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Establishing a Design Space for an Existing Generic Tablet Dosage Form for Efficient Manufacturing and Quality Assurance at Jepharm in Palestine

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Declaration

I hereby declare that this present master's thesis Titled

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has been written by myself and is my work. All formulas and concepts utilized in this work were quoted in compliance with the good science practice law; either it was taken literally from printed, non-printed contents or the internet. Also, this work has not been submitted, in whole or in part, for any other degree or professional qualification.

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Abstract

Quality has become a critical factor in the success of an organization. Quality management and planning through the implementation of Quality by Design (QbD) to establish a Design Space(s) and utilize Quality Improvement methods used in this research study have been proven to maximize efficacy, safety and increase manufacturing productivity while reducing the manufacturing cycle time. This research study is to utilize QbD to establish a Design Space(s) for efficient manufacturing and quality assurance at Jepharm in Palestine. More specifically, this study helps to reduce the manufacturing cycle time of an existing JR tablet pharmaceutical product with the ultimate focus on the patient. Qualitative data were collected to define the Critical to Quality (CTQs) characteristics while Palestinian Ministry of Health was contacted to understand the guidelines of QbD implementation in Palestine. Quantitative empirical 2018 and 2019 overall cycle time retrospective data for all products at Jepharm were collected and JR tablet was identified with the worst overall cycle time. Also, 2017 to 2019 retrospective data for the manufacturing of JR tablet were collected. The relationship between Critical Material Attributes, Critical Process Parameters and Critical Quality Attributes was identified for JR tablet. Design Expert 13 software was used to build the Design Space models. Four Design Spaces were established; the first one is for the response dissolution, the second one is for the response friability, the third and fourth ones are for the response API 2 Assay after compression and after coating. In August 2020, thirteen batches were executed, new processing data collected and the design spaces were finalized utilizing Design Expert 13 and Quality Risk Management. It was found that the manufacturing cycle time is the main and most critical process factor

affecting the overall cycle time of JR tablet. Final mixing and coating stages are the most critical unit operations affecting the manufacturing cycle time. Oscillating and sieving unit operations were modified to remove none value added activities while improving the compression operation due to better powder-mixture's flow-ability, hence, eliminating capping and chipping of tablets. API 2 assay was found to be the most Critical Quality Attribute of JR tablet manufacturing process. In order to help better distribute API 2 in the final mixture and eliminate degradation of API 2, granulated material was dried to LOD <1.5% and geometric mixing was introduced before the final mixing stage. Mixing time was increased from 15 minutes to 30 minutes giving more time for homogenous mixing of API 2 since its concentration in the batch is about 0.3% and no baffles are present in the Bin Mixer. In addition, API 2 was found to be affected by temperature in the coating stage's warming step with the inlet air temperature reaching a maximum of 63^{o}C leading to an out-of-specification of API 2 assay with 15% reduction. The inlet air temperature to the coating machine was reduced to <32^{o}C eliminating product degradation. These results are very important because the improvements made reduced the manufacturing cycle time by 45% and ensured that API 2 assay stays within (95% - 110%) limit which frequently failed this limit leading to reprocessing of batches. The control strategy was developed and training was completed accordingly. In July 2021, all of the uncovered improvements were validated by executing four actual production batches with excellent results.

Keywords: Quality by Design, Design Space, Six Sigma, DMAIC, Lean Six Sigma, VSM, Quality Management, Quality Risk Management, Cycle Time, Process Improvement.

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List of abbreviations

- AR: Acceptable Range
- BP: British Pharmacopeia
- CHMP: Committee for Medicinal Products for Human Use
- CMA: Critical Material Attribute
- COA: Certificate of Analysis
- COC: Certificate of Conformance
- CPP: Critical Process Parameter
- CQA: Critical Quality Attribute
- CT: Cycle Time
- CTQ: Critical to Quality obtained from customer
- DS: Design Space
- DPMO: Defects per Million Opportunity
- DMAIC: Define Measure Analyze Improve Control
- DMADV: Define Measure Analyze Design Verify
- DFSS: Design for Six Sigma
- DOE: Design of Experiment
- EMA: European Medicines Agency
- ERP: Enterprise Resource Planning
- EXACT: Exchange Access Control and Tracking System Software
- FBD: Fluid Bed Dryer
- FDA: Food and Drug Administration of USA
- FMEA: Failure Mode and Effect Analysis

- FQA: Final Quality Attribute
- GMP: Good Manufacturing Practice
- HEPA Filter: High Efficiency Particulate Air Filter
- ICH: International Conference on Harmonization
- IQA: Intermediate Quality Attribute
- ISPE: International Society for Pharmaceutical Engineering
- Jepharm: Jerusalem Pharmaceuticals Co. Ltd.
- JR Tablet: Fixed combination tablet consisting of Folic Acid and Iron salt.
- LSS: Lean Six Sigma
- LOD: Loss on Drying
- MCC: Micro Crystalline Cellulose
- MHLW: Minister of Health, Labor and Welfare Drug Approval System of Japan
- MPR: Manufacturing Procedure Record
- NIST: National Institute of Standards and Technology
- PAT: Process Analytical Technology
- PC: Project Charter
- PCD: Problem Context Diagram
- PDA TR 60: Parenteral Drug Association Technical Report 60
- PFD: Process Flow Diagram
- PM: Process Map
- PMI: Process Management International company
- PV: Process Validation
- QbT: Quality by Testing

- QbD: Quality by Design
- QRM: Quality Risk Management
- QP: Qualified Person
- QA: Quality Assurance
- QAI: Quality Assurance Inspector
- QC: Quality Control Lab
- QMS: Quality Management System
- RPM: Revolution per Minute
- RPN: Risk Priority Number
- SS: Six Sigma
- SIPOC: Supplier Input Process Output and Customer
- SMEs: Small and Medium-Sized Enterprises
- SMG: Super Mixer Granulator
- TPP: Target Product Profile
- TQPP: Target Quality Product Profile
- QTPP the same as TQPP: Quality Target Product Profile
- VSM: Value Stream Map

List of definitions

- **Jerusalem Pharmaceuticals Company** (Jepharm, 2018)**:**

Jerusalem Pharmaceutical Company (Jepharm) is an industrial Palestinian company which was established in 1969 as a private company. The company grew and in 1978 became a Joint-stock company. The company expanded to become a regional Middle East company not just in Palestine, but also in Jordan and Algeria. The company delivers its products to more than 17 countries in Middle East region and North Africa. The company manufactures more than 300 medicinal products for human and veterinary use. These products are manufactured under the umbrella of Good Manufacturing Practice and safety standards ISO 9001, ISO 14001 and ISO 45001. The company also distributes house hold products. JR product is one of the medicinal products manufactured in Palestine.

- **Quality by Design and Design Space** (ICH, 2011)**:**

Some Pharmaceutical companies use QbD to establish Design Space(s) (DS) as their approach to developing and producing their pharmaceutical products. QbD is a science and Quality Risk Management based-approach that emphasizes on the understanding of the drug product manufacturability including the processes and their controls to produce quality medicinal products. While Design Space is a method of finding a combined interaction relationship of critical or not critical variables which when monitored and controlled can produce pharmaceutical products with the required quality requirements and product quality attributes. QbD is used to understand the relationship between variables so that they can use their optimum combination and interaction to create a more stable and an optimum Design Space. As (Lepore & Spavins, 2008) noted, “the design space is arrived

at by an iterative process such that is not a true design space until it has been demonstrated that an 'appropriate understanding of attributes needed to assure the Quality Target Product Profile has been achieved". They use the Input Variables including material attributes such as particle size and process parameters such as temperature, pressure and or flow rate that have been demonstrated to provide assurance of Product Quality Attributes (ICH, 2009). The drug product general quality attributes include characteristics such as Safety, Quality, Efficacy, Strength, Purity and Identity.

- **Lean Six Sigma** (Wikimedia, 2020)**:**

Lean Six Sigma combines Lean method with Six Sigma method are employed to achieve an overall process improvement by eliminating the eight types of wastes such as Defects, Over-Production, Waiting, Non-Utilized Talent, Transportation, Inventory, Motion, and Extra-Processing. Lean Six Sigma uses team efforts to systematically eliminate waste and reduce variation in the process. Kaizen, Value Stream Mapping, Visual Management and Line Balancing are all tools used to successfully implement Lean Six Sigma (LSS). When LSS is used effectively, it can lead to quality improvement, cycle time reduction and eventually cost reduction.

- **Six Sigma** (Wikimedia, 2020)**:**

Six Sigma (6σ) is an improvement method which uses various tools and techniques to improve processes. Bill Smith, an American Engineer, was the first to introduce Six Sigma in 1986 while working at Motorola. On the other hand, Jack Welch used it as a business improvement strategy in 1995 at General Electric. A process is said to be Six Sigma if 99.99966% of all opportunities to produce products with an expected statistical outcome

of almost defects free, 3.4 defects per million opportunities (DPMO) indicating the percentage of defect-free products the process creates or a yield of a product from the process. Six Sigma as a technique with its tools improves the quality of products produced by a particular process through the identification of variability in the process and then trying to eliminate them in order to reduce defects in products. Six Sigma ensures stability in the process, hence, consistent quality outcome and defects free products leading to cycle time reduction, cost savings and higher profitability. For process improvements, Six Sigma follows two methods either DMAIC or DMADV. DMAIC is an acronym for Define, Measure, Analyze, Improve and Control. DMAIC refers to a process improvement cycle used for improving, optimizing and stabilizing existing processes. While DMADV is an acronym for Define, Measure, Analyze, Design and Verify. DMADV or also called Design for Six Sigma (DFSS) is used for new products development and implementation. DMADV can also be used during the improve phase of the DMAIC since it is possible while improving a process a new machine or instrument or piping system is needed to optimize a process or reduce cycle time. In this case DFSS can be used in parallel to DMAIC.

- **Quality Risk Management (QRM)** (ICH, 2011)**:**

Quality Risk Management (QRM), is a tool used to investigate the risk of a particular process or operation. QRM contains five phases including Risk Assessment, Risk Control, Risk Review, Risk Communication and Risk Tools. Risk Assessment contains risk identification, risk analysis and risk evaluation. Risk assessment takes the qualitative information gathered during the QRM study and helps translate it into quantitative data for ranking purposes. This ranking process happens during the evaluation process where

severity, probability of occurrence and detectability can be used to obtain the Risk Priority Number (RPN) which is used to rank the risks for implementation. The results of the QRM study is to uncover corrective and or preventative actions for continuous improvement.

- **Design of Experiment (DOE)** (Wikimedia, 2020)**:**

Formal Experimental Design is a Design of Experiment used to identify the relationship between factors. It is an organized and structured approach in order to find relationships among in-process processes and their output.

- **Acceptable Range (In specification Limit)** (Wikimedia, 2020)**:**

Keeping other parameters constant, operation within this range will result in a finished material which can be an intermediate or finished product with the required quality specifications and criteria meeting customer requirements and satisfaction.

- **Suppliers Input Process Outputs and Customers Diagram (SIPOC):**

It is a Process Management International (PMI) SIPOC diagram. The SIPOC diagram is a summary of all of the inputs from suppliers to a process including controllable inputs such as raw materials and uncontrollable inputs such as weather and indicates the outputs of this process and customer Critical to Quality Attributes.

- **Problem Context Diagram (PCD):**

It is a Process Management International (PMI) diagram. The PCD diagram provides a quick overview of the upstream processes that affect the main process which affect the downstream processes.

- **Project Charter:**

It is a Project Management International (PMI) company's Project Charter (PC). The PC is initially prepared to give an overview of the study objectives, scope, team members, an overall timeline of the study and any projections of possible future obstacles.

- **Process Flow Diagram** (Wikimedia, 2020)**:**

A diagram for the entire process which may include several stages or processing steps. It shows all of the inputs and all of the outputs of each stage or step. It covers all of the processing steps from the start to the end until a final product is achieved.

- **Process Map according** (QBDVision, 2020)**:**

A diagram which shows input materials, process components, materials attributes, process parameters, unit operations, intermediate attributes and final attributes of each step or stage of the process.

- **Pareto Chart** (Wikimedia, 2020)**:**

A chart used to give an overview of the most significant problems or issues or defects in a process. The chart shows bars and a line graph. The bar indicates the total defects or problems or issues descended from tallest bar to shortest bar. The line graph gives the cumulative % of the defects or problems or issues. In general, the 20/80 rule when applied; it indicates that the few most significant 20% of problems or defects or issues make up 80% of the overall problems or defects of a process. This means that if we solve the most top significant 20% of problems or defects or issues, 80% of the overall problems of the process are resolved.

- **Value Stream Mapping (VSM)** (Wikimedia, 2020)**:**

Value Stream mapping is completed for all process steps from the start to the end. VSM indicates the lead time and the actual process time for each step and the total lead time and the total processing time of the entire process to calculate the overall cycle time of the process. VSM is an LSS tool which is completed for a product before improvements and after improvements to show the effect of improvements made on cycle time.

- **Overall Cycle Time:**

The cycle time starts from weighing of raw materials and ends at Qualified Person or Responsible Pharmacist final signature to release the product to market.

- **Manufacturing Cycle Time:**

The cycle time starts from raw materials receiving until the end of packaging of the entire product.

- **Process Analytical Technology (PAT)** (Wikimedia, 2020)**:**

Helps to design, analyze and control manufacturing processes while in operation to monitor performance and critical to quality attributes of raw materials and in-process materials. It is an online monitoring for parameters such as CPPs to ensure TQPP. This is so that the finished product is with the required quality specifications.

- **Material:**

Material includes starting materials, excipients, solvents, reagents, intermediates and packaging and labelling materials.

- **Components of a medicinal product** (ICH, 2009)**:**

A drug product contains an active ingredient (drug substance) and excipients.

- **Active Ingredient (Drug substance)** (ICH, 2009)**:**

"The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability" (ICH, 2009). The drug substance is also called active ingredient which makes the drug product effective to the patient with direct effect providing the required remedy. Examples of physicochemical and biological properties to examine are assay, water content, particle size, crystal properties, bulk density and tapped density.

- **Excipients** (ICH, 2009)**:**

"The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, dissolution rate)" (ICH, 2009). These excipients are mixed with the drug substance and may or may not appear in the final finished product such as solvents. Excipients must be compatible with the drug substance and with other excipients in the mixture. Excipients can be lubricants and or disintegrates which have different functions such as being preservatives for the drug product throughout its shelf life. They are added to the drug substance to protect it, to cover unpleasant odors and to make the product looks and tastes good for the patient. Excipients have no therapeutic effect on the patient.

- **Target Product Profile (TPP)** (ICH, 2011)**:**

TPP of a drug product is considered the profile of the product which covers indication and usage, dosage and administration, dosage forms and strength, adverse reactions, warnings and precautions, drug interactions, use in specific population, over-dosage, description, clinical pharmacology, nonclinical toxicology, storage…etc. Normally, in order to achieve all required TPPs, TQPP are executed which are the quality attribute that a product should contain to attain the TPP. TQPP is executed in the form of tests such assay, content uniformity, dissolution, stability…etc.

- **Target Quality Product Profile (TQPP)** (ICH, 2011)**:**

The target quality product profile is the design basis for product development. TQPP contains the quality characteristics of the medicinal product which must be available or met to ensure Safety, Quality, Efficacy, Strength, Purity and Identity of the drug product. For a tablet product, for example, these quality attributes include assay, dissolution, content uniformity of dosage form…etc.

- **Critical Quality Attributes (CQA)** (ICH, 2011)**:**

CQAs are the attributes that must be available in the finished product as a result of monitored and controlled processes. An effective and successful design space ensures such control and results. Tablet dosage form CQAs have a direct effect on the quality of the drug product and its characteristics such as Safety, Quality, Efficacy, Strength, Purity, Identity and on the finished product release and shelf-life stability.

- **Critical Process Parameter (CPP)** (ICH, 2011)**:**

Critical Process Parameters are identified as the process variables which can have an impact on the finished product critical quality attributes mentioned in the TQPP: An example of a CPP is temperature set point in a coating machine or a temperature set point in a Fluid Bed Dryer. The variability of the CPP especially within the design space of a process must be monitored and controlled to ensure that the tablet dosage form finished product has the required quality and the required Critical Quality Attributes (CQA).

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Chapter One: Introduction

1.1 Overview

This chapter aims to explain quality and the importance of effectively planning and managing quality in pharmaceutical manufacturing. Quality and Quality Management are terms of importance while if understood and practiced effectively and efficiently can help even a very small company become competitive globally. Over the last seven decades, quality Gurus emerged with their own definitions of quality. Juran defined quality as "Fitness for use" while Crosby defined it as meeting customer requirements. Quality of a process can be measured through its variation in results which may have an effect on product quality. Montgomery (2021, p. 6) in his book said that "Quality is inversely proportional to variability" which means that quality improvement can be achieved by reducing variability in the process which is then reflected to consistently producing a quality product within specifications. On the other hand, Quality Management means that the businesses, services or finished products are produced in a consistent manner within predefined specification limits to attain the required quality for customer satisfaction. This means that there are written procedures and specifications to ensure that products are produced with quality each and every time the same way consistently with almost no to minimum defects so that they are quickly delivered to a demanding market place with no delays. Quality management covers quality planning, quality assurance, quality control and continuous improvement. It involves people, processes or services and products together during quality evaluation and improvements. Pharmaceutical manufacturers have been facing many business challenges to cope with the fast development of drug products in this

advanced global technological environment. Changes in rules, regulations and guidelines in the pharmaceutical industry enabled pharmaceutical companies to shift their strategy from using traditional methods of drug manufacturing to the new methods which enabled them to sustain their competitive edge in this global economy. In order to compete on a global scale and even survive in the local market place, small pharmaceutical companies must follow up and implement the new regulations and guidelines of pharmaceutical development and manufacturing to produce quality medicinal products. In this new technological edge, the main goal to survival and growth is customer satisfaction regardless of borders. Small pharmaceutical companies must be able to compete on a global scale in order to gain market share and increase their profit and eventually growth. It has been proven that large successful pharmaceutical companies were able to produce quality medicinal products efficiently in different ways as long as they abide by the set regulatory rules and guidelines to consistently attain quality in their medicinal products and supply them globally. All of the efforts spent in quality management are again to obtain customer satisfaction which if it is met, it will increase a company's revenues and eventually growth. The achievement of quality can be checked through the usage of quality management methods with related tools which play an important role in measuring quality. Among the main quality management methods known to measure success of continuous quality improvements are Six Sigma and Lean Six Sigma with their related tools. However, designing the achievement of quality is an approach which has been gaining attention from the FDA and EMA. The new approach to designing quality into products is using QbD.

