1 QTPP of ethionamide 250 mg tablets

QTPP Elements		Target	Justification
Dosage form		Tablet	Product is pharmaceutically equivalent and has the same dosage form
Dosage design		Uncoated immediate release tablet	Product is pharmaceutically equivalent and has the same dosage design
Route of administration		Oral	Product is pharmaceutically equivalent and has the same route of administration
Dosage strength		250 mg	Product is pharmaceutically equivalent and has the same dosage strength
Pharmacokinetics		Immediate release tablet where plasma T_{max} is reached at 2 hours with a C_{max} of 2µg/ml. $t_{1/2}$ at 2 to 3 hours.	Bioequivalence requirement. Needed to ensure rapid onset and efficacy.
Drug product quality attributes	Physical attributes	Round yellow, shallow concave, bevelled edged tablet with debossing on one side and scored	Tablet identification and to facilitate the splitting of tablet into fractions for partial dosage
	Identification	Targets for product identification are set according to pharmacapoeial standards	Pharmaceutical equivalent requirement: must meet the same compendia or other applicable (quality) standards
	Assay	250.0 mg (237.5 – 262.5 mg) 95.0 – 105.0% label claim	Pharmaceutical equivalent requirement: must meet the same compendia or other applicable (quality) standards
	Dissolution	Not less than 80% of ethionamide is released within 45 minutes (Q = 75%)	Pharmaceutical equivalent requirement: must meet the same compendia or other applicable (quality) standards
	Residual solvents	N/A	Formulation does not contain a solvent based damping medium. Purified water is the damping medium selected
	Water content	LOD: to be established	Formulation and manufacturing process should meet the acceptable quality standard. The moisture content after drying the wet granule needs to be established
	Microbial limits	Total aerobic microbial count (TAMC): Not more than 10^3 cfu/g Total combined yeasts and mould (TYMC): Not more than 10^2 cfu/g Escherichia coli: Absent	Pharmaceutical equivalent requirement: must meet the same compendia or other applicable (quality) standards

QTPP Elements		Target	Justification
Drug product quality attributes	Degradation products (by thin layer chromatography) (TLC)	Any secondary spot in the chromatogram obtained with the test solution is not more intense that the spot in the chromatogram obtained with test solution (a) (2.0%). At most one secondary spot in the chromatogram obtained with the test solution can be more intense that the spot in the chromatogram obtained with the test solution (b) (0.5%)	As per in-house method that has been validated
	Uniformity of dosage units (by weight variation)	<u>Stage I</u> The acceptance value of the first 10 dosage units is less than or equal to L1% <u>Stage II</u> The final acceptance value of the 30 dosage units is less than or equal to L1% and no individual content of any dosage unit is less than [1-(0.01) (L2)] M or more than [1 + (0.01) (L2)] M. (L1 = 15.0%; L2 = 25.0%; T = 100%)	Pharmaceutical equivalent requirement: must meet the same compendia or other applicable (quality) standards (USP <905>)
Stability		At least 24 month shelf-life at room temperature	Pharmaceutical equivalent requirement: Equivalent or better than shelf-life requirement
Container closure system		Container closure system qualified as suitable for this drug product	Need to achieve target shelf life and to ensure tablet integrity until tablets are administered
Administration/Concurrence with labelling		Similar food effect as reference product	Reference product labelling indicates that ethionamide is readily absorbed from the GIT and is widely distributed throughout the body and tissue fluids. Advised to be taken with food to minimise GIT irritation

The QTPP of ethionamide tablets is a functional summary of the product attributes to ensure that the product is fit for its intended use. The characteristics that make up the QTPP are designed into the product. The established QTPP would be a quantitative surrogate for aspects of clinical safety and efficacy that can be used to optimise the formulation and manufacturing process. The QTPP includes the dosage form, dosage design, dosage strength, route of administration and drug product quality attributes, all of which should be pharmaceutically equivalent to the reference counterparts. Although factors such as the stability, container closure system and administration labelling are important and have been identified as part of the QTPP, the focus of the study is optimising the formulation and manufacturing process and will not be examined and discussed. The depicted QTPP will lay down the basis for determining the cQAs.

4.3 Identification of the critical quality attributes (cQAs)

Once the QTPP for ethionamide was established, defined and translated into the relevant targets, the cQAs were identified. All possible process and product variants and their effect on safety and efficacy are listed in Table 4.2 below.

Table 4.2 summarises the cQAs of ethionamide tablets and denotes that dissolution is the cQA that has the potential to be impacted by the formulation and process variables. Dissolution will be evaluated in the subsequent optimisation studies. On the contrary, physical attributes such as tablet friability, hardness, and disintegration time are not identified as potential quality attributes for ethionamide tablets, yet these are still considered important elements of the QTPP and may still be essential from a business perspective i.e. manufacturability. The ability of tablets to resist attrition to ensure the correct amount of drug is administered and that the appearance of the tablet does not alter during handling is an important property (Alderborn, 2013). Tablet friability is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in handling. The resistance of tablets to capping or breaking before usage depends on its hardness. However, if tablets are too hard, they may not disintegrate in the required time period under test conditions. In addition, the disintegration test does not offer any guarantee that the resultant particles will release the drug substance in solution at the correct rate. The experimental work will increase the knowledge about these physical attributes and will be monitored through cGMP and quality risk management.

Table 4.2 Identification of the cQA for ethionamide 250 mg tablets

Quality attributes of the drug product	Target		Is this a cQA? (No/Yes)	Justification
Physical Attributes	Appearance	Round yellow, shallow concave, bevelled edged tablet with debossing on one side and scored	No	Appearance, colour and shape are not directly linked to safety and efficacy. The target is to ensure patient acceptability. Therefore appearance is not critical.
	Odour	Unpleasant	No	An unpleasant odour does not directly link to safety and efficacy.
	Size	Similar to reference product/current dossier	No	For comparable ease of swallowing as well as patients' acceptance and compliance with treatment regimens, the target for the tablet dimensions are set similar to the reference product. Tablet size is not directly linked to safety and efficacy.
	Score configuration	Scored	No	Dosage for adults is 15 mg/kg/day as a single dose (maximum of 1 g/day) and for children under the age of 10 years the dosage is 10 mg/kg/day increased to 15-20 mg/kg/day in two divided doses (maximum 1 g/day) (Gibbon, 2013). Tablets are scored for facilitate the splitting of the tablets as the dosage may require for half a tablet to be used. The API forms 50% of mass of the dosage unit; thus the score configuration does not affect safety and efficacy.
	Friability	Proposed: Not more than 1.0% m/m after 4 minutes	No	Routine test per compendia requirement for tablets. A target of not more than 1.0% m/m after 4 minutes of mean weight loss assures a low impact on safety and efficacy. Tablets that are no friable at the time of administration minimises customer complaints.

Quality attributes of the drug product	Target		Is this a cQA? (No/Yes)	Justification
Physical Attributes	Disintegration	Not more than 15 minutes (900 seconds)	No	Routine test per compendia requirement for tablets. Tablet disintegration testing is used as a quality assurance measure and may not predict how well the dosage form will release its active ingredient *in vivo* but will ultimately affect dissolution. Disintegration is a precursor to dissolution and is therefore not critical.
	Diameter	11.18 mm (10.62 – 11.74 mm)	No	Target for tablet dimensions are set similar to the reference product. Tablet diameter to fall outside of its acceptable range may not cause harm to patients. Tablet diameter is not critical to safety and efficacy.
	Thickness	To be established	No	Tablet thickness is not directly related to safety and efficacy. Therefore tablet thickness is not critical since related to hardness. Dimensions should be similar to the reference product, however thickness needs to be established based on results from research study.
	Hardness	To be established	No	Hardness is not critical since related to dissolution. To be established based on results from research study.
	Mass	Proposed: 500 mg ± 3%	No	Tablet mass range set between 485–515 mg tablets (target: 500 mg) Uniformity of mass is a quality assurance requirement, but is not directly linked to safety and efficacy.
Identification	Positive for ethionamide		No	Critical for safety and efficacy, but can be controlled by Quality Management Systems (QMS). Formulation and process parameters does not impact identity.
Assay	Half tablet	50% of label claim	No	Pre-formulation studies have shown that the assay for ethionamide is within the specification (95.0 – 105% label claim). Therefore assay is not a critical attribute.
	Whole tablet	100% of label claim	No	

Quality attributes of the drug product	Target		Is this a cQA? (No/Yes)	Justification
Uniformity of dosage units	Half tablet	Conforms to United States Pharmacopoeia (USP)	No	Tablets are required to meet a weight variation test where the API comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. However, the weight of the API forms 50% of the tablet mass. Therefore, uniformity of dosage units is not critical.
	Whole tablet		No	
Dissolution	Half tablet	Conforms to United States Pharmacopoeia (USP)	Yes	Dissolution is a rate-limiting step for drug absorption. Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This cQA will be investigated throughout formulation and process development.
	Whole tablet		Yes	
Water Content	Loss on Drying (LOD)	Current: N/A (To be established)	No	Pre-formulation studies suggest that degradation and microbial growth of the drug product is not a critical attribute. Moisture content of intermediate bulk material (after drying wet granule) needs to be established.
Degradation products/related substances/impurities		N/A (as per in house validated requirements)	No	Can be controlled based on requirements for reference product.
Residual solvents		N/A	No	N/A
Microbial Limits		Meets relevant pharmacopoeial criteria	No	Pre-formulation studies suggest that microbial limit is not a critical attribute and can be controlled by quality management system (QMS).

4.4 Quality Risk Assessment

4.4.1 Risk Assessment of Excipients

A risk assessment of the excipients was performed to evaluate the impact that each raw material could have on the drug product cQA as discussed in Section 3.2.3. The outcome of the risk assessment is shown in Table 4.3.

Table 4.3 Initial risk assessment of the excipients

Drug Product cQA	Drug Substance Attributes	Risk Ranking
Dissolution	SSG quantity	**Medium**
	Magnesium stearate quantity	**Medium**
	MCC quantity	**Medium**
	Lactose monohydrate quantity	Low
	MCC: lactose monohydrate ratio	**Medium**
	Purified water quantity	**Medium**
	Povidone binder quantity	**High**

Based on the formal risk assessment of the excipients used in the proposed formulation, magnesium stearate is a 'medium' risk factor. Magnesium stearate is used as the lubricant in the formulation. Lubricants are important for the tablet ejection take-off steps during tablet compression as the lubricant aids in reducing friction between the tablet and the metal surfaces of the compression machine. Magnesium stearate can influence tablet dissolution, hardness, friability and disintegration. A slow dissolution profile generates a potential risk and possible bio-inequivalence to the reference product. Wang *et al*. (2010) reported that studies have shown that lubricants such as magnesium stearate had a more pronounced adverse effect on *in vitro* dissolution of immediate release tablets. This is due to the combined effects of their large surface area and hydrophobic behaviour that hinders water penetration to affect dissolution. As the amount of magnesium stearate in the formulation increases, the amount of magnesium stearate coating the API particle surface area increases. The lubricant coating around the API adds an extra hydrophobic layer, which

further reduces dissolution rate. Therefore over processing with magnesium stearate reduces dissolution rates (Kushner & Moore, 2010; Moore *et al.*, 2010; Shah & Mlodozeniec, 1977; Wang *et al.*, 2010).

Microcrystalline cellulose (MCC) and its combined ratio with lactose monohydrate (MCC: lactose monohydrate) were also identified as being 'medium' risks. The risk is acceptable, however further investigation is needed to reduce its risk. The combination of the two excipients is used to enhance the requirements of the single component. The ratio of MCC to lactose monohydrate may impact dissolution via tablet hardness; however, hardness can be controlled during compression. A review by Pifferi and co-workers (1999) suggests that when using MCC, low compressibility forces are sufficient to produce compactions that are resistant and yet elastic with low friability. Following compaction, the particles deform plastically and form hydrogen bonds between adjacent molecules, giving rise to a predominantly resistant compaction. Despite this resistance, these compactions disintegrate quickly (Pifferia *et al.*, 1999). Lactose, a water soluble excipient act by forming pores within the tablet matrix and allowing rapid dissolution and the potential of the quantity of lactose to impact the product quality is 'low'. Although lactose is water-soluble, a study by Husen and co-workers (2012) demonstrated slower release behaviour compared to MCC. Though MCC is insoluble in water, at a higher concentration, it has a faster release rate and a shorter dissolution time. Due to its inherent disintegration properties this causes tablet erosion of the polymer matrix and faster drug release.

Incorrect quantity of purified water added to the formulation may result in either over- or under granulation of the powder. The amount of water used for high shear wet granulation is essential as the process is susceptible to over wetting and uncontrollable agglomerate growth. This potentially influences granule and final drug product quality. An over granulated powder bed hinders powder flow, compression and ejection of tablets, which impacts hardness, disintegration and dissolution profiles (Agrawal *et al.*, 2011; Shi *et al.*, 2011). The quantity of water is a 'medium' risk.

Adding a superdisintegrant like SSG to the formulation improves tablet disintegration and ultimately the dissolution rate. The incorrect quantity of SSG may lead to a poor dissolution profile as a result of a slow disintegration time; and subsequently demonstrate an in-equivalent bioavailability. The disintegrant is added either intragranularly, extragranularly or both. Lang (1982) showed that an equal distribution of superdisintegrant in both intragranular and extragranular phases resulted in better dissolution than total incorporation (Rahman *et*

al., 2011). The quantity of SSG is categorised as a 'medium' risk. In addition, disintegrants counteracts the binder function as it opposes the efficacy of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder the more effective the disintegrant agents should be in order for the tablet to release the API (Farhana *et al.*, 2013). Povidone binder quantity impacts binder activation and ultimately dissolution. Potential effect of failure may hinder compression and the dissolution profile. Similarly, Chalmers and Elworthy (1976) has demonstrated that an increased concentration of povidone in the binder solution, decreased the rate of tablet dissolution. The quantity of povidone binder is a 'high' risk factor.

4.4.2 Risk Assessment of Manufacturing Process Stages

A risk assessment of the overall manufacturing process was performed to identify the processing parameters that may affect tablet dissolution. The initial risk assessment of the process stages is shown in Table 4.4.

Table 4.4 Initial risk assessment of the manufacturing process stages

Drug Product cQA	Process Stages	Risk Ranking
Dissolution	Dry mixing	Low
	Dosing	**High**
	Wet mixing	**High**
	Wet milling	Low
	Drying	**Medium**
	Dry milling	**Medium**
	Blending	**High**
	Compression	**High**

During binder addition, the granulating medium is poured into the moving powdered mix. The expectation is that due to the movement of the powder and the wetting properties of the liquid, the binder is distributed on the powered surfaces rendering them sticky enough to allow particle-particle coalescence upon mutual collisions. The subsequent process is wet

massing, where the movement of the particles in the mixer grow and consolidate due to their sticky surfaces. Fluid distribution is critical as granules are bound by capillary and viscous forces created by liquid bridges between primary particles. When liquid droplets are imbibed into the dry mix, granule nuclei are formed which typically have relatively low saturation. As granulation proceeds, more nuclei are formed while existing nuclei begin to collide with each other leading to growth and consolidation (Michaels *et al.*, 2009; Tardos, 2005).

Granules are created through a combination of mechanical energy, the quantity and addition rate of binder and to some extent the concentration of the binder in the solution. Over granulating is over processing or over working the powders while the granulation medium is added. This occurs when the mixing time exceeds the end point and/or adding too much binding solution. An overworked granulation may not flow well, compress or eject properly and impact hardness, disintegration and dissolution. The impeller rotational speed affects the quality of the mixing between the powder and the granulating medium; the collisions between particles; and between the particles and the equipment. Controlling impeller speed creates an even distribution of the granulating medium over the powder bed and reduces the effect of localised wetting; thus creating a homogenous granulation (Benali *et al.*, 2009). Failure to obtain a homogenous granulation may potentially cause over granulation and negatively impact tablet dissolution. Therefore, dosing and wet mix are ‘high’ risk factors. Controlling moisture content, particularly for formulations containing hygroscopic excipients, such as povidone, are essential as this potentially affects process performance and ultimately batch reproducibility (Shi *et al.*, 2011). An adequate moisture content level is required for the binding of granules during compression in the die cavity. Furthermore, tablet compression may potentially impact the extent of dissolution. Over drying granules can cause capping in compression, marking on tablets, hard granules, poor flow and negatively impact the content uniformity. Counter to over drying, under drying granules can cause sticking, marking and poor flow. As the moisture content after drying the wet granule i.e. loss on drying (LOD) needs to be established, the risk is graded ‘medium’.

The milling step controls the final granule size distribution. Particle size reduction is a simple means to enhance the dissolution rate of poorly soluble drugs. The percentage fines in the granule blend may impact tablet hardness and dissolution. Harun and co-workers (2013) investigated the effect of particle size on the dissolution and demonstrated that the particle size of the final granules in tablet formulation affected the dissolution. The risk for dry milling is categorised as ‘medium’.

Effective blending is essential to ensure a homogenous mix. Exceeding the mixing time with a predetermined quantity of extra glidant and lubricant may potentially result in segregation. Over-lubrication due to excessive number of revolutions during the blending stage may impact disintegration and ultimately the dissolution of the tablets (Twitchell, 2013). The risk for this process stage is therefore classified as 'high'.

Moore and co-workers (2010) reported that several other authors have demonstrated that the tablet hardness increases as the lubrication mixing time decreases or as the amount of magnesium stearate (lubricant) decreases. In addition, the extent to which the granules are over-lubricated can also be quantified by the amount of compression force needed to compress a tablet to a particular hardness. The amount of applied force required to produce tablets having similar hardness increases as the amount of lubrication time with magnesium stearate increases. Thus, increasing tablet hardness may impair dissolution (Huang *et al.*, 2011). Therefore, the risk is categorised as 'high'.

Dry mix and wet milling are categorised a 'low' risk factors as the severity and probability of these factors impacting the extent of dissolution are 'low'. These factors are controlled within the manufacturing process.

4.4.3 Risk Assessment of Active Pharmaceutical Ingredient

A risk assessment of the API was performed to identify the characteristics that may affect tablet dissolution. The outcome of the initial risk assessment of the API is shown in Table 4.5.

Table 4.5 Initial risk assessment of the API

Drug Product cQA	API attributes	Risk Ranking
Dissolution	Particle size distribution	**High**
	Solubility	**High**
	Impurity	Low
	Residual Solvent	Low
	Chemical Instability	Low

Particle size distribution of the API that potentially has poor flow may negatively impact the compression stages. Smaller particles have the tendency to agglomerate as a result of increased van der Waals forces and cause non uniform distribution of the API. The dissolution rate can differ according to different particle sizes. Particle size can have a significant effect on the rate of dissolution as a smaller particle size with a larger surface area have shown to improve the dissolution profile (Savjani *et al.*, 2012).

Drug solubility, dissolution and gastrointestinal permeability are important parameters that control the rate and extent of drug absorption and bioavailability. Water solubility is an essential property that has an important role in drug absorption after oral administration. The drug solubility is an equilibrium measure, however, the dissolution rate at which the dosage form passes into solution is also important when the dissolution time is limited (Khadka *et al.*, 2014). The solubility of the API may impact dissolution. Ethionamide is practically insoluble in water which may potentially cause for failure in that it may result in below therapeutic levels. However this is the API characteristic thus the formulation and manufacturing process need to mitigate this risk. Weakly basic drugs such as ethionamide would dissolve faster when solvent pH is relatively low and tend to have a slower dissolution at higher solvent pH. When solvent pH is equal to the drug pKa, this weakly basic drug will exhibit the lowest solubility (Song *et al.*, 2004; Vale *et al.*, 2012). Therefore, the API particle size distribution (PSD) and the solubility of the API are graded as ‘high’ risk factors as these may potentially affect the extent of dissolution.

The dissolution is mainly affected by the solubility and its particle size distribution and is disparate from chemical stability. The formulation does not contain a solvent based granulation medium, instead a granulation medium containing purified water and povidone will be used. Impurity levels are controlled in the drug substance specifications ranges and are unlikely to affect the extent of dissolution. Product history suggests that the chemical stability, residual solvent and chemical instability are ‘low’ risk factors.

4.4.4 Failure Mode Effects Analysis

The FMEA method identified the cMAs and cPPS influencing the product cQA that has the potential of not meeting the QTPP. It also describes the effects of specific failure modes related to the respective formulation and process variables and it anticipates the possible causes of failure and the likelihood of failures before it may occur. The modes are prioritised

according to the seriousness of their effects, how frequently they occur and how easily they can be detected.

Table 4.6 is a partial listing of the cMAs and cPPs considered when doing the FMEA. The failure modes are categorised into those from the API, excipients and the manufacturing process. The process failure modes were further categorised by unit operations, which include dosing, wet mix and drying. The cMAs and cPPs with a RPN $\geq$ 50 were considered as high risk factors and will be further investigated using DoE. These factors include API particle size (µm), povidone binder quantity (% m/m), impeller speed during dosing (rpm), massing time (s), impeller speed during wet mix (rpm) and moisture content after drying wet granule (% m/m). The advantage of using this risk assessment tool, is that it facilitates systematically gathering the knowledge within the multidisciplinary team and it allows the information on the risks to be captured for future use. This is important for companies in which turnover results in the loss of institutional memory.

Table 4. 6 FMEA analysis of ethionamide 250 mg tablets depicting RPN of the failure modes

Attributes	Item	Process Step/Input	Potential Failure Mode	Potential Effect of Failure	Severity	Potential Cause for Failure	Occurrence	Current Risk Control	Detection	RPN
API	API particle size	Dissolution	Low solubility in purified water	Below therapeutic level	8	Chemical property of API	8	Control dissolution	1	64
Excipients	Povidone binder quantity	Dissolution	Low binding activation, slow dissolution	Compression problem, bio inequivalent to reference product	8	Incorrect quantity of binder in formulation	5	Quality control	2	80
Manufacturing process	Dosing	Dissolution	Impeller speed during dosing	Over granulation	8	Equipment changes, operator training	7	Determine range for impeller speed	1	56
	Wet mix	Dissolution	Massing time	Over granulate and under granulate	9	Unknown range (to be established)	8	Determine speed and duration of impeller	3	216
			Impeller speed	Over granulate and under granulate	9	Unknown range (to be established)	8		3	216
	Drying	Dissolution	Moisture content of intermediate bulk material	Over or under drying may cause physical tablet defects and poor granule flow. This may potentially affect the content uniformity and uniformity of mass	8	Temperature and time	5	Drying time and moisture content to be established	3	120

4.5 Design of Experiments

4.5.1 Screening trial batches

A screening experimental design identifies the significant factors affecting the product cQA. To best use the screening design, a risk analysis was performed and six factors were identified as potential high risk factors. These include API particle size, povidone binder quantity, impeller speed during dosing, massing time, impeller speed during wet mix and moisture content of the intermediate bulk material (after drying the wet granule). The screening design used in the study was a 2^{6-3} fractional factorial design. Being a resolution III design, the experimental design can estimate the significance of the main effects with high efficiency and accuracy, but it cannot separate the main effects from possible interactions (Myers *et al.*, 1995). However, as the goal of this design is to simply determine which of the factors has a significant effect on the responses such a design was considered to be sufficient to achieve this outcome. The effect of the six factors on the responses are summarised in Table 4.7 below

4.5.1.1 Effect of factors on the responses

Table 4.7 Screening trial batches: Summary of the tablet characteristics

Formulation	Average tablet hardness	Friability	Disintegration time	Average tablet mass	Average tablet thickness	Extent of dissolution
Units	**N**	**% m/m**	**s**	**mg**	**mm**	**% drug release at 15 minutes**
F-1	42.80 ± 5.14	0.90	156	498.61 ± 1.82	4.89 ± 0.01	100 ± 1.3
F-2	34.80 ± 2.20	2.70	31	501.87 ± 3.76	5.06 ± 0.02	105 ± 1.5
F-3	80.40 ± 3.75	0.20	538	499.97 ± 2.15	4.85 ± 0.02	47 ± 11.7

Formulation	Average tablet hardness	Friability	Disintegration time	Average tablet mass	Average tablet thickness	Extent of dissolution
Units	**N**	**% m/m**	**s**	**mg**	**mm**	**% drug release at 15 minutes**
F-4	78.40 ± 6.02	0.15	524	488.95 ± 2.37	4.80 ± 1.25	41 ± 4.4
F-5	29.80 ± 2.49	9.61	33	499.50 ± 3.32	5.20 ± 0.03	97 ± 2.8
F-6	49.20 ± 4.78	1.07	107	502.36 ± 2.60	5.03 ± 0.02	95 ± 1.4
F-7	39.50 ± 6.35	1.02	352	488.32 ± 1.90	4.83 ± 0.03	102 ± 2.8
F-8	58.50 ± 0.01	1.16	37	500.35 ± 3.84	5.27 ± 0.02	99 ± 1.9

Table 4.7 summarises the tablet characteristics of the screening trial batches. The effect of the selected input variables on each response will be discussed below in section 4.5.1.1.1 to 4.5.1.2.