1.2 General background

1.2.1 Quality management methods and related tools

The Quality by Design (QbD) concept was first outlined by Joseph M. Juran in "Juran on Quality by Design" publication. Montgomery (2021, p. 22) talked about Juran Trilogy. One of the three Trilogy of Juran is designing for quality and innovation of products and services. Juran believed that most quality issues and problems are related to the way that quality is planned. "Dr Juran believed that quality could be planned, and that most quality crises and problems could be averted with improved quality planning and the way in which a product was designed in the first place." (Schlindwein & Gibson, 2018, P. 117). In the 1970s, Toyota pioneered many QbD concepts in their operations. While in 1990, medical devices began to incorporate the QbD aspects with the aim of continuous improvement. The Food and Drug Administration of the United States of America FDA was the first to adopt Juran's quality by Design. "FDA continues to make progress under the Pharmaceutical Quality for the 21st Century – A Risked Based Approach formally known as *Pharmaceutical CGMP Initiative for the 21st Century – a Risk Based Approach*." (FDA, 2007). This approach was instituted to try to modernize the FDA regulations of pharmaceutical quality. The FDA's look at QbD concept is similar to what Juran viewed QbD, their focus is that "quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks." (FDA, 2007). FDA's emphasis on QbD began with the recognition that "increased testing does not necessarily improve product quality and that quality should be built into the product" (Schlindwein & Gibson, 2018, P. 118). The first company to

approve a product using QbD was Merck & Co's Januvia in 2006. Process Analytical Technologies (PAT) is a tool which can help through the implementation of QbD. It is a tool used during the design and analysis of pharmaceutical manufacturing and new development so that new manufacturing technologies are encouraged. The goal is to try to use the knowledge gained from experience to improve process understanding and to predict the quality of the product through calculated risks and the use of scientific understanding to measure and control the performance of the product. PAT gives you the ability to analyze processes online and make effective decisions, however, not all companies have PAT which can be a challenge, for it requires high amount of capital spending, to pharmaceutical companies especially in Palestine. The FDA assembled and instituted many working groups under their supervision and met with a number of outside organizations to actively follow up on the development of the QbD concept. The concept of QbD is to facilitate a design for a product and the processes involved during development by studying the risks and providing mitigations of those risks prior to introducing the product into manufacturing. This initial step is based on effectively planning quality into the product, analyzing the processes to be used during the manufacturing of this product, making scientifically calculated decisions and understanding the risks involved in order to maximize the product safety, quality and efficacy while enhancing the product manufacturability. "Therefore, successful implementation of QbD in manufacturing process means a full understanding of each unit operation involved in the process, which also means using QbD tools to identify all critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs), and then developing corresponding control strategy" (Badawy & Narang, 2018, P. 703&704). Many

pharmaceutical companies have been encouraged by the FDA to follow the footsteps of Merck & Co's Januvia to develop QbD for their products. In this research study, QbD concept and approach to develop a Design Space(s) and other quality management methods such as Six Sigma and Lean Six Sigma will be used to efficiently improve the manufacturing of an existing JR generic tablet drug product at Jepharm in Palestine.

1.2.2 Pharmaceutical drug manufacturing

In pharmaceutical manufacturing, medicinal products are said to be quality manufactured if their analyzed results are found to be within an accepted and approved set of specification limits. In order to monitor the quality of pharmaceutical products, quality assurance or Quality Management System (QMS) comes to play the role of managing and controlling all of the processes of the drug product's life cycle. As mentioned in (Health Canada, 2011), GMP is considered part of Quality Assurance or QMS to ensure that drug products are consistently produced and controlled according to the quality standards appropriate for their intended use and as required by the marketing authorization. What is meant by the quality standards is that product qualities such as quality, efficacy, safety, strength, purity and identity characteristics. These characteristics of finished pharmaceutical products must be met in order for the final release of these products to the marketplace. "Product and process information related to product quality and patient safety should be used to ensure that manufacturing systems are designed and verified to be fit for their intended use" (Schlindwein & Gibson, 2018, P. 285). This is a worldwide Good Manufacturing Practice (GMP) regulation which can help small companies such as Jepharm in Palestine, for example, to compete with Global companies such as Pfizer if they manufacture their medicinal products under the GMP umbrella. Any drug product contains active drug

substance(s) and excipient(s). The manufacturing of such product must be completed under the umbrella of Good Manufacturing Practice (GMP) so that it can be released for sale in the marketplace as prescribed medicinal product or over the counter. Quality of medicinal products is very important for the patient's health. Out of specifications medicinal products can have or is said to may have higher impurities and toxic or being less effective for the patient. Therefore, effectively controlling the manufacturing process plays a key role in producing stable quality medicinal products within the required specification limits.

1.2.2.1 Tablet dosage form

A pharmaceutical drug product can be defined as a substance or mixture of substances manufactured or has been processed to the point where it is now in a form in which it may be administrated in individual doses. Depending on the method/route of administration, dosage forms come in several types. Common dosage forms include pill, tablet or capsule, liquid drinkable or syrup among many others, see Table1.

Table 1: Pharmaceutical dosage forms.

Pharmaceutical Dosage Forms		
Solid Dosage Forms	Solids	Tablets, Powders and Granules, Capsules
	Semi-Liquids	Creams, Ointments, Suppositories
Liquids Dosage forms	Liquid Oral	Suspension, Emulsions, Syrups
	Liquid Sterile	Injections, Infusions

Tablets dosage forms are preferred due to the ease of manufacturing, convenience in administration, accurate dosing and stability compared to liquids. According to the mode of administration and design, tablets can be classified as presented in Table 2.

Table 2: Classifications of tablets dosage form.

Classification of Tablets Dosage Forms	
Mode of Administration	**Form of Design**
Per-Oral	Compressed Tablets
Buccal	Multiple Layer Tablets
Sublingual	Coated Tablets
Chewable	Sustained Release Tablets
Effervescent	Sugar Coated Tablets
Vaginal	Film Coated Tablets
	Enteric Coated Tablets

The manufacture of tablets is a complex multi-stage process under which the starting materials change their physical characteristics a number of times before the final dosage form is produced. Particle size or the size of granules plays an important role during the production of tablets. According to particle size, powders are classified into two types:

- Monodisperse: A bulk powdered material consisting of only one size, which is unusual.
- Poly-disperse: A bulk powdered material with a range of particle sizes. Most of the powders are poly-disperse. Powders can also be classified as in Table 3.

Table 3: Classification of powders particle size.

Powders Size Classification	
Very Coarse	>1000 Micrometer
Coarse	355-1000 Micrometer
Moderately Coarse	180-355 Micrometer
Fine	125-180 Micrometer
Very Fine	90-125 Micrometer

Powder beds are usually consisting of individual particles of different sizes, shapes and size of distributions. Tablets can be made in virtually any shape. The thickness of a tablet is determined usually by the amount of tablet material. The tablet weight should be in specification during the tablet compression process to ensure the proper amount of drug or active material in the tablet or content uniformity of a tablet. Tablet weight can be varied

by many factors such as large particle or granule size, poor flow-ability and compressibility of powders or granules, improper mixing and many others. In order to ensure the continuation of proper amount of drug in the tablets or content uniformity of a tablet, tablet weight is routinely measured by taking samples of tablets throughout the compression process. Also, tablets require a certain amount of mechanical strength to withstand the shocks of handling during its manufacturing, packaging, shipping and dispensing. The hardness of tablets is the principle measure of mechanical strength. It indicates tablet durability and evaluates tablet strength. Tablets must be able to withstand a reasonable amount of abuse from a consumer. If a tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specification time limit delaying the required dosage unit for the patient. If the tablet is too soft, it may not be able to withstand the handling during subsequent processing and ends up supplying higher dosage for the patient in short period of time. The process of tableting can be achieved in three methods direct compression, dry granulation and wet granulation. The simplest is direct compression where the active substance and excipients are mixed together and then tableting and coating are completed sequentially. Dry granulation is more complex where the active substance is mixed with the excipients followed by processing the mixture through a roller compactor, milling it, mixing it with suitable excipients and finally tableting it. Wet granulation on the other hand is the most complex of the three methods. The manufacturing process of a wet granulation solid dosage form goes through different stages or steps of manufacturing, see Figure 1.

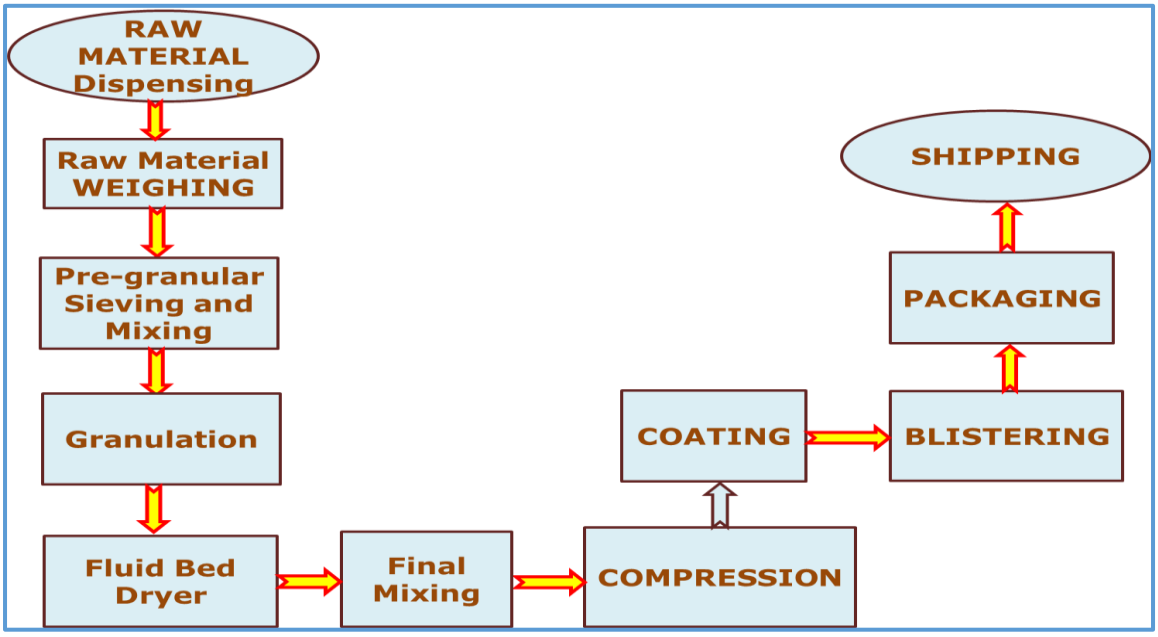


Figure 1: Overview of wet granulation tablet dosage form.

The wet granulation process starts with raw materials dispensing to the weighing section in order to exactly weigh all required materials according to the batch formula. The materials are prepared for the granulation stage through sieving and or dry mixing to ensure correctness of particle size and homogeneity of the dry mixture prior to granulation. Granulation means wet granulation where a granulation either water or alcohol based solution is prepared and fed to the granulator to make the granules which are dried in the fluid bed dryer. The dried granulated material is either sieved and or milled when needed so that they are ready for final mixing where a lubricant is added to help in eliminating sticking through the compression process to make tablets defects free. The tablets are then coated and sent to be blistered and packaged for shipment to the market. With this brief description of manufacturing tablets through a wet granulation process, the next section will explain all of these manufacturing stages in more details and give a thorough

description to gain understanding of the processes since JR tablet product is manufactured through a wet granulation process.

1.2.2.2 JR tablet process description

1.2.2.2.1 Raw material dispensing

JR tablet product contains active ingredients and excipients. These raw materials are dispensed from the weighing section according to a master formula which contains the materials name, APIs and excipients, and quantities required to produce JR product.

1.2.2.2.2 Raw material weighing

All dispensed raw material is initially checked by the weighing supervisor and then by the QC personnel to ensure that the material is dispensed according to the master formula for JR tablet. Then, the material is transferred to a special weighing room where all materials are weighed exactly to the milligram according to the master formula. After weighing is complete, a QC officer verifies and checks that all the materials identity and their quantity or weight are correct.

1.2.2.2.3 Raw material sieving, mixing and wet granulation

Raw materials including APIs and excipients are sieved before mixing to ensure particle size uniformity. The raw material is mixed and processed according to the manufacturing procedure record (MPR) which contains a step-by-step procedure with three verification checks of each step of manufacturing. The verification checks are completed by the operator, the tablet section supervisor and the Quality Assurance (QA) inspector. The overall sieving, granulation, final mixing, tableting and coating steps are critical steps since we are forming the final tablet as a product. After we prepare the granulation solution, the

granulation step starts in the Super Mixer Granulator (SMG). The SMG contains a side chopper and a bottom impeller to provide effective and efficient mixing and granulation,

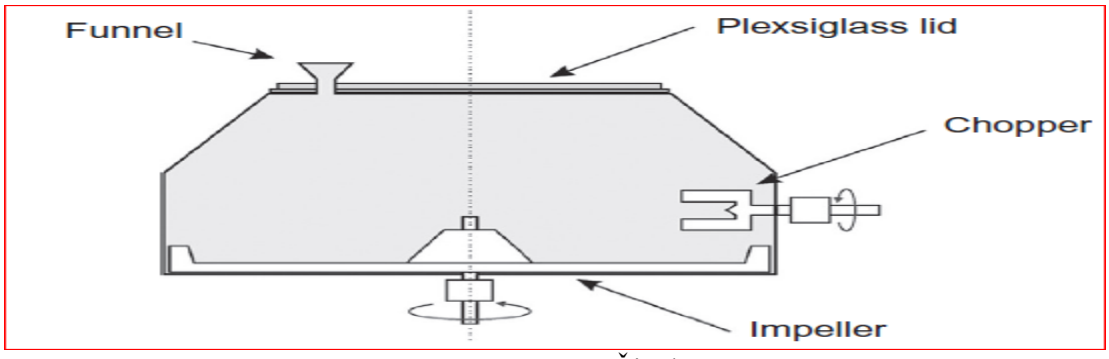


Figure 2: Super granulator (Žižek et al., 2013).

see Figure 2.

The SMG can be run at two impeller speeds of low speed of 105 RPM or high speed of 160 RPM while the chopper speed can run at low-speed of 1720 RPM or high speed of 3440 RPM. The process of wet granulation starts with dry blending of certain components to achieve a homogenous mixture. Then, the binder solution is added to help form the wet larger granules. “Granulation is a process of size enlargement whereby small particles are gathered into larger permanent aggregates in which the original particles can still be identified” (Kristensen & Schaefer, 1987). The binder solution is continuously added with continued mixing to reach the end point of granulation. To determine the end point of granulation, Kristensen and Schaefer (1987) mentioned that “the end point may be defined as the mixing time or amount of granulation liquid that produces a certain amount of granules with a specific diameter”. The granulation process overview is shown in Figure 3.

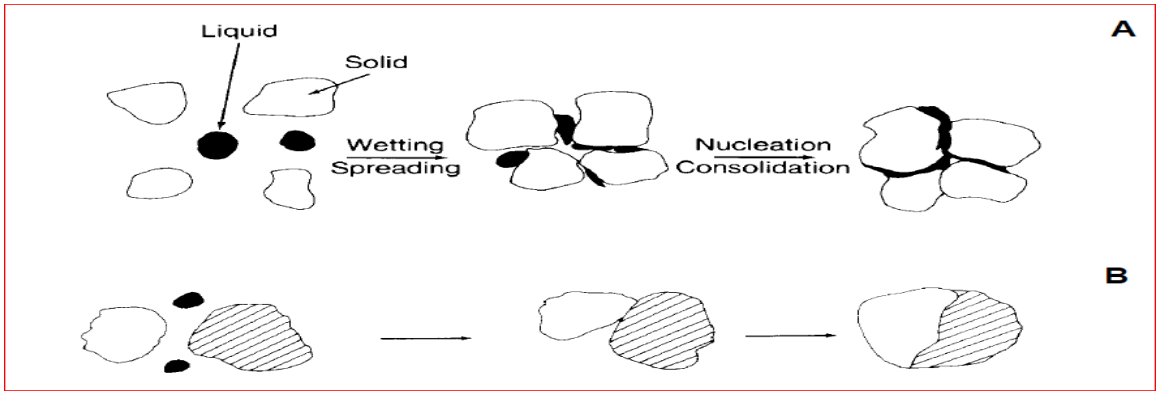


Figure 3: Illustration of granule growth by nucleation (A) and by coalescence (B) (Kristensen & Schaefer, 1987).

"In general, granulation is performed mainly to prevent segregation of the constituents of the powder, to improve flow properties, compaction characteristics, appearance, to minimize dust, and to densify the material" (Parikh, 2005, p. 2). These properties of the wet granulated material are very important which help in producing a more effective and efficient tableting. After the granulation step, the granulated material is transferred to the next manufacturing step which is the Fluid Bed Dryer operation.

1.2.2.2.4 Fluid bed drying (FBD)

FBD is an equipment used in the pharmaceutical industries to reduce the excess solvent or moisture content of pharmaceutical powder and granules by the application of heat, see Figure 4.

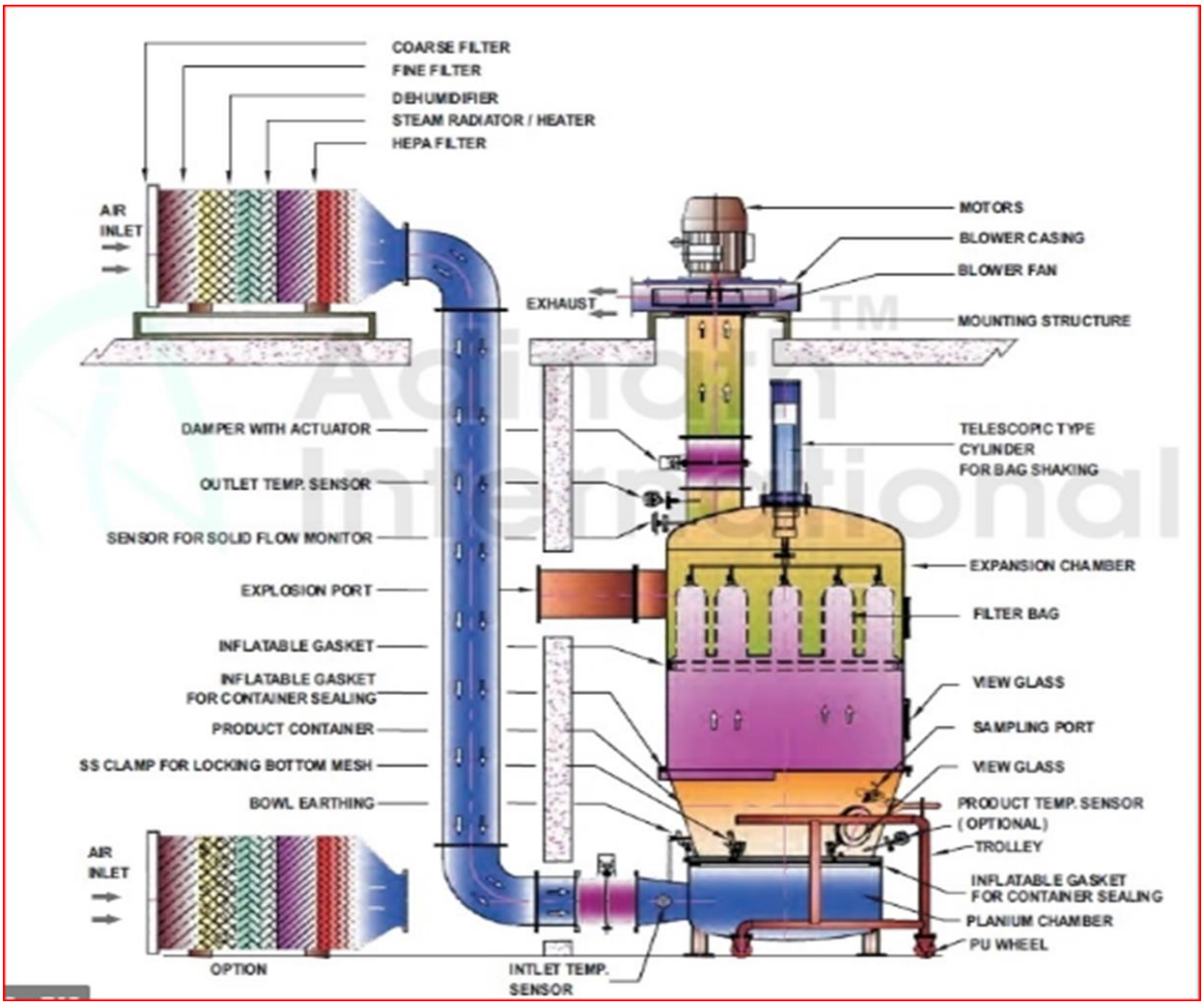


Figure 4: Fluid bed dryer (Adinath, 2013).

A detachable container or bowl or product bin is placed at the bottom of the FBD. The product bowl has a perforated bottom with a mesh screen support so that the materials or wet granulated materials to be dried are placed above it. The perforated mesh screen is used to provide better air distribution and uniformity of hot air speeding through this screen

when the fan is in operation. The fan is mounted in the upper part of the FBD so that when the fan is in operation, a vacuum is created inside the product chamber lifting and suspending the wet granulated materials for drying. The granules are lifted from the bottom of the product container or bowl and suspended in the air stream providing efficient heat transfer between the hot air and the wet granules. This condition is called a Fluidized state in which the hot air surrounds every wet granule to completely and uniformly dry all of the granules. The vacuum created by the blower fan supplies fresh air from the outside air which passes through a coarse filter, a fine filter and a set of HEPA filters to ensure that the air is purified to 99.995%. Then, the air goes through a steam-based heat exchanger to heat the incoming filtered air to the required setup temperature before sending it through the perforated screen. Bag filters or exhaust filters are placed above the suspended granules being dried so that fine powders are recovered through the bag filter's shaking mechanism to prevent product loss. The drying operation in the FBD is timed according to the MPR. Samples are collected by the QC to analyze the moisture content in the granulated dried powder. The measuring instrument gives the results as % LOD or Loss on Drying. The instrument checks and compares weight loss after heating the sample material to a certain temperature for a fixed period of time. For JR tablet, the existing LOD is set to be between 2% to 3% in order to proceed to the next manufacturing step which is the final mixing of all ingredients prior to the tableting process.

1.2.2.2.5 Final mixing

The dried granulated material is sieved through a mesh 40 screen and any remaining materials above the mesh 40 is milled using a mesh 30 screen until all of the dried materials passes through mesh 40. The prepared dried material is transferred to the Bin Mixer and

API 2, MCC and stearic acid are added later. This mixture is mixed for 15 minutes. A sample is collected and sent to the QC lab for analysis of API 1 and API 2 Assay. If the Assay of API 1 and API 2 are within specification limits, the mixture is moved to the next stage which is the tableting or compression stage.

1.2.2.2.6 Tablet compression

After set-up, the compression or tableting production of all of the mixed and dried powders will be performed according to the batch MPR. The tablet machine uses the upper and lower punches to pre-compress the powder to remove trapped air while the main compression force uses the upper and lower punches to compress the powder to form the tablet shape including size and thickness. The punch size, the die size and the machine set up plays an important role in tablet weight and hardness besides particle size. The weight control unit represented by the weight adjustment ramp plays a key role in the weight of each tablet besides the die. Figure 5 shows the tablet machine making one tablet.

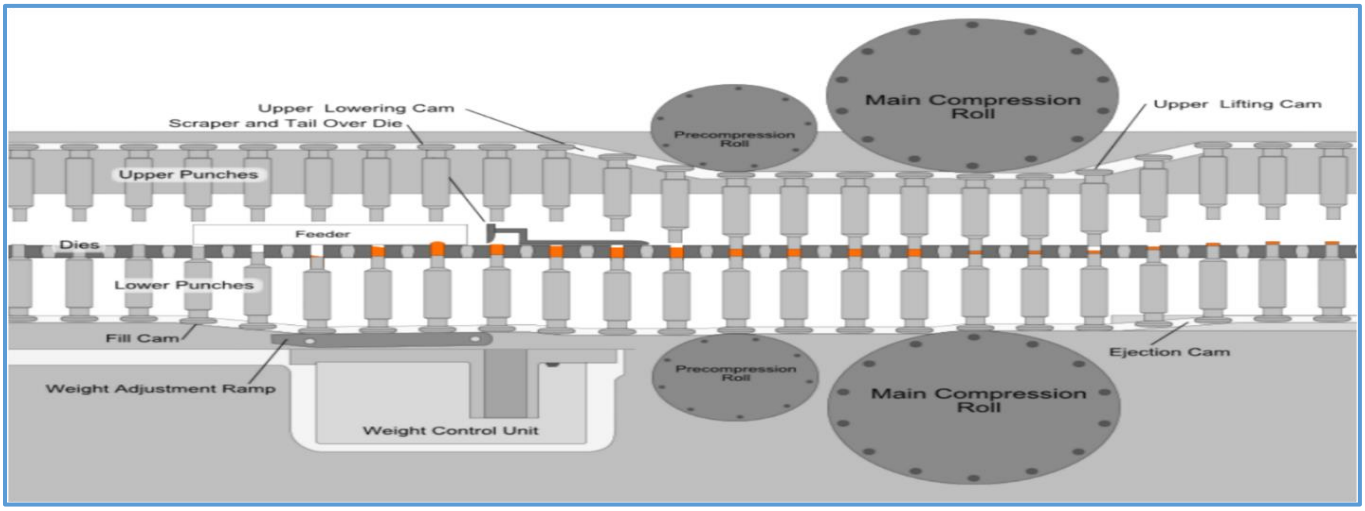


Figure 5: Tablet compression machine (Dahl, 2008).

During compression, the operator frequently takes samples of tablets to test tablets according to the required specification limits. The operator collects samples every 30 minutes, 10 tablets randomly to determine the tablet weight and hardness. The tablets from the tablet machine are fed to a de-duster to remove excess powder. Finally, the tablets are fed to a metal detector which removes any tablets containing metals above a certain specified limit. After completing the compression step, a test request form is sent to the QC lab to collect samples for analysis of disintegration when needed, dissolution, assay and friability which are critical tests after the completion of the compression step. If the results are within specification limits, the QA inspector reviews the results and gives approval to proceed to the next stage which is the coating stage.

1.2.2.2.7 Tablet coating

The coating stage is used to coat or cover tablets with a thin layer of a pre-mixed solution. This layer is used to protect the tablet from the outside environment and or provide and correct the tablet taste and or provide needed color to the tablet. After the completion of the coating process, a test request form is sent to the QC again for analysis. The QC collects samples and completes the required analysis of dissolution, assay, weight, hardness and dimensions. After reviewing the results of the after coat analysis, the QA inspector gives approval for production to proceed to the next stage which is blistering.

1.2.2.2.8 Tablet blistering

Production sends a request form to the warehouse one day before blistering requesting PVC and Aluminum materials which are used to make the blisters of JR tablet. After completion of blistering, a test request form is sent to the QC section to collect samples for visual analysis of the blister including printed codes and expiry dates correctness, clearness and

readability while also inspecting the number of tablets filled in each blister. A leak test is finally completed to ensure that each blister is sealed tightly. The QA inspector receives the results from the QC lab and the QA gives an approval to proceed to the next stage which is packaging.

1.2.2.2.9 Blister packaging

Production sends a request form to the warehouse one day before packaging requesting printed boxes and Leaflet materials which are used to prepare and make the final JR box. Each JR box contains 30 tablets or 2 blisters and one leaflet.

1.2.2.2.10 Quality release and shipping

After completion of all of the manufacturing stages and their related in process testing, the QC manager reviews the results and gives a final QC release by preparing and signing a certificate of analysis (COA) for JR tablet. Then, the QC manager sends the batch file to the QA manager who reviews all of the results again and who ensures that all documentations have been completed according to approved procedures. Once confirmed, the QA manager approves JR batch file and sends it to the Qualified Person (QP) who is a doctor of pharmacy. The QP reviews all results and documentation of the batch file again and gives a final approval for JR tablet product release to the market. The supply chain manager receives the finished quantity of JR tablet into a software called EXACT and calls the transportation company to transfer the final quantity to the finished product store warehouse which is located outside the manufacturing site for distribution and shipments to the market place.

1.3 Scope of the study

The scope of the study covers the manufacturing stages of an existing JR tablet dosage form at Jepharm, Palestine. These manufacturing stages include raw materials dispensing, raw materials Sieving, Wet Granulation, Drying, Mixing, Tableting and Coating. Actual manufacturing batches of JR tablets will be supervised, data collected and analyzed and compared to an existing 2017, 2018 and 2019 processing retrospective data. Critical Material Attributes (CMA), Critical Process Parameters (CPP) and the Target Product Profile (TPP) with their related Target Quality Product Profile (TQPP) and related Critical Quality Attributes (CQAs) will all be identified and their relationship established utilizing QRM. QbD to establish a Design Space(s) for the existing retrospective data will be used to help give directions for the manufacturing process of an actual JR tablet product, represented by the Manufacturing Procedure Record (MPR) while improvement opportunities necessary will be uncovered in order to improve the product quality and or to reduce the manufacturing cycle time. Safe operating ranges for all CMAs, CPPs, CQAs and TQPPs will be defined and tied with the patient's requirements represented by the TPP which all be monitored and controlled using the control strategy. Quality Management methods such as Six Sigma and Lean Six Sigma with their related tools will be utilized to manage through and measure the success of the quality improvements made as a result of this research study.

1.4 Problem statement

Ideally, JR tablet dosage form overall product cycle time should be 28 days on average as a set KPI standard based on the manufacturing process of wet granulation. This includes QC testing and QA analysis and approval with no variations in test results and no out of

specification quality limits are obtained, hence, no reprocessing of intermediate products is required to release the product to the market place. However, JR tablet overall cycle time exceeds the standard set KPI (28 days) limit by 225% due to reprocessing which leads to delaying JR tablet product to the market in order to ensure that the QC tests results are within the required specification quality limits at every stage of the manufacturing process. This Quality by Testing (QbT), traditional method, to release JR tablet product to markets is a time-consuming process which can take days to release products to the marketplace since it involves QC testing after each critical stage and QA analysis and approval of results after each reprocessing contributing to higher overall cycle time. On the other hand, Jepharm has to re-register or get re-approval from PMOH for changes made to their marketed products which can be costly depending on the change and the number of times changes are made. While QbD approach has proven to be more successful than QbT. However, the utilization of QbD with known Design Space(s) in the pharmaceutical companies require Process Analytical Technology (PAT) to easily implement it. However, Jepharm doesn't have PAT. Also, Jepharm does not have a management tool to manage QbD implementation work according to ICHQ8/Q9/Q10 guidelines which were adopted by the FDA and EMA. This research study will evaluate QbD to establish Design Space(s) for an existing JR tablet product at Jepharm. The implementation of QbD to establish Design Space(s) will be according to ICHQ8/Q9/Q10 guidelines without using PAT. The excessively high JR overall cycle time will be investigated and efficiency improvements of the manufacturing process will be completed with actual manufacturing batches. As a consequence, the overall JR tablet cycle time will be reduced.

1.5 Study goal and objectives

1.5.1 Goal of the study

The main goal of this research study is to reduce the overall cycle time of JR tablet dosage form product through the utilization of QbD. Since JR product is an existing product and has been manufactured for almost 30 years at Jepharm, a different approach will be used in order to improve the manufacturing efficiency and reduce the overall cycle time without affecting the Quality, Efficacy, Safety, Purity, Identity and Strength characteristics. This approach will be to resolve the manufacturing issues and reduce variations in processes by utilizing Quality by Design (QbD) to establish Design Space(s) method according to ICHQ8/Q9/Q10 guidelines. Six Sigma and Lean Six Sigma with their related tools will be applied as necessary to help better manage this study and measure the improvements made to the manufacturing process of JR product.

1.5.2 Study objectives

The main objective of this research study is to improve the manufacturing efficiency and reduce the overall cycle time of JR tablet product by resolving manufacturing issues and reducing process variations through the utilization of Quality by Design (QbD) to establish Design Space(s) and Quality Management tools within the Quality Management System. This main objective can be achieved by:

1.5.2.1 Utilizing QRM, scientific and technical experiences and Design Expert Software to establish Design Space(s) for the selected JR tablet product's processes.

1.5.2.2 Eliminating Quality Control (QC) in process testing and analysis.

1.5.2.3 Reducing Quality Assurance management and control follow up during the manufacturing process of JR tablet product.

1.5.2.4 Providing improvement opportunities for a more efficient pharmaceutical JR manufacturing process and improve JR product quality and manufacturing efficiency.

1.5.2.5 To assess the level of implementation of QbDvision for JPHARM product.

1.6 Research questions

1.6.1 Why aren't the Palestinian Ministry of Health and Pharmaceutical Companies use QbD and Design Space instead of QbT and encourage its implementation similar to the FDA?

1.6.2 What are the input CMA and the CPPs which demonstrate and ensures a tablet dosage form product Critical Quality Attributes (CQAs) of a pharmaceutical product?

1.6.3 What is the level of implementation of QbD/Design Space ICH guidelines at JEPHARM?

1.6.4 What are the personnel and technical requirements needed to maintain Design Space(s) to consistently produce in specification tablet dosage form product?

1.6.5 How can we utilize Six Sigma and Lean Six Sigma to measure quality improvements for JR tablet product at JEPHARM?

1.7Research significance and justifications

Quality by Testing is a time-consuming process which can take days to release products to markets while utilizing QbD to establish a Design Space takes few hours to quickly release

products to markets. This reduces the number of tests to be completed by the Quality Control QC lab during in-process manufacturing of JR tablet including production waiting time for QC analysis and Quality Assurance Time to give release from one manufacturing stage to another. Also, frequent reprocessing of JR tablet leads to increasing the overall cycle time. JR Tablet dosage form product has the highest overall cycle time which exceeds the standard set KPI (28 days) limit by 225%. In addition, re-registrations from the Palestinian Ministry of Health for changes made to pharmaceutical products are time-consuming and can be costly depending on the change and the number of times changes are made. While utilizing QbD to establish a Design Space improves processes understanding and innovation, reduces variability and provides diligent follow up by operators and QA personnel to monitor and control processes using the control strategy. QbD is a proactive predictive process which ensures right first time consistent manufacturing of JR tablet. In addition, utilizing QbD to establish a Design Space allows companies not to submit for changes as long as they stay and operate within the approved Design Space. This will save on Re-registration fees, Re-registration time and the number of time re-registration is requested.

1.8Thesis methods

1.8.1 QRM will be initially used to identify and evaluate all of material attributes, process parameters and link those with their effect on the target product profile. As a result of the QRM; the CMAs, CPPs and the critical TQPP and CQAs of product will be selected and identified.

1.8.2 QbD will be used to establish a design space(s) for the CMAs, CPPs and CQAs to ensure TQPP in order to achieve the TPP as the final patient attributes of the

product. It is important to determine the CQAs such as dissolution and assay which may have an impact on safety and efficacy of the drug product performance and manufacturability.

1.8.3 QbDvision software will be used as a management tool to tabulate all process parameters, material attributes, CMAs, CPPs, CQAs, TQPPs and TPPs, provide the process map with the risk indications of the parameters and attributes.

1.8.4 Design Expert 13 will be used to build the Design Space(s) in order to establish the control strategy.

1.8.5 Six Sigma and Lean Six Sigma Tools will be used to measure and manage the improvements made from utilizing QbD and technical expertise of JR product production.

1.4 Thesis structure

Chapter One is an introduction of Quality and quality management methods and related tools used during this research study with a brief introduction of pharmaceutical tablet dosage form drug manufacturing process. This chapter lists the scope of the study, the problem statements, the goals and objectives, research questions and the significance and justifications of the research study. Chapter Two talks about the literature review of books, research studies, journals and research papers which were read and referenced during this research study. These literature reviews give supporting evidences and direction to the findings of this research study outcomes. Chapter Three explains the methods and tools used to answer the research questions. SS and LSS methods and tools were used during the research study including QRM. Manufacturing process retrospective data, process flow

diagram and process mapping were used during the QRM execution and DOE studies which helped identify all of the materials attributes and process parameters measured and their criticality. Also, this chapter discusses the method and approach of developing and implementing the Design Space(s) and QbD guidelines and standards. Chapter Four aims to explain the results of the research study and their analysis and discussion. It shows how the research questions were answered utilizing the methods and tools mentioned in chapter three. SS DMIAC process was used to structure the phases of this research study from the Define Phase to the Control Phase. LSS tool VSM was used to show the cycle time of the existing JR manufacturing process before improvements and the VSM after improvements have been made. This chapter also shows the actions recommended and their implementation status as a result of the QRM. Finally, the chapter shows the results of the four Design Spaces and the established control strategy which will ensure producing JR tablets consistently within specification limits with the required quality and safety characteristics. Chapter Five is a discussion of the results chapter covering the limitations, obstacles and delays experienced during the research study. The chapter gives a brief comparison between other similar researches related to thesis outcomes and results. It explains the differences and similarities in results and gives supporting evidences for closure effectiveness of differences. Finally, the chapter lists the benefits of this research study to Jepharm as a company and the benefits to the fields of study. Chapter Six finalizes this research study with a conclusion and recommendations for researches similar to this research study.

Chapter Two: Literature Review

2.1 Overview

This chapter identifies related existing studies to this research study concept. These studies explained the importance of managing quality either by utilizing quality management methods such as Six Sigma or Lean Six Sigma and their importance in improving quality of products or using QbD as a new method of effectively ensuring the quality of products with an effective front end design loading. Quality management in organizations has gained interest for the past few decades. There have been several approaches to managing quality. These approaches include the usage of several methods such as Six Sigma, Lean Six Sigma, Lean, Kaizen with related tools have been proven to positively improve the performance of organizations in several existing studies. Sectors which have the personnel resources and expertise to implement these methods with related tools report an effective outcome and improvement results in their businesses. These quality management methods with tools have been used worldwide in large co-operations. These co-operations managed to have a department for the utilization and implementation of such quality management methods and related tools. Experts in quality management tools say “If you can't measure, you will not manage. We don’t have faulty people, but we have faulty processes” with this phrase attributed to W. Edwards Deming. While (Schlindwein & Gibson, 2018, P. 303) wrote in their book “Of course, you cannot control what you cannot measure” which is an indication that in order to understand a process, you must measure it correctly for analysis. Once variables are measured and data are generated, Six Sigma (SS) or Lean can be used to effectively manage the process and quantify improvements. SS is a management approach

tool that aims at reducing the variations and defects in a process. “Its goal is to reduce defects by 3.4 opportunities per millions which is almost zero defect.” (Augusto et al., 2014). While “Lean is another approach in quality management that aims at reducing the wastes and activities that increase the cost of production and services.” (Hu et.al, 2015). Combining lean and Six Sigma is a new method called Lean Six Sigma which has been proven to be more successful in providing continuous improvement in some case studies. “This approach has a synergistic effect of six sigma and lean which makes this strategy more effective than both of them” (Chiarini, & Bracci, 2013). The implementation of such approaches in organizations depends on the availability of many success factors. In the west of Ireland, a study was completed to understand the critical success factors which affect the implementation of quality management approaches. “While, top management commitment, understanding the Lean Six Sigma (LSS) methodology, tools and techniques, integrating LSS to business strategy, organizational cultural change and training and education were the most important success factors in the west of Ireland” (Iyede et al., 2018). Palestinian pharmaceutical companies and their management show interest in implementing Six Sigma and related tools, but the high initial investment cost and the lack of available experts in these methods and related tools discourage them. One of the new methods to effectively managing quality is Quality by Design (QbD). “FDA’s emphasis on quality by design began with the recognition that increased testing does not improve product quality” (Lionberger et al., 2008).