4.5.1.1.1 Effect on tablet hardness

The Pareto chart compared the relative magnitude and the statistical significance of the main effects influencing tablet hardness. The effects are plotted in decreasing order of the absolute value of the effects as shown in Figure 4.1. The initial model F-value of 20.21 implied that the model is non-significant, where p=0.169. Massing time (s), as a non-significant term (p=0.951) and a term that showed the least impact on the response was removed from the model. Thereafter, the R^2 (pred) improved from 47.64% to 86.83%. The adjusted model with an F-value of 48.21 indicates the model is significant, implying that there is only a 2.00% chance that an F-value this large could occur due to noise (R^2 = 99.18%; p = 0.020). ANOVA analysis (Table 4.8) shows the significant factors influencing tablet hardness are moisture content (% m/m) and povidone binder quantity (% m/m).

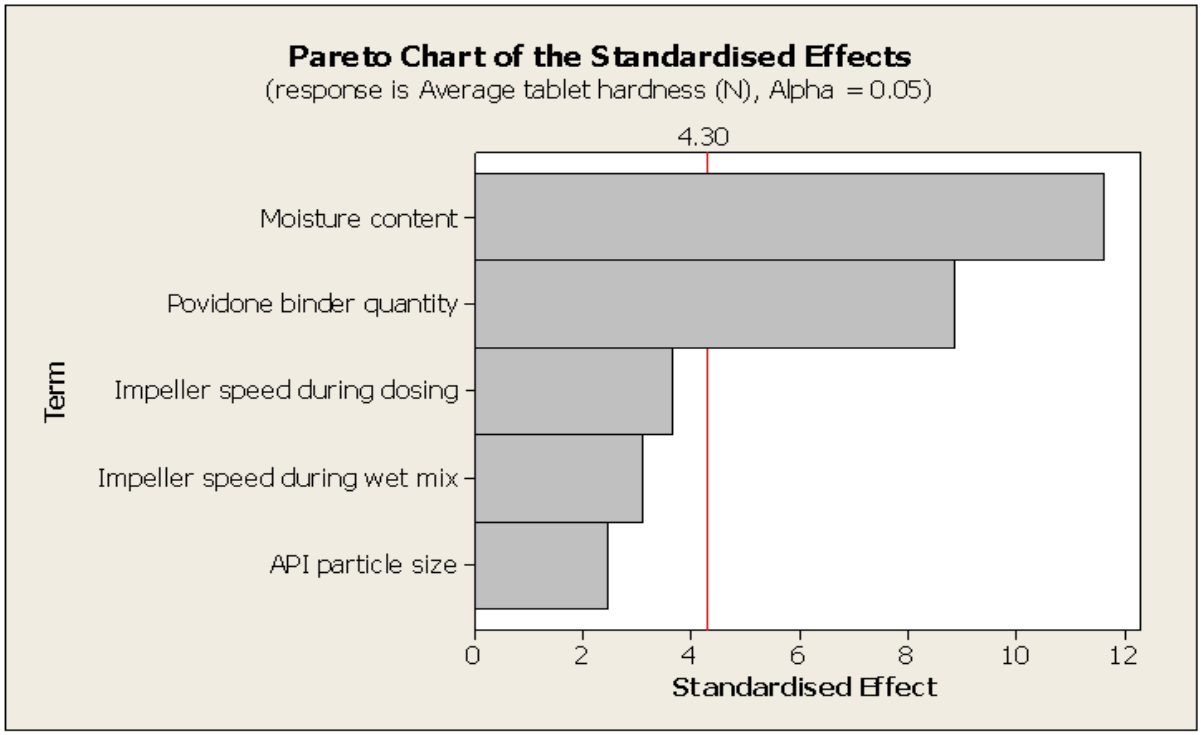


Figure 4.1 Pareto analysis of the adjusted model for the influence of the input variables influencing tablet hardness

Table 4.8 Summary of the ANOVA results of the adjusted model for tablet hardness

Term	Units	F-value	p-value	Comment
Model	-	48.21	0.020	Significant
API particle size	D_{50}, µm	5.90	0.136	Non-significant
Povidone binder quantity	% m/m	78.34	0.013	Significant
Impeller speed during dosing	rpm	13.12	0.068	Non-significant
Impeller speed during wet mix	rpm	9.49	0.091	Non-significant
Moisture content	% m/m	134.19	0.007	Significant

Table 4.7 shows that tablets formulated with a 5% m/m povidone binder quantity and dried to a moisture content of 3% m/m had the highest tablet hardness. Tablet hardness for these

batches i.e. F-4 and F-3 ranged from 78.40 N ± 6.02 to 80.40 N ± 3.75, respectively. On the contrary, granulation batches dried to a moisture content of 1% m/m showed lower compressibility and tablet hardness. This implies that moisture content after drying the wet granule had a prominent effect on tablet hardness. The two-dimensional contour plot **Figure 4.7**Figure 4.4 represents the interactive relationship between moisture content and povidone binder quantity and their influence on tablet hardness. At higher povidone binder quantities and increased moisture content, there was an increase in the average tablet hardness. Mangwandi and co-workers (2012) similarly observed that increasing the concentration of the binder increases the viscosity of the binder solution. It is expected that the strength of the granules would increase as the content of the povidone binder quantity is increased (Mangwandi *et al.*, 2012).

Batches F-2, F-5, F-6 and F-7 were dried to a moisture content of 1% m/m and the average tablet hardness for these batches were 34 N, 29 N, 49 N and 39 N, respectively. At the lower moisture content, tablets were friable. This demonstrates that moisture content is important for the mechanical strength of tablets. The moisture content increases the compact strength by increasing the tensile strength of the powder bed through a reduction in the density variation within the tablet. The reduction in tablet density variation can be accredited to the lubrication of the die wall (Nokhodchi, 2005). Garr and Rubinstein (1992) have demonstrated that moisture content is an important element for the mechanical strength of tablets. Reducing moisture content, increases the die-wall friction which contributes to an increase in stress ratio (Garr & Rubinstein, 1992). At an optimum moisture level, the die-wall friction is reduced which is due to the reduction in stress ratio. The increase in compact strength may be due to the hydrodynamic lubrication effect of moisture, which promotes compaction force transmission and formation of hydrogen bonds.

Although batches F-3 and F-4 compressed to an average tablet hardness of 80.40 N ± 3.75 and 78.40 N ± 6.02, their extent of dissolution at 15 minutes, were 47% and 41%, respectively. However, after 45 minutes, the extent of dissolution for these batches was above 80%. A higher compression may increase the specific surface and may enhance the dissolution. On the other hand, the high compression may also inhibit the wettability of the tablet, owing to the formation of a firmer and more effective sealing layer of the lubricant. The higher compression may also produce slower dissolution, at least in the initial period, because of an increased difficulty of fluid penetration into the compressed tablets (Jambhekar, 1997).

4.5.1.1.2 Effect on friability

Friability is the measure of the tablets ability to withstand abrasion and shock without crumbling during manufacture, packing, shipping and consumer use. This attrition resistance method determines the reduction in tablet mass and change in appearance by mimicking the kind of forces to which a tablet is subjected to during handling. Another application of the friability test is to detect incipient capping, as tablets with no visible defects can cap or laminate when stressed by an attrition method (Alderborn, 2013). The specification for tablet friability is not more than 1% in mass can be lost during friability testing (after 100 rotations/drops). When capping occurs during the friability testing, irrespective of the percentage loss, the outcome is a non-conforming batch and the possible cause needs to be investigated (World Health Organisation, 2013b).

The model F-value of 1.92 showed that the model is non-significant. There is only a 50.20 chance that an F-value this large could occur due to noise (R^2= 92.03%, p=0.502). The Pareto and ANOVA analysis shows that none of the selected input variables have a significant influence on friability as shown in Figure 4.2 and Table 4.9. The backward elimination technique did not show any significant terms in the model.

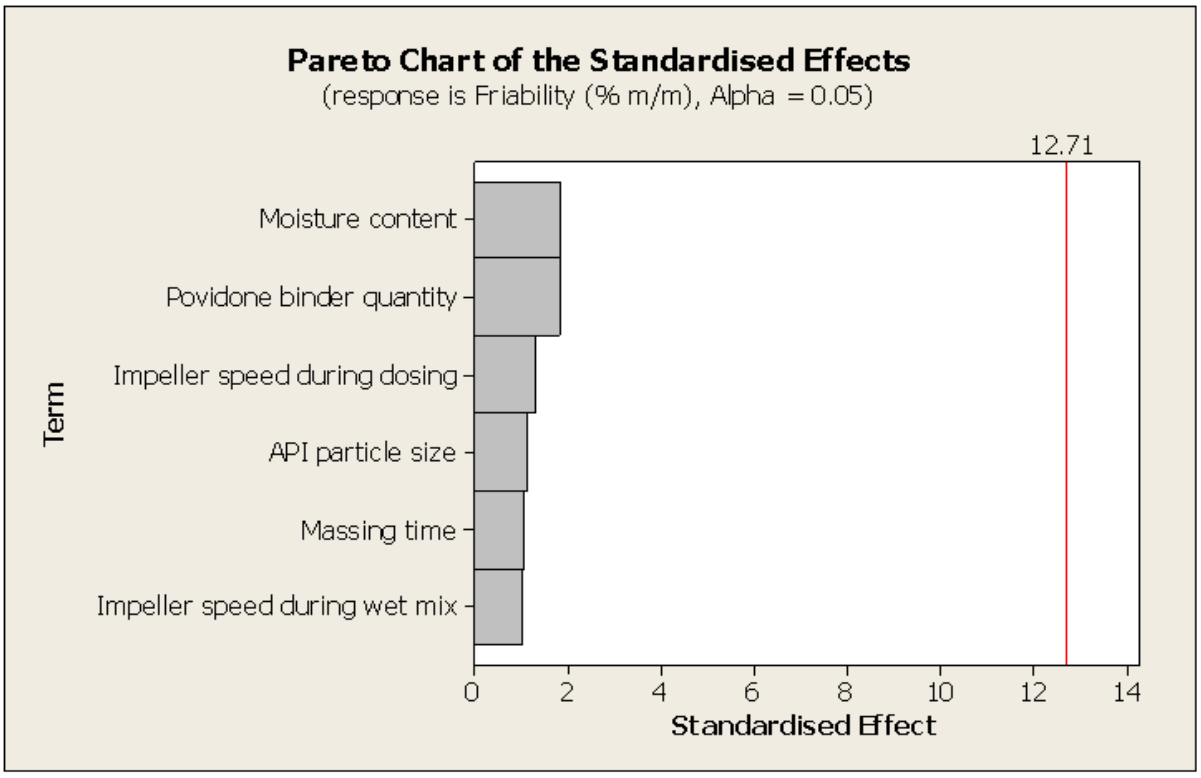


Figure 4.2 Pareto chart of the standardised effect for the input variables on friability

Table 4.9 ANOVA analysis of the initial model for the effect of the input variables on friability

Term	Units	F-value	p-value	Comment
Model	-	1.92	0.502	Non-significant
API particle size	D_{50}, µm	1.23	0.468	Non-significant
Povidone binder quantity	% m/m	3.24	0.323	Non-significant
Impeller speed during dosing	rpm	1.67	0.419	Non-significant
Massing time	s	1.13	0.481	Non-significant
Impeller speed during wet mix	rpm	1.02	0.497	Non-significant
Moisture content	% m/m	3.26	0.322	Non-significant

Table 4.7 shows friability improved as the average tablet hardness for each formulation increased. Although friability was lowest for formulation F-3 and F-4, povidone binder quantity was set at 5% m/m and the extent of dissolution at 15 minutes was slower, compared to the other batches. The low friability percentage for the formulations correlates to the average tablet hardness. Friability results showed that as the moisture content of the tablets decreased, the tablets became more friable. At higher povidone binder levels and increased moisture contents, the resistance to attrition improved.

4.5.1.1.3 Effect on disintegration time

The breakdown of tablets into smaller particles or granules is the first step for the drug substance to be in solution so it may be readily available for absorption. Disintegration tests are valuable in accessing the importance of material attributes and process parameters on the biopharmaceutical properties of tablets. However, complying with the specifications does not guarantee that the dosage unit will have an acceptable release profile and clinical effect

(Alderborn, 2013). For an uncoated immediate release tablet formulation, the pharmacopoeial limit for disintegration is 15 minutes (World Health Organisation, 2013b).

The initial model F-value of 23.08 indicates that the model is non-significant. There is only a 15.80% possibility that an F-value this large may occur due to noise. Massing time (s) has the smallest possibility of influencing disintegration (p=0.560) and as a non-significant term, it was removed from the model. Accordingly, the R^2 (pred) increased from 54.11% to 80.70%. The adjusted model with an F-value of 32.76 indicates the model is significant, implying that there is only a 3.00% chance that an F-value this large could occur due to noise (R^2 = 98.79%, p=0.030). The Pareto chart (Figure 4.3) compared the relative magnitude and the statistical significance of the main effects influencing disintegration time and ANOVA analysis of the model are summarised in Table 4.10. The significant factors influencing disintegration time are povidone binder quantity (% m/m) and moisture content (% m/m).

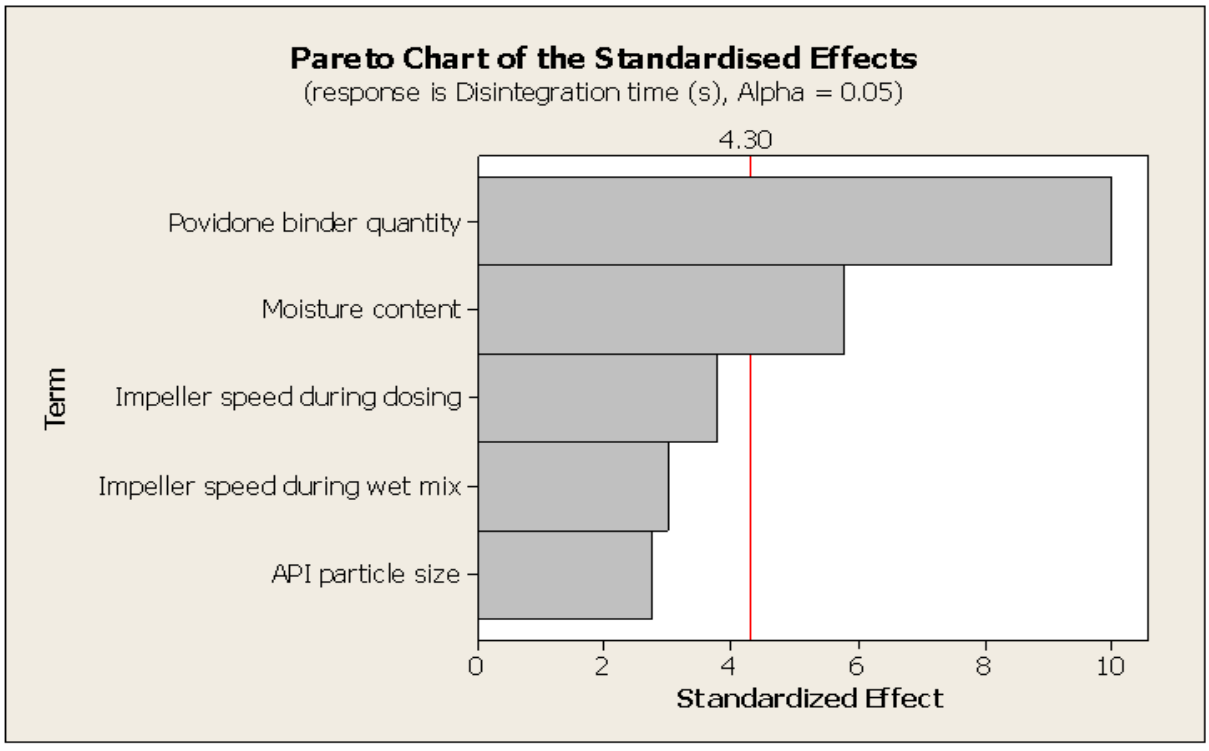


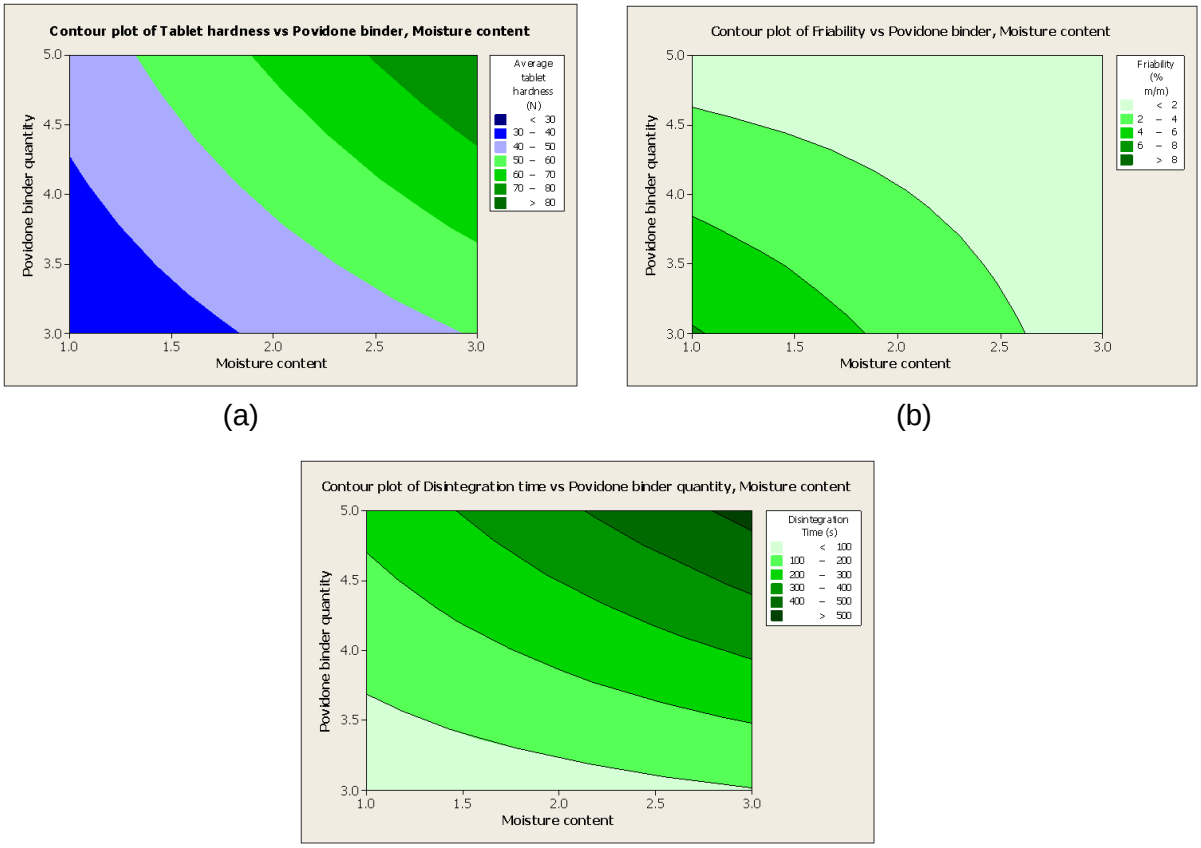
Figure 4.3 Pareto analysis of the adjusted model for the influence of the input variables influencing disintegration time

Table 4.10 ANOVA analysis of the adjusted model of tablet disintegration time

Term	Units	F-value	p-value	Comment
Model	**-**	32.76	0.030	Significant
API particle size	D_{50}, µm	7.56	0.111	Non-significant
Povidone binder quantity	% m/m	99.73	0.010	Significant
Impeller speed during dosing	rpm	14.02	0.064	Non-significant
Impeller speed during wet mix	rpm	9.01	0.095	Non-significant
Moisture content	% m/m	33.45	0.029	Significant

According to the data obtained from the screening trial, all the formulations were well within the pharmacopoeial disintegration time limit (Table 4.7). Formulation F-2 had the fastest disintegration time of 31 seconds and the lowest average tablet hardness of 34.80 N ± 2.20 compared to formulation F-3 that had the slowest disintegration time of 538 seconds (i.e. 8 minutes and 58 seconds) and highest average tablet hardness of 80.40 N ± 3.75. Batches F-6 and F-7, both contained 5% m/m povidone binder and dried to a 1% m/m moisture level and were compressed at 49.20 N ± 4.78 and 39.50 N ± 6.35 respectively. Although, both batches disintegrated within the acceptable times, friability test results were above 1% m/m.

Figure 4.4 shows that at a higher moisture content and higher povidone binder quantity, disintegration time was longer, tablets had a lower percentage friability and a higher average tablet hardness. Binders impart their cohesive qualities to the tablet formulation which ensures tablets remain intact after compression as well as improving the free-flowing qualities by the formulation of granules of desired hardness (Gaikwad & Kulkarni, 2013). The quantity of binder used has considerable influence on the characteristics of the compressed tablets. A higher percentage of binder quantity causes an extended disintegration time (Rupp, 2006).



(a) (b)

(c)

Figure 4.4 Contour plots showing the effect of povidone binder quantity and moisture content on the selected responses (a) tablet hardness (b) friability (c) disintegration time

4.5.1.2 Effects on product cQA

The disintegration test simply identifies the time required for the tablet to fragment under test conditions. The disintegration test does not offer any guarantee that the resultant particles (fragments) will release the drug in solution at the correct rate. The dissolution test describes the overall rate of all the processes involved in the release of the product into a bioavailable form for its systematic absorption (Alderborn, 2013; Nyol *et al.*, 2013).

The effect on the extent of dissolution for the initial model F-value of 15.60 demonstrates that the model is non-significant. There is only a 19.10% possibility that an F-value this large may occur due to noise. Impeller speed during wet mix as a non-significant term and as a term that had the lowest impact on dissolution (p=0.814) was removed from the analysis.

Accordingly, the R^2 (pred) increased from 32.34% to 81.56%. The adjusted model with an F-value of 34.31 indicated that the model is significant, implying that there is only a 2.90% chance that an F-value this large could occur due to noise (R^2= 98.85%, p=0.029). The significant factors were povidone binder quantity (% m/m), moisture content (% m/m) and impeller speed during dosing (rpm) relative to other factors influencing the extent of dissolution as shown in Figure 4.5 and Table 4.11.

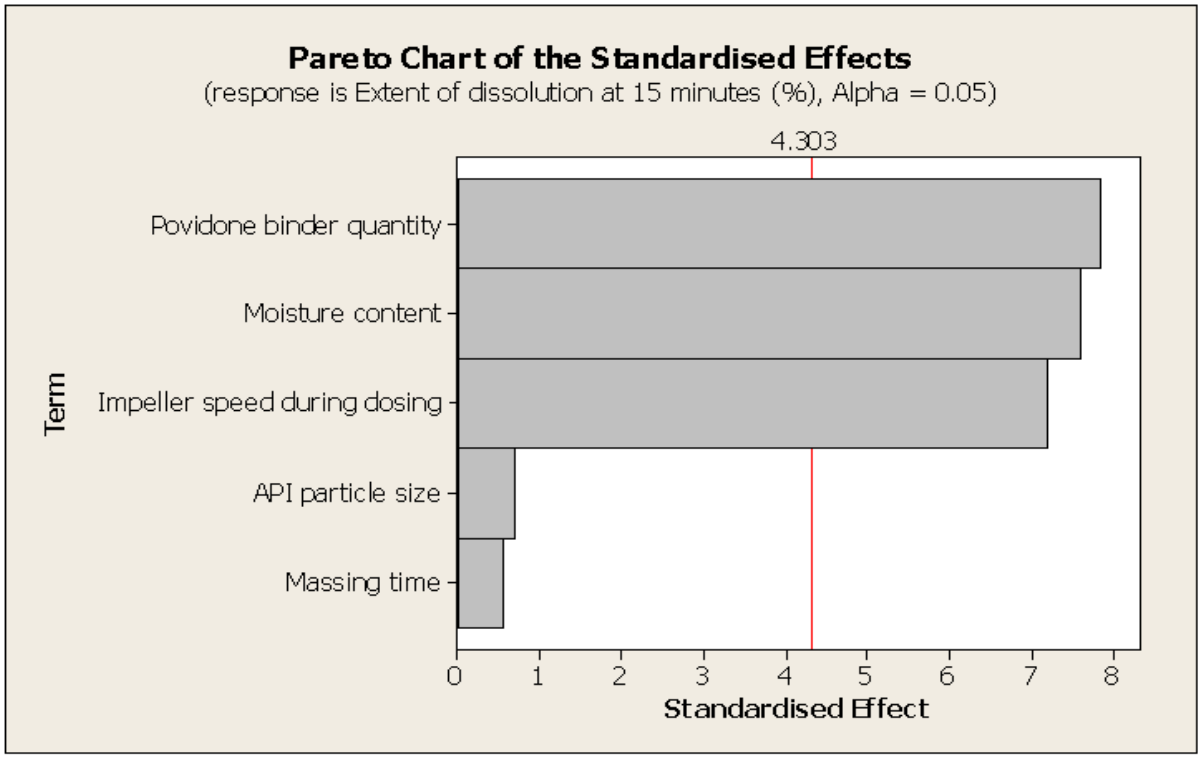


Figure 4.5 Pareto analysis of the adjusted model for the influence of the input variables influencing the extent of dissolution at 15 minutes

Table 4.11 ANOVA analysis for the extent of dissolution at 15 minutes for the screening trial batches

Term	Units	F-value	p-value	Comment
Model	-	34.31	0.029	Significant
API particle size	D_{50}, µm	0.46	0.568	Non-significant
Povidone binder quantity	% m/m	61.72	0.016	Significant
Impeller speed during dosing	rpm	51.54	0.019	Significant
Massing time	s	0.29	0.642	Non-significant
Moisture content	% m/m	57.54	0.017	Significant

The dissolution samples were analysed by UV-spectrophotometry as described in Section 3.3.4.1. The mean cumulative release dissolution profile (n=6) at time intervals 10, 15, 20, 30 and 45 minutes are shown in Figure 4.6.