2.2 Qbd-design space in pharmaceutical manufacturing concepts

Jepharm and other Palestinian Pharmaceutical companies use Quality by Testing (QbT), traditional method, to release their products to the market place instead of Quality by Design (QbD). In QbT, a sample is collected at the end of every critical stage in the manufacturing of any pharmaceutical product by the Quality Control laboratory (QC lab) to ensure that the resulted material of this stage is within the required set of specification limits. This is a time-consuming process where production, at every critical stage of manufacturing, waits until the QC lab completes the required analysis and submits the results to the Quality Assurance (QA) Inspector for review. The QC analysis and the QA inspector review may take hours to complete in order for production to proceed to the next manufacturing stage. This lead time between critical manufacturing stages affects the manufacturing and eventually the overall cycle time of the products causing delays in releasing products to the market place and possibly ending in lost sale. Cycle time reduction and responsiveness to market demand are major requirements for manufacturing excellence. Manufacturing cycle time is the total time from the start to the end of a process which includes the total processing time during which a stage is acted upon to bring it closer to an output and delay time during which a unit of work is spent waiting to take the next action to begin a new stage. “Cycle time has been used as a key measurement tool for evaluating the performance of a number of leading-edge management concepts, including supply-chain management, just-in-time management, enterprise resource planning, theory of constraints management, and lean management” (Lander, 2014). “Cycle time reduction is a valuable tool to any company’s business; it uses time as a strategic weapon to compete and win in this competitive market. It can open up significant new working capital and cost

reduction opportunities in areas of operations in a company often missed because of adoption of other cost reduction approaches" (Lander, 2014). Many benefits can be gained from reducing cycle time. In general, cycle time reduction would lead to faster time-to-market and, if other cost factors are kept in check, an opportunity for higher profitability. A shorter cycle time improves the company's ability to respond to changing customer demands and reduces the work-in-process inventory for any given level of throughput. Reducing variability in cycle time is very important as it will lead to more accurate prediction of the product completion time, and it is a critical factor in accurate planning. Improvement in cycle time has been linked to reduced inventories, reduced costs, and increased capacity. Reducing cycle time translates to faster response to customer needs. Researchers have found that pharmaceutical companies can capture significant savings by addressing cycle time issues, especially if the company prioritizes its improvement efforts. Utilizing known improvement tools has been proven to mostly lead to reduce cycle time and eventually cost savings. Pharmaceutical industries have introduced many cost-saving measures utilizing Six Sigma (SS) and Lean Six Sigma (LSS) which consist of many integrated tools and they are among the most popular. These improvement tools when used correctly have eventually led to providing more efficient processes which helped reduce the cycle time of products. This thesis aims to identify the technical elements of QbD for the establishment of a Design Space and provide some guidance as to how to achieve and use Design Space in an existing Pharmaceutical tablet dosage form manufacturing while utilizing QRM, Six Sigma and Lean Six Sigma methodologies and related tools to measure and manage the manufacturing improvement efficiency as a result of this study and reduce the manufacturing cycle time. Improving quality of a product while reducing its cycle time

provides an opportunity for customer satisfaction and growth potentials. Quality as a term can sometimes be misunderstood since there are many definitions of quality as each person may define quality according to his or her experience with a particular product. The gurus of quality such as Juran defined quality as “Fitness for use” while Crosby defined it as conformance to requirements. This means that we should effectively manage and control our processes to be able to produce products within the customer specifications or requirements so that the customer is satisfied and his perception of the product is satisfactory so he doesn’t just buy our product again but he urges his friends and family for it. In relation to modern QbD, Juran defined quality with two meanings, the presence and reliability of attributes which create customer satisfaction. It is obvious that Juran believed that creating attributes for products through QbD leads to customer satisfaction if those attributes are kept within the design specification limits and are consistent and reliable in producing quality products within these design limits. Montgomery (2021, p. 6) in his book said that “Quality is inversely proportional to variations”. Variation is the enemy of process stability. Quality improvement in manufacturing can be achieved if processes’ variability is reduced as much as possible so that the output quality of the product is optimized as much as possible to achieve customer satisfaction and be able to compete in this advanced technological age. The quality of pharmaceutical drug products is a result of many inputs including the drug substance, excipients and primary packaging materials. While the control environment of manufacturing and the utilities used in manufacturing such as water and air plays a very important role in defining the quality of the final drug product so that it contains the least amount of impurities as possible. “In a 2004 paper, Janet Woodcock (Director for the Center for Drug Evaluation and Research) defined pharmaceutical quality

as a product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer" (Woodcock, 2004). Therefore, we have to ensure that we consistently produce and control the manufacturing process according to the quality standards and requirements appropriate for the drug product intended use and as required by the marketing authorization regarding quality, efficacy, safety, strength, purity and identity characteristics. "A CQA is a quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure the product meets its intended safety, efficacy, stability and performance" (Berridge, 2007; Lionberger et al., 2008). These characteristics are required to release the product batch to the marketplace. The traditional way of determining the acceptance criteria that the final drug product has such characteristics is through Quality by Testing which means that the quality of the drug product is controlled through laboratory testing. Samples are collected at the end of every critical stage of manufacturing by the Quality Control (QC) laboratory personnel. The QC laboratory completes the analysis of the collected samples and compares them to a validated test method approved by USP and BP pharmacopeia as being within the required set of specification limits. This method of analysis depends mostly on the laboratory personnel who completes the analysis where human errors are possible. "Consequently, QbT is not a powerful means of ensuring quality and has been limiting factors" (Sangshetti et al., 2017). In addition, QbT for some products increases the manufacturing cycle time and delays such products to be quickly released to markets. This can be a result of repeated tests, quality assurance evaluation time of results and the possibility of re-processing of some drug product leading to further extension of the drug product's cycle time. "Through QbD the process is much more predictable and

flexible to responding to disturbances and changes in process parameters to ensure quality is met" (Lionberger et al., 2008). QbD is based on science, Quality Risk Management and technical knowledge and experiences in understanding the processes and their controls to produce quality drug products. The QbD process starts by defining the Quality Target Product Profile (QTPP) which defines the required performance characteristics of the finished pharmaceutical product. Initial QRM and the involved experts' prior scientific and product knowledge and experiences are an asset in identifying related DOE experiments to define and refine the relationships and interactions between the drug product TQPP and CQAs, the CPPs and the CMAs. "CQAs are for output materials while CMAs are for input materials including drug substance, excipients, in-process materials" (Zhang & Mao, 2017). QbD is "Primarily science driven through empirical models, scientific literature and frameworks, design of experiments (DOEs) and based on sound risk assessment". (Nadpara et al., 2012; Singh & Sharma, 2015). Several DOE studies may be possible until concrete evidences are generated to provide validation and stability in the control strategy of the selected tablet dosage form manufacturability. "Design space is determined by an iterative process. The process is not complete until successive iterations demonstrate appropriate understanding of attributes needed to assure the Pharmaceutical Target Product Profile" (Lepore, 2008). This successive iteration better defines the Design Space and the control strategy. "A design space is usually a specified space of process parameters that has been demonstrated to provide acceptable quality". (Lionberger et al., 2008; FDA, 2004). The best definition of Design Space can be found in the International Conference on Harmonization (ICH). ICH defines the Design Space as: "The multidimensional combination and interaction of input variables (e.g., material attributes) and process

parameters that have been demonstrated to provide assurance of quality." "Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval." (ICH, 2009). Submitting a Design Space is a snap view of the manufacturing process and the control strategy implemented. After Design Space approval, additional knowledge and information may be generated during the product life cycle. This newly generated knowledge and information can be used to optimize processes and their Design Spaces. However, initially all process variables should be identified. A research study indicated that "An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs" (Lionberger et al., 2008). As a result, interacting or critical and non-interacting or non-critical variables are identified and refined until an optimum quality product attributes are consistently generated within the required specification limits. "The classification of process parameters as critical or noncritical is essential to evolve the control strategy toward the QbD based goal. Full classification of all parameters as either non-critical or critical can lead to reduced end-product testing". (Lionberger et al., 2008). Variables during the DOE are identified and their relationship and interaction are formed to create a multivariate analysis to identify the causes and effects of variability during manufacturing of a tablet dosage form product. Once the CMAs of all raw material and the CPPs of the manufacturing processes has been defined, the interaction between them is evaluated and analyzed to understand their relationship and implications if any. "If performed and articulated well, Design Space together with an appropriate Control Strategy will reduce

and focus end product testing, while increasing process performance and robustness" (ICH, 2009). The control strategy of the Design Space monitors the CMAs and ensures that the CPPs stays within the boundary of the Design Space in order to consistently produce the product with the required CQAs. "Process parameters are process inputs that are directly controllable, whereas the process outputs that are not directly controllable are attributes. If the attribute ensures product quality, it is deemed to be a CQA. Therefore, a process parameter is deemed to be critical when its variability has an impact on a CQA and, therefore should be monitored or controlled to ensure that the process produces product of the desired quality" (Schlindwein & Gibson, 2018, P. 136). Following the identification of all critical factors which can be material attributes or process parameters and their effect on the responses which are the CQAs for the drug product, factorial designs are used. "Factorial designs are used to study the effect of design variables on the response and the presence of interactions between the design variables" (Westerhuis,1997). "Even when defined as critical, not all CQAs will have the same impact on safety and efficacy (ICH, 2011). Therefore, in practice, risk assessments are a must to finalize and determine criticality of variables and the impact of attributes on the safety and efficacy of patient. Through risk assessment, we are able to establish selected Design Space models for existing products. The available processing retrospective data can be used to build the required Design Space(s) for selected stages. The Design Space models included normal operating ranges can be managed under the Quality Management System or Quality Assurance section. "Design Space is identified as the region where acceptable product can be produced." (ICH, 2009). Figure 6 gives an overview of the relationship between the knowledge space, the design space and the control space or normal operating ranges. The

control space includes normal operating ranges which are considered routine manufacturing as part of the Design Space where they will typically be checked and performed on a daily basis while manufacturing of the product. It is intended to prevent operating in regions which are known to cause product failure.

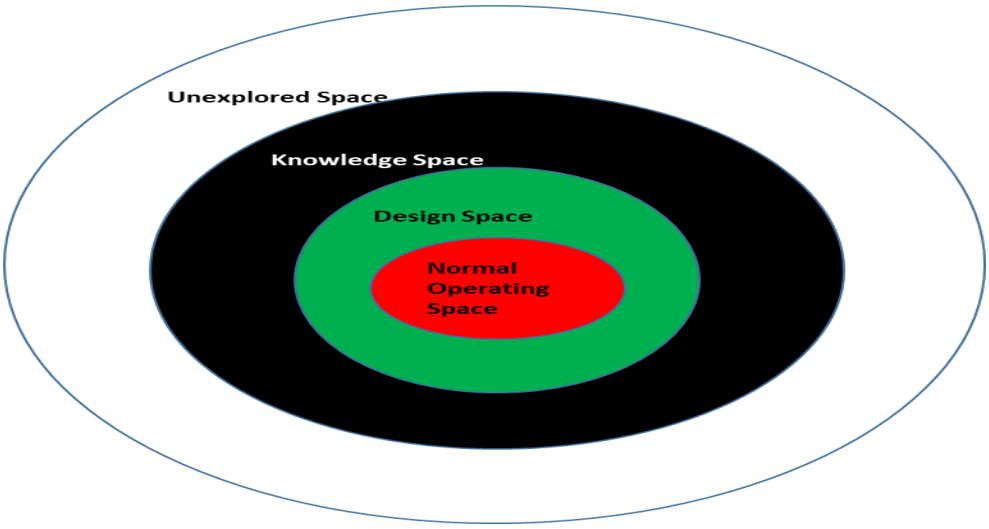


Figure 6: Over view of spaces in relation to Design Space

The DS is the area where a consistent quality within specification product is produced which includes process parameters and material attributes. These parameters and attributes are obtained through iterative use of risk assessment and DOE which are performed to obtain knowledge, a knowledge space, about the product. “The Knowledge Space is a summary of all process knowledge obtained during product development for new products or during the risk assessment and DOE evaluation for existing products” (Lepore, 2008). It contains information about critical and non-critical attributes and process parameters including operating ranges and or areas known to produce unacceptable drug product. “The Knowledge Space only contains information regarding regions that have been investigated,

and beyond its boundaries is considered to be undefined or unexplored space." (Lepore, 2008). Therefore, new risk assessment and scientific expert involvement were required to define such boundaries when needed during this research study. The CQAs within the knowledge space don't usually meet the acceptance limits, however, this area is filtered through risk assessments and scientific experience to finally arrive at the design space. The main purpose of the developed Design Space(s) is to be able to monitor the CMAs of the raw material and the CPPs of the manufacturing processes in order to produce tablets with the required CQAs mentioned in the Quality Target Product Profile (QTPP) to effectively and efficiently control the quality of product and reduce the manufacturing cycle time. "Analyzing QTPPs help link the manufacturing processes with the product and patient for patient health care and benefits" (FDA, 2009; Heider et al., 2014). It is very important to well understand all of the unit operations and define all of the inputs and outputs including controllable and uncontrollable input variable so that during the risk assessment you are able to make the right decision in selecting the CMAs and CPPs to save time since establishing a design space is an iterative process until you arrive at a Design Space with least variability which provides process stability. The manufacturing process failure modes in each unit operation should be known and the effects of these failures on the CQAs should be accurately evaluated. Multivariate analysis can be used to develop the design space(s) to support the definition of the normal operating ranges from the design space for an effective and successful unit operation process. "The use of QbD to identify those factors that influence the risks and bring the process under control can be achieved through the use of multivariate analysis to develop the design space and spiking experiments to support specifications" (Looker et al., 2010). The design space is not a set stone which prevents

failure of successive batches. This is why the normal operational ranges or the control space are set tighter than the Design Space limits to ensure successful and consistent results while operating within this tight control strategy. The validation for all of the unit operations understudy represented by the newly established control strategy should be completed to verify that all processes are stable in producing consistent quality pharmaceutical products with the required quality standards appropriate for their intended use and as required by the marketing authorization regarding quality, efficacy, safety, strength, purity and identity characteristics.

2.3 Research gap

The research gap found in literature can be summarized in trying to develop an "Integrated examples demonstrating practical application of Design Space, criticality, and Control Strategy are necessary to further refine the concept. Also, to find the extent to which Design Space determination includes analysis of critical and non-critical aspects, and what is eventually regulated." (Lepore, 2008). Vezina (2017) in her thesis researched the gaps in QbD; she wrote in her thesis that "Most literature reviews discuss the characteristics of QbD and QbD tools principally speaking in comprehensive terms, theory and definitions. Furthermore, those few case studies provided seem to focus predominantly on unit operations rather than plant wide and that regulation bodies like the FDA are addressing a diverse drug market in a very broad way that may cause manufacturers to be hesitant in adopting QbD principles". "Although QbD can be applied to all product types with both small and large molecules, there are currently still challenges, particularly with complex biopharmaceutical products and processes, where complete characterization is not practical" (Rathore & Winkle, 2009). This research study will provide an integrated

example of utilizing QbD and establishing Design Spaces with actual tablet dosage form manufacturing data with practical presentation of the Design Spaces with recommendations and showing how the establishment of these Design Spaces and their control strategies can successfully and consistently produce drug products. The Design Spaces covered the entire wet granulation tablet dosage form plant and not just one-unit operation which is what I have come across during literature review. This research study will be the first in the Palestinian context with actual production batches.

2.4 QbD guidelines and standards

"The American Food and Drug Administration (FDA), European Medicines Agency (EMA) and Japan's Ministry of Health Labor and Welfare (MHLW) authorities accept QbD to establish a Design Space as long as it is completed within their required guidelines ICH Q8 (R2), ICH Q9 and ICH Q10" (Schlindwein & Gibson, 2018, P. 118). The International Conference on Harmonization (ICH) creates their guidelines based on EMA(EU), MHLW and FDA regulations, guidelines and requirements. The process validation (PV) of pharmaceutical products traditional approach is to validate the manufacturing process through the completion of three actual batches, as required by 2014 EMA CHMP and Annex 15 guidelines, in order to register the product with the regulatory authority. The new QbD approach to process validation focuses on the design to identify the critical process parameters, material attributes and link their effect on the CQAs of the product to develop the manufacturing process control strategy. "PV of the finished drug product is a strict GMP requirement, and manufacturers must comply with the current GMP regulations for finished pharmaceuticals" (FDA 21CFR 210 and 211, 2014; EudraLex, 2015).

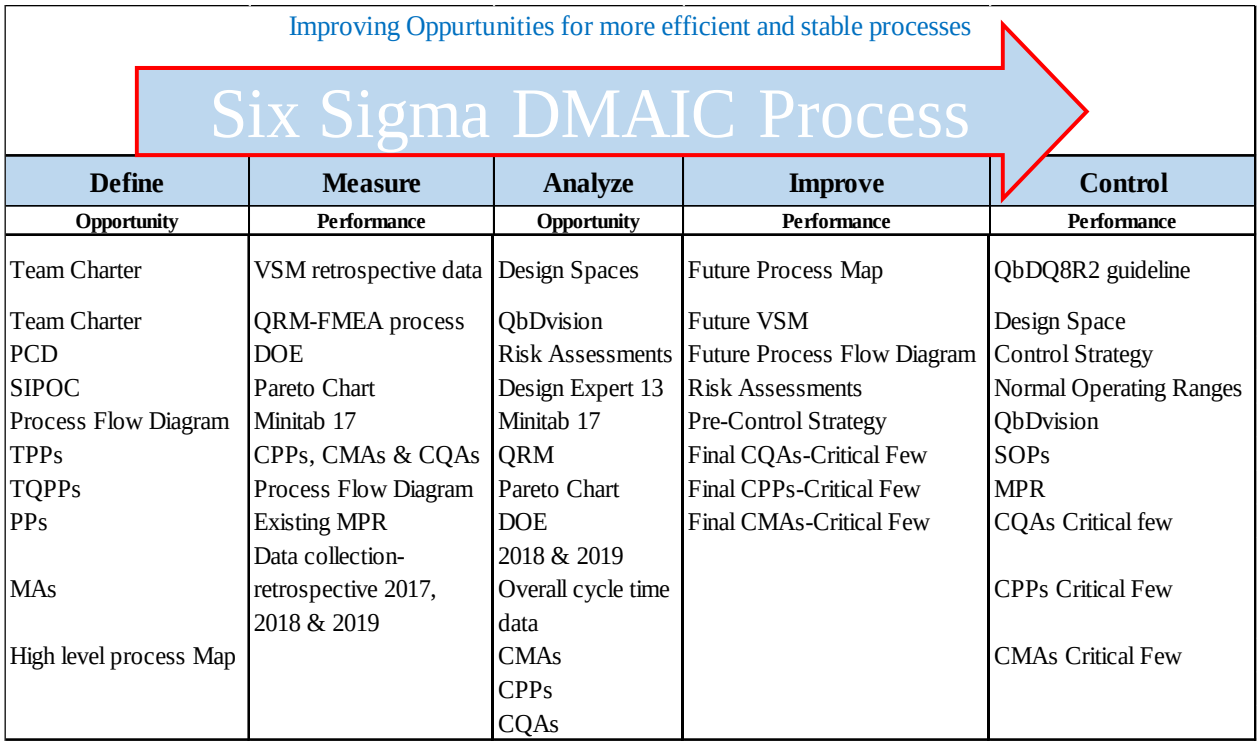
Chapter Three: Research methodologies

3.1 Overview

This chapter's objective is to give a summary of the Quality Management methods and tools used, including Six Sigma, Lean Six Sigma, QbD to establish a Design Space and other quality management methods and tools, to answer all of the research study questions and resolve the problem statement. One part of this study is qualitative while working with Jepharm's upper management and the Palestinian Ministry of Health in order to obtain approval or a direction on how they are going to accept Design Spaces and the regulations instituted. The other part is empirical retrospective data which will be gathered for the overall cycle time and for the materials, process parameters and quality attributes of an existing tablet product. The worst-case performing tablet dosage form product will be selected for this study from the product line of Jepharm's General facility in Al Bireh, Ramallah Palestine.

3.2 Quality management methods and tools

Six Sigma DMAIC is used as an organization and management tool for this research study. The structure of the results and analysis of this study follows the DMAIC process using the Define, Measure, Analyze, Improve and Control phases as shown in Figure 7.



Define	Measure	Analyze	Improve	Control
Opportunity	**Performance**	**Opportunity**	**Performance**	**Performance**
Team Charter	VSM retrospective data	Design Spaces	Future Process Map	QbDQ8R2 guideline
Team Charter	QRM-FMEA process	QbDvision	Future VSM	Design Space
PCD	DOE	Risk Assessments	Future Process Flow Diagram	Control Strategy
SIPOC	Pareto Chart	Design Expert 13	Risk Assessments	Normal Operating Ranges
Process Flow Diagram	Minitab 17	Minitab 17	Pre-Control Strategy	QbDvision
TPPs	CPPs, CMAs & CQAs	QRM	Final CQAs-Critical Few	SOPs
TQPPs	Process Flow Diagram	Pareto Chart	Final CPPs-Critical Few	MPR
PPs	Existing MPR	DOE	Final CMAs-Critical Few	CQAs Critical few
MAs	Data collection-retrospective 2017, 2018 & 2019	2018 & 2019 Overall cycle time data		CPPs Critical Few
High level process Map		CMAs		CMAs Critical Few
		CPPs		
		CQAs		

Figure 7: Six Sigma DMAIC process for JR tablet.

Each phase of the DMAIC process calls for certain tools to be completed systematically so that this research study completes one cycle of improvement.

3.2.1 Define phase

During the Define phase, a Project Charter (PC) is initially prepared to give an overview of the study objectives, scope, team members, an overall timeline of this research study and any projections of possible future obstacles. Also, a Supplier Inputs Process Outputs and Customers (SIPOC) process diagram is developed to provide a quick summary of the inputs and outputs of JR tablet manufacturing process while a Problem Context Diagram (PCD) is developed to provide a quick overview of the upstream processes that affect the manufacturing of JR product process which in turn has an effect on the downstream processes. A process flow diagram (PFD) is developed for the manufacturing process of

JR tablet to provide an indication of the existing processing steps of JR tablet. The Critical to Quality (CTQs) are defined by the customer, Jepharm in this case study, which are the required expected outcome of the study. CTQs identify what the customer needs are such as information which will be translated into measurable product and process required results. For the manufacturing process, all of the TPPs, TQPPs, Quality Attributes, Materials and their attributes, unit operations including equipment and process parameters are identified for JR tablet product using retrospective batch files from 2017, 2018 and 2019.

3.2.2 Measure phase

3.2.2.1 Retrospective data

2018 and 2019 empirical retrospective data for the overall manufacturing and quality release cycle time of all products manufactured at Jepharm were collected. These cycle time data are taken from the monthly Jepharm production dashboard historical data. Quality by Testing (QbT) historical 2017, 2018 and 2019 retrospective data from the Quality Control (QC) department are utilized for the in-process, intermediate and finished product analysis as a baseline for the CQAs and CMAs which all are shown on the batch file of products. All of the raw materials and their attributes are taken from EXACT software with the help from the IT department. The Critical Material Attributes (CMAs) of the drug substance and excipients specifications are verified using the Drug Master File with the help from the R&D department. The Critical Process Parameters of the process equipment and instrumentations are obtained from the completed JR batch files and verified by the qualifications and calibrations engineering department and the validation department. The registered JR existing tablet dosage form product Critical Quality

Attributes (CQAs) represented by the Target Quality product profile (TQPP) and Target Product Profile (TPPs) are obtained from the Regulatory Affairs department who registered the product with the Palestinian Ministry of Health (PMOH). All of the parameters and attributes are tabulated in excel templates provided by QbDvision software. These templates are filled, reviewed by the R&D department and approved by the quality and regulatory affair departments and then uploaded into QbDvision software.

3.2.2.2 Drug product selection approach and tools used

The 2018 and 2019 JR tablet's overall cycle time retrospective data is sorted and filtered to identify the tablet dosage form product with the highest overall worst-case manufacturing and quality release cycle time using a Pareto chart. The product with the highest overall manufacturing and quality release average cycle time will be selected for this research study as a baseline. The most probable causes contributing to high drug product manufacturing and release cycle time should be identified. A detailed process flow diagram (PFD), process flow map (PM) and the Value Stream Map (VSM) were developed following the infield actual manufacturing stages, QC in process sampling and QA in process inspection checks. The PFD shows the start and end of the manufacturing process of the selected tablet product from raw materials receiving to the packaging stages. The process map shows the input materials list and their attributes, the process components, the process parameters, the unit operations, the intermediate attributes and the final product attributes. Also, the process map shows the CMAs, the CPPs and the CQA of JR with the link between the attributes and process parameters. Then, a VSM for the existing selected product before improvements was developed to show the lead time and processing time of the selected tablets product so that we can obtain the cycle time. The VSM shows the stages

from raw materials receiving to the coating stages. Design of Experiment (DOE) was used to help understand factors effects on responses which helped to resolve issues related to the manufacturing of JR product specifically in the coating stage. The trials DOE data were fed to Design Expert 13. Design Expert Software (DES) was used to develop and establish the Design Space(s) for the selected manufacturing unit operation processes. Microsoft Excel was used for data gathering for QbDvision software and to organize and complete simple mathematical calculations. Minitab software was used to initially define the correlations between several factors and for graphical analysis such as Pareto chart, moving average chart, moving range chart and normality analysis of data. “Prior knowledge involves many disciplines including biopharmaceutics, material classification, kinetics, thermodynamics, and experimental design techniques” (ICH, 2009). Then, a Quality Risk Management (QRM) for the entire selected product is completed by utilizing Failure Mode and Effect Analysis (FMEA) tool. ICH QRM process flow chart, Figure 8, was used with the FMEA as a risk management tool to complete the risks identification, analysis and evaluation. According to ICH Q9 module during risk assessments, the identification of risks and their documentation is a very important step in the QbD approach. QRM was initially performed to understand the risks related to the manufacturing and quality release of the selected product and provide mitigations to better manage and control the identified risks. The ICH QRM process flow chart was taken from ICHQ9 website to be followed and used as a guide while performing the QRM.

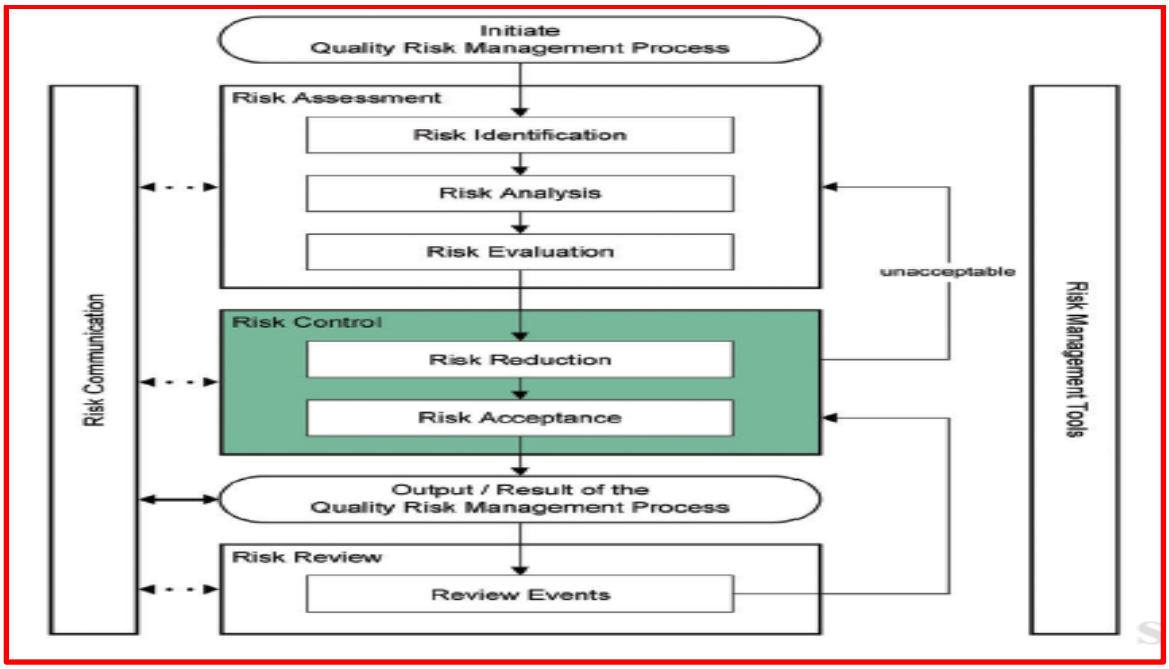


Figure 8: ICH quality risk management process flow chart.

The FMEA, see the completed FMEA in Appendix 01, tool was selected since it allows us to study each failure mode separately for each processing step including each component and identify opportunities to improve process performances and the ability to prioritize recommended actions on the bases of criticality. Many scenarios were reviewed and evaluated in order to identify, analyze and evaluate the potential failures and their effects on the quality of the selected tablet product starting from receiving of raw materials until packaging of the product. The QRM covers raw materials receiving, raw materials dispensing, raw materials weighing, raw materials sieving, granulation stage, drying stage, final mixing stage, compression stage, coating stage, blistering stage and final packaging stage and the quality release of the product.

Risk Identification:

During the identification step, the following points are addressed:

- What might go wrong.
- Specifying the location of failure.
- Evaluating all steps which may occur affecting the critical quality attributes of the product.
- Focusing on the mentioned failure modes.

Risk Analysis:

In this step, the qualitative risks are converted to quantitative data. Three factors were selected to calculate the Risk Priority Number (RPN):

- **S:** Severity of the potential failure effect.
- **P:** Likelihood of occurrence (Probability).
- **D:** Ability to detect the failure.

Risk Evaluation:

During risk evaluation, the RPN is calculated as follows:

RPN = Severity × Probability of Occurrence × Detectability

Acceptance Criteria: Table 4 is taken from ICH web site Q9. This table clarifies the components of the risk assessment process for the purpose of determining the RPN values.

Table 4: ICH Q9 risk ranking matrix.

Ranking	Severity (S)	Probability (P)	Detection (D)
10	Death	More than once a day	Impossible to detect
9	↓	3 – 4 times a day	Remote
8	Permanent injury	Once a week	Very slight
7	↓	Once a month	Slight
6	Temporary injury	Once in three month	Low
5	↓	Once in half – one year	Medium
4	Reported/ dissatisfied	Once a year	Moderately high
3	↓	Once in 1 – 3 years	High
2	Notice/ no report	Once in 3 – 5 years	Very High
1	↓	Less than once in 5 years	Virtually certain

Characterization of severity, probability and detectability:

- An equal number of levels are sometimes helpful. Some companies prefer to use 3, 4, 5, 6 or 10 levels, but an even number of levels avoids the mid-point.
- Use different scales: Linear: 1, 2, 3, 4 or Exponential: 1, 2, 4, 8 or Logarithmic: 1, 10, 100, and 1000 or Self-made: 1, 3, 7, 10 with multiplying different scales to differentiate the outcome.

The numbering criteria selected for all Jepharm rankings is according to Table 4 above.

Risk ranking is performed based on Table 4 as follows:

- Maximum RPN = 10 X 10 X 10 = 1000 (High Risk)
- Medium RPN = 5X5X5 = 125 (Medium Risk), (In general).
- Minimum RPN = 1 X 1 X 1 = 1 (Very Low Risk)

- A high priority RPN means that this function or component is critical and that validation measures must be taken.

- A medium priority RPN means that this function or component is potentially critical and that validation measures should be taken.

➢ A low priority RPN means that this function or component is not critical and that there are no validation actions or measures to be taken.

After calculating all **RPNs**, Jepharm controls actions for all risks when:

- **RPN** equals to or more than **100.**
- **Any Severity** equals to or more than **5.**
- Any remaining critical parameters after taking action require further controls.

Risk Control and Review:

ICH Q9 states that risk control is the process of decision making to reduce and/or accept risks. Risks acceptance and risk reduction are considered as iterative steps and are subject to constant review, feedback, and communication between the team performing the FMEA and management. If the risk is still unacceptable, further risk reduction steps should be identified. ICH Q9 states that risk reduction is the implementation of control strategies to mitigate or avoid the risk. Risk reduction can be achieved by addressing the severity and/or probability of harm as well as providing improvement in the detection of hazard. As a result of the QRM and the FMEA, all of the risks are identified, analyzed and evaluated. The risk scores, RPNs, are determined by combining the probability or likelihood of a problem, the severity or outcome, or potential undesired consequences on the product, personnel, patient and the environment and the detectability or ability to find the failure. After completing the QRM; the CQAs, CMAs and CPPs are determined which ensure that the selected tablet manufacturing output quality is consistent with the required Quality, Safety, Efficacy, Purity, Identity and Strength characteristics. At this point, all of the selected tablet product

processes are defined and the data collected and understood. The data are ready for analysis.

Software packages used:

- **QbDvision:** Cloud-based software solution for managing pharmaceutical process development which is aligned with ISPE's Pharma 4.0 initiatives. It manages products during its lifecycle while enabling teams to transform fragmented data and siloes knowledge into true process intelligence.
- **Design Expert 13:** Statistical software package from Stat-Ease Inc. that is specifically dedicated to performing design of experiments (DOE).
- **Minitab 17:** A statistical analysis program by NIST automates calculations and the creation of graphs, allowing the user to focus more on the analysis of data and the interpretation of results.
- **EXACT:** Exact is a Dutch software company that offers accounting, ERP, and other software for small and medium-sized enterprises (SMEs).
- **Microsoft Excel:** used to tabulate data and complete simple calculations and graphical analysis.

3.2.3 Analyze phase

All of the materials and their attributes, process parameters, unit operations and process equipment, test methods are identified, tabulated and uploaded into QbDvision software. With the help of QRM process mentioned and scientific background and experience, Critical Material Attributes of raw materials (CMA) and Critical Process Parameters (CPPs) are defined and selected to ensure a consistent in process Critical Quality Attributes of intermediates required to produce the final required QTPP and CQAs which achieve the

required TPPs for selected tablet finished drug product. This includes the Input Variables being controllable and non-controllable and Process Parameters which are demonstrated to provide assurance of the selected tablet product TQPP. QbDvision helps in linking all attributes and parameters through risk assessments so that all critical parameters and attributes are defined. According to Schlindwein and Gibson (2018, P. 324) “It is essential in any QbD submission to identify/describe the QTPP, the Critical Quality Attributes (CQAs), the Critical Process Parameters (CPPs) and the control strategy”. The approach to define the Design Space(s) and control strategy for the JR tablet product is as indicated in Figure 9.

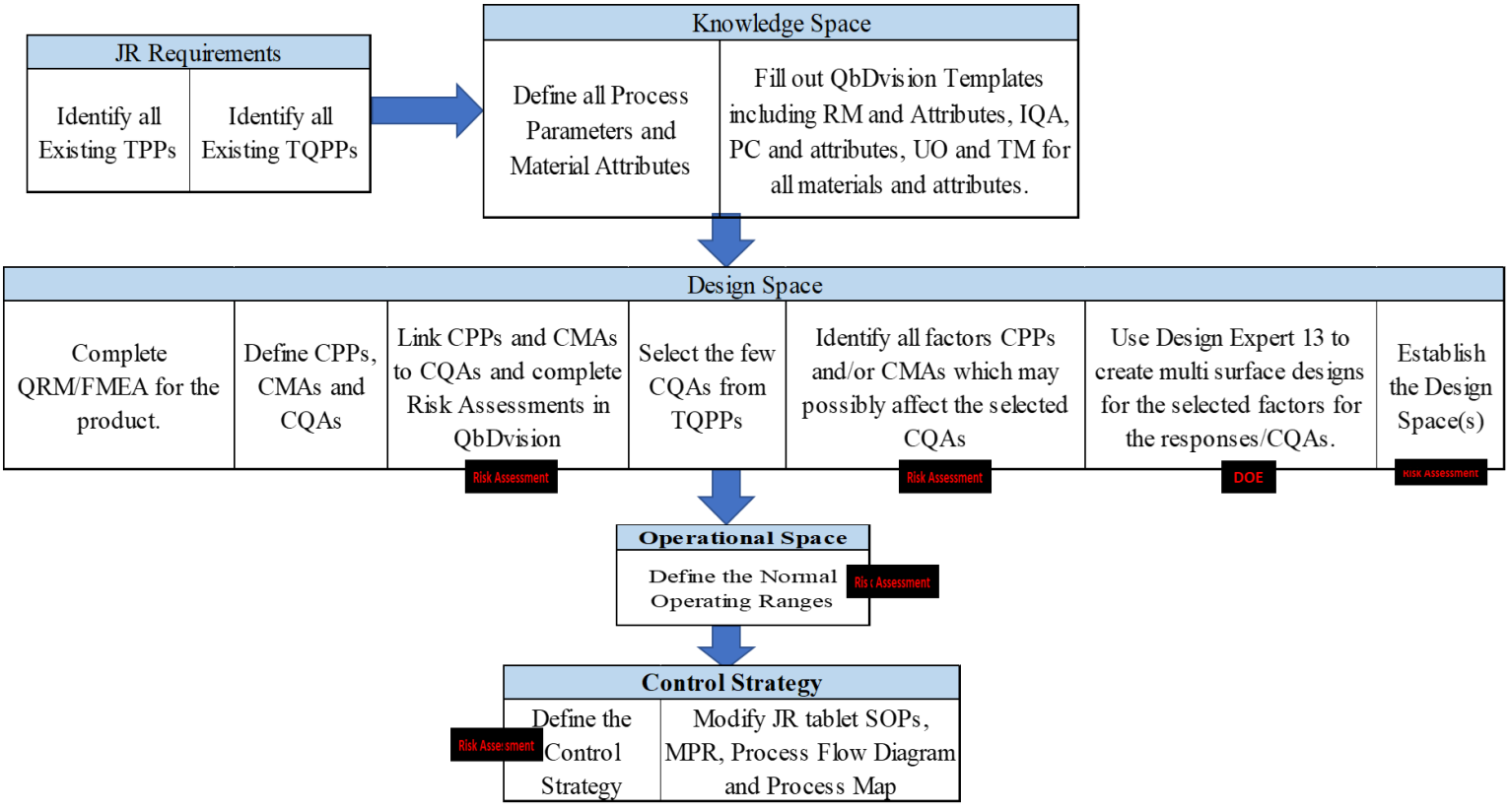


Figure 9: Steps taken to define the design space and control strategy.

As a result of the analyze phase, all improvement opportunities are defined and recommended actions are written. A process deviation form is filled so that the recommended results and directions of the newly-developed design spaces are implemented which will help improve the efficiency of the selected tablet manufacturing processes and eventually reduce the overall cycle time.

3.2.4 Improve phase

During the improve phase, all of the recommended actions and solutions to improve the selected tablet product manufacturing efficiency and reduce cycle time were quantified and sorted. At this point, all of the CPPs, CMAs and CQAs have been analyzed and the critical few have been selected and their interactions were identified. Actual manufacturing batches were completed to verify and validate solutions to recommended changes. Some changes may be possible while executing the actual manufacturing batches. However, by the end of the improve phase, the control strategy was in draft, modified and ready for approval. Approval from production, quality, engineering and R&D departments and upper management were given to initiate a change control for all changes to be reflected on procedures and methods.

3.2.5 Control phase

In the control phase, the control strategy was developed and the manufacturing procedure record or step-by-step manufacturing procedure was modified to reflect the newly-generated operating ranges as a result of the Design Spaces and the actual manufacturing of batches. A process flow diagram, a process map, a Value Stream Map and the operating procedures were established for the newly-improved, after improvement, JR tablet product process. These documents were instituted in the Quality Management system to train

personnel such as QC, QA and operators to effectively monitor and control the processes to provide operation stability to consistently produce JR tablet product with the required Quality, Safety, Efficacy, Purity, Identity and Strength characteristics as a result of the new Design Space models. Finally, QbDvision software was updated to reflect the final links between attributes and parameters and their risks and interactions shown on the final process map of JR tablet.

3.3 Palestinian Ministry of Health (PMOH) and Jepharm regarding QbD

An interview with two key PMOH technical experts who give quality batch file releases to Jepharm products was completed in order to understand their prospective regarding the implementation of QbD to establish design space in the Palestinian context. The following questions were asked to these two PMOH subject matter experts:

1) Do PMOH accept or approve QbD to establish a Design Space for drug products?
2) Are there guidelines which Jepharm can follow in implementing QbD in Palestine?
3) Have the PMOH approved a drug product using QbD?
4) Do the PMOH have the expertise to review and approve QbD for drug products?