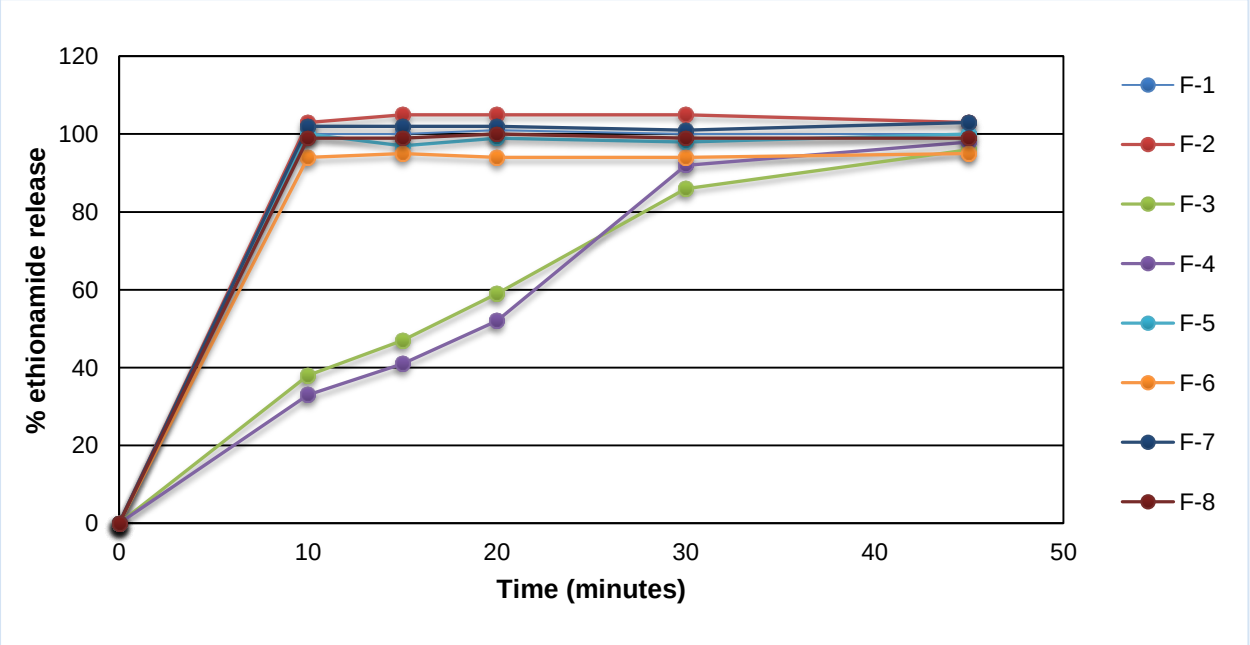
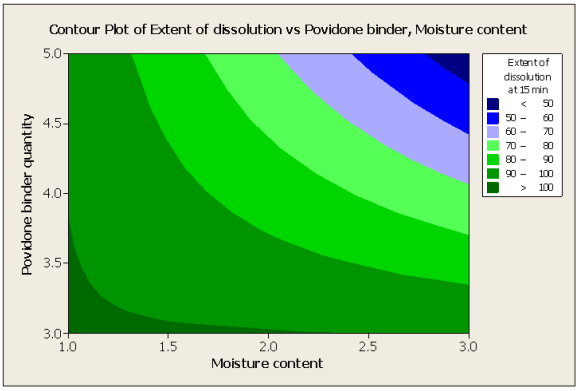


Figure 4.6 Screening trial batches: A release dissolution profile of ethionamide 250 mg tablets

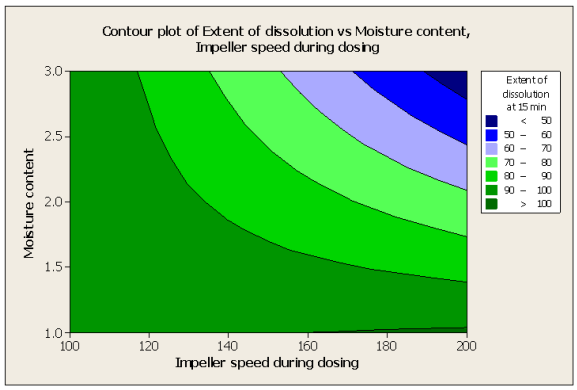
At time point 15 minutes the extent of dissolution varied from 41% (F-4) to 102% (F-7) for the various factor combinations (Table 4.7). Screening trial batches F-3 and F-4 containing 5% m/m povidone binder, dosed at an impeller speed of 200 rpm and dried to a moisture content of 3% m/m, held the better attrition resistance (<1% m/m after 4 minutes) and tablet compressibility. However, at the selected input variable settings, the extent of the dissolution at 15 minutes was the slowest compared to the other screening trial batches. Notably, tablets compressed at the lower ranges, disintegrated at a faster rate and showed a higher % ethionamide release during dissolution testing at the 15 minute time point. At lower moisture content, granules were more brittle and tablets were found to be more friable. This may be due to an increase in the die wall friction, which contributes to an increase stress ratio at lower moisture content levels.

During wet massing, granule coalescence and growth may take place but large granules may also undergo breakage until a steady state PSD is achieved. In addition, during wet massing granule densification may take place which can affect granule liquid saturation and the mechanical properties (Badaway *et al.*, 2012). Woyna-Orlewicz and Jachowics (2011) reported that the impeller blade speed affects collisions between granules and at high levels of impeller speed during wet mix and massing time, could lead to the manufacture of tablets of unacceptable dissolution. However, for this study, impeller speed during wet mix and the duration thereof, did not impact the responses.

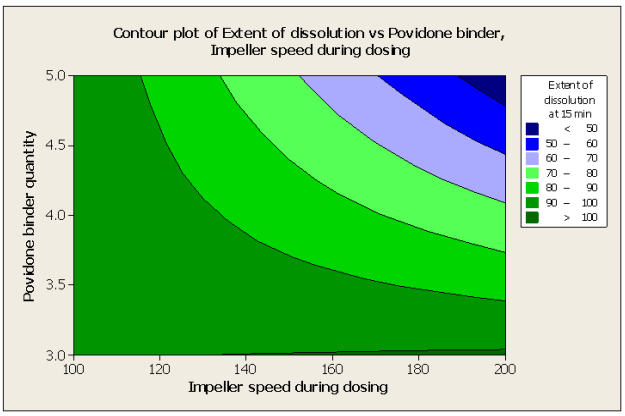
Additionally, dosing plays an important role in the compression characteristics of the granules and on the extent of dissolution. Increasing the impeller speed generally leads to a decrease in granule size and an increase in growth rate. At higher impeller speeds better distribution of the binder over the powder bed is ensured (Benali *et al.*, 2009; Chitu *et al.*, 2011a). A powder bed that is cohesive may flow better if its moisture content is increased. However, too much moisture may result in capillary bonding between particles and flow may be compromised by the increased particle-particle adhesion. In addition, the higher compression reduces the extent of dissolution due to the reduction of fluid penetration into the compressed tablets. Figure 4.7 (a), (b) and (c) represents a 2-dimentional graphical contour plot of the relationship between povidone binder quantity, impeller speed during dosing and moisture content, and their influence on the extent on dissolution.



(a)



(b)



(c)

Figure 4.7 Contour plots showing the effect of povidone binder quantity, moisture content and impeller speed during dosing on the extent of dissolution at 15 minutes

Screening trial batches have shown that to distend the extent of dissolution while still maintaining an acceptable tablet hardness, a friability of less than 1% m/m loss and a disintegration time within the acceptable limit, the povidone binder quantity can be maintained constant at a recommended 4% m/m (Figure 4.8). Therefore, the RSM will focus primarily on the optimisation of the manufacturing process. The factors evaluated in the succeeding experimental plan are moisture content after drying (% m/m) and impeller speed during dosing (rpm).

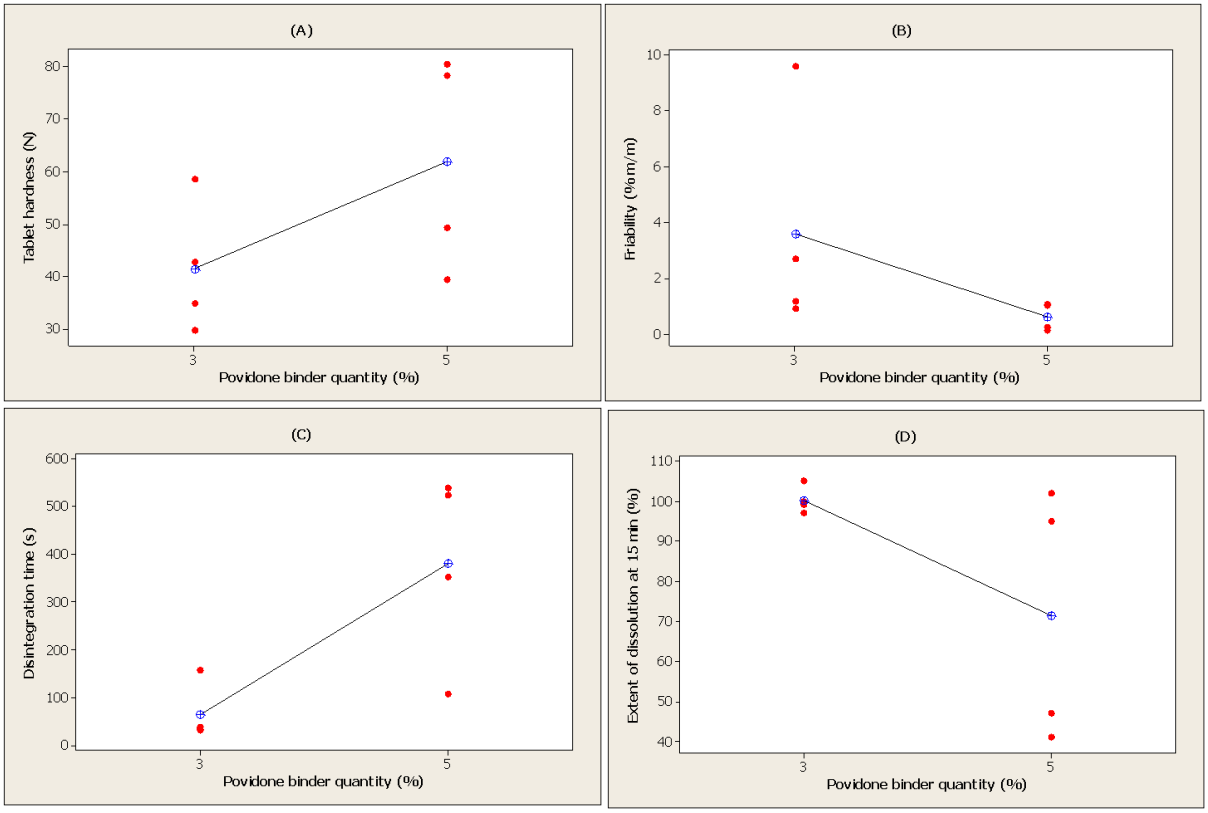


Figure 4.8 Graphical representation of the effects of the quantity of povidone binder between the range of 3% m/m to 5% m/m on (a) tablet hardness (b) friability (c) disintegration and (d) the extent of dissolution at 15 minutes

Although ethionamide is practically insoluble in water at neutral pH, the dissolution medium used during dissolution testing is a 0.1 M HCl medium that facilitates the complete dissolution as ethionamide is a weakly basic drug. It was shown that API particle size range did not impact dissolution and, therefore, does not pose a high risk of obtaining a low therapeutic level. By reason of having a larger quantity of API available with a particle size D_{50}, 95.18 µm compared to 267.00 µm and maintaining batch to batch consistency, the low level (-1) was selected for the subsequent RSM study. Impeller speed during wet mix and duration of the wet mix did not have a significant influence on dissolution, suggesting that at these ranges, a homogenous granulation can be obtained. For the RSM, the non-significant factors, massing time was set at centre point level, API particle size at low level and impeller speed during wet mix at low level. The final tablet composition of ethionamide 250 mg tablets is summarised in Table 4.12. This formulation will be used in the subsequent response surface methodology.

Table 4.12 Formulation composition of ethionamide 250 mg tablets

Formula ingredient	Quantity per unit dose	Total Quantity
Ethionamide	250.00 mg	1425.00 g
Microcrystalline cellulose	64.50 mg	367.65 g
Lactose monohydrate	150.50 mg	857.85 g
Sodium starch glycolate	5.00 mg	28.50 g
Povidone	20.00 mg	114.00 g
Purified water	q.s.	350.00 ml
Sodium starch glycolate	5.00 mg	28.50 g
Magnesium stearate	5.00 mg	28.50 g
Total	**500.00 mg**	**2850.00 g**

4.5.2 Pivotal trial batches

Once the significant factors affecting the product cQA were identified, it was essential to optimise the levels of the selected manufacturing process variables. Optimisation is considered as an efficient and economical method to understand the relationship between independent and dependent variables (Bushra *et al.*, 2008). Based on the screening trial study results, impeller speed during dosing and moisture content after drying the wet granule were selected for the optimisation study, using response surface methodology, more specifically a CCRD. In this two factor CCRD, 13 experimental runs were generated, containing four cube points, five centre points in cube, four axial points and zero centre points in the axial. The experimental runs were completed according to the experimental plan depicted in Section 3.2.4.2. The level for each factor is neither too close nor too far away from each other so that the edge of failure is exceeded. Consequently, this reduces the probability to miss the optimum effect. Each experiment represents a different condition with a different set of factors. CCRD for the pivotal trial batches were performed to create a broader design space. Knowing that the investigated input variables have a significant

impact on the product cQA, it is important to set their operational ranges at levels that provide a quality product with a robust manufacturing process. In contrast to the screening design where the generated model is only sufficient for qualitative determination of the main effects, the CCRD allows the generation of a more predictive model.

4.5.2.1 Effect of significant factors on the responses

Table 4.13 summarises the tablet characteristics of the pivotal trial batches. The effect of the impeller speed during dosing and the moisture content on the selected responses will be discussed below in Section 4.5.2.1.1 to 4.5.2.2.

Table 4.13 Pivotal trial batches: Summary of the tablet characteristics

Formulation	Average tablet hardness	Friability	Disintegration time	Average tablet mass	Average tablet thickness	Extent of dissolution (at 15 minutes)
Units	**N**	**% m/m**	**s**	**mg**	**mm**	**%**
FT-1	66.30 ± 6.77	0.08	180	496.63 ± 4.23	4.81 ± 0.04	99 ± 2.20
FT-2	73.30 ± 7.01	0.08	370	502.41 ± 3.19	4.91 ± 0.05	78 ± 15.50
FT-3	71.70 ± 2.83	0.15	208	499.01 ± 4.06	4.77 ± 0.02	100 ± 1.00
FT-4	91.00 ± 6.53	0.07	336	498.43 ± 4.43	4.82 ± 0.02	81 ± 14.50
FT-5	66.70 ± 5.50	0.11	201	502.34 ± 2.86	4.89 ± 0.04	96 ± 1.00
FT-6	78.90 ± 5.95	0.09	347	505.90 ± 3.93	4.88 ± 0.03	91 ± 2.40
FT-7	72.50 ± 6.02	0.05	293	496.90 ± 2.83	4.82 ± 0.02	92 ± 1.70

Formulation	Average tablet hardness	Friability	Disintegration time	Average tablet mass	Average tablet thickness	Extent of dissolution (at 15 minutes)
Units	**N**	**% m/m**	**s**	**mg**	**mm**	**%**
FT-8	67.40 ± 4.67	0.11	305	501.72 ± 2.77	4.92 ± 0.03	99 ± 1.40
FT-9	66.90 ± 5.13	0.05	276	500.98 ± 2.28	4.88 ± 0.03	97 ± 0.80
FT-10	73.30 ± 5.66	0.05	250	500.23 ± 2.35	4.87 ± 0.03	95 ± 2.50
FT-11	63.00 ± 5.89	0.05	345	498.00 ± 3.30	4.95 ± 0.18	78 ± 11.20
FT-12	69.30 ± 5.40	0.08	230	499.50 ± 2.62	4.93 ± 0.04	91 ± 10.80
FT-13	69.30 ± 3.56	0.17	227	504.47 ± 1.76	4.89 ± 0.03	96 ± 1.50

4.5.2.1.1 Effect on tablet hardness

The quadratic model was used for the analysis of tablet hardness. ANOVA analysis of the model for the response showed that the model (quadratic) chosen for the analysis did not have a significant fit relative to the noise with an F-value of 1.21 ($p=0.395$, $R^2= 46.29\%$) and a lack of fit test showed that there was a non-significant lack of fit relative to the pure error ($p=0.212$). None of the terms for this model were significant ($p>0.05$). An Adj R^2 of 7.93% was obtained, the Pred R^2 of -1.745 (0.00%) implies that the overall mean would be a better predictor of tablet hardness and a signal to noise ratio of 3.79 indicates that this model will not be used to create the design space. ANOVA analysis for the effect on tablet hardness is shown in Table 4.14.

Table 4.14 ANOVA analysis for linear, interaction and squared effects on tablet hardness.

Source		F-value	p-value	Comment
Regression		1.21	0.395	Non-significant
Model	Linear	0.43	0.665	Non-significant
Terms	Impeller speed during dosing	0.86	0.386	Non-significant
	Moisture content	0.01	0.928	Non-significant
Model	Square	2.21	1.81	Non-significant
Terms	Impeller speed during dosing * Impeller speed during dosing	2.75	0.141	Non-significant
	Moisture content * Moisture content	1.13	0.322	Non-significant
Model	Interaction	0.75	0.414	Non-significant
Terms	Impeller speed during dosing * Moisture content	0.75	0.414	Non-significant
Lack of Fit		2.37	0.212	Non-significant

Figure 4.9 represents the contour and surface plot of the effect of impeller speed during dosing and moisture content on tablet hardness which represents a saddle graph. Near the centre (saddle) of the graph, increasing either input variable (i.e. dosing impeller speed or moisture content) while decreasing the other leads to an increase in the average tablet hardness. The quadratic equation (Equation 4.1) derived from the model used to makes predictions about the response is shown below, where A is the dosing impeller speed during dosing and B is moisture content.

$$Tablet\ Hardness = 20.72 - 3.12\ A + 183.13\ B + 0.476\ AB + 0.0069\ A^2 - 44.28\ B^2$$

[Equation 4.1]

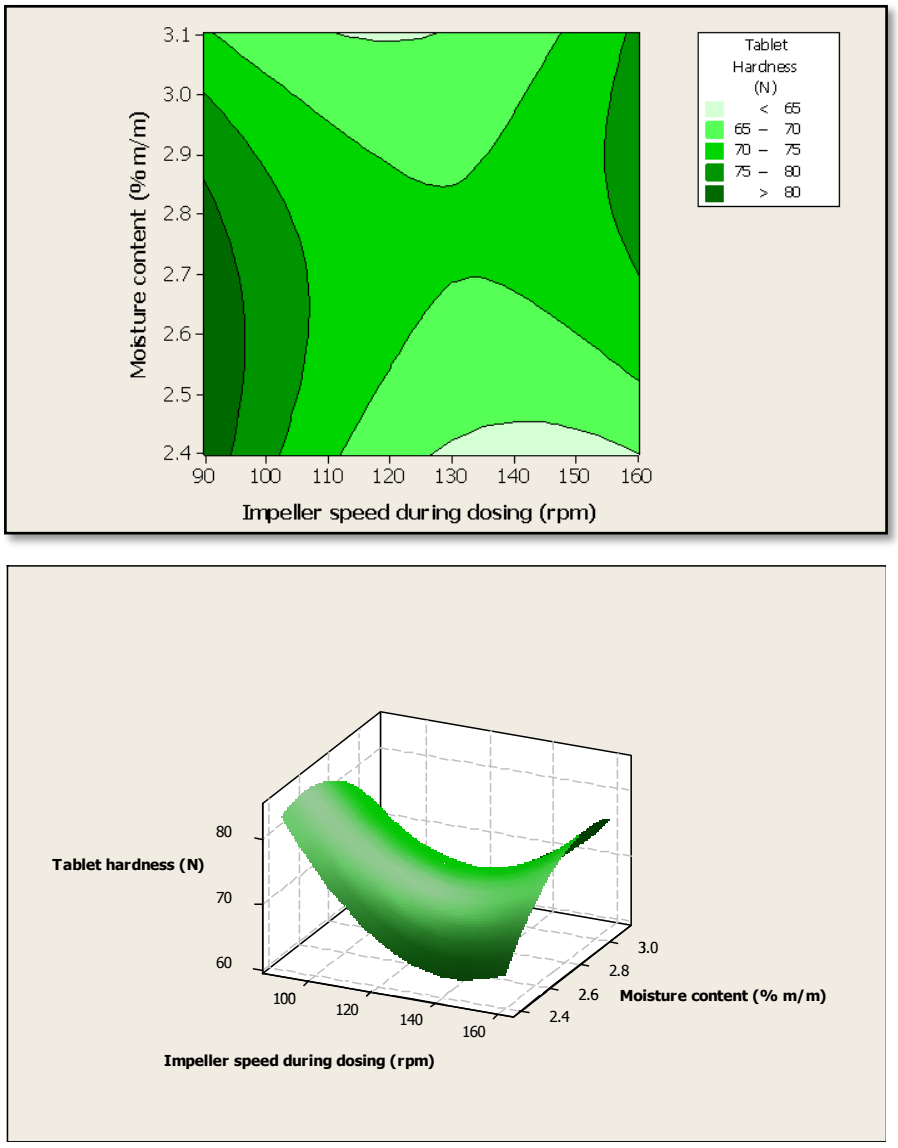


Figure 4.9 Contour plot and surface plot of the effect of impeller speed during dosing and moisture content on tablet hardness

Table 4.13 summarises the tablet characteristics and % drug release for dissolution at 15 minutes for the pivotal trial batches. All the batches demonstrate an acceptable friability and disintegration time. Of the batches, batch FT-4 had the highest residual (8.655) and highest standard residual with an absolute value greater than 2 (2.06). This suggests that tablet hardness for batch FT-4 does not follow the proposed regression equation well, and may not fit well by the response surface model. However the analysis of the model has shown a non-significant lack of fit for tablet hardness. The minimum and maximum values for the average tablet hardness, where the batches had shown a standard residual less than 2 may be used to establish a suitable hardness range. A potential range for the average tablet hardness

may be set between 66 N and 78 N and a tablet thickness range between 4.77 mm and 4.95 mm.

4.5.2.1.2 Effect on friability

The linear model was used for the analysis of friability. ANOVA analysis of the model for the response showed that the model (linear) chosen for the analysis has a significant fit relative to the noise with an F-value of 4.86 (p=0.034, R^2= 49.29%) and a lack of fit test showed that there was a non-significant lack of fit relative to the pure error (p=0.379). Of the factors analysed, only moisture content (% m/m) was significant with an F-value of 9.59 (p=0.011). The Pred R^2 of 8.55% is not as close to the Adj R^2 of 39.15% as one would expect. The signal to noise ratio of 6.45 indicates adequate signal and that this model may be used to navigate the design space.

No interaction between the factors were evident, indicating that, while moisture content had an effect on friability, there was no significant interaction (p=0.809). Therefore, the effect of dosing impeller speed on friability does not depend on moisture content and one factor can be changed independent of the other between impeller speed during dosing and moisture content. ANOVA analysis for the effect on friability is shown in Table 4.15.