PMOH experts indicated that ICHQ8/Q9/Q10 guidelines should be followed when implementing QbD to establish a design space. They indicated that QbD implementation is up to the company and must be in accordance of the aforementioned guidelines. Also, they indicated that PMOH has not approved any drug product using QbD nationally nor regionally nor internationally. These subject matter experts mentioned that PMOH has the experts to review and approve QbD documents similar to the normal batch file release with the differences being on the documentation requirements. Also, they have mentioned that QbD is a scientific proof of a drug product acceptance criteria in the design phase following

ICHQ8/Q9/Q10 guidelines, PMOH experts have the technical background necessary to review and give approval. Jepharm acceptance of implementing QbD as a company was discussed with upper management and acceptance was given to follow ICHQ8/Q9/Q10 guidelines as indicated by the PMOH, FDA and EMA. In order to ensure that ICHQ8/Q9/Q10 guidelines are followed, Jepharm asked us to use QbDvision software to try and load JR tablet to complete a demo-trial to find out whether or not to purchase this software and implement it for all of their products.

3.4 Data analysis tests:

The retrospective data for all of the identified materials attributes, process parameters and quality attributes were collected and tabulated in excel. Minitab software will be used to study correlations between variables, normality plots, X and R charting and descriptive statistics. Design Expert 13 will be used to build all of the surface design plots in order to define all Design spaces. QRM methodology and FMEA tool will be used to evaluate the risks and classify all CMAs, CPPs and CQAs. Several risk assessments will be required until arriving at the final control strategy. QbDvision software will be used to manage through the implementation of QbD according to ICHQ8/Q9/Q10 guidelines.

Chapter Four: Results and Data Analysis

4.1 Overview

This chapter shows that JR Tablet is the product selected for this case study. This chapters' objective is to present the data collected and to analyze and discuss the primary data which were collected from the actual thirteen batches of JR tablet manufactured during August of 2020, and to compare this data to the retrospective 2018 and 2019 data. The Design Spaces built were based on the retrospective data and the newly-collected data. The results of the built Design Spaces and the directions given from Design Expert 13 software were used during the execution of the 13 batches trial. Process ranges were used during processing. As a result of this data analysis, improvements made were identified and measured easily using Design Expert 13 software. Also, SS and LSS structured methods and tools were used to effectively manage this study. DMAIC process structure was used throughout this research study.

4.2 Quality management methods and tools

Six Sigma DMAIC process was used to report the results, analysis and discuss the outcome of the developed Design Spaces while Lean Six Sigma's VSM was used to show the improvements made to JR tablet product before and after this case study. The DMAIC process covered the Define, Measure, Analyze, Improve and Control phases.

4.2.1 DMAIC-define phase

A one-on-one meeting with the deputy manager for technical affairs and her adviser of Jepharm was done to obtain the customer requirements and their satisfaction criteria as a result of this research study. During this meeting, QbD was briefly presented with the

known benefits of QbD to industries and the study objective of reducing the overall cycle time and improving the efficiency of the manufacturing process. After the presentation, the deputy manager was asked the following questions:

- Is it ok to proceed with this case study presented? Will you support it?
- What are your CTQs requirements in implementing QbD at Jepharm?
- What satisfies Jepharm as a result of implementing QbD?
- Is it ok to utilize needed staff to support this study?
- It may be possible to use the tablet section to complete production of the yearly batches as a trial while changes will be approved by R&D, QA and production, is this ok?

As a result of the meeting, the deputy manager gave the ok to proceed and use the tablet section with the needed resources. QbD turned out to be a strategic plan that Jepharm has had since 2018. The deputy manager has a PHD in pharmaceutical manufacturing and she knew about the topic and she seemed very interested. The deputy manager mentioned that Jepharm Critical to Quality Attributes (CTQs) are as follows:

- Reduce the overall cycle time of JR tablet product by at least 30%. A reduction of the overall cycle time by 45% below the standard KPI limit is considered an excellent study performance.
- Reduce the manufacturing cycle time by at least 20% to free up and make space to help the company produce other batches of other products.
- Institute protocols and procedures to consistently produce JR tablets with the required quality within approved specifications right first time every time.

- Develop a Design Space(s) for selected processes of JR tablet for the purpose of cycle time reduction while being able to copy to other products in the near future.
- Ensure that all of the critical material attributes, critical process parameters and critical to quality product attributes are not affected as a result of changes made from this research study.

Keeping all of these CTQs in mind, retrospective data was collected for the manufacturing process and for the overall cycle time. Pareto chart, discussed in the measure phase, was used to help identify that JR tablet has the worst overall cycle time with manufacturing efficiency issues at JEPHARM. A PMI Study Charter Form shown in Appendix 02 was completed to define the study title, sponsor, problem definition and purpose, business case, key players, scope, barriers and risks and their mitigations. Then, a PMI Supplier Inputs Process Outputs and Customers SIPOC Form in Appendix 03 was prepared to tabulate an overview of a high-level process steps of JR tablet from raw material weighing to shipping. SIPOC is a process which summarizes the inputs and outputs of the JR manufacturing process in a table form. This SIPOC form tabulates the process measures, present data, goal performance, source of variation and waste and impact on performance for all of the high-level processing steps. Also, a Problem Context Diagram (PCD) depicted in Figure 10 was prepared using the template which was taken from PMI.

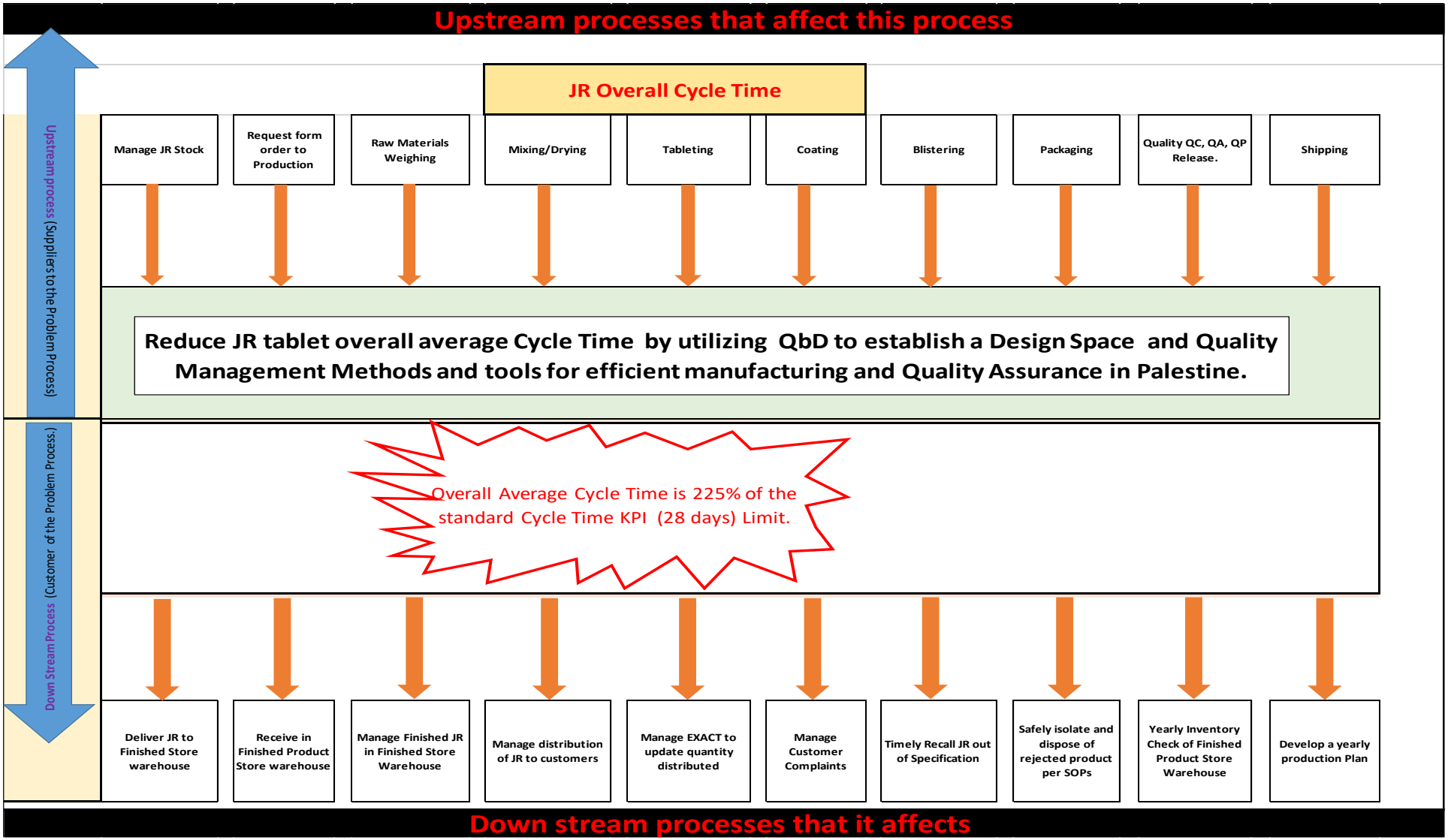


Figure 10: PMI's problem context diagram for JR tablet.

Figure 10 provides a quick overview of the upstream processes that affect the manufacturing of JR tablet dosage form product process which in turn affects the downstream processes. The SIPOC and the PCD give a big picture overview of JR manufacturing and release cycle processes with their effect on the downstream processes. JR detailed manufacturing process flow diagram, shown in Appendix 04 was prepared in order to define and give an initial overview of the manufacturing process. On the other hand, the PMOH was contacted regarding the guidelines for QbD to establish a design space. PMOH indicated to use ICHQ8/Q9/Q10 as a guideline similar to the FDA. Jepharm upper management were contacted and their direction was to use QbDvision software which follows ICH guidelines.

4.2.2 DMAIC-measure phase

A detailed manufacturing Process Flow Diagram (PFD) in Appendix 04 and process flow map in Appendix 05 for JR wet granulation tablet dosage form product were developed. These process diagrams cover the manufacturing steps from the initiation or request to manufacturing of JR tablets by the production department to the blistering stage. The PFD covers all of the Quality Control checks and the Quality Assurance inspections and reviews completed throughout the manufacturing of JR product. While the process map covers all stages, materials attributes, unit operations, equipment and the final quality attributes of each stage of the manufacturing process. Jepharm produces more than 150 tablet dosage form products. To select the product with the highest cycle time, actual overall cycle time data for all tablet dosage form manufactured in 2018 and 2019 were collected. The top 11 products with the highest overall cycle time were identified. Through Pareto Chart analysis, shown in Figure 11, of manufacturing and quality release overall cycle time; JR tablet

dosage form was identified with the highest cycle time of 63 days compared to the KPI (28 days) limit.

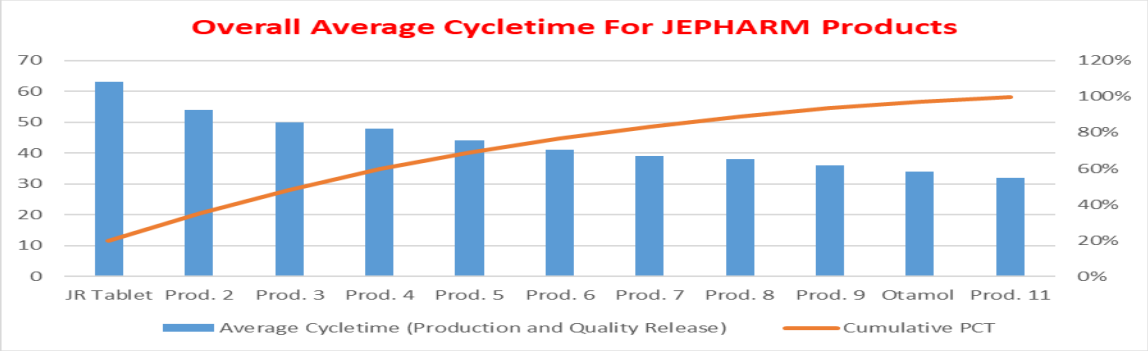


Figure 11: Highest overall cycle time of eleven Jepharm products.

In addition, JR tablet manufacturing is considered a nightmare for the production department with many difficulties including frequent reprocessing of some manufacturing stages. Based on the Pareto chart results, JR product was selected for improvement of its manufacturing process efficiencies and related cycle time. A Lean Six Sigma Value Stream Mapping(VSM) and its calculations, depicted in Appendix 06, was established for JR manufacturing before improvement for all manufacturing stages starting from receiving of raw materials at the manufacturing floor until the coating stage since these stages were considered critical stages in the manufacturing of JR tablets. The VSM indicates a baseline of 16.74 days on average cycle time. This cycle time calculation covered 2018 and 2019 manufacturing stages data for JR tablets product. The overall cycle time of JR tablet of 63 days indicated in the CTQ requirements covers the cycle time from weighing of raw materials until receiving of finished product to warehouse. The Manufacturing Procedure Record (MPR) for JR is a step-by-step procedure which was prepared during this phase of the study, as shown in Figure 12.

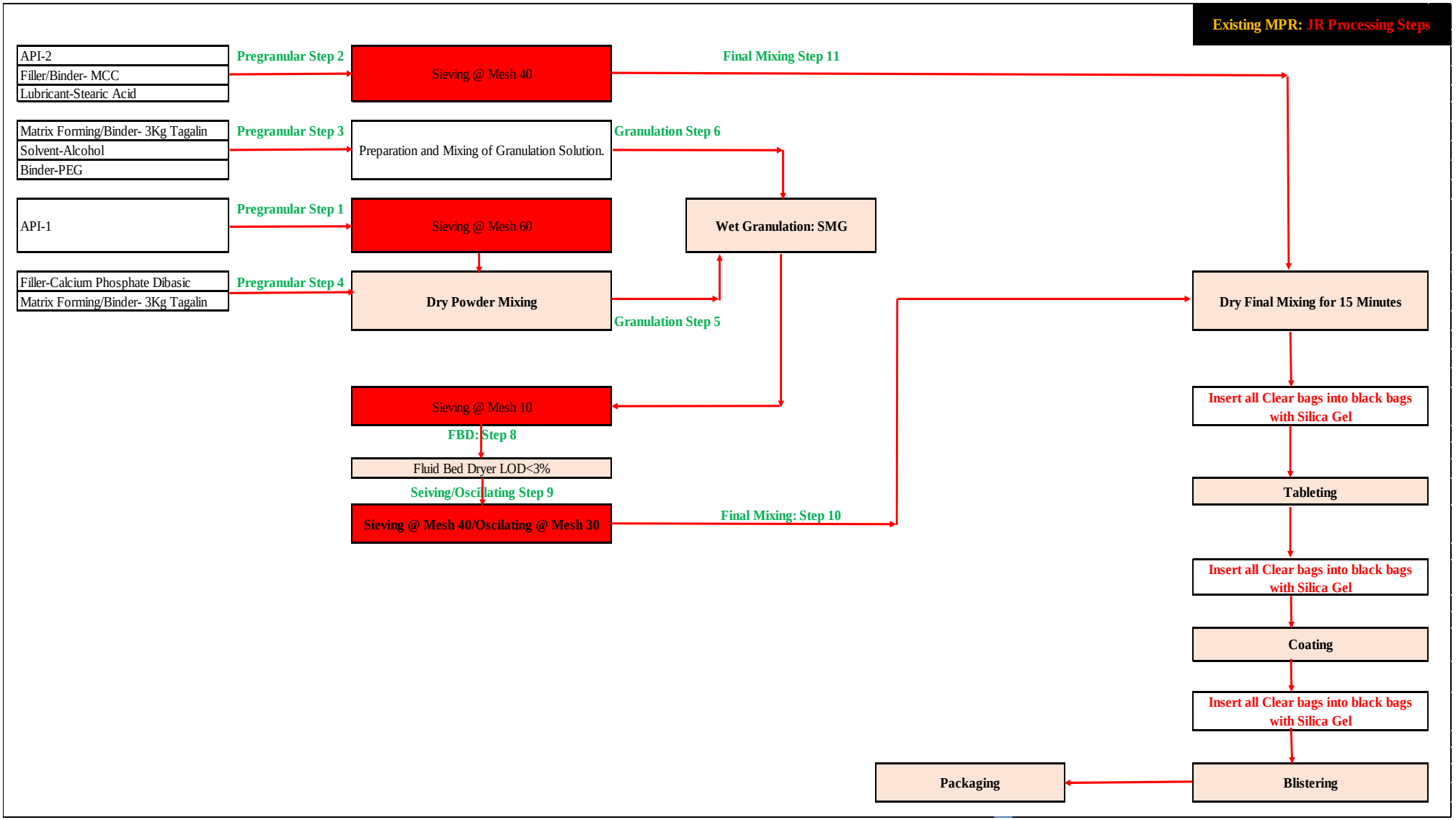


Figure 12: Manufacturing procedure record for JR tablet before improvements.

During the measure phase, the TPP, TQPP, CQA, IQA, CMA, CPP were identified for JR product. Since JR is an existing product and has been in manufacturing for several years, Figure 13 shows the sequence which was followed to obtain the required information and data prior and during the establishment of the Design Spaces.

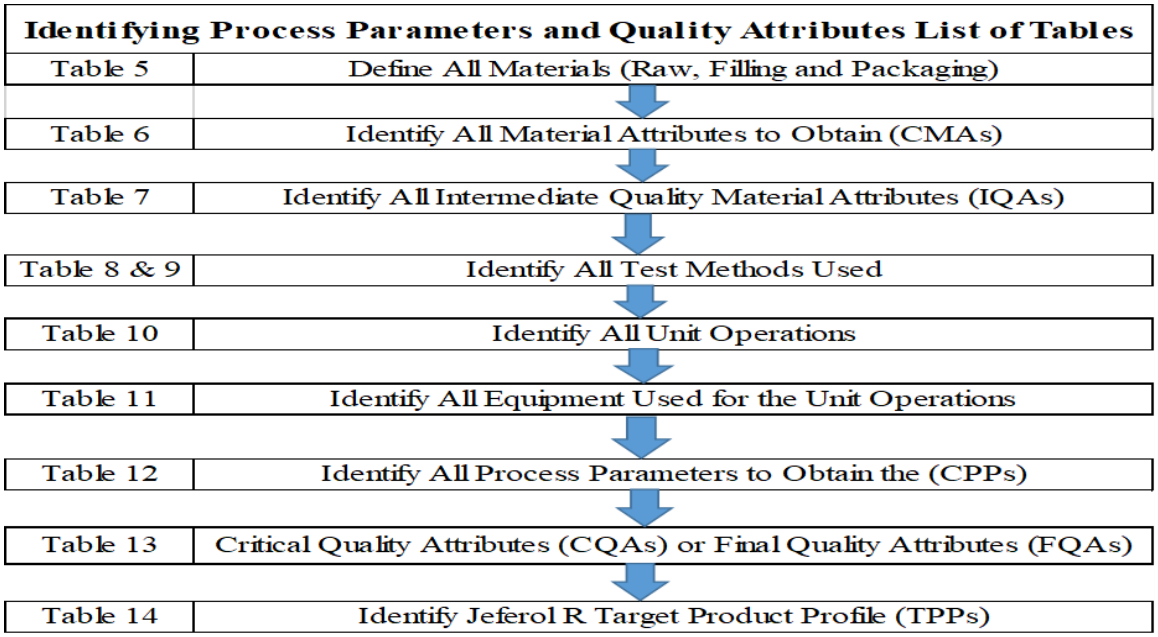


Figure 13: Sequencing steps taken to collect information and data for an existing JR tablet.

JR tablet raw materials, as shown in Table 5, were identified during the measure phase.

Table 5: JR tablet materials.