Table 4.15 ANOVA analysis for the linear model on friability

Source		F-value	P-value	Comment
Regression		4.86	0.034	Significant
Model	Linear	4.86	0.034	Significant
Terms	Impeller speed during dosing	0.13	0.723	Non-significant
	Moisture content	9.59	0.011	Significant
Lack of Fit		1.43	0.379	Non-significant

Figure 4.10 represents the contour and surface plot of the effect of impeller speed during dosing and moisture content on tablet friability, which represents a stationary ridge surface graph. This graph suggests that the ranges used for moisture content and impeller speed

during dosing will result in a friability of less than 1% m/m, which is acceptable according to the pharmacopeia standard. The linear equation (Equation 4.2) derived from the model used to makes predictions about the response is shown below, where A is the dosing impeller speed during dosing and B is moisture content.

$$Friability = 0.421 + 1.507 \times 10^{-4} A - 0.128\, B$$

[Equation 4.2]

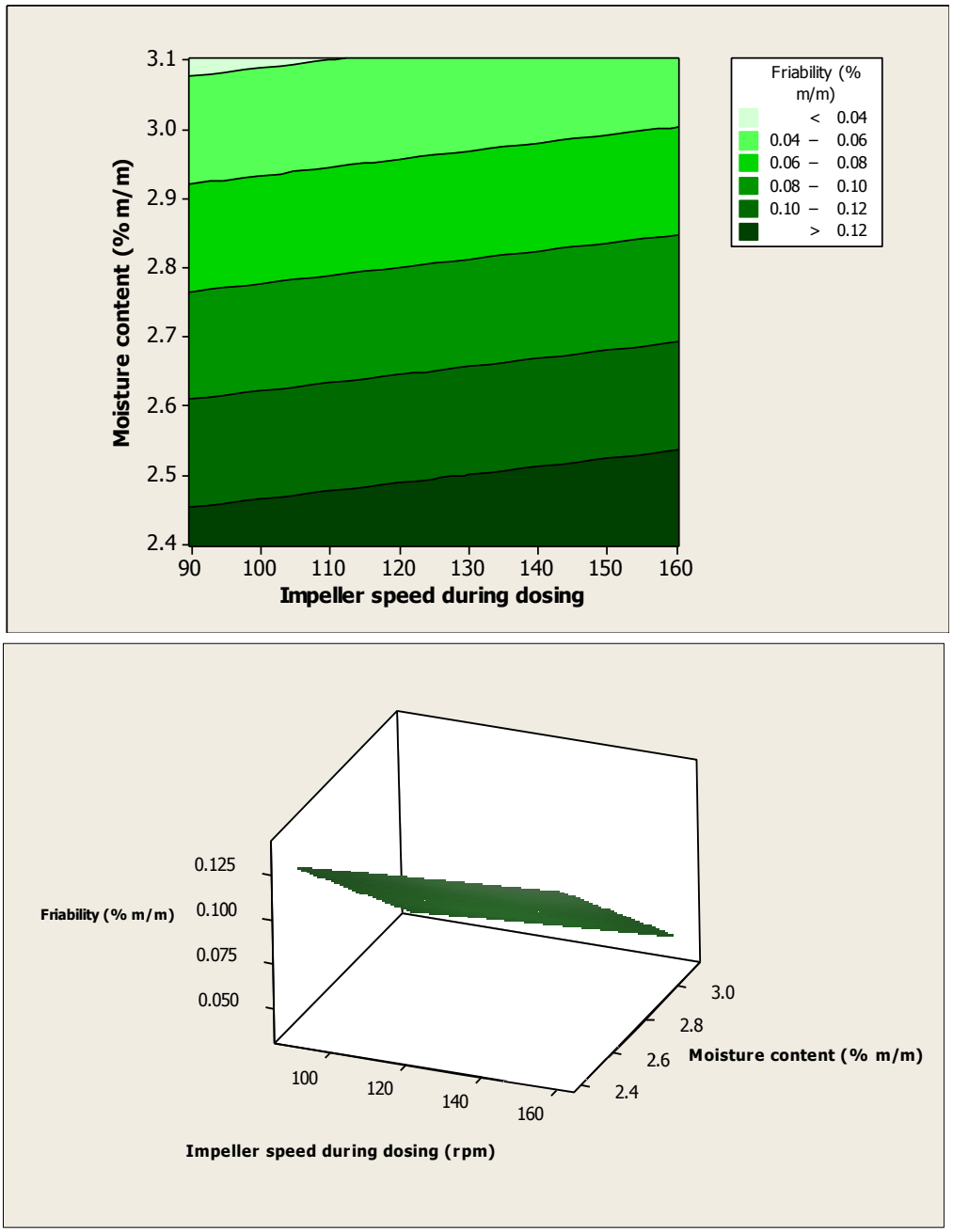


Figure 4.10 Contour plot and surface plot of the effect of impeller speed during dosing and moisture content on friability

4.5.2.1.3 Effect on disintegration time

The quadratic model was used for the analysis of the disintegration time. ANOVA analysis of the model for the response showed that the model (quadratic) chosen for the analysis has a non-significant fit relative to the noise with an F-value of 1.91 (p=0.211, R^2= 57.72%) and a lack of fit test showed that there was a non-significant lack of fit relative to the pure error (p=0.766). There are no significant model terms as p>0.05, as shown in Table 4.16. An Adj R^2 of 27.52% was obtained and the Pred R^2 of -0.194 (0.00%) suggests that the overall mean may be a better predictor of disintegration time. The range of predicted values at design points to the average prediction error of 5.01 was obtained. This model will not be used to create the design space.

Table 4.16 ANOVA analysis for the linear, interaction and squared effects on disintegration time

Source		F-value	p-value	Comment
Regression		1.91	0.211	Non-significant
Model	**Linear**	1.29	0.334	Non-significant
Terms	Impeller speed during dosing	0.01	0.924	Non-significant
	Moisture content	2.57	0.153	Non-significant
Model	**Square**	3.27	0.099	Non-significant
Terms	Impeller speed during dosing * Impeller speed during dosing	3.23	0.115	Non-significant
	Moisture content * Moisture content	2.47	0.160	Non-significant
Model	**Interaction**	0.43	0.531	Non-significant
Terms	Impeller speed during dosing * Moisture content	0.43	0.531	Non-significant
Lack of Fit		0.39	0.766	Non-significant

Figure 4.11, a contour and surface plot of moisture content and dosing impeller speed during dosing and their effect on the disintegration time represents a saddle graph. Near the centre (saddle) of the graph, increasing either input variable (i.e. dosing impeller speed or moisture content) while decreasing the other leads to an increase in the disintegration time. The polynomial equation (Equation 4.3) derived from the model used to makes predictions about the response are shown below, where A is the dosing impeller speed during dosing and B is moisture content.

$$Disintegration\ time = 271.60 + 1.89\ A + 30.50\ B - 17.75\ AB + 36.70\ A^2 - 32.05\ B^2$$

[Equation 4.3]

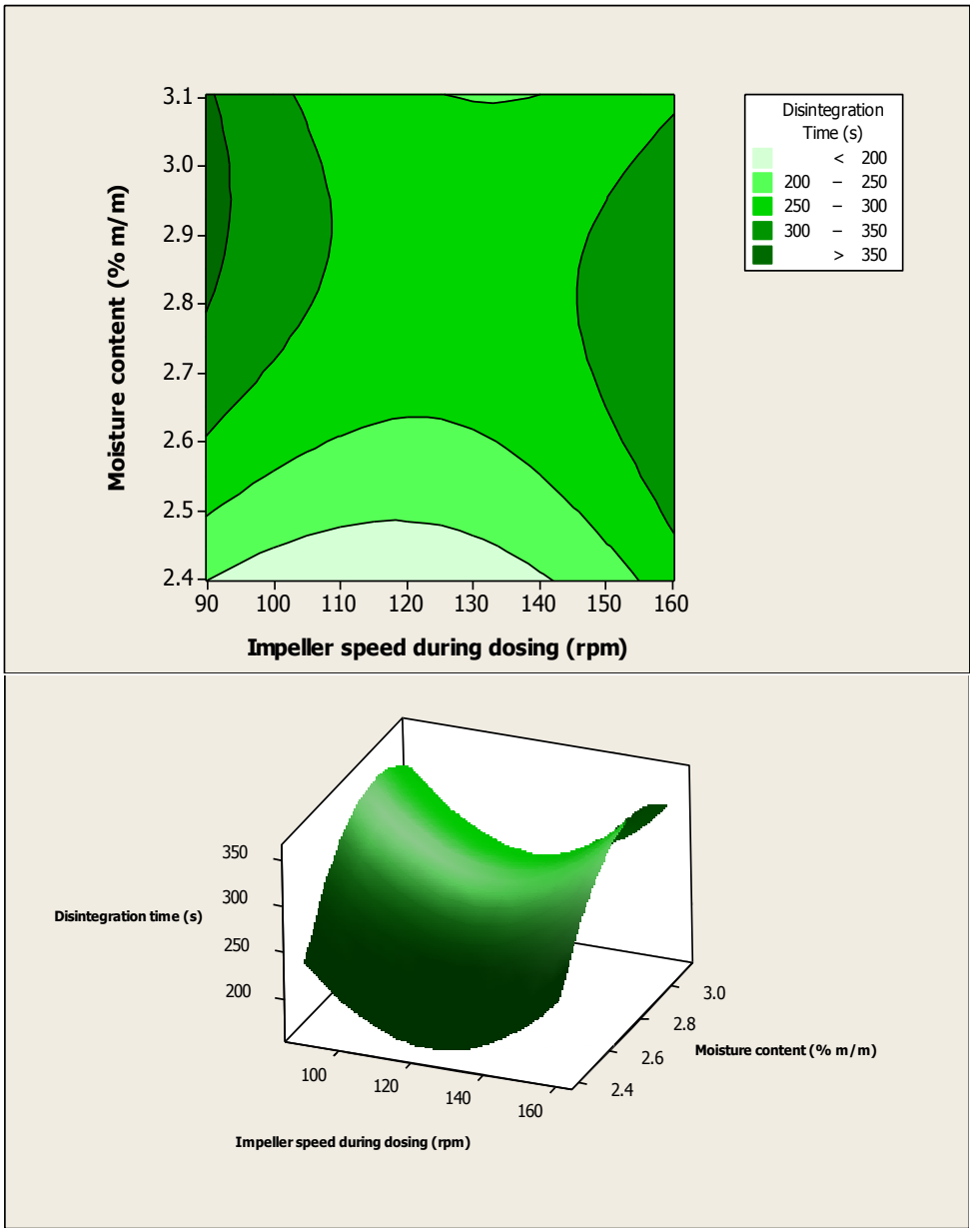


Figure 4.11 Contour and surface plot of the effect of impeller speed during dosing and moisture content on disintegration time

4.5.2.2 Analysis of product cQA

A quadratic model (polynomial equation) was used to analyse the extent of dissolution. ANOVA analysis of the model for the response showed that the model (quadratic) chosen for the analysis had significant fit relative to the noise with an F-value of 4.90 (p=0.030) and a lack of fit test showed that there was a non-significant lack of fit relative to the pure error (p=0.125), indicating that this model may be used to evaluate the design space. Of the squared terms for this model, dosing impeller speed has a significant effect with an F-value of 14.38 (p=0.006). This implies that there is significant curvature in the response surface. Analysis of the main effects for the extent of dissolution showed that only moisture content was significant, where p=0.047. No significant interactions where noted between the selected factors. ANOVA analysis for dissolution at 15 minutes are summarised in Table 4.17.

Table 4.17 ANOVA analysis of the for the linear, square and interaction effects on the extent of dissolution at 15 minutes

Source		F-value	p-value	Comment
Regression		4.90	0.030	Significant
Model	**Linear**	2.99	0.115	Non-significant
Terms	Impeller speed during dosing	0.18	0.688	Non-significant
	Moisture content	5.80	0.047	Significant
Model	**Square**	7.54	0.018	Significant
Terms	Impeller speed during dosing * Impeller speed during dosing	14.38	0.006	Significant
	Moisture content * Moisture content	0.00	0.958	Non-significant

Source		F-value	p-value	Comment
Model	**Interaction**	3.44	0.106	Non-significant
Terms	Impeller speed during dosing * Moisture content	3.44	0.106	Non-significant
Lack-of-Fit		3.58	0.125	Non-significant

The polynomial equation (Equation 4.4) derived from the model used to makes predictions about the response is shown below, where A is the dosing impeller speed during dosing and B is moisture content.

$$Dissolution = 195.97 + 0.89\,A - 97.74\,B + 0.72\,AB - 0.011\,A^2 - 1.60\,B^2$$

[Equation 4.4]

The quadratic model was adequate to characterise the data since a non-linear relationship exists between impeller speed during dosing and the product cQA. This demonstrates the benefit of using a 5-level design as opposed to a 2-level factorial design, where the range of experimental data was wide enough to detect the statistically significant variation. As shown in Figure 4.12 to maximise the extent of dissolution of the immediate release tablet above 85% drug release at 15 minutes, impeller speed during dosing should be within the region of 90 rpm to 150 rpm and a 2.5 % m/m to 2.8% m/m range for the moisture content level.

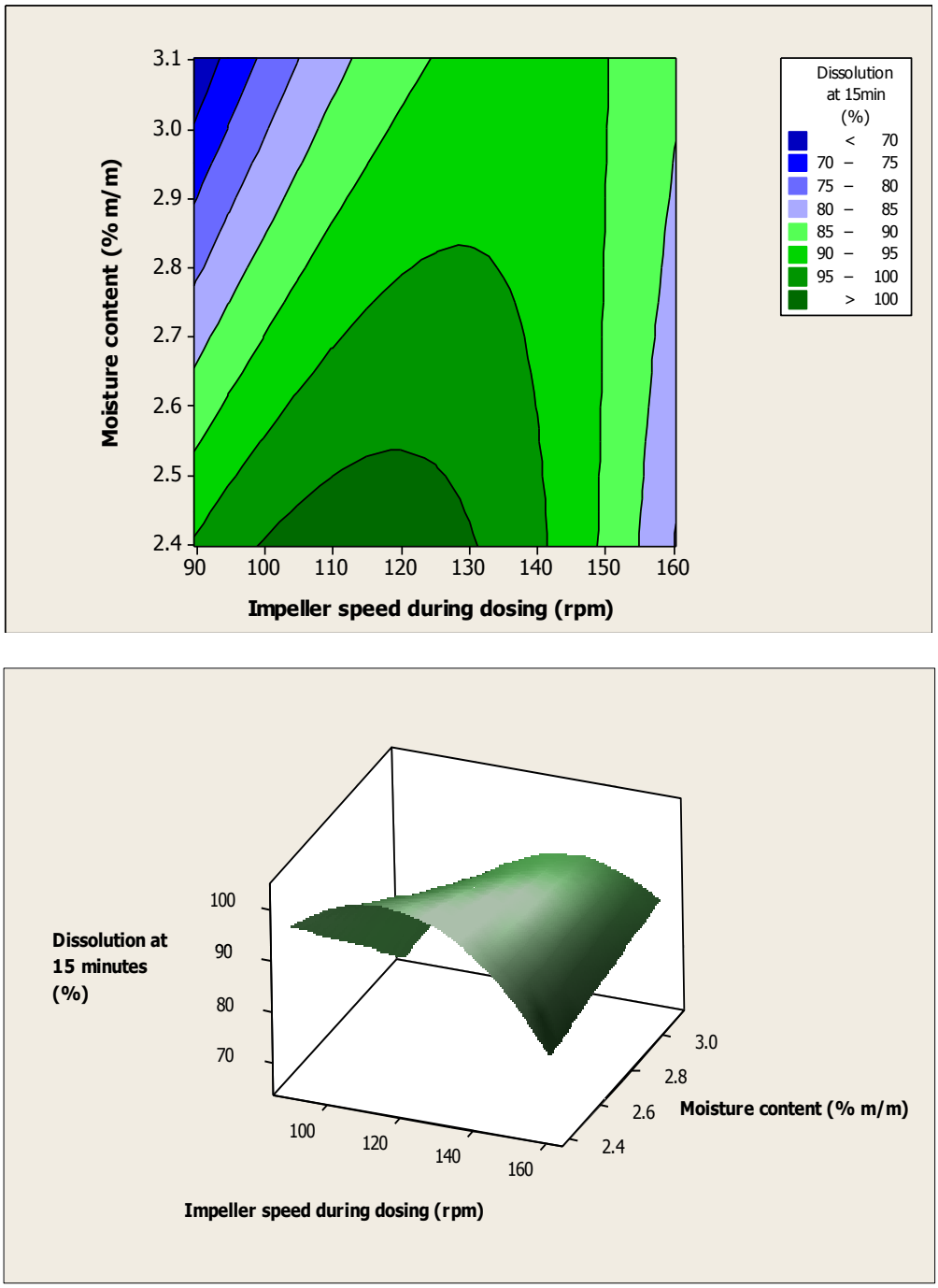


Figure 4.12 Contour and surface plot of the effect of moisture content and impeller speed on the extent of dissolution at 15 minutes

The impeller speed during dosing allowed for efficient distribution of the granulating medium over the powered bed, rendering the particle surfaces sticky enough to allow coalescence. Badaway and co-workers (2012) reported that at a higher moisture content a higher fraction of the void spaces within the granule are filled with liquid, which increases liquid saturation of

the granule, thus enhancing granule coalescence. The moisture content may be required for the binding of granule during compression in the die cavity. The higher liquid saturation makes the granule easily deformable and results in more liquid available to the granule surface both of which increases the probability of effective coalescence upon granule collision (Badaway *et al.*, 2012). In addition, moisture may act as a lubricant which reduces inter-particulate friction within the granule. Hence, facilitating particle movement within the granules in response to densifying forces in the high shear granulation (Iveson *et al.*, 2001). Similarly Nokhodchi and co-workers (1995) demonstrated that moisture played a significant role in the compaction process. This may be due to the water forming a 'monomolecular' layer around the API particles. This tightly bound water can be regarded as part of the surface molecular structure of the particles, which facilitates the formation of interparticle hydrogen bonding that may increase van der Waals forces, thus smoothing out the surface micro irregularities and reducing interparticle separation. In addition, the formation of pendular bonds on the particle surfaces would be expected to contribute to compact strength. At the impeller speed and moisture content ranges for the pivotal trial batches, tablets have shown an acceptable hardness and met the specification for friability and disintegration time in addition to having an acceptable dissolution profile which may be the consequence of adequate fluid penetration into the compressed tablet during drug release analysis.

In general, physical defects such as capping and chipping caused by low moisture levels or sticking and picking caused by high moisture levels are typical tablet defects (Rana & Hari-Kumar, 2013). However, these defects were not evident, and the physical appearances were found to be satisfactory. At the ranges for the selected input variables, friability and disintegration time were within the specifications. For a drug to be readily available to the body it must be in solution and the first fundamental step towards solution is the breakdown of a tablet into smaller particles. The limit for an uncoated immediate release tablet to disintegrate is 15 minutes (900 seconds). Most batches presented fast disintegration time, except batch F-2 that had a disintegration time of 6 minutes 10 seconds and tablets from batch F-11 disintegrated at 5 minutes 45 seconds, but were still well within the required limit of 15 minutes as shown in Table 4.13.

The results of the disintegration only identified the time required for the tablet to break up under test conditions. Thus, it offers no assurance that the resultant particles will release the drug in solution at the appropriate rate. The average tablet hardness for all batches was kept within the range of 63 N – 91 N throughout experimentation as shown in Table 4.13. The dissolution profiles for all formulations are shown in Figure 4.13. The y-axis represents the %

ethionamide release, with the x-axis representing the time interval, in minutes. The 15 minute interval was chosen to study the effects of the selected input variables on dissolution profile. All the batches demonstrated an acceptable dissolution profile as the % drug release after 15 minutes was above 80%.

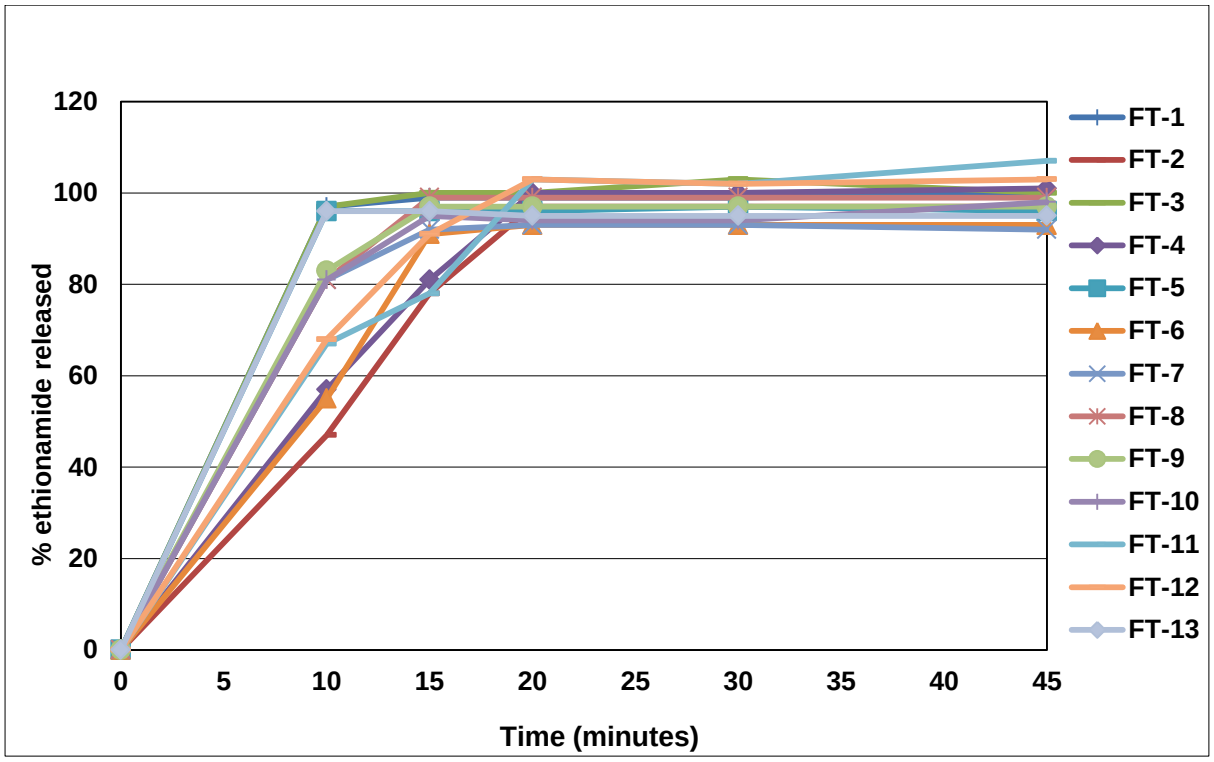


Figure 4.13 Pivotal trial batches: A release dissolution profile of ethionamide 250 mg tablets

Key parameters that had been demonstrated to affect ethionamide product cQA were used to construct the design space as shown in Figure 4.14. The design space is the acceptable region within which the quality of the product can be built (International Conference on Harmonisation, 2009a).

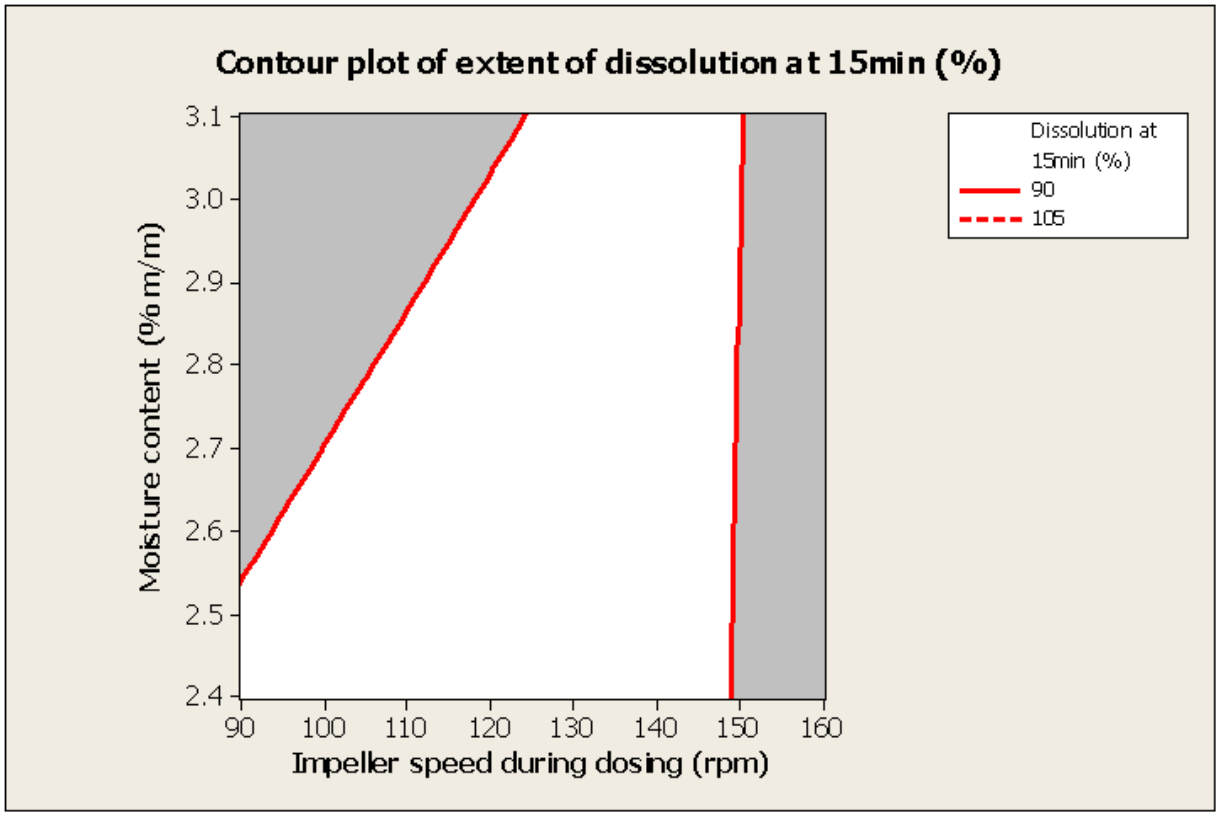


Figure 4.14 Design space: A contour plot of the interaction between the significant factors on the product cQA

The design space is the multidimensional interaction between impeller speed during dosing and moisture content, to determine their influence on the extent of dissolution. The white zone represents the area of acceptable quality (design space) and the red-lines represents the edge of failure. Movement beyond the edge of failure into the grey zone is the area of potential risk where the dissolution is below the acceptable internal control limit. The design space makes QbD a reality and the wider the design space the more robust and flexible the process is to accommodate the variations (Charoo *et al.*, 2012). A vital step of product optimisation is to achieve an appropriate response function for both dependencies and independencies within the design space.

4.5.3 Process optimisation

4.5.3.1 Optimisation using desirability function

Desirability function was calculated for the extent of dissolution at 15 minutes. The composite desirability with the aid of Minitab® 16.0 software was 0.707. The weight and importance for the response were allotted 1 and 5, respectively. Figure 4.15 shows the response optimisation plot for dissolution where the optimal setting for impeller speed during dosing is 115 rpm and moisture content is 2.5% m/m. At these settings, the % drug release at 15 minutes is calculated at 100.6%.

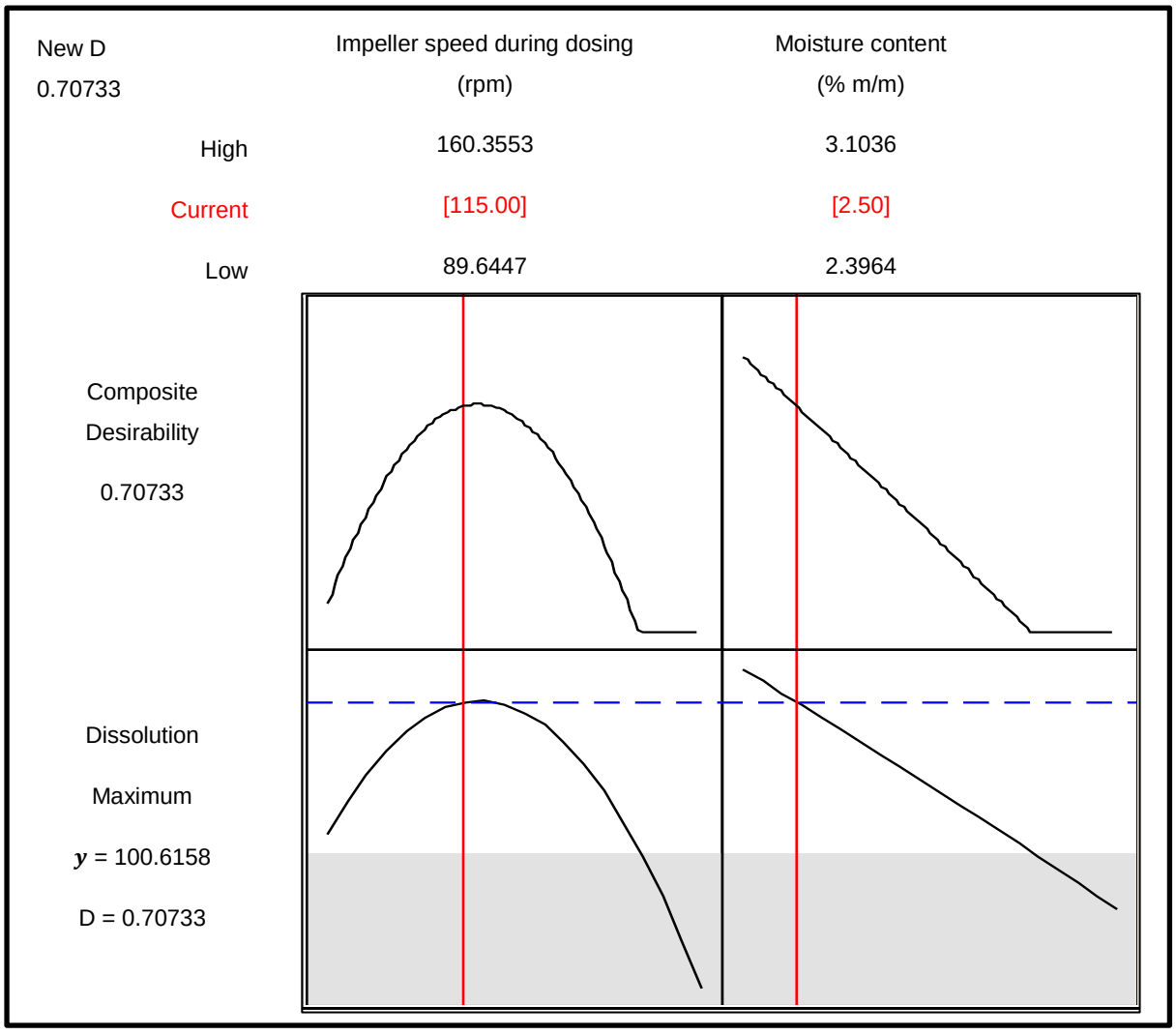


Figure 4.15 Response optimisation plot for the extent of dissolution at 15 minutes

4.5.3.2 Analysis of validation batch

To test the accuracy and robustness of the developed model, the model was validated by producing the optimised batch and testing it against the measured responses. The overall optimisation plot, Figure 4.15 identified the levels at which the significant factors are optimised in order to obtain a maximum dissolution response. This optimum point represented a predictive point, thus in order to validate the predictive ability of the hypothesised model for the product cQA around the optimised conditions, the agreement between predicted and measured responses were verified. Therefore, ethionamide tablets were prepared according to the optimised conditions and subjected to the release test. The confidence interval for each response at the 95% confidence level was used. The actual values for each response are compared to the predicted values and are summarised in Table 4.18. The optimised product met all the required specification. The actual % drug release for ethionamide is 93.0% ± 1.4 and the predicted value was 100.6%. The actual values were within the 95% prediction interval (PI) for each observed response, indicating statistical equivalence of the experimental drug release profile and the predicted one.

Table 4.18 Summary of the predicted and measured responses of the hypothesised model at the optimised conditions

Response	Units	Predicted mean	Actual mean	95% PI low	95% PI high
Dissolution at 15 minutes	**%**	100.6	93.0 ± 1.4	87.56	113.75
Disintegration time	S	207.00	213.00	61.60	352.00
Friability	% m/m	0.12	0.19	0.05	0.19
Tablet hardness	N	72.58	69.30 ± 2.83	53.97	91.19

In order to assess the reliability of the model for product cQA, percentage bias was calculated. Bias (%) has the ability to access the model performance. The percentage bias measures the average tendency of the simulated values to be larger or smaller than the observed ones. The optimal value of bias (%) is 0.00, with low magnitude values indicating

accurate model simulation. Positive values indicate overestimation bias, whereas negative values indicate model underestimation bias (Moriasi *et al.*, 2007). In order to assess the reliability of the model, the model for the product cQA was evaluated. Bias or percent relative error between the experimental value and predicted value was calculated by using Equation 4.5 below.

$$\text{Bias } (\%) = \frac{\text{predicted value} - \text{experimental value}}{\text{predicted value}} \times 100$$

[Equation 4.5]

A bias value of 7% indicates that the model generated is over estimated as the expected value is greater than zero. This serves to be true as the estimated value was calculated at 100.6% and the observed response was 93% drug release at 15 minutes. Therefore, the predictive equation expresses an overestimation of the influence of the significant factors on the extent of dissolution. However, the measured data are within the 95% confidence intervals and 95% prediction interval for all the responses including the product cQA. Therefore the model equation may be used to describe the real dependencies.

The initial step in DoE is performing a screening trial to identify the significant factors and the fractional factorial design reduces the number of runs to a significant few. Reduced designs are often necessary to make simultaneous investigations of multiple independent variables feasible (Collins *et al.*, 2009). However, one of the downfalls of using fractional factorial design (2^{6-3}), as the elimination of design points done purely for economic reasons, is that it limits the statistical power of the model. Therefore, any removal of experimental conditions to form a reduced design may have a significant effect. This may be a potential cause for the variance in the % drug release; however the measured data are with the 95% prediction interval.

4.6 Risk mitigation and control strategy

The control strategy is defined as a planned set of controls derived from current product and process understanding that assures process performance and product quality (International Conference on Harmonisation, 2009b). The control of quality of the finished product is closely linked to the criticality and therefore to each dimension of the design space. By

determining the extent of dissolution as the cQA, the allowed variability of impeller speed during dosing and moisture content after drying wet granule is indicated.

The risk mitigation and control strategy is an integrated outline of how quality is built into the product. Although the implementation of a control strategy is no new concept in pharmaceutical industry, pharmaceutical products always had a more or less unequivocal control concept. However, the use of risk assessment in creating a control strategy is unique to QbD. Figure 4.16 illustrates the FMEA analysis before and after the implementation of a control strategy.

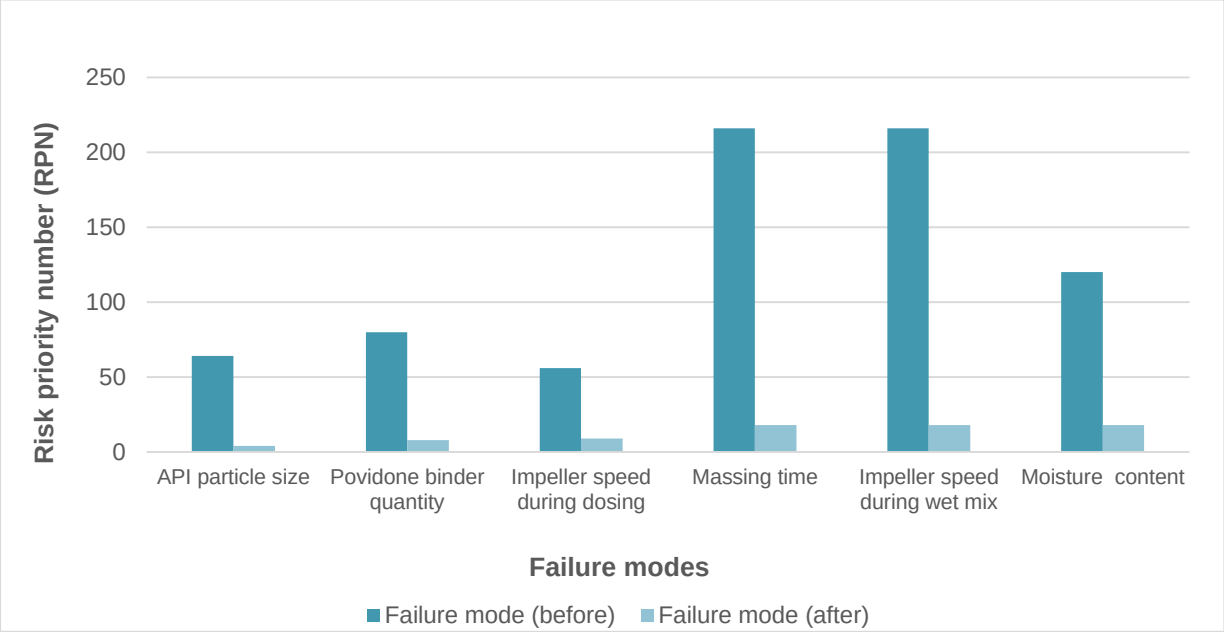


Figure 4.16 FMEA analysis of ethionamide tablets depicting RPN of failure modes before and after implementation of control strategy

Ethionamide is insoluble in water and its potential effect of failure may result in a below therapeutic level. Generally, weakly basic drugs like ethionamide (pKa = 4.49) tend to have a slower dissolution rate at higher pH levels as more drug exists in its ionised form (Pandit, 2007; Troy *et al.*, 2006). A study by Vale and co-workers (2012) showed that the solubility of pure ethionamide in an aqueous buffer at pH 1.2 was 4 mg/ml but decreased to 741 µg/ml in the pH range of 5.5 – 7.4. This finding concurs with the weakly basic nature of the drug substance (Vale *et al.*, 2012). However, its solubility is a physicochemical property of the API. Nonetheless, DoE has demonstrated that API particle size distribution with a D_{50} range 95.18 to 267.00 µm does not have a significant effect on dissolution in a 0.1 M HCl medium.

Therefore, the potential effect and cause of failure is lower. API particle size, D_{50} may range from 95.18 to 267.00 µm and remain within the design specification. The FMEA analysis of API particle size after implementing a control strategy is shown in Equation 4.6.

$$[\mathrm{S}]\ 4\ \times [\mathrm{O}]\ 1 \times [\mathrm{D}]\ 1 = 4\ \mathrm{RPN} \qquad \textbf{[Equation 4.6]}$$

The severity [S] that the API may have a potential effect of failure and the likelihood of occurrence [O] is reduced as the API particle size range has been established within the design space. The ability to detect [D] that the API particle size range does not meet the specification is almost certain, as all raw materials are analysed upon receiving and analysed to confirm supplier certificate of analysis. This is a quality control measure and forms part of cGMP (Medicines Control Council, 2010).

DoE has established that a quantity of 4% m/m povidone binder is sufficient to cause optimal binding activation. Tablets were hard enough to withstand abrasion and handling, disintegrate within 15 minutes (900 seconds) and demonstrated an acceptable dissolution profile. Therefore, the potential effect and cause of failure is well controlled at a 4% quantity and should be maintained within design space specification. The FMEA analysis of the povidone binder quantity after implementing a control strategy is shown in Equation 4.7.

$$[\mathrm{S}]\ 2\ \times [\mathrm{O}]\ 2 \times [\mathrm{D}]\ 2 = 8\ \mathrm{RPN} \qquad \textbf{[Equation 4.7]}$$

The severity [S] of the quantity of povidone binder impacting the release dissolution is reduced as the optimum quantity of povidone binder has been identified and the potential effect of failure is very minor. The probability of occurrence [O] is lowered and the ability to detect any variation [D] in the quantity of povidone binder is high as this will be recorded in the batch manufacturing record. Checking the quantity of the dispensed raw material is a quality control measure and recorded in accordance to good documentation practice which constitutes an essential part of the quality assurance system (Medicines Control Council, 2010).

Impeller speed during wet mix between 100 and 200 rpm and the massing time between 120 and 360 seconds did not impact the extent of dissolution. For a massing duration of 180 seconds at an impeller speed of 100 rpm during wet mix, the pivotal trial batches and the validation batch generated a homogenous mix and tablets were able to withstand abrasion, disintegrate within 15 minutes (900 seconds) and showed an acceptable dissolution profile. At these settings, product quality will be achieved within the design space. The potential

cause and effect of failure has been mitigated. The FMEA analysis of the impact of the impeller speed during wet mix and the time during massing time after implementing a control strategy is shown in Equation 4.8.

$$[S]\ 2\ \times [O]\ 3 \times [D]\ 3 = 18\ \mathrm{RPN} \qquad \textbf{[Equation 4.8]}$$

The severity [S] of risk that the impeller speed during wet mix and the massing time has on the potential failure mode and the probability of failure occurring is reduced as both their effects on the product cQA are non-significant. Since the optimised settings have been identified and as each step of the manufacturing process is documented according to good documentation practice, the ability to detect the potential failure mode [D] is higher.

Impeller speed during dosing has been identified as one of the significant factors to influence dissolution. The validation batch indicated that at the optimal setting where the granulating medium is added to the powered bed over the 90 second period at an impeller speed of 115 rpm would result in 93% drug release at time point 15 minutes. The potential cause of failure and its effect on the product cQA is reduced and controlled within the design space specification. The FMEA analysis of the impeller speed during dosing after implementing a control strategy is shown in Equation 4.9.

$$[S]\ 3 \times [O]\ 1 \times [D]\ 3 = 9\ \mathrm{RPN} \qquad \textbf{[Equation 4.9]}$$

The optimised setting for the impeller speed during dosing has been identified, thus the severity of the failure mode [S] to cause over granulation or local wetting is reduced. The likelihood of occurrence [O] of the potential effect of failure is unlikely as this is controlled within the design space. The ability to detect such failure [D] is high as this will form part of the batch manufacturing record and recorded. Personnel involved in the batch manufacturing process should be involved in ongoing training session based on education, experience and working habits of staff, as well as on periodic assessment of previous training (Medicines Control Council, 2010).

The control for moisture content of the intermediate bulk material after drying the wet granule is set within the design space specification. The DoE batches showed no physical defects to suggest granules are over- or under- dried. Accordingly, impeller speed is a set input value entered onto the human machine interface (HMI) screen of the high shear mixer granulator

compared to measuring the moisture content level. To mitigate the risk of not obtaining the target moisture content level of 2.5% m/m, it is feasible to set a tighter in-process control range within the design space of 2.4% m/m to 2.6% m/m. The prediction response for design points 2.4% m/m and 2.6% m/m using the model for dissolution are 102% and 98%, respectively. The predicted values are within the 95% prediction interval. Since moisture content has a significant role in the compaction process, the average hardness range for the moisture content between 2.4% m/m and 2.6% m/m should be within the range of 68 N and 72 N. The FMEA analysis of the moisture content of the intermediate bulk material after drying the wet granule is shown in Equation 4.10.

$$[\mathrm{S}]\ 3 \times [\mathrm{O}]\ 2 \times [\mathrm{D}]\ 3 = 18\ \mathrm{RPN} \qquad \textbf{[Equation 4.10]}$$

The severity [S] of the moisture content impacting the product cQA and the likelihood of the failure mode occurring [O] has been reduced as the target and range of moisture content has been established. The ability to detect these failures [D] are high, and controlled within the validated design space.

The RPN for all the possible failure modes are below 50 which make them fall in the low risk range. The scalability of the design space can be revaluated in the transfer from pilot to commercial scale up batch manufacturing. Thus is may be further refined based on additional experience gained during the life-cycle of the product. However, certain unit operations are scale dependent and may require additional experimental work. Implementing quality risk management tools summarised in ICH Q10 guidelines (2009) may facilitate continual improvement of ethionamide 250 mg tablets.

In addition, the control strategy for the manufacturing process stages is maintaining the in-process tablet characteristics of hardness, friability and disintegration time within the required ranges. The machine settings required to produce tablets with the desired hardness, friability and disintegration time at the start of each run and during the in-process control checks within the run, will routinely check if tablet attributes are within ranges. End product testing will form a component of the control strategy as it confirms product quality. Although these tablet characteristics were not initially identified as critical to product quality, analysing tablet friability, hardness, and disintegration time aided in better understanding the product and its manufacturing process. When identifying the cQA from the drug quality attributes of the QTPP, the tablet thickness, hardness and moisture content needed to be established. Table 4.19 summarises the updated QTPP.

Table 4.19 Updated QTPP of the drug quality attributes after implementing the control strategy

Quality Attributes of the Drug Product	Target		Is this a cQA? (No/Yes)	Justification
Physical attributes	Hardness	Target: 69.3 N Range: 68 N – 72 N	No	Established based on results from research study
	Thickness	Range: 4.82 mm – 4.92 mm	No	RSM batches have indicated that tablets compressed within the range of 68 N – 72 N, would produce tablets with a thickness range between 4.82 mm and 4.92 mm
Water Content	Loss on Drying (LOD)	Target: 2.5% m/m Range: 2.4 – 2.6 %m/m	No	Moisture content of intermediate bulk material (after drying wet granule) established based on outcome of research study. Optimum setting within design space specification.

The risk mitigation strategy is to ensure a product consistency during production by monitoring the normal operating ranges for the material attributes and process parameters. Thus, the design space of knowledge is created and should be controlled at the optimised setting. Working at this setting, within the design space specification reduces the risk for all the potential failure modes. Under the QbD approach, these specifications are for the confirmation of product quality, not the manufacturing consistency and process control. In addition, this does not replace the review and quality control steps called for under the cGMP.

Therefore, this project highlights the usefulness of QbD in pharmaceutical product optimisation by focusing on one pilot project that will create standards and set the path for the implementation to other pharmaceutical products in the future and ties up to the aims of pharmaceutical goals of providing a safe, effective and quality assured product. The QbD

principles provided an effective means to achieve a greater understanding of the ethionamide formulation and its wet granulation method of manufacture.

CHAPTER 5 – CONCLUSIONS AND RECOMMENDATIONS

The study presented a systematic approach of optimising the formulation and manufacturing process of ethionamide 250 mg tablets using QbD. A historical database of the API, excipients and process data exist for legacy products and this information can be used to reengineer and optimise pharmaceutical products. Optimising a long withstanding product using the modernised approach is void of the limitations of the traditional approach of QbT which assures product quality by in-process and end product testing.

Dissolution was identified as the quality attribute derived from the QTPP to be critical to patients should it fall outside of its acceptable range. The material attributes and process parameters were assessed using qualitative descriptors as part of the first evaluation followed by the FMEA method. API particle size, povidone binder quantity, impeller speed during dosing, massing time, impeller speed during massing and the moisture content after drying the wet granule were identified as risk factors with a high RPN .

In an endeavour to accomplish the objectives, two experimental protocols were applied for evaluating the high risk factors and defining the relationship between the input variables and the quality attribute desired. Statistical designs were created and analysed using Minitab® statistical software. The screening trial using a fractional factorial design was used to estimate the significance of the main effects.

ANOVA analysis revealed that impeller speed during dosing, moisture content and povidone binder quantity were significant factors. Results also revealed that to increase the extent of dissolution while still maintaining an acceptable tablet hardness that is able to withstand abrasion during handling and a disintegration time within the acceptable limit, povidone binder quantity can be maintained constant at a recommended 4% m/m. Therefore, impeller speed during dosing and moisture content were further examined in the subsequent optimisation study, using RSM, more specifically a CCRD. Tablets showed an acceptable hardness and met the specification for friability and disintegration time in addition to having an acceptable dissolution profile. Risk factors that had been demonstrated to affect dissolution i.e. dosing impeller speed and moisture content were used to construct the design space.

The optimised manufacturing process was then chosen using the desirability factor and the optimised product corresponded reasonably well with those predicted for the desired quality

attribute. Impeller speed during dosing was set at 115 rpm and moisture content was set at 2.5% m/m. In addition, the control strategy was developed to mitigate risks. The RPN of the updated risk assessment depicted that all the failure modes were categorised as 'low' risk. Apart from identifying the factors that affect the product cQA, the study also established acceptable ranges for characteristics that were previously unknown, thus updating the QTPP. Therefore, the shift in paradigm from the traditional approach to QbD provided an astute insight for building quality into an immediate release oral solid dosage form. The study highlights the usefulness of QbD in optimising legacy products at a pilot scale. The information obtained from the risk assessment and the DoE can be useful to the accumulation of institutional knowledge and beneficial to other immediate release oral solid dosage forms.

Recommendations for this study would be to further investigate the additional cost of a QbD development strategy compared with the traditional approach as the reward in the long run should outweigh the initial expenditure. In addition, it is recommended to further investigate the comparative *in vitro* dissolution study of the optimised product, which may be included in the QTPP. Dissolution testing should be carried out in USP apparatus II at 50 rpm using 900 ml in the following dissolution media: (1) 0.1 M HCl, (2) a pH 4.5 buffer and (3) a pH 6.8 buffer. A minimum of 12 dosage units (n=12) of the product should be evaluated. Samples should be collected at 10, 15, 20, 30 and 45 minutes. The moisture content of the optimised formulation should be determined by the Karl Fischer titration method which may be included in the QTPP.