Name	Category	Unit Operation	Function	Description
API-1	Drug Substance (API)	Sifting 1	API	API
Tagalin	Excipient	Dry mixing	Matrix Forming	Extended Release Polymer
Calcium Phosphate Dibasic	Excipient	Dry mixing	Filler	Excipient
Alcohol	Excipient	Binder Solution preparations	Solvent	Solvent
Tagalin	Excipient	Binder Solution preparations	Binder	Excipient
PEG	Excipient	Binder Solution preparations	Binder	Excipient
API-2	Drug Substance (API)	Final Mixing	API	API
MCC	Excipient	Pre-mixing	Filler/Binder	Excipient
Stearic Acid	Excipient	Lubrication	Lubricant	Excipient
Methylene Chloride	Excipient	Coating Solution Preparations	Solvent	Solvent
Methanol	Excipient	Coating Solution Preparations	Solvent	Solvent
Opadry	Excipient	Coating Solution Preparations	Coating Polymer	Coating Polymer
PVC	Packaging	Blistering	Primary Packaging material	Packaging material
Aluminum Foil	Packaging	Blistering	Primary Packaging material	Packaging material
Box	Packaging	Packaging	Secondary Packaging material	Packaging material
Leaflet	Packaging	Packaging	Secondary Packaging material	Packaging material

This table shows all materials used to make JR tablets including excipients, active materials and filling and packaging materials. Also, the table shows where in the unit operation does each material enter or is processed. In order to identify the Critical Materials Attributes during the QRM, Appendix 07 for all materials attributes, was created. Also, the Intermediate Materials Attributes (IQA) were also tabulated, as shown in Appendix 08. These intermediate materials are produced during the manufacturing process from the granulation to the packaging stage. Test Methods are developed and used as a consistent procedure for analysis of raw materials, intermediate materials and finished product before, during and after all stages of manufacturing. These Test Methods or Control Methods are shown in Appendix 09. The unit operations for JR tablet manufacturing were identified as shown in Appendix 10. Appendix 11 shows the process components (equipment) used during the unit operations and why they are used or their functions. Also, Appendix 11 shows the required Certificate of Analysis (COA) or Certificate of Conformance (COC)

for each equipment. The process parameters were identified for JR manufacturing as shown in Appendix 12. This table was used during the risk assessment in order to identify the critical process parameters (CPPs) for JR manufacturing. The Intermediate Quality Attributes of JR manufacturing must be met in order to produce the final JR Tablet Finished Product with the required quality attributes. Table 6 shows the Critical Quality Attributes (CQAs) for JR product manufacturing which were identified during the risk assessment and TQPP evaluation, as shown in Appendix 13.

Table 6: Critical quality attributes for JR tablet.

Critical Quality Attribute (CQA)			Acceptance Criteria						
Name	Type	Category	Data Space	Measure	Measurement Units	LSL	Target	USL	Target Justification
Assay-API1	Chemical	Drug Product	Control	Range	%	95	100	110	USP limit
Assay-API2	Chemical	Drug Product	Control	Range	%	90	105	115	USP limit
Content Uniformity-API1	Chemical	Drug Product	Control	Upper Limit (NMT)	Aceptance Value			15	USP limit
Content Uniformity-API2	Chemical	Drug Product	Control	Upper Limit (NMT)	Aceptance Value			15	USP limit
Dissolution 1hour-API1	Physical	Drug Product	Control	Range	%	40	50	60	In house limit
Dissolution 3hour-API1	Physical	Drug Product	Control	Lower Limit (NLT)	%	75			In house limit

These CQAs results which are part of the TQPP must be within the acceptance criteria for the product to be released to the market place with the required (TQPP). “A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TQPP” (Lionberger et al, 2008). The criticality of variables was determined through their effect on the TQPP. The design space was established by the combined use of DOE, multivariate analysis, risk assessments and process optimization of the JR drug product manufacturing stages while ensuring that the desired CQAs are attained in order to validate the Design Space with consistent reliability of achieving the same results throughout the manufacturing of JR tablet dosage form product. As a result, the final Target Product Profile shown in Table 7 can be achieved, keeping all other parameters and attributes as

designed and practiced according to approved procedures, if the TQPP shown in Appendix 13 are achieved.

Table 7: Target product profile for JR tablet.

TPP Section	Target
Indications and Usage	Deficiency Anemia
Dosage and Administration	Oral
Dosage Forms and Strengths	Film Coated Tablet with strength 50 mg/0.4 mg
Contraindications	Hemochromatosis. Hemosiderosis.
Warnings and Precautions	Hepatitis. Pancreatitis. Peptic ulcer or GI inflammation. Achlorhydria. Monitor hematocrit. API-2 may mask pernicious anemia. Repeated blood transfusions. Elderly.
Adverse Reactions	Nausea, abdominal discomfort and pain, constipation, diarrhea, masks occult bleeding, black stools.
Drug Interactions	Inhibits tetracycline absorption.
Use in Specific Populations	Not recommended for children.
Drug Abuse and Dependence	None
Overdosage	None
Description	Extended release tablets.
Clinical Pharmacology	None
Nonclinical Toxicology	None
Clinical Studies	None
References	Novartis reference product.
How Supplied/Storage and Handling	15 tablets per (PVC brown/Aluminum) blister/2 blisters per box.
Patient Counseling Information	According to physician's recommendations.

All of the above tables and Appendixes were taken into consideration during the QRM, Design Spaces establishment, Design of Experiments results and the changes made to the Manufacturing Procedure Record (MPR) were all considered in order to consistently achieve the TPP shown in Table 7 while making improvements to the JR manufacturing cycle time. The identification of all of the related materials attributes and process parameters for JR manufacturing was a very important initial step for JR quality by design and design spaces development. The reason for the identification of all of the materials attributes and process parameters is that not to just define the critical materials attributes and critical process parameters, but also to understand their effects during the risk assessment and DOE and how they are linked to the TPPs of JR product.

4.2.3 DMAIC-analyze phase

During the analyse phase, the detailed Process Flow Diagram of the JR manufacturing process was used to help effectively complete a Quality Risk Management (QRM) for JR product. The QRM and DOE studies completed through Design Expert 13 helped identify the critical materials attributes and the critical process parameters and which unit operation processes require a Design Space. A design Space model for each selected JR process was established and implemented in July 2020 utilizing 2018 and 2019 retrospective data. Using the Design Space models and the uncovered improvement opportunities eventually led to reducing the cycle time of JR. The QRM for the JR substances and drug product attributes was initially completed. The risk assessment criteria for the drug substance attributes is shown in Table 8.

Table 8: Criteria for risk assessment of drug substance attributes.

Risk Assessment of Drug Substance Attributes
A risk assessment of JR Tablet's attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs.
The outcome of the assessment and the accompanying justification is provided.
The relative risk that each attribute presents was ranked as high, medium or low.
The high risk attributes warranted further investigation whereas the low risk attributes required no further investigation.
The medium risk is considered acceptable based on current knowledge.
Further investigation for medium risk may be needed in order to reduce the risk.

The level of risk was identified according to Table 9.

Table 9: Risk levels for drug substance risk assessment.

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

The drug substance attributes and JR drug product CQAs were identified and an initial risk assessment was completed as shown in Appendix 14. As a result of the initial risk assessment, a summary of the risks for JR CQAs were identified as indicated in Table 10.

Table 10: Initial risk assessment of the drug product attributes.

Initial Risk Assessment of the Drug Product Attributes										
Drug Product CQAs	API	Drug Substance Attributes								
		Solid State Form	Particle Size Distribution (PSD)	Hygroscopicity	Solubility	Moisture Content	Residual Solvents as Impurity	Process Impurities	Physical & Chemical Stability	Flow Properties
Assay	API-1	Low	Low	High	Low	Low	Low	Low	Medium	Low
	API-2	Low	medium	High	Low	Low	Low	Low	Medium	Low
Content Uniformity	API-1	Low	Low	High	Low	Low	Low	Low	Low	Low
	API-2	Low	High	High	Low	Low	Low	Low	Low	Low
Dissolution	API-1	High	High	High	High	Low	Low	Low	Low	Low
	API-2	Low	Low	High	Low	Low	Low	Low	Low	Low
Degradation Products	API-1	medium	Low	High	Low	Low	Low	Low	Medium	Low
	API-2	medium	Low	High	Low	High	Low	Low	High	Low

As seen in Table 10, Hygroscopic, the ability of JR product substances to attract and uphold water from the surrounding environment, is a critical drug substance attribute which affects all CQAs. Therefore, moisture control during manufacturing was identified as the main contributing element to the degradation of JR in general and the active drug substances API 1 and API 2. The effect of moisture on API 1 is related to converting its color while the effect on API 2 is decomposition. Particle size of API 1 is a critical attribute which affects dissolution of JR while particle size affects API 2 distribution in JR during the mixing stage. The detailed JR product process flow diagram shown in Appendix 04 was used while performing the Quality Risk Management (QRM); specifically, it was used during the risk methodology Failure Mode and Effects Analysis (FMEA) risk management tool, as shown in Appendix 01, which was selected for the subject case study. As a result of the FMEA risk ranking and based on the acceptance criteria, the following

recommended actions, shown in Table 11, were taken to minimize, mitigate and or eliminate the potential risks of JR product manufacturing process cycle:

Table 11: QRM FMEA recommended actions for JR tablet.

JR Tablet QRM (Material Receiving to Packaging)		
No.	**Recommended Actions**	**Status**
1	Install Cameras inside all manufacturing areas.	Done
2	Samples should be placed in a special carry box before transferring to QC lab to protect from light and humidity.	Not Done
3	Preparation should be done inside a booth at the QC lab.	Not Done
4	An automatic transfer system should be installed to transfer the liquid solution to the super mixer granulator.	Done but not used during trials
5	A table should be created to list the particle size of API-1 and the required Ethanol needed for dispensing. The warehouse should dispense according to this table.	Done
6	Since API-1 is tested by the QC lab at receiving and a clearance is given after analysis of its particle size, there is no need to sieve API-1 using mesh 60, use mesh 10.	Done
7	A design space should be built to cover Fluid Bed Dryer and the final mixing stage since API-2 Assay failure has been an issue.	Done
8	A design space should be built for the compression and the coating stages since API-2 Assay failure is frequent.	Done
9	API-2 should be Geometrically mixed with Avicel and with dried granulated material prior to final mixing which should help in better distributing API-2 in the final mixture.	Done
10	All tablet section hoses should be put on qualification with periodic replacement and each group of products should be tracked and labeled with colored hoses.	Not Done
11	An interlock should be installed to stop the coating solution feed to the coating machine in case the incoming air temperature drops to less than $35^{o}C$.	Not Done
12	An interlock should be installed to stop the coating machine in case the vacuum pressure is lost.	Not Done
13	It is recommended that a second Oscillator and tablet machines are to eliminate bottlenecks in the manufacturing process.	Done

After completing thirteen actual production batches of JR product, data were collected and tabulated, as shown in Appendix 15. Initially, the first two batches manufactured in 2020 were produced according to the existing Manufacturing Procedure Record (MPR) in order to validate the retrospective data obtained from 2017, 2018 and 2019 for JR manufacturing. Then, changes to the MPR were applied based on the QRM, DOE, Design Spaces and

scientific and technical expertise of myself and other staff at Jepharm. The establishment of a Design Space(s) for a particular unit operation or a combination of unit operation was evaluated. “A design space might be determined per unit operation or a combination of unit operations which, from a regulatory perspective, can provide additional flexibility.” (Schlindwein & Gibson, 2018, P. 65). A multivariate data was generated from JR manufacturing and an analysis was performed. “Multivariate analysis searches for interdependences among all variables. Various methods have been developed for the analysis of the multivariate data” (Westerhuis, 1997). As a result, three Design Spaces were developed in Design Expert software using Response Surface Design while each Design Space was a combination of unit operations. “Graphical techniques such as surface plots and contour plots can be used to show the relation between the independent process variables and the dependent responses. The model can also be used to acquire knowledge of the process” (Westerhuis, 1997). The Design Space for the Granulation to compression stage, Figure 14 was established. UV-Visible Spectrophotometer was used to measure the % release of API 1 from JR tablet, a dissolution test, to investigate the response dissolution at specific times after one hour and after three hours. In this case study, a dissolution after three hours as the response with three factors including particle size, hardness and content of API 1 were chosen.

ANOVA for Quadratic model

Response 1: Dissol. After Compr 3hr

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Block	157.04	4	39.26			
Model	906.73	9	100.75	42.21	< 0.0001	significant
A-API-1 Particle Size	23.19	1	23.19	9.72	0.0047	
B-API-1 Content	18.82	1	18.82	7.89	0.0097	
C-Hardness	1.76	1	1.76	0.7367	0.3992	
AB	278.74	1	278.74	116.78	< 0.0001	
AC	23.97	1	23.97	10.04	0.0041	
BC	21.61	1	21.61	9.05	0.0061	
A^2	129.66	1	129.66	54.33	< 0.0001	
B^2	260.23	1	260.23	109.03	< 0.0001	
C^2	54.07	1	54.07	22.65	< 0.0001	
Residual	57.28	24	2.39			
Lack of Fit	46.28	17	2.72	1.73	0.2351	not significant
Pure Error	11.00	7	1.57			
Cor Total	1121.05	37				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 42.21 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB, AC, BC, A^2, B^2, C^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 1.73 implies the Lack of Fit is not significant relative to the pure error. There is a 23.51% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	1.54	**R^2**	0.9406
Mean	93.84	**Adjusted R^2**	0.9183
C.V. %	1.65	**Predicted R^2**	0.8390
		Adeq Precision	31.2767

The **Predicted R^2** of 0.8390 is in reasonable agreement with the **Adjusted R^2** of 0.9183; i.e. the difference is less than 0.2.

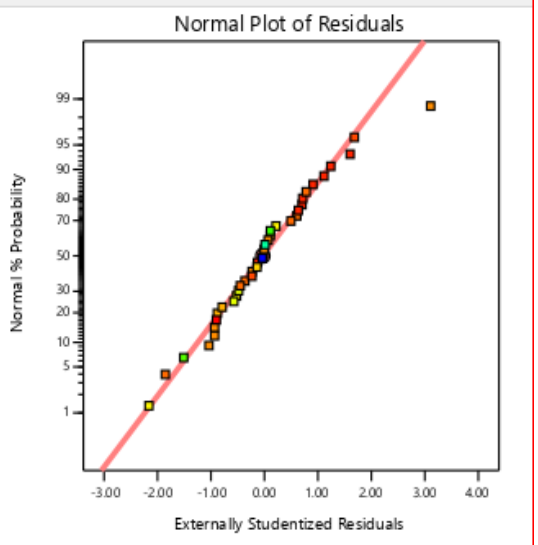
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 31.277 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients in Terms of Coded Factors

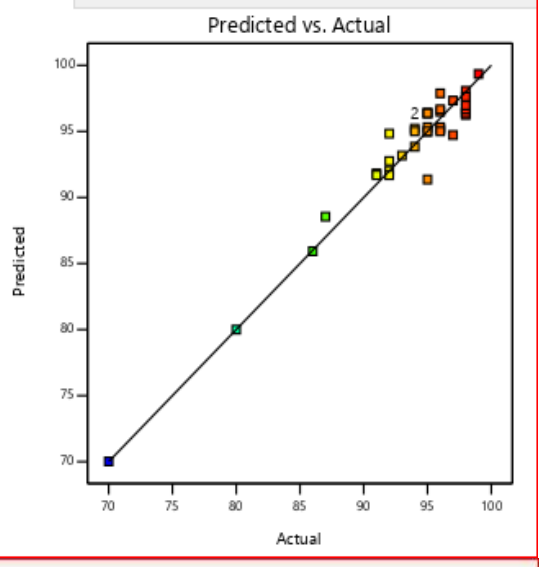
Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	106.94	1	1.27	104.31	109.56	
2017	-4.23	4				
2018	2.04					
2019	7.35					
2020	-5.79					
Block 5	0.6279					
A-API-1 Particle Size	-3.50	1	1.12	-5.82	-1.18	11.29
B-API-1 Content	2.15	1	0.7652	0.5696	3.73	3.32
C-Hardness	-0.6623	1	0.7716	-2.25	0.9303	2.26
AB	17.70	1	1.64	14.32	21.08	8.89
AC	-4.52	1	1.43	-7.46	-1.58	4.24
BC	3.43	1	1.14	1.08	5.78	3.55
A^2	-11.63	1	1.58	-14.89	-8.38	6.43
B^2	-17.30	1	1.66	-20.72	-13.88	6.64
C^2	6.12	1	1.29	3.47	8.78	2.94

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

Normal Plot

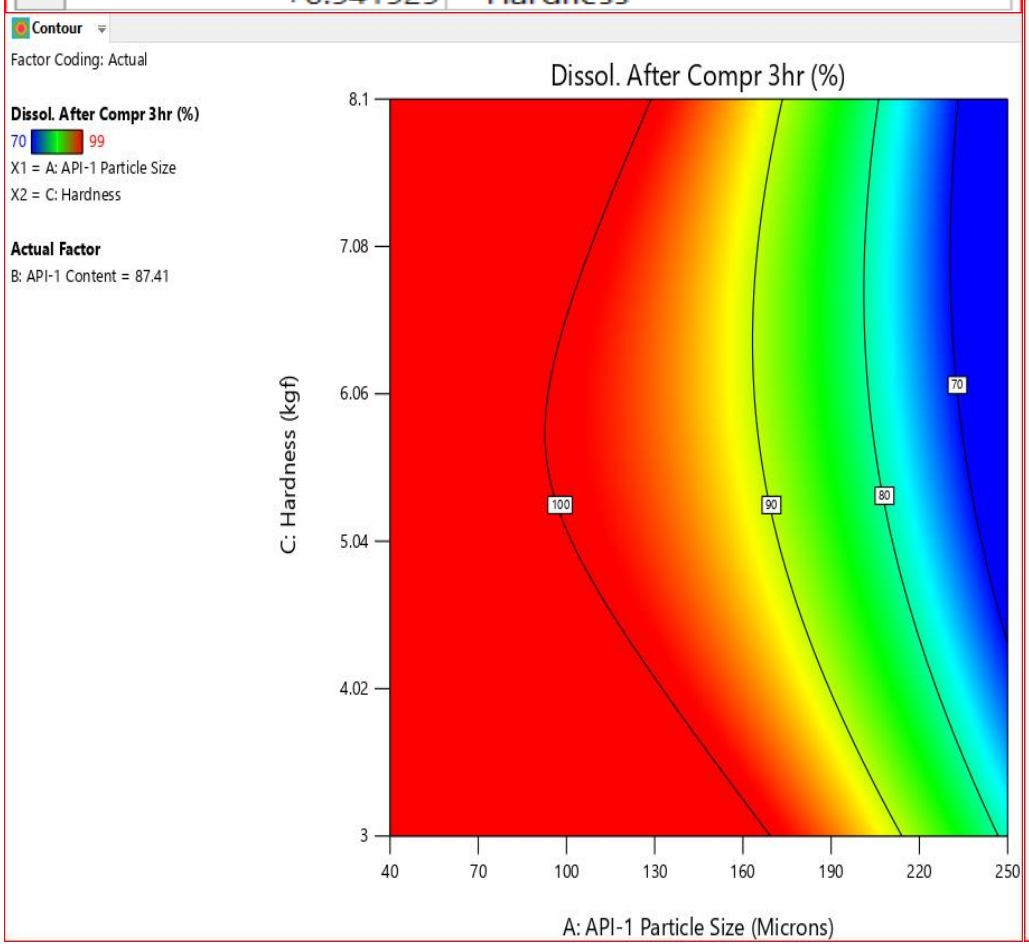


Box-Cox | Pred. vs. Actual



Dissol. After Compr 3hr	=
-1.19608E+05	
-13.79924	* API-1 Particle Size
+2741.40659	* API-1 Content
-121.27070	* Hardness
+0.160516	* API-1 Particle Size * API-1 Content
-0.016877	* API-1 Particle Size * Hardness
+1.28048	* API-1 Content * Hardness
-0.001055	* API-1 Particle Size²
-15.69259	* API-1 Content²
+0.941929	* Hardness²