This study needs to be carried forward to show that QbD can be applied to not only small scale product development but also scaled up to full production batches. The scale up from small scale to production size may depend on the design of the equipment which may be potentially scalable in terms of its dimensionless features or components. Consequently, proposing the design space across scales should be described in terms of scale independent parameters and if possible in terms of dimensionless numbers, which are naturally scale independent. Once determined, the design space can be scaled by keeping the dimensionless numbers constant. The design space may therefore continue to evolve as additional knowledge and information is generated throughout the product life-cycle.

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APPENDICES

APPENDIX A – Concept article for the Drug Development and Industrial Pharmacy

Formulation and Process Optimisation of Ethionamide 250 mg Tablets Using Quality by Design Principles

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Key Words: Quality by design, ethionamide, risk assessment, failure mode effects analysis (FMEA), fractional factorial design, central composite design (CCRD)

Abstract

The aim of this study was to optimise ethionamide 250 mg tablets using Quality by Design (QbD). A quality target product profile (QTPP) was established and a risk assessment was performed using a qualitative risk assessment followed by the failure mode effects analysis (FMEA). A fractional factorial design was used to identify the significant factors affecting dissolution, the critical quality attribute (cQA). The central composite rotatable design (CCRD) was subsequently used to investigate the effects of the significant factors on the response. Six factors were considered as a high risk compared to others, namely the active pharmaceutical ingredient (API) particle size, povidone binder quantity, impeller speed during dosing, massing time, impeller speed during wet mix and the moisture content after during the wet granule. Pareto ranking analysis indicated that povidone binder quantity, impeller speed during dosing and moisture content after drying the wet granule were significant factors. Although povidone binder quantity was significant, results revealed that povidone binder can be maintained constant at a recommended 4% m/m. Optimisation with response surface methodology (RSM) clarified the relationship between impeller speed during dosing and moisture content and the cQA, and a design space was established. To test the accuracy and robustness of the developed model, the model was validated by producing the optimised batch. A good agreement was observed between the predicted and actual values; thus confirming the robustness of the model. QbD provided a judicious insight for building quality into ethionamide immediate release tablets.

1. Introduction

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product [1]. Continuous quality improvement is a critical step for the pharmaceutical industry to maintain a competitive advantage in the market. In this era of competition, quality has prime magnitude, and failure to meet such quality-allied goals produces challenges for industry [2].

Under the traditional approach of Quality by Testing (QbT), product specifications are set by observing data from a small number of batches believed to be an acceptable quality and then setting acceptance criteria that require future batches to be the same. Specifications are tight as these are used to assure consistency of the manufacturing process. Testing of products can only be performed on a small sample, simply because the majority of the tests are destructive in nature and if the entire batch were tested to assure its quality, there would be no product. Since a few tablets out of a batch of several million are tested, industries are usually expected to conduct extensive in-process tests and post-production tests to ensure the outcome meets the predefined specifications, if not, batches are reworked or discarded. The combination of stringent manufacturing steps and excessive testing is what assures quality under the traditional approach [3-5].

The Food and Drug Administration (FDA) identified a succession of continuing issues in the pharmaceutical industry that the traditional approach of QbT had not solved. These problems include among others, the lack of mitigation of potential risks, and the lack of process understanding [6]. The FDA acknowledged that more controls are required for pharmaceutical manufacturers and for better regulatory decision-making. Thus, ensuring decisions are based on sound-science and not an empirical approach.

To improve the competence and modernise the pharmaceutical industry, the FDA initiated the, “Pharmaceutical cGMPs for the 21st century: A risk-based approach” [7]. An important part of this initiative was to shift the focus of the pharmaceutical industry away from the empirical approach of QbT to a more systematic approach. This led to the implementation of Quality by Design (QbD). QbD focuses on building quality into the product by identifying factors that are critical to patients and translating them into attributes that the product should have. The emphasis is on preventing quality associated problems and not just correcting them [1, 7-9].

The concept of QbD was first outlined in the 1960s and later pioneered by Toyota to improve their early automobiles. Since then, industries like technology, telecommunications, aeronautics and companies manufacturing medical devices began incorporating QbD into their products, which significantly improved their product efficacy [10]. QbD is the successor to the traditional approach of QbT that the FDA agency has employed until the late 1900s and early 2000s. QbD focuses on building quality into the product through proper planning and highlights that the mere analysis of the final product, post-production, will not suffice. This is achieved by understanding the product and its manufacturing process, the risks involved in product manufacturing and the best method to mitigate those risks. Understanding the product and its process aids in detecting quality-associated problems early enough to permit actions without compromise to cost, available resources or product quality [11-13].

The International Conference on Harmonisation (ICH) guidelines, Q8: Pharmaceutical Development, ICH Q9: Quality Risk Management and ICH Q10: Pharmaceutical Quality System provides the roadmap on how QbD affects, ensures, maintains and optimises product quality. The core objective of QbD is to develop a robust formulation and manufacturing process that facilitates any adjustment of potential variables within a design space [1, 4].

The model drug selected for this study is ethionamide, a second-line drug used in the treatment of multiple drug resistant tuberculosis (MDR-TB). Ethionamide, an immediate release tablet was introduced onto the market in the early 1960s, thus creating the opportunity of taking a long existing product i.e. a legacy product, and optimising it using the QbD approach. At present, there is only one South African pharmaceutical company manufacturing ethionamide 250 mg tablets [14]. In South Africa, the percentage of new tuberculosis (TB) cases with MDR-TB is 1.8% (95% CI: 1.4 – 2.3%) and an estimated number of retreatment TB cases with MDR-TB is 6.7% (95% CI: 5.4 – 8.2%). These estimates are unchanged since 2011 [15]. With the growing number of MDR-TB cases in South Africa, the need to fulfil the demand requires the manufacture of the drug on a wider scale. Hence, the need to implement QbD in the manufacture of ethionamide to ensure market demands are satisfied without compromising product quality, effectiveness and cost. Thus, QbD provides a better overall business model.

2. Methods

2.1 Materials

The following raw materials were utilised in this study: ethionamide (Liaoning Beiqi Pharmaceutical Co. Ltd, China); microcrystalline cellulose (Gujurat Microwax, India); lactose monohydrate (DMV – Fonterra Exc, New Zealand); sodium starch glycolate (Amishi Drugs and Chemicals, India); Povidone K25 (BASF SE, Germany); magnesium stearate (Faci Asia Pacific PTE Ltd, Singapore). All raw materials were kindly donated by Aspen Pharmacare, Port Elizabeth.

2.2 Preparation of ethionamide tablets

For each batch, the raw materials were weighed (Mettler Toledo balance SR 32001; Switzerland) in accordance with the experimental plan. The batches were manufactured at a 10 litre scale using Granulator Rapid Mixer and Wet Granulator (RMG 10 LTR, India).

Granulating medium was prepared by mixing Povidone K25 and purified water (Heidolph Electrical Stirrer; Model Number: 50115; Germany). Ethionamide, lactose monohydrate, sodium starch glycolate (SSG) and microcrystalline cellulose (MCC) were dry mixed with the impeller speed set at 200 rpm and chopper speed set at 2500 rpm for 240 seconds (Rapid Mixer & Wet Granulator; Model Number: RMG 10 LRT; India). The granulating medium was added to the bowl over a 90 second period, at a chopper speed of 1500 rpm and the impeller speed set according to the experimental plan. The granules were wet milled through a 6.0 mm screen at 300 rpm (Quadro Co-Mill; Model Number 197; Canada) and dried in a 40 °C pre-heated fluid bed dryer (Retsch Fluid Bed Dryer: Model Number TG100; Germany) until a specified percentage moisture content (loss on drying) was reached. After being dried and milled through a 1.5 mm screen, SSG was sieved through a size 40-mesh screen, added to the bulk material and blended (IMA Pharma CanguroTurbula Bin; Model Number: J50; Italy) for 10 minutes at 11 rpm. Magnesium stearate, was screened through a size 40-mesh, added to the granules and blended for five minutes at 11 rpm. The final blend was subsequently compressed into tablets using a Karnavati Mini Press (Karnavati Mini Press II; Model Number: UNIK – PC 20 MT; India).

2.3 Quality target product profile (QTPP) of ethionamide tablets

The quality target product profile (QTPP) is listed as the quality properties that the drug product should have to ensure the desired quality is achieved (International Conference on Harmonisation, 2009a). The QTPP is a strategic foundation for product development and optimisation, emphasising the statement ‘planning with the end in mind’ and forms the basis

of determining the critical quality attributes (cQAs) [5, 16]. Based on the clinical, pharmacokinetic and its physicochemical characteristics, the QTPP of ethionamide 250 mg tablets was established. The QTPP includes the dosage form, dosage design, dosage strength, route of administration and drug product quality attributes, all of which is pharmaceutically equivalent to its reference counterpart. The QTPP for ethionamide tablets is depicted in Table 1.

2.4 Identifying the product critical quality attributes (cQAs)

The critical quality attributes (cQAs) are physical, chemical and biological properties that should be within an appropriate range to ensure the desired product quality. Identifying the product cQA from the QTPP is based on the severity of harm to the patient, should the product attribute fall outside its acceptable range [1]. Consequently, dissolution is the product cQA, as the dissolution of the drug substance under physiological conditions is essential for its systemic absorption.

2.5 Risk assessment

The ICH Q9 guideline introduced the concept of quality risk management for evaluating, communicating, controlling and reviewing quality associated risks across the product life cycle [8]. A qualitative risk assessment was used as part of the first evaluation to determine if the risks are significant enough to warrant a more detailed analysis. Risks were characterised into those from the API, the excipients and the manufacturing process. The criteria used to evaluate each risk was based on its combined severity and probability, and the risk were categorised using qualitative descriptors such as ‘low’, ‘medium’ and ‘high’**.** The ‘low’ risk attributes do not require any further analysis, whereas the ‘high’ risk attributes are unacceptable and require further analysis. In general, ‘medium’ risks were also considered acceptable; however investigations were conducted in order to reduce such

risks. Table 2 summarises the risk ranking system in terms of the severity and the probability of the risks [17].

Subsequent to the qualitative risk assessment, the FMEA method was used to analyse the 'medium' and 'high' risks by identify the failure modes that have the greatest chance of causing product failure, i.e. not meeting the QTPP. The failure modes were characterised into those from the API, excipients and the manufacturing process. The process failure modes were further categorised by unit operations. The failure modes were prioritised according to the seriousness of their consequences, how frequently they occur and how easily they can be detected. The relative risks were ranked according to risk priority number (RPN).

The risks were rated on a scale of one to 10 for each of the causes i.e. severity (S), probability of occurrence (O) and detection (D). Based on this scaling system, a high severity event would be given a 10, whereas a low severity event would be given a score of one. With probability, if something were quite certain to happen, then a 10 would be given, whereas if something were very unlikely to happen, a score of one would be allocated. For detection, if there is a good detection system in place, a score of one is given, whereas a non-existent detection system would be given a 10 [18]. These severity, occurrence and detection numbers were multiplied together to give a RPN (Equation 1).

$$RPN = [S] \times [O] \times [D] \qquad \textbf{[Equation 1]}$$

The RPN was generated for all risk factors and the factors with the highest RPN follows greater priority and were evaluated. The failure modes with a RPN $\geq$ 50 were further examined in the subsequent DoE. Table 3 depicts the FMEA for ethionamide tablets with their respective RPN for each failure mode.

2.6 Fractional factorial design screening study

Based on the risk assessment results, a 2^{6-3} fractional factorial design was used to screen significant factors influencing the selected cQA. The selected formulation and manufacturing input variables selected included: API particle size, povidone binder quantity, impeller speed during dosing, massing time, impeller speed during wet mix and moisture content after drying wet mix. Each factor was set at two levels, either a low (-) or high (+) and are summarised in Table 4. The matrix of the experiments for the fractional factorial design screening study is summarised in Table 5.

2.7 Central composite rotatable design optimisation study

Relied on the results of the 2^{6-3} fractional factorial design screening study, a response surface methodology (RSM) was applied to determine if the levels of the significant factors from the screening experiments will produce a response that is in close proximity to the optimum and select the optimum settings of the selected variables. In this two factor CCRD, 13 experiments were generated for the optimisation study and are summarised in Table 6 and Table 7. The relationship between the significant factors and the product cQA was defined in the design space.

2.8 Statistical analysis

Replicate measurements were represented as a means ± standard deviation (SD). Statistical designs and analysis were carried out using the software package Minitab® statistical software version 16.0 (Minitab Inc., United Kingdom). Experimental runs were randomised to exclude any bias. The applied fractional factorial design is a resolution III design, so only the main effects were considered. Pareto ranking analyses were used to select the significant

factors, where the length of the horizontal bar represented the magnitude of the impact on the response.

Analysis of variance (ANOVA) was performed to evaluate the model significance. A p-value $\leq$ 0.05 was considered statistically significant. The coefficient of determination (R^2), adjusted R^2 (Adj R^2) and predicted R^2 (Pred R^2) were also applied to determine the suitability of the model. The R^2 value is the maximum squared regression coefficient that can be achieved by the model using only the variables in it, which is an indication of how well the model fits the experimental data. The Adj R^2 is a modified form of R^2 considering the number of terms used within the model and the Pred R^2 is an estimation of how well the model predicts a response value. In addition the lack-of-fit estimated the error variance independently of the model. A significant 'lack-of-fit' ($p>0.05$) indicates that the variability measured by the replicates does not explain the gap between predicted and experimental data points. For the CCRD analyses, the regression analyses enabled a prediction equation to be obtained

2.9 Granule characterisation

2.9.1 Moisture content

The moisture content after drying the wet granule was measured using a Moisture Analyser (Mettler Toledo LJ16, Switzerland). The granule sample (2 g – 3 g) was placed in a heating pan, weighed and heated at a temperature of 105 °C and a drying time set to the automatic switch-off criterion (2 mg/30 seconds) The percent reduction in the weight due to moisture loss i.e. loss on drying (LOD) was determined.

$$Moisture\ content = \frac{initial\ weigh - final\ weight}{initial\ weight}\ x\ 100$$

[Equation 2]

2.10 Tablet characterisation

2.10.1 Dissolution testing

Dissolution studies were performed using a United States Pharmacopoeia (USP) I dissolution apparatus (Hanson SR II 6-flask Dissolution Test Station; Model Number 64-705-045, United States of America), equipped with six vessels. Nine hundred millilitres (ml) of 0.1 M hydrochloric acid (HCl), as the dissolution medium was added to each of 6 vessels sited in the water bath at a temperature of 37 °C ± 0.5 °C. Baskets were set to rotate at 100 rpm. One tablet was transferred to each of the six baskets and at time zero, the baskets were immersed in the dissolution medium. Ten ml aliquots were withdrawn at 10, 15, 20, 30 and 45 minute intervals from each vessel into separate test tubes. Two ml of the filtered sample was transferred into a 50 ml volumetric flask and made up to volume with 0.1 M HCl.

The dissolution medium was prepared by transferring 8.5 ml of HCl (32% v/v) (Merck KGaA, Germany) into 10 litres of purified water (Riggtek DissoPrep X8, Germany). The standard solution was prepared by weighing and transferring approximately 55 mg of ethionamide working standard into a 100 ml volumetric flask, adding 60 ml of the dissolution medium and sonicating until dissolved (Branson Ultasonic 8510, United States of America). The solution was allowed to cool to room temperature and the solution was made to volume with the dissolution medium. Two ml of this solution was transferred into a 100 ml volumetric flask and made up to volume with the dissolution medium. The dissolution was measured using UV-VIS Spectrophotometer (UV-Pharmaspec 1700 UV-visible spectrophotometer, Japan). Ethionamide concentration of each sample (n=6) at each time interval and the absorbance of the standard (five replicates) was spectrophotometrically determined at 274 nm with a 1 cm cell and the dissolution medium as the blank. Data acquisition was performed using UV Probe® 2.43 software. The percentage drug release per tablet was calculated using Equation 3 below. The parameters used in the formula for the dissolution test is shown in Table 8.

$$\%\ ethionamide\ released\ per\ tablet = \frac{Asam\ \times mass\ of\ standard\ \times 2\ \times 900\ \times 50 \times C\ \times 100}{Astd\ \times 100\ \times 100\ \times label\ claim\ \times 2 \times 100}$$

[Equation 3]

2.10.2 Disintegration Test

Disintegration time was measured using Erweka Tablet Disintegration Test Unit (Model Number: ZT 304; Germany). Six tablets were randomly selected from each batch (n=6) for the disintegration test. One tablet was introduced on each of cylindrical (glass) tubes. Water was used as the disintegration medium at 37 °C ± 0.5 °C. The time it took for each tablet to disintegrate was recorded as the disintegration time and presented in seconds.

2.10.3 Hardness Testing

Ten tablets were randomly selected from each formulation batch and tablet strength i.e. hardness was measured using a hardness tester (Erweka Hardness tester; Model Number: TBH 320TD; Germany). The average hardness and mean SD of the 10 tablets from each batch was calculated.

2.10.4 Friability

Twenty tablets were randomly taken from each formulation batch. Tablet samples were weighed accurately (Mettler Toledo AG204; Switzerland) and placed in a friabilator (PharmaTest Friabilator PTF 3; Germany). Tablets were rotated at 25 rpm for four minutes, totalling 100 revolutions. Finally tablets were removed from the friabilator, de-dusted and weighed. The weight difference between the initial and final weight was recorded. The percentage friability was determined by using Equation 4.

$$\%\ friability = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

[Equation 4]

3. Results

3.1 Quality target product profile (QTPP) of ethionamide tablets

The purpose of this exercise was to identify the quality characteristics that ethionamide should possess in order to deliver the desired therapeutic effect. The parameters that will be focused on in the study were selected and enlisted as the QTPP for ethionamide tablets (Table 1). These characteristics that make up the QTPP will be designed into the product and will lay down the basis for determining the cQA.

3.2 Identification of the critical quality attribute

Dissolution was identified as the product cQA as this is a rate-limiting step for drug absorption. Failure to meet the dissolution specification can impact bioavailability. The formulation and process variables that may affect the dissolution profile, thus will be investigated. The extent of dissolution at time point 15 minutes was measured.

3.3 Risk assessment

As outlined in the ICH Q9 guideline, the risk identification and risk analysis are the two basic components of the risk assessment. Risk assessments were performed on the API,

excipients and the manufacturing process. The qualitative risk assessment was used as part of the initial risk assessment to narrow down the list of potential risk factors. The 'medium' and 'high' risk factors were further analysed using the FMEA method and aided in identifying how each potential risk may impact the product cQA. Each risk factor was scored in terms of severity, detectability and probability. The RPN scores using FMEA methodology is summarised in Table 3. Six risk factors were identified in the risk assessment study that has the potential to impact dissolution. These independent factors included: API particle size, quantity povidone binder, impeller speed during dosing, massing time, massing impeller speed and moisture content after drying the wet granule. These six factors would be used in the screening trial to obtain the significant factors influencing the cQA.

3.3.1 Influence of various factors on the product cQA by fractional factorial screening study

Six factors were identified in the risk assessment to have a potential impact on dissolution. A screening experimental design minimises the number of experiments required to identify the significant factors affecting the product cQA. The effect on the extent of dissolution at 15 minutes for the initial model F-value of 15.60 demonstrates that the model is non-significant. There is only a 19.10% possibility that an F-value this large may occur due to noise. Impeller speed during wet mix as a non-significant term and as a term that had the lowest impact on dissolution (p=0.814) was removed from the analysis. Accordingly, the Pred R^2 increased from 32.34% to 81.56%. The adjusted model with an F-value of 34.31 indicated that the model is significant, implying that there is only a 2.90% chance that an F-value this large could occur due to noise (R^2= 98.85%, p=0.029). The significant factors were povidone binder quantity (% m/m), moisture content (% m/m) and impeller speed during dosing (rpm) relative to other factors influencing the extent of dissolution as shown in Figure 1 and Table 9.

The mean cumulative release dissolution profile (n=6) at time intervals 10, 15, 20, 30 and 45 minutes are shown in Figure 2. Table 10 summarises the tablet characteristics for the screening trial batches. Screening trial has shown that to distend the extent of dissolution while still maintaining acceptable tablet hardness, a friability of less than 1% loss and disintegration time within the acceptable limit, indicating that povidone binder quantity can be maintained constant at a recommended 4% m/m (Figure 3). The RSM will focus primarily on the optimisation of the manufacturing process. The factors evaluated in the succeeding experimental plan are moisture content after drying (% m/m) and impeller speed during dosing (rpm).

3.4 The response surface obtained by the central composite rotatable design

This study aimed at understanding the effects and interactions between the selected input variables on the product cQA. The levels used for the selected variables and the experimental results are listed in Table 7. ANOVA analysis for dissolution at 15 minutes are summarised in Table 11.

A quadratic model (polynomial equation) was used to analyse the extent of dissolution. ANOVA analysis of the model for the response showed that the model (quadratic) chosen for the analysis had a significant fit relative to the noise with an F-value of 4.90 (p=0.030) and a lack of fit test showed that there was a non-significant lack of fit relative to the pure error (p=0.125), indicating that this model may be used to evaluate the design space. Of the squared terms for this model, dosing impeller speed had a significant effect with an F-value of 14.88 (p=0.006). This implies that there is significant curvature in the response surface. Analysis of the main effects for the extent of dissolution showed that only moisture content was significant, where p=0.047. No significant interactions where noted between the selected factors. Contour and surface plots were also analysed to visualise the effects of

moisture content and impeller speed during dosing and their interactions on the cQA. As shown in Figure 4 to maximise the extent of dissolution of the immediate release tablet above 85% drug release at 15 minutes, impeller speed during dosing should be within the region of 90 rpm to 150 rpm and a 2.5% m/m to 2.8% m/m range for the moisture content level. The polynomial equation derived from the model used to makes predictions about the response is shown below, where A is the dosing impeller speed during dosing and B is moisture content.

$$Dissolution = 195.97 + 0.89\,A - 97.74\,B + 0.72\,AB - 0.011\,A^2 - 1.60\,B^2$$

[Equation 5]

3.5 Establishment and evaluation of the design space

Key parameters that had been demonstrated to affect ethionamide product cQA were used to construct the design space as shown in Figure 5. The design space is the acceptable region within which the quality of the product can be built [1].

3.6 Optimisation using desirability function

Desirability function was calculated for the extent of dissolution at 15 minutes. The composite desirability with the aid of Minitab® 16.0 software was 0.707. The weight and importance for the response were allotted one and five, respectively. The response optimiser indicated that the optimal setting for impeller speed during dosing is 115 rpm and moisture content is 2.5% m/m. At these settings, the % drug release at 15 minutes is calculated at 100.6%.

3.7 Validation of the optimised formulation and manufacturing process

To test the accuracy and robustness of the developed model, the model was validated by producing the optimised batch and testing it against the measured responses. Ethionamide tablets were prepared according to the optimised conditions and were subjected to the release test. The confidence interval for each response at a 95% confidence level was used. The actual values for each response are compared to the predicted values and are summarised in Table 12. The optimised product met all the required specification. The actual % drug release for ethionamide is 93.0% ± 1.4 and the predicted value was 100.6%. The actual values were within the 95% prediction interval (PI) for each observed response, indicating statistical equivalence of the experimental drug release profile and the predicted one.

3.8 Determination of a control strategy

The control strategy is defined as a planned set of controls derived from current product and process understanding that assures process performance and product quality [9]. The control of quality of the finished product is closely linked to the criticality and therefore to each dimension of the design space. By determining the extent of dissolution at 15 minutes as the cQA, the allowed variability of impeller speed during dosing and moisture content after drying wet granule is indicated.

The risk mitigation and control strategy is an integrated outline of how quality is built into the product. Although the implementation of a control strategy is no new concept in pharmaceutical industry, pharmaceutical products always had a more or less unequivocal control concept. However, the use of risk assessment in creating a control strategy is unique

to QbD. Figure 6 illustrates the FMEA analysis before and after the implementation of a control strategy. The RPN after implementing the control strategy for all the possible failure modes are below 50 which make them fall in the low risk range.

4. Discussion

A screening trial was used to identify the significant factors influencing the cQA and using a fractional factorial design reduces the number of runs to a significant few. To best use the screening design, a risk analysis was performed and six factors were identified as potential high risk factors. These include API particle size, povidone binder quantity, impeller speed during dosing, massing time, impeller speed during wet mix and moisture content of the intermediate bulk material (after drying the wet granule).

A 2^{6-3} fractional factorial design was used in the screening trial. Being a resolution III design, the experimental design can estimate the significance of the main effects with high efficiency and accuracy, but it cannot separate the main effects from possible interactions (Myers & Montgomery, 1995). However, as the goal of this design is to simply reduce the high risk factors to be studied in the subsequent experiments, such a design was considered to be sufficient to achieve this outcome. As shown in Figure 1 and Table 9, of the six factors only povidone binder quantity (% m/m), moisture content (% m/m) and impeller speed during dosing (rpm) were significant relative to other factors influencing the extent of dissolution. At time point 15 minutes the extent of dissolution varied from 41% (F-4) to 102% (F-7) for the various factor combinations. Screening trial batches F-3 and F-4 containing 5% m/m povidone binder, dosed at an impeller speed of 200 rpm and dried to a moisture content of 3% m/m, held a better attrition resistance (<1% m/m after four minutes) and tablet compressibility. Tablet hardness for these batches i.e. F-4 and F-3 ranged from 78.40 N ± 6.02 to 80.40 N ± 3.75, respectively (Table 10). Notably, tablets compressed at the lower

ranges, disintegrated at a faster rate and showed a higher % ethionamide release during dissolution testing at the 15 minute time point. Batches dried to a moisture content of 1% m/m were found to be more friable and had a prominent effect on tablet hardness. At higher povidone binder quantities and at increased moisture content, tablet hardness increased and friability improved. Friability results showed that as the moisture content decreased, the tablets were more friable. Although friability was lowest for formulation F-3 and F-4, the extent of dissolution at 15 minutes was slower compared to the other batches. The low friability percentage for the formulations correlates to the average tablet hardness. According to the data obtained from the screening trial, all the formulations were well within the pharmacopoeial disintegration time limit (Table 10). Formulation F-2 had the fastest disintegration time of 31 seconds and the lowest average tablet hardness of 34.80 N ± 2.20 compared to formulation F-3 that had the slowest disintegration time of 538 seconds (i.e. 8 minutes and 58 seconds) and highest average tablet hardness of 80.40 N ± 3.75. Batches F-6 and F-7, both contained 5% m/m povidone binder and dried to a 1% m/m moisture level and were compressed at 49.20 N ± 4.78 and 39.50 N ± 6.35 respectively. Although, both batches disintegrated within the acceptable times, friability test results were above 1% m/m.

Increasing the concentration of the binder increases the viscosity of the binder solution and it is expected that the strength of the granules would increase as the content of the povidone binder quantity increased [19]. Moisture content increases the compact strength by increasing the tensile strength of the powder bed and decreasing the density variation within the tablet. Garr and Rubinstein [20] have demonstrated that moisture content is an important element for the mechanical strength of tablets. Reducing moisture content, increases the die-wall friction which contributes to an increase in stress ratio [20]. At an optimum moisture level, the die-wall friction is reduced which is due to the reduction in stress ratio. The increase in compact strength may be due to the hydrodynamic lubrication effect of moisture, which promotes compaction force transmission and formation of hydrogen bonds. Although batches F-3 and F-4 compressed to an average tablet hardness of 80.40 N ± 3.75 and 78.40

N ± 6.02, the extent of dissolution at 15 minutes, were 47% and 41%, respectively. However, after 45 minutes, the extents of dissolution for these batches were above 80%. A high compression may increase the specific surface and may enhance the dissolution. On the other hand, the high compression may also inhibit the wettability of the tablet, owing to the formation of a firmer and more effective sealing layer of the lubricant. The higher compression may also produce slower dissolution, at least in the initial period, because of an increased difficulty of fluid penetration into the compressed tablets [21]. Figure 7 shows that at a higher moisture content and higher povidone binder quantity, disintegration time was longer. Binders impart their cohesive qualities to the tablet formulation to ensure the tablet remains intact after compression as well as improving the free-flowing qualities by the formulation of granules of the desired hardness. The quantity of binder used had considerable influence on the characteristics of the compressed tablets. A higher percentage of binder quantity causes an extended disintegration time [22].

Dosing plays an important role in the compression characteristics of the granules and also in the extent of dissolution. Increasing the impeller speed generally leads to a decrease in granule size and an increase in growth rate. At higher impeller speeds better distribution of the binder over the powder bed is ensured [23]. A powder bed that is cohesive may flow better if its moisture content is increased. However, too much moisture may result in capillary bonding between particles and flow may be compromised by the increased particle-particle adhesion. In addition, the higher compression reduces the extent of dissolution due to the reduction of fluid penetration into the compressed tablets. Figure 8 (a), (b) and (c) represents a 2-dimentional graphical contour plot of the relationship between povidone binder quantity, impeller speed during dosing and moisture content, and their influence on the extent of dissolution.

The screening trial demonstrated that to distend the extent of dissolution while still maintaining an acceptable tablet hardness, friability of less than 1% m/m loss and

disintegration time within the acceptable limit, povidone binder quantity can be maintained constant at a recommended 4% m/m. Ethionamide is practically insoluble in water and the dissolution medium used during the dissolution testing is a 0.1 M HCl medium. Results showed that API particle size did not impact dissolution and, therefore does not pose a high risk to obtaining a low therapeutic level. By reason of having a larger quantity of API available with a particle size D_{50}, 95.18 µm compared to 267.00 µm and maintaining batch to batch consistency, the low level (-1) was selected for the subsequent RSM study. Impeller speed during wet mix and duration of the wet mix did not have a significant influence on dissolution. Suggesting that at these ranges, a homogenous granulation can be obtained. For the RSM, the non-significant factors, massing time was set at centre point level, API particle size at low level and impeller speed during wet mix at low level.

Following the screening trial, the significant factors, moisture content after drying (% m/m) and impeller speed during dosing (rpm) were evaluated using a CCRD. In contrast to a screening trial that determines the main effects, a response surface design mapped the response surface over a particular region of interest, thus predicting, in advance, the changes in response that will result if there are any adjustments to the input variable [24, 25].

The quadratic model was adequate to characterise the data since a non-linear relationship existed between impeller speed during dosing and the product cQA. This demonstrates the benefit of using a 5-level design as opposed to a 2-level factorial design, where the range of experimental data was wide enough to detect the statistically significant variation. As shown in Figure 4, to maximise the extent of dissolution of the immediate release tablet above 85% drug release at 15 minutes, impeller speed during dosing should be within the region of 90 rpm to 150 rpm and a 2.5% m/m to 2.8% m/m range for the moisture content level. The impeller speed during dosing allowed for efficient distribution of the granulating medium over the powered bed, rendering the particle surfaces sticky enough to allow coalescence.

Badaway and co-workers [26] reported that at a higher moisture content a higher fraction of the void spaces within the granule are filled with liquid, which increases liquid saturation of the granule, thus enhancing granule coalescence. The moisture content may be required for the binding of granules during compression in the die cavity. The higher liquid saturation makes the granule easily deformable and results in more liquid available to the granule surface both of which increases probability of successful coalescence upon granule collision [26]. In addition, moisture may act as a lubricant which reduces inter-particulate friction within the granule. Hence facilitating particle movement within the granules in response to densifying forces in the high shear granulation [27]. Similarly Nokhodchi and co-workers [28] demonstrated that moisture played a significant role in the compaction process. This may be due to the water forming a 'monomolecular' layer around the API particles. This tightly bound water can be regarded as part of the surface molecular structure of the particles, which facilitates the formation of interparticle hydrogen bonding that may increase van der Waals forces, thus smoothing out the surface micro irregularities and reducing interparticle separation. In addition, the formation of pendular bonds on the particle surfaces would be expected to contribute to compact strength. At the impeller speed and moisture content ranges for the pivotal trial batches, tablets have shown an acceptable hardness and met the specification for friability and disintegration time, in addition to having an acceptable dissolution profile which may be the consequence of adequate fluid penetration into the compressed tablet during drug release analysis.

In general, physical defects such as capping and chipping caused by low moisture levels or sticking and picking caused by high moisture levels are typical tablet defects [29]. However, these defects were not evident, and the physical appearances were satisfactory. At the ranges set for the input variables, friability and disintegration time met the specifications. The hardness for all batches were kept constant throughout experimentation between 63 N – 91 N. Most batches presented fast disintegration time, except batch F-2 that had a disintegration time of 6 minutes 10 seconds and tablets from batch F-11 disintegrated at 5

minutes 45 seconds, but were still well within the required limit of 15 minutes (900 seconds) as shown in Table 13. Figure 9 illustrates the dissolution profiles for all formulations. The y-axis represents the % ethionamide release, with the x-axis representing the time interval, in minutes.

Figure 5 illustrates the design space which is the multidimensional interaction between impeller speed during dosing and moisture content, to determine their influence on the extent of dissolution. The white zone represents the area of acceptable quality (design space) and the red-lines represent the edge of failure. Movement beyond the edge of failure into the grey zone is the area of potential risk where the dissolution is below the acceptable internal control limit. A vital step of product optimisation is to achieve an appropriate response function for both dependencies and independencies within the design space.

Figure 6 shows the FMEA before and after the implementation of a control strategy. Ethionamide is insoluble in water and its potential effect of failure may result in a below therapeutic level. Generally, weakly basic drugs like ethionamide (pKa = 4.49) tend to have a slower dissolution rate at higher pH levels as more drug exists in its ionised form [30]. A study by Vale and co-workers [31] showed that the solubility of pure ethionamide in an aqueous buffer at pH 1.2 was 4 mg/ml but decreased to 741 µg/ml in the pH range of 5.5 – 7.4. This finding concurs with the weakly basic nature of the drug substance. However, its solubility is a physicochemical property of the API. Nonetheless, DoE has demonstrated that API particle size distribution with a D_{50} range 95.18 µm to 267.00 µm does not have a significant effect on dissolution in a 0.1 M HCl medium. Therefore, the potential effect and cause of failure is lower. API particle size, D_{50} may range from 95.18 to 267.00 µm and remain within the design specification. DoE has established that a quantity of 4% m/m povidone binder is sufficient to cause optimal binding activation. Tablets were hard enough to withstand abrasion and handling, disintegrate within 15 minutes (900 seconds) and demonstrated an acceptable dissolution profile. Therefore, the potential effect and cause of

failure is well controlled at a 4% m/m quantity and should be maintained within the design space specification.

Impeller speed during wet mix between 100 to 200 rpm and the massing time between 120 and 360 seconds did not impact the extent of dissolution. For a duration of 180 seconds at an impeller speed of 100 rpm during wet mix, the pivotal trial batches and the validation generated a homogenous mix and tablets were able to withstand abrasion, disintegrate within 15 minutes (900 seconds) and showed an acceptable dissolution profile. At these settings, product quality will be achieved within the design space. The potential cause and effect of failure has been mitigated.

Impeller speed during dosing has been identified as one of the significant factors to influence dissolution. The validation batch indicated that at the optimal setting where the granulating medium is added to the powered bed over the 90 second period at an impeller speed of 115 rpm would result in 93% drug release at time point 15 minutes. The potential cause of failure and its effect on the product cQA is reduced and controlled within the design space specification.

The control for moisture content of the intermediate bulk material after drying the wet granule is set within the design space specification. The DoE batches showed no physical defects to suggest granules are over- or under- dried. Accordingly, impeller speed is a set input value entered onto the human machine interface (HMI) screen of the high shear mixer granulator compared to measuring the moisture content level. To mitigate the risk of not obtaining the target moisture content level of 2.5% m/m, it is feasible to set a tighter in-process control range within the design space of 2.4% m/m to 2.6% m/m. The prediction response for design points 2.4% m/m and 2.6% m/m using the model for dissolution are 102% and 98%, respectively. The predicted values are within the 95% prediction interval. Since moisture content has a significant role in the compaction process, the hardness range for the moisture

content between 2.4% m/m and 2.6% m/m should be within the range of 68 N and 72 N. The RPN for all the possible failure modes are below 50 which make them fall in the low risk range. Implementing quality risk management tools summarised in ICH Q10 guidelines (2009) may facilitate continual improvement of ethionamide 250 mg tablets. In addition, the control strategy for the manufacturing process stages is maintaining the in-process tablet characteristics of hardness, friability and disintegration time within the required ranges. End product testing will form a component of the control strategy as it confirms product quality.

5. Conclusion

The study presented a systematic approach of optimising the formulation and manufacturing process of ethionamide 250 mg tablets using QbD. By nature a historical database of the API, excipients and process data exist for legacy products and this information can be used to optimise pharmaceutical products. Optimising a long withstanding product using the modernised approach of QbD are void of the limitations of the traditional approach of QbT which assures product quality by in-process and end product testing. Therefore, the shift in paradigm from the traditional approach to QbD provided an astute insight for building quality into an immediate release oral solid dosage form.

Acknowledgments

Thank you to Aspen Pharmacare, Port Elizabeth and Nelson Mandela Metropolitan University for their financial support for this project.

Declaration of interest

The authors report no declarations of interest

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Table 1 Summary of the QTPP for ethionamide 250 mg tablets

QTPP Elements		Target	Justification
Dosage form		Tablet	Product is pharmaceutically equivalent and has the same dosage form
Dosage design		Uncoated immediate release tablet	Product is pharmaceutically equivalent and has the same dosage design
Route of administration		Oral	Product is pharmaceutically equivalent and has the same route of administration
Dosage strength		250 mg	Product is pharmaceutically equivalent and has the same dosage strength
Drug product quality attributes	Physical attributes	Round yellow, shallow concave, bevelled edged tablet with debossing on one side and scored	Tablet identification and to facilitate the splitting of tablet into fractions for partial dosage
	Dissolution	Not less than 80% of ethionamide is released within 45 minutes (Q = 75%)	Pharmaceutical equivalent requirement: must meet the same compendia or other applicable (quality) standards

Table 2 The risk ranking system in terms of the severity and the probability of the risks (Source: Frank *et el.,* 2008)

	Probability		
Severity	**Low**	**Medium**	**High**
High potential to impact product quality	Medium	High	High
Medium potential to impact product quality	Medium	Medium	High
Low potential to impact product quality	Low	Low	Medium

*This table has been amended and sourced from the Product Quality Research Institute (PQRI), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, United States of America; website: http://www.pqri.org/index.asp

Table 3 The FMEA for ethionamide tablet with their respective RPN for each failure mode

Formulation/process parameter component	Failure mode	Failure effects	S	Potential causes	O	Detectability method	D	RPN
API particle size	Low solubility in purified water	Below therapeutic level	8	Chemical property of the API	8	Control dissolution	1	64
Povidone binder quantity	Low binding activation, slow dissolution	Compression problem, bio-inequivalent to reference product	8	Incorrect quantity of binder in formulation	5	Quality control	2	80
Dosing	Impeller speed during dosing	Over granulation	8	Equipment changes, operator training	7	Determine range for impeller speed	1	56
Wet mix	Massing time	Over granulate and under granulate	9	Unknown range (to be established)	8	Determine speed and duration of impeller	3	216
	Impeller speed	Over granulate and under granulate	9	Unknown range (to be established)	8		3	216
Drying	Moisture content of intermediate bulk material	Over or under drying may cause physical tablet defects and poor granule flow. This may potentially affect the content uniformity and uniformity of mass	8	Temperature and time	5	Drying time and moisture to be established	3	120

Table 4 Formulation and process factors and their levels for the screening trial batches using a 2^{6-3} fractional factorial design

Independent variables (factors)		**Levels**		
		Units	**Low (-1)**	**High (+1)**
1	API particle size	D_{50} (µm)	95.18	267.00
2	Povidone binder quantity	% m/m	3	5
3	Impeller speed during dosing	rpm	100	200
4	Massing time	s	120	360
5	Impeller speed during wet mix	rpm	100	200
6	Moisture content	% m/m	1	3

Table 5 Matrix of the experiments for the fractional factorial design screening study and results for the product cQA

Standard Order	Run Order	Critical material attributes and process parameters						Product cQA
		API particle size	Binder quantity (povidone)	Impeller speed during dosing	Massing time	Impeller speed during wet mix	Moisture content	Dissolution
Units		D_{50} (µm)	% m/m	rpm	s	rpm	% m/m	% drug release at 15 minutes
1	1	267.00	3	100	360	200	3	100 ± 1.3
5	2	267.00	3	200	360	100	1	105 ± 1.5
8	3	95.18	5	200	360	200	3	47 ± 11.7
7	4	267.00	5	200	120	100	3	41 ± 4.4
6	5	267.00	3	200	120	200	1	97 ± 2.8
4	6	95.18	5	100	360	100	1	95 ± 1.4
3	7	267.18	5	100	120	200	1	102 ± 2.8
2	8	95.18	3	100	120	100	3	99 ± 1.9

Table 6 Significant factors and their levels for CCRD

Factors		Units	Factor Level				
			-α	**-1**	**0**	**+1**	**+α**
Impeller speed during dosing	X_1	rpm	89.64	100.00	125.00	150.00	160.36
Moisture content	X_2	% m/m	2.40	2.50	2.75	3.00	3.10

Table 7 Matrix of experimental plan of CCRD and results of cQA

Run Order (Formulation)	Standard Order	Point Type	Blocks	Risk Factors		Product cQA
				Impeller speed during dosing	Moisture content	Dissolution
Units				rpm	% m/m	% drug release at 15 minutes
1	10	0	1	125.00	2.75	99 ± 2.20
2	6	-1	1	160.36	2.75	78 ± 15.50
3	1	1	1	100.00	2.50	100 ± 1.00
4	5	-1	1	89.64	2.75	81 ± 14.50
5	7	-1	1	125.00	2.40	96 ± 1.00
6	11	0	1	125.00	2.75	91 ± 2.40
7	4	1	1	150.00	3.00	92 ± 1.70
8	9	0	1	125.00	2.75	99 ± 1.40
9	13	0	1	125.00	2.75	97 ± 0.80
10	12	0	1	125.00	2.75	95 ± 2.50
11	3	1	1	100.00	3.00	78 ± 11.20
12	8	-1	1	125.00	3.10	91 ± 10.80
13	2	1	1	150.00	2.50	96 ± 1.50

Table 8. Parameters used in the formula for the dissolution test

A_{sam}	Absorbance of ethionamide in the sample solution
A_{std}	Average absorbance of ethionamide in the standard solution
Mass of standard	Mass of ethionamide working standard taken to prepare the standard solution (55 mg)
C	Potency of the ethionamide working standard, expressed in percentage (100.6%)
Label Claim	Amount of ethionamide present in each tablet i.e. dosage unit, expressed in mg (250 mg)
Requirement: Not less than 80% of active is release per dosage unit within 45 minutes	

*Note: The values in the brackets represent the mass weighed, volume of the standard solution, volume of the dissolution medium, label claim and the potency of ethionamide

Table 9 Screening trial: ANOVA analysis of the adjusted model for the product cQA

Term	Units	F-value	p-value	Comment
Model	-	34.31	0.029	Significant
API particle size	D_{50} (µm)	0.46	0.568	Non-significant
Povidone binder quantity	% m/m	61.72	0.016	Significant
Impeller speed during dosing	rpm	51.54	0.019	Significant
Massing time	s	0.29	0.642	Non-significant
Moisture content	% m/m	57.54	0.017	Significant

Table 10 Screening study: A summary of the tablet characteristics

Formulation	Average tablet hardness	Friability	Disintegration time
Units	**N**	**% m/m**	**s**
F-1	42.80 ± 5.14	0.90	156
F-2	34.80 ± 2.20	2.70	31
F-3	80.40 ± 3.75	0.20	538
F-4	78.40 ± 6.02	0.15	524
F-5	29.80 ± 2.49	9.61	33
F-6	49.20 ± 4.78	1.07	107
F-7	39.50 ± 6.35	1.02	352
F-8	58.50 ± 0.01	1.16	37

Table 11 ANOVA analysis of the for the linear, square and interaction effects on the extent of dissolution at 15 minutes

Source		**F-value**	**p-value**	**Comment**
Regression		**4.900**	**0.030**	**Significant**
Model	Linear	2.990	0.115	Non-significant
Terms	Impeller speed during dosing	0.180	0.688	Non-significant
	Moisture content	5.800	0.047	Significant
Model	Square	7.54	0.018	Significant
Terms	Impeller speed during dosing * Impeller speed during dosing	14.38	0.006	Significant
	Moisture content * Moisture content	0.000	0.958	Non-significant
Model	Interaction	3.440	0.106	Non-significant
Terms	Impeller speed during dosing * Moisture content	3.440	0.106	Non-significant
Lack-of-Fit		3.58	0.125	Non-significant

Table 12 Summary of the predicted and measured responses of the hypothesised model at the optimised conditions

Response	Units	Predicted mean	Actual mean	95% PI low	95% PI high
Dissolution at 15 minutes	**%**	100.6	93.0 ± 1.4	87.56	113.75
Disintegration time	s	207.00	213.00	61.60	352.00
Friability	% m/m	0.12	0.19	0.05	0.19
Tablet hardness	N	72.58	69.30 ± 2.83	53.97	91.19

Table 13 RSM study: Summary of the tablet characteristics

Formulation	Average tablet hardness	Friability	Disintegration time	Average tablet mass
Units	**N**	**% m/m**	**s**	**mg**
FT-1	66.30 ± 6.77	0.08	180	496.63 ± 4.23
FT-2	73.30 ± 7.01	0.08	370	502.41 ± 3.19
FT-3	71.70 ± 2.83	0.15	208	499.01 ± 4.06
FT-4	91.00 ± 6.53	0.07	336	498.43 ± 4.43
FT-5	66.70 ± 5.50	0.11	201	502.34 ± 2.86
FT-6	78.90 ± 5.95	0.09	347	505.90 ± 3.93
FT-7	72.50 ± 6.02	0.05	293	496.90 ± 2.83
FT-8	67.40 ± 4.67	0.11	305	501.72 ± 2.77
FT-9	66.90 ± 5.13	0.05	276	500.98 ± 2.28
FT-10	73.30 ± 5.66	0.05	250	500.23 ± 2.35
FT-11	63.00 ± 5.89	0.05	345	498.00 ± 3.30
FT-12	69.30 ± 5.40	0.08	230	499.50 ± 2.62
FT-13	69.30 ± 3.56	0.17	227	504.47 ± 1.76

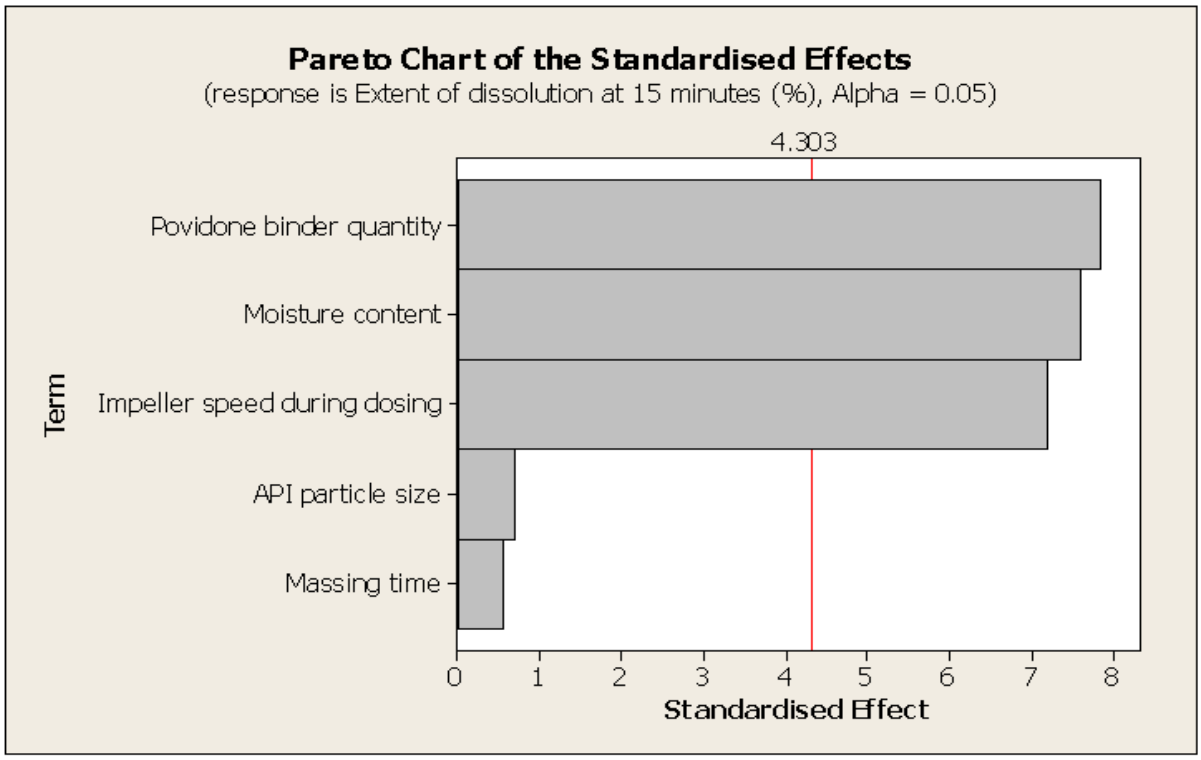


Figure 1 Pareto analysis for the adjusted model of the influence of the input variables influencing the extent of dissolution at 15 minutes

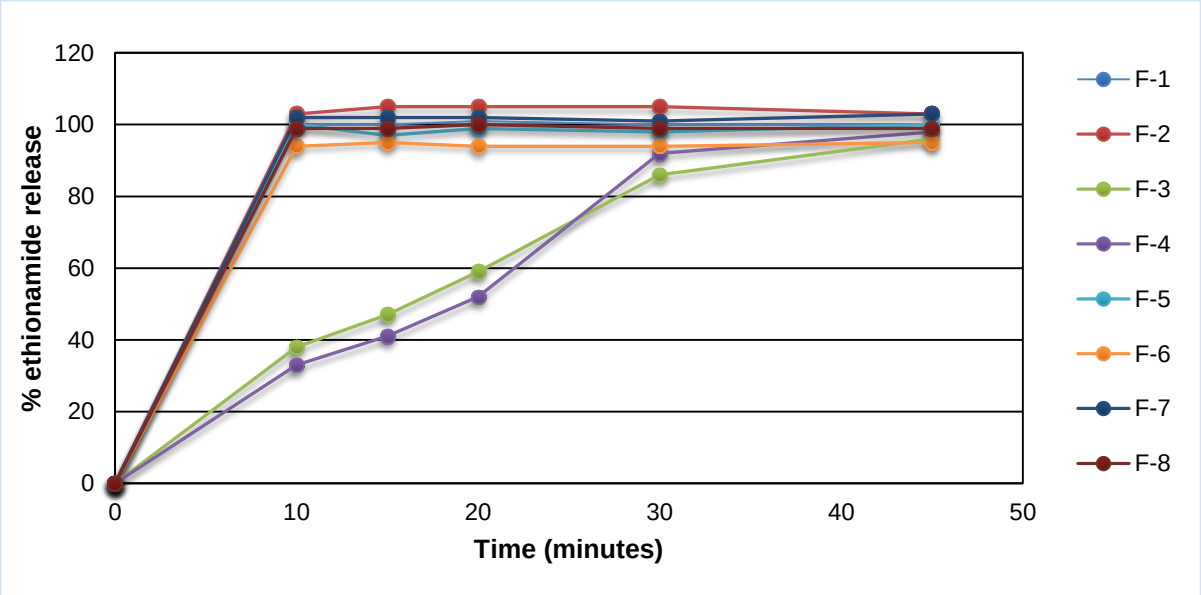


Figure 2 Screening trial batches: A release dissolution profile of ethionamide 250 mg tablets

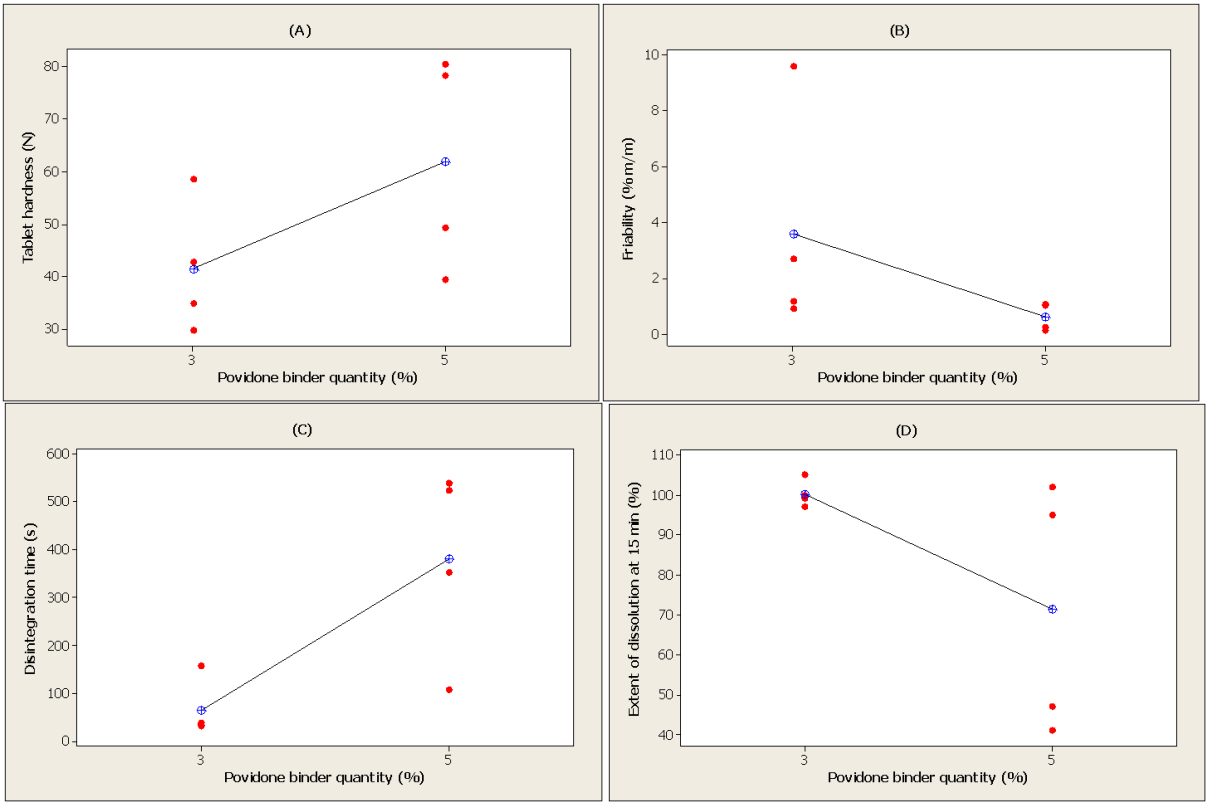


Figure 3 Graphical representation of the effect of the quantity of povidone binder between the range of 3% m/m to 5% m/m on (a) tablet hardness (b) friability (c) disintegration and (d) the extent of dissolution at 15 minutes

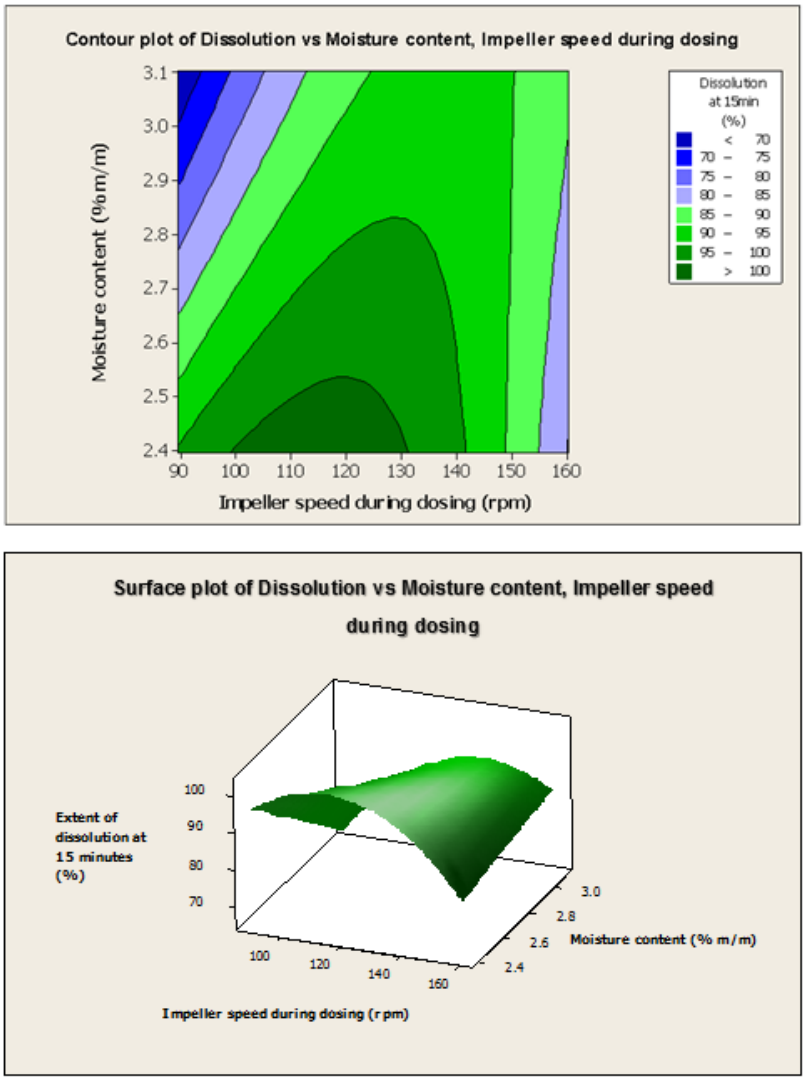


Figure 4 Contour and surface plot of the effect of moisture content and impeller speed on the extent of dissolution at 15 minutes

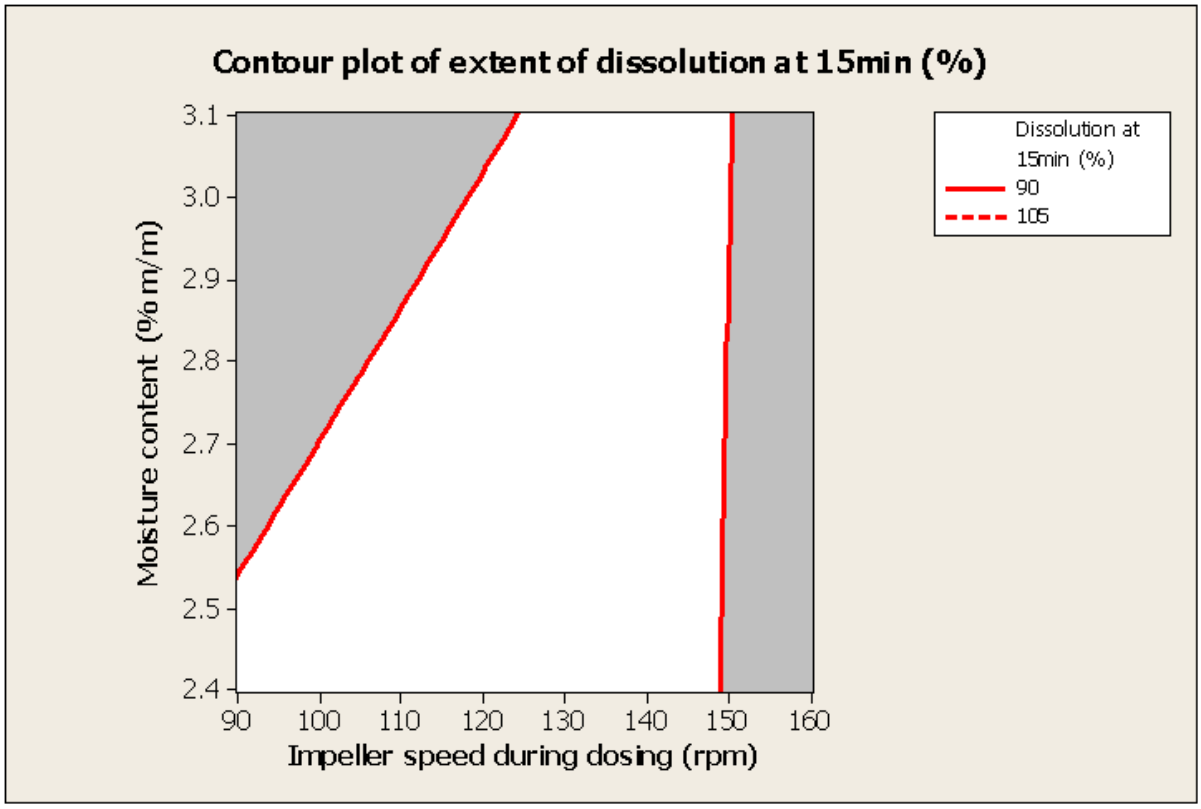


Figure 5 Design space: A contour plot of the interaction between the significant factors on the product cQA

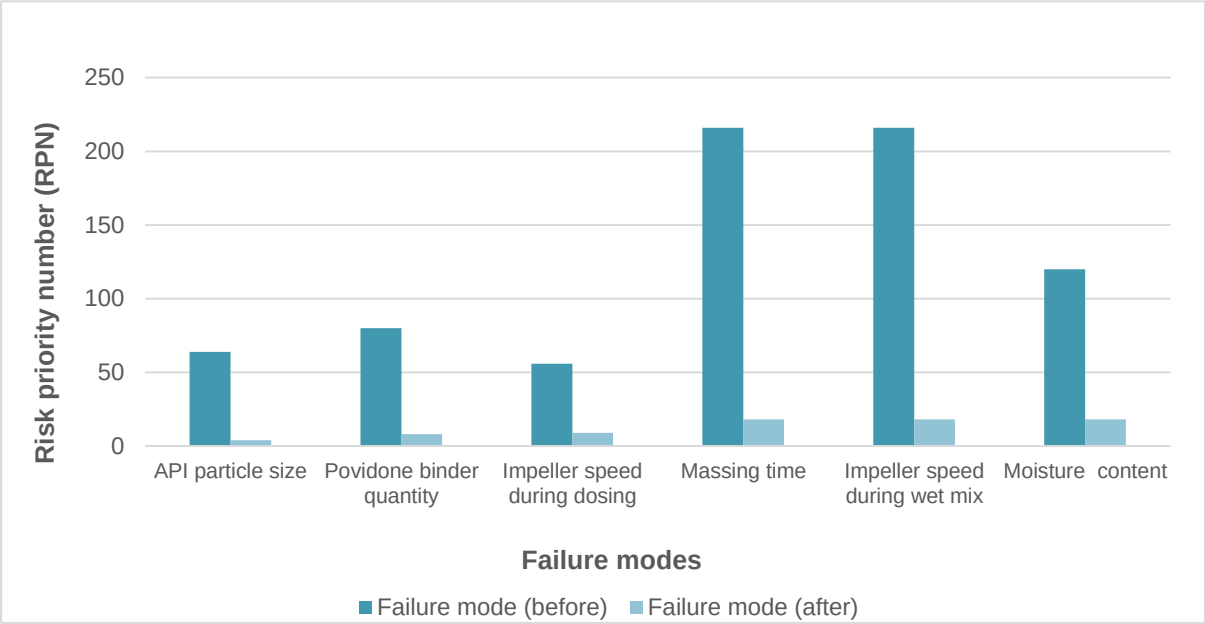
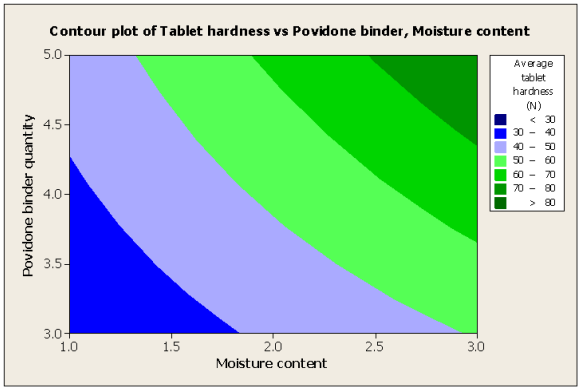
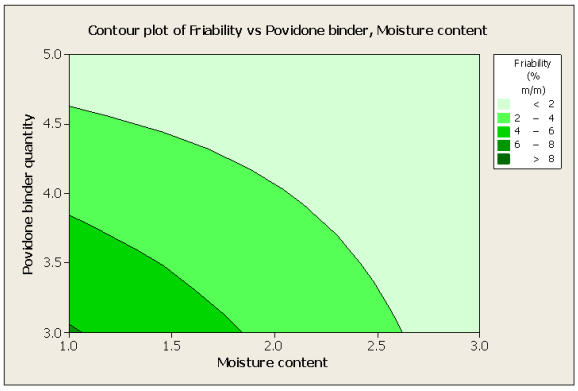


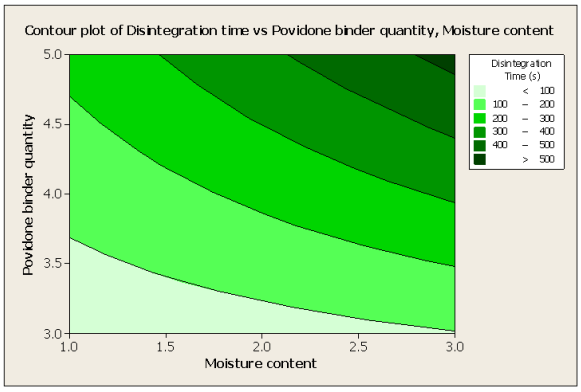
Figure 6 FMEA analysis of ethionamide tablets depicting RPN of failure modes before and after implementation of control strategy



(a)



(b)



(c)

Figure 7 Contour plots showing the effect of povidone binder quantity and moisture content on the selected responses (a) tablet hardness (b) friability (c) disintegration time

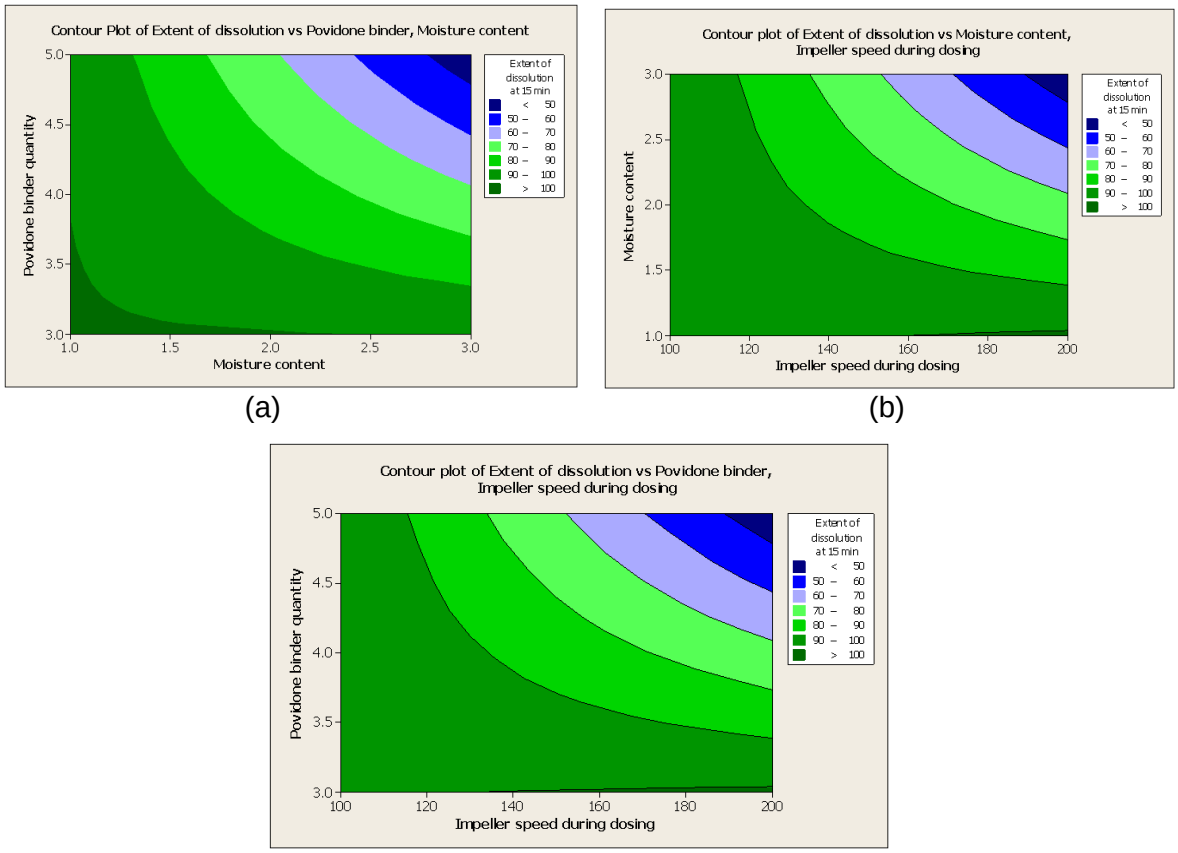


Figure 8 Contour plots showing the effect of povidone binder quantity, moisture content and impeller speed during dosing on the extent of dissolution at 15 minutes

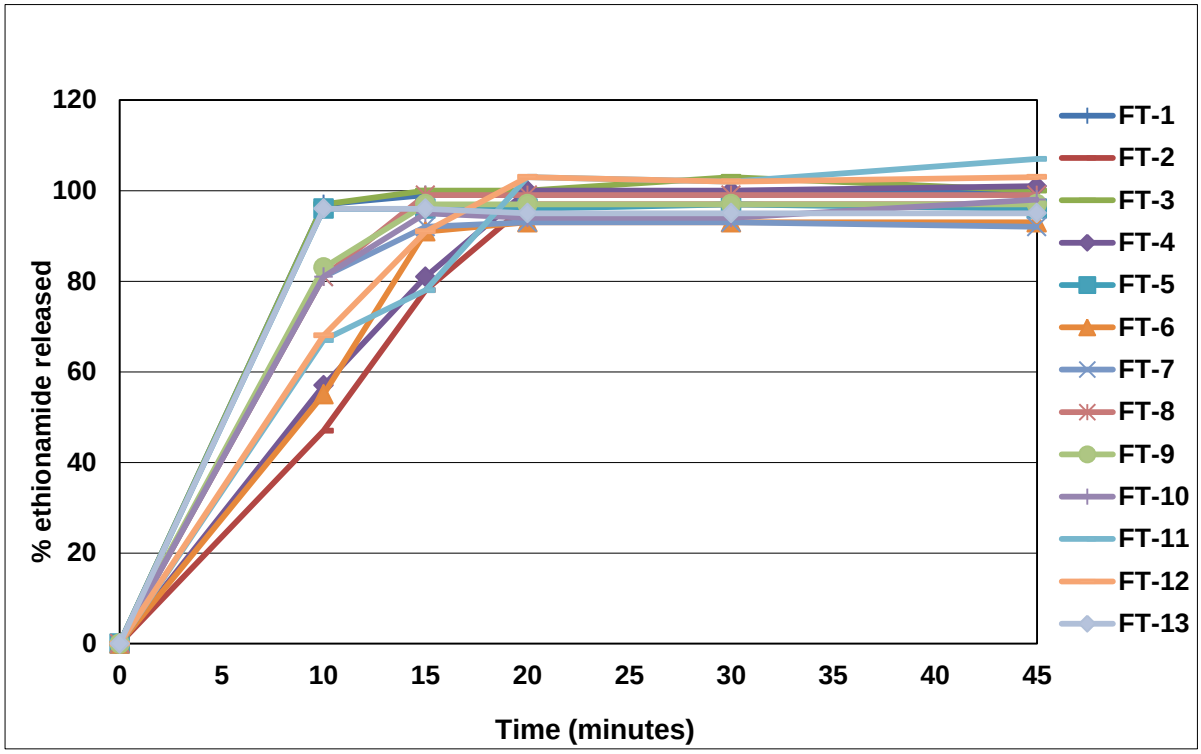


Figure 9 RSM study: A release dissolution profile of ethionamide 250 mg tablets

LIST OF FIGURES

APPENDIX B – Abstract Submitted to the Academy Pharmaceutical Society of South Africa (APPSA) Conference

Entry: The young scientist award

Held at the Summerstrand Hotel, Port Elizabeth, 12 -14 September 2014

Formulation and Process Optimisation of an Immediate Release Tablet Using Quality by Design

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Purpose: Designing a pharmaceutical product and its manufacturing process that is efficient, safe and fit for its intended use for patients is the primary focus of pharmaceutical development. Quality by Design (QbD) emphasises that the product quality should be built into the product and not merely tested post-production. This systematic concept of QbD is the successor of the empirical Quality by Testing (QbT) and forms part of the modern approach to pharmaceutical quality. The aim of the study is to optimise the formulation and manufacturing process of an immediate release tablet using QbD.

Methodology: The methodology employed in this investigation was done in accordance with the International Conference on Harmonisation Q8 and Q9 guidelines. Established the quality target product profile (QTPP). Identified the critical quality attributes (cQAs) of the product. Performed a risk assessment to identify the critical material attributes and process parameters that may impact the cQAs. Design of experiments (DoE) was applied to the risk factors. The screening trial batches using a 2-level fractional factorial design screened the factors to determine which of the critical factors identified during the risk assessment are significant. Following the screening trial, the pivotal study using a central composite rotatable design (CCRD) determined the effects of the significant factors on the cQAs.

Results: The risk assessment identified the active pharmaceutical ingredient (API) particle size; quantity of binder content (povidone); impeller speed during dosing; massing time; impeller speed during wet mix; and moisture content (after drying wet granule) as factors

that may impact the extent of dissolution (%) at 15 minutes (cQA). ANOVA analysis of the experimental designs showed that the model (quadratic) chosen for the analysis had a significant fit (p=0.030). The response optimiser, indicated that to reach optimum desirability for the extent of dissolution (%) at 15 minutes, i.e. 100.6%, impeller blade speed during dosing should be 115 rpm and moisture content at 2.5% m/m.

Conclusion: QbD provided an effective means to optimise the formulation and manufacturing process of the immediate release tablet by determining the influence of the selected input variables on the product cQA.