Contour



3D Surface

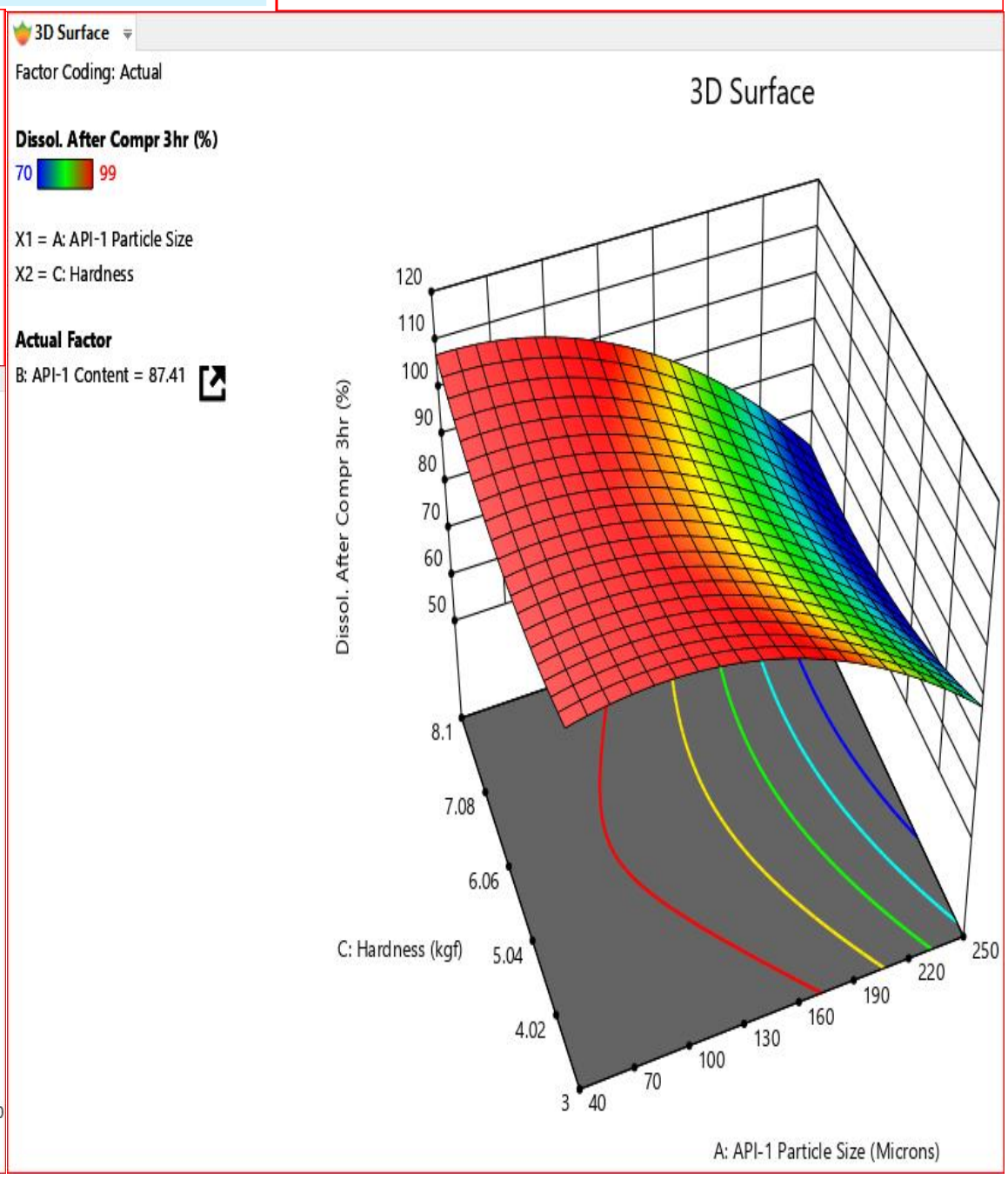


Figure 14: Design space (Granulation to Compression Stages) for Response Dissolution.

The sample size is 38 actual production batches. There are three factors with two levels for each factor. The factor interaction was given by Design Expert 13, as depicted in Table 12.

Table 12: Design Expert 13 factor interaction for Response Dissolution.

m	Intercept		AC^3	⚠	A^3B^3
m	A-API-1 Particle Size	⚠	B^3C	⚠	A^3B^2C
m	B-API-1 Content		BC^3	⚠	A^3BC^2
m	C-Hardness	⚠	A^4	⚠	A^3C^3
m	AB	⚠	B^4	⚠	A^2B^3C
m	AC		C^4	⚠	A^2BC^3
m	BC	⚠	A^2B^2C	⚠	AB^3C^2
m	A^2	⚠	A^2BC^2	⚠	AB^2C^3
m	B^2	⚠	AB^2C^2	⚠	B^3C^3
m	C^2	⚠	A^3B^2	⚠	A^4B^2
	ABC	⚠	A^3BC	⚠	A^4BC
	A^2B	⚠	A^3C^2	⚠	A^4C^2
	A^2C	⚠	A^2B^3	⚠	A^2B^4
	AB^2	⚠	A^2C^3	⚠	A^2C^4
	AC^2	⚠	AB^3C	⚠	AB^4C
⚠	B^2C	⚠	ABC^3	⚠	ABC^4
	BC^2	⚠	B^3C^2	⚠	B^4C^2
⚠	A^3	⚠	B^2C^3	⚠	B^2C^4
⚠	B^3	⚠	A^4B	⚠	A^5B
	C^3	⚠	A^4C	⚠	A^5C
⚠	A^2B^2	⚠	AB^4	⚠	AB^5
⚠	A^2BC		AC^4		AC^5
	A^2C^2	⚠	B^4C	⚠	B^5C
⚠	AB^2C		BC^4		BC^5
⚠	ABC^2	⚠	A^5	⚠	A^6
⚠	B^2C^2	⚠	B^5	⚠	B^6
⚠	A^3B		C^5		C^6
⚠	A^3C	⚠	$A^2B^2C^2$		
⚠	AB^3				

m	The term will be included in the model.
⚠	Indicates the term is aliased with another term, or was not estimated in the Fit Summary calculations. Including the term in the model is not recommended.
🔒	A user-forced term. Automatic model selection will always produce a model that includes this term.
🔒	Indicates that the term is required to be in the model by the program.

Design expert 13 gives a fit summary for the suggested model based on the p-value, lack of fit, adjusted R^2 and predicted R^2, as shown in Table 13.

Table 13: Model fit summary for the Response dissolution.

Fit Summary

Response 1: Dissol. After Compr 3hr

	Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
	Linear	0.2289	0.0001	0.0453	-1.7873	
	2FI	< 0.0001	0.0018	0.5575	-0.6460	
	Quadratic	**< 0.0001**	**0.2351**	**0.9183**	**0.8390**	**Suggested**
	Cubic	0.0746	0.4320	0.9410		**Aliased**

R^2 estimates the proportion of variation in the response dissolution that can be attributed to the model rather than to random error. An R^2 closer to 1 indicates a better fit to the data than does an R^2 closer to 0. An R^2 near 0 indicates that the model is not a much better predictor of the dissolution than is the dissolution mean, in this case. Figure 14 shows that R^2 is 0.94, it indicates that 94% of the variation in the response dissolution are explained by particle size of API 1, content of API 1 and hardness of API 1 factors, and the remaining 6% of the variability is still unaccounted for. Since R^2 is 0.94, it indicates a better fit for the Quadratic model. However, R^2 alone does not tell us if the selected model is a good fit. Every time we add a factor, R^2 increases which makes it not a good indicator of a model fit. This is why we also look at R^2 Adjusted which accounts for the number of factors in order to compare models and select the best fit. Adjusted R2 is more appropriate when evaluating model fit by evaluating the variance in the response dissolution which is accounted for by API 1 particle size, API 1 content and hardness while comparing alternative models. Table 13 above shows that Quadratic was suggested by Design Expert

13 as the better fit model. Figure 14 shows that R^2 Adjusted value is 0.92, which suggests a good model fit with high predictive power. On the other hand, R^2 predicted gives an idea of how good our model is and how useful in predicting future % dissolution results. "The predicted R-squared indicates how well a regression model predicts responses for new observations. A key benefit of predicted R-squared is that it can prevent you from overfitting a model" (Frost, 2021). An over-fit model starts to model the random noise which is impossible to predict, for example. Lower predicted R^2 means that we have too many factors in the model. Figure 14 shows that the predicted R^2 is 0.84 indicating that the Quadratic model has an 84% prediction power for the response dissolution using the factors API 1 particle size, API 1 content and hardness with the remaining 16% variability unaccounted for. As a result of evaluating R^2, adjusted R^2 and predicted R^2, we conclude that the quadratic model selected to model the three factors API 1 particle size, API 1 content and hardness for the response dissolution is a good fit and can be used to predict future % dissolution for JR tablet product. Also, Figure 14 clearly shows that the ANOVA for Quadratic model for the Response Dissolution after three hours is statistically significant with p-value <0.05. The factors particle size and API-1 percentage (%) content highly affects the dissolution of JR tablet. Dissolution is a Critical Quality Attribute for JR. A p-value for particle size <0.05 indicates that particle size is statistically significant factor for the response Dissolution of JR after 3 hours after the compression stage. The acceptance limit for dissolution after 3 hours is >75%. The lower the particle size of API-1 at a hardness between 5.04 to 6.06 kgf would guarantee a dissolution value of >75% with API 1 content of 87%. As can it be seen in the Contour and the 3D plots, the particle size must be below 230 Micrometers to ensure that the dissolution value is >75%. Also, the model

shows that the factor hardness is not significant since the p-value = 0.3992 which is higher than 0.05. In this case study, the excipient Tagalin plays a very important role in delaying dissolution. During the granulation stage, Tagalin coats on API 1 particles so that it delays its release when the patient takes JR medicine. Tagalin is considered a dissolution rate retardant and a binder. As the particle size of API 1 decreases, the surface area of API 1 particle increases, hence, giving more surface for Tagalin coating on it. Therefore, allowing more percentage of Tagalin coating on API 1 particles so that as the Tagalin coating increases, the dissolution rate decreases. "Nanosciences are mainly dependent on particle behavior; smaller the particle size greater number of the particle is on the surface hence increases the surface area for absorption, dissolution profile and in vivo drug release profile" (Babu et al., 2014). As mentioned earlier, Tagalin is also a binder meaning that it provides API 1 the capability of effective chaining when granulated and tableted in addition to the coating mechanism. The more the availability of Tagalin as a binder on site of API 1 particles, the higher the hardness at a constant compression force and therefore the slower the dissolution rate. Therefore, hardness in this case study is affected by the availability of % Tagalin as a binder with no direct relation to tablet machine compression force since for JR tablet a disintegration test is not required and therefore not completed and only a dissolution test is completed. In literature and based on experience, Hardness generally affects dissolution for immediate release tablets. However, in this case study, JR is a sustained release tablet which means a slow or extended-release tablet. Generally, the higher the hardness, the lower the dissolution rate since tablets when compressed at higher compression pressure tend to prolong disintegration time leading to slower rate of dissolution. “As always, it is useful to check that the model makes scientific sense. For

example, as we increase the load, we would expect the tablet should get harder. The harder the tablet, the slower the dissolution" (Schlindwein & Gibson, 2018, P. 178). In this case study, the compression force is constant for all JR tablet batches and what varies is the effectiveness of Tagalin coating on API 1 particles, hence, the granulation end point is based on operator experience and not on measurements. The second multi surface design space was completed for Response Friability. Friability is a very important and critical product CQA for intermediate core tablets before coating has a USP/BP of <1% and reducing Friability helps improve the product final % Yield. Friability measures percentage weight loss generated during testing of not less than 6.5 grams of tablets turned 100 times. The higher the % of weight loss the higher the Friability. The effect of API 1 particle size, API 1 % content and hardness on the response Friability was studied with the results shown in Figure 15.

ANOVA for Quadratic model

**Response 1: Friability **

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Block	1.17	4	0.2920			
Model	1.12	9	0.1247	46.65	< 0.0001	significant
A-API-1 Particle Size	0.0120	1	0.0120	4.48	0.0448	
B-API-1 Content	0.0135	1	0.0135	5.05	0.0341	
C-Factor Hardness	0.2224	1	0.2224	83.22	< 0.0001	
AB	0.0363	1	0.0363	13.59	0.0012	
AC	0.0092	1	0.0092	3.43	0.0765	
BC	0.0754	1	0.0754	28.22	< 0.0001	
A^2	0.1767	1	0.1767	66.14	< 0.0001	
B^2	0.0580	1	0.0580	21.69	< 0.0001	
C^2	0.0003	1	0.0003	0.1069	0.7465	
Residual	0.0641	24	0.0027			
Lack of Fit	0.0408	16	0.0025	0.8742	0.6122	not significant
Pure Error	0.0233	8	0.0029			
Cor Total	2.35	37				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 46.65 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, AB, BC, A^2, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The **Lack of Fit F-value** of 0.87 implies the Lack of Fit is not significant relative to the pure error. There is a 61.22% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	0.0517	**R^2**	0.9459
Mean	0.3447	**Adjusted R^2**	0.9257
C.V. %	14.99	**Predicted R^2**	NA[1]
		Adeq Precision	42.7658

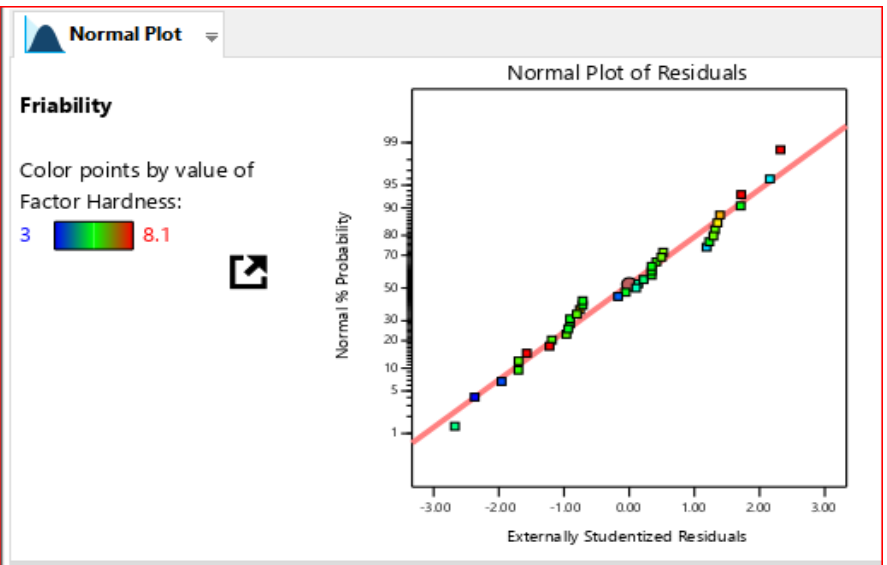
[1] Case(s) with leverage of 1.0000: Pred R^2 and PRESS statistic not defined.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 42.766 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients in Terms of Coded Factors

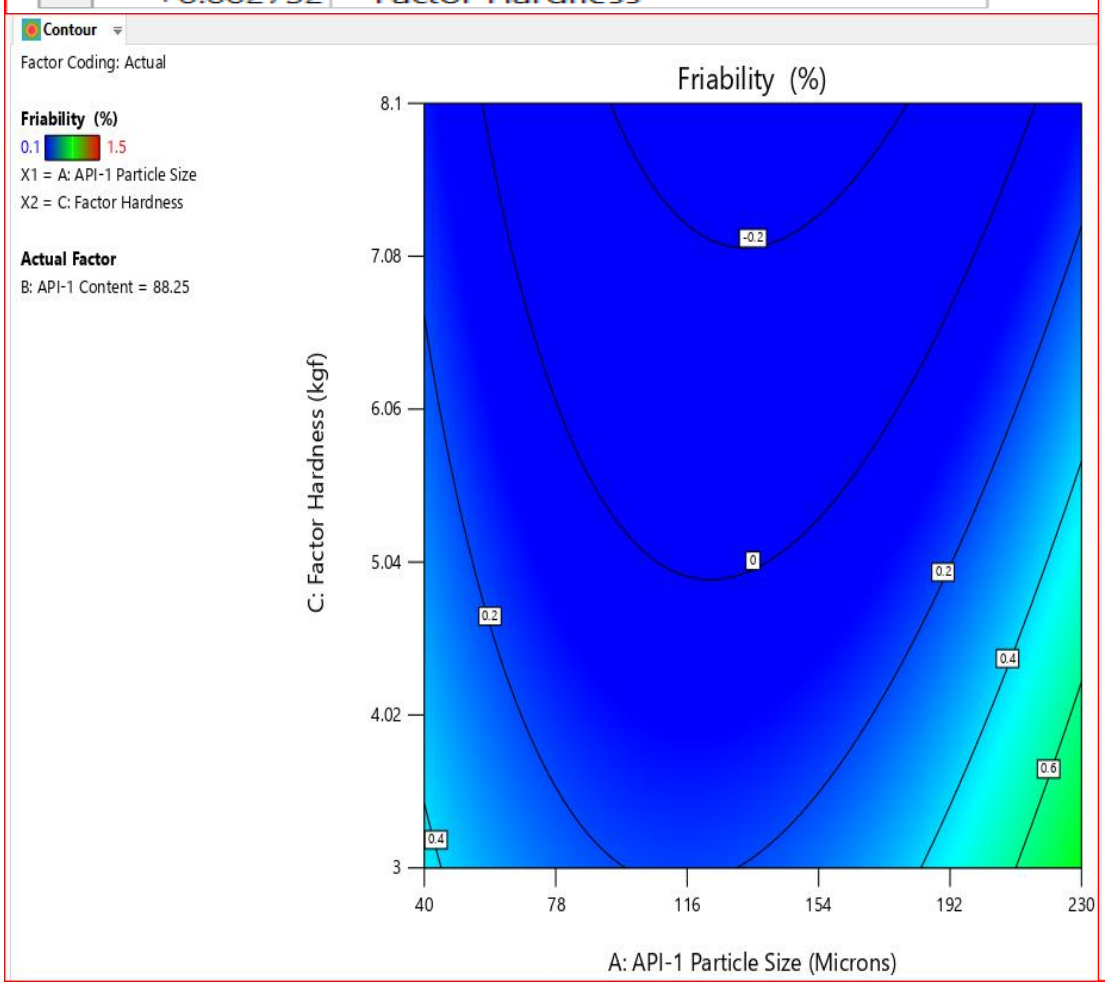
Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	-0.0546	1	0.0461	-0.1497	0.0405	
2017	-0.0480	4				
2018	-0.1128					
2019	-0.1181					
2020	-0.0928					
Block 5	0.3717					
A-API-1 Particle Size	0.0792	1	0.0374	0.0020	0.1564	11.05
B-API-1 Content	-0.0637	1	0.0283	-0.1222	-0.0052	4.30
C-Factor Hardness	-0.2443	1	0.0268	-0.2995	-0.1890	2.50
AB	-0.2105	1	0.0571	-0.3283	-0.0926	9.09
AC	-0.0941	1	0.0508	-0.1990	0.0108	5.19
BC	-0.2301	1	0.0433	-0.3195	-0.1407	5.33
A^2	0.3967	1	0.0488	0.2960	0.4974	7.45
B^2	0.3242	1	0.0696	0.1805	0.4679	11.25
C^2	0.0179	1	0.0547	-0.0951	0.1309	5.18

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.



Final Equation in Terms of Actual Factors

Friability	=
+2229.21002	
+0.177313	* API-1 Particle Size
-51.19967	* API-1 Content
+7.50916	* Factor Hardness
-0.002110	* API-1 Particle Size * API-1 Content
-0.000388	* API-1 Particle Size * Factor Hardness
-0.085927	* API-1 Content * Factor Hardness
+0.000044	* API-1 Particle Size²
+0.294055	* API-1 Content²
+0.002752	* Factor Hardness²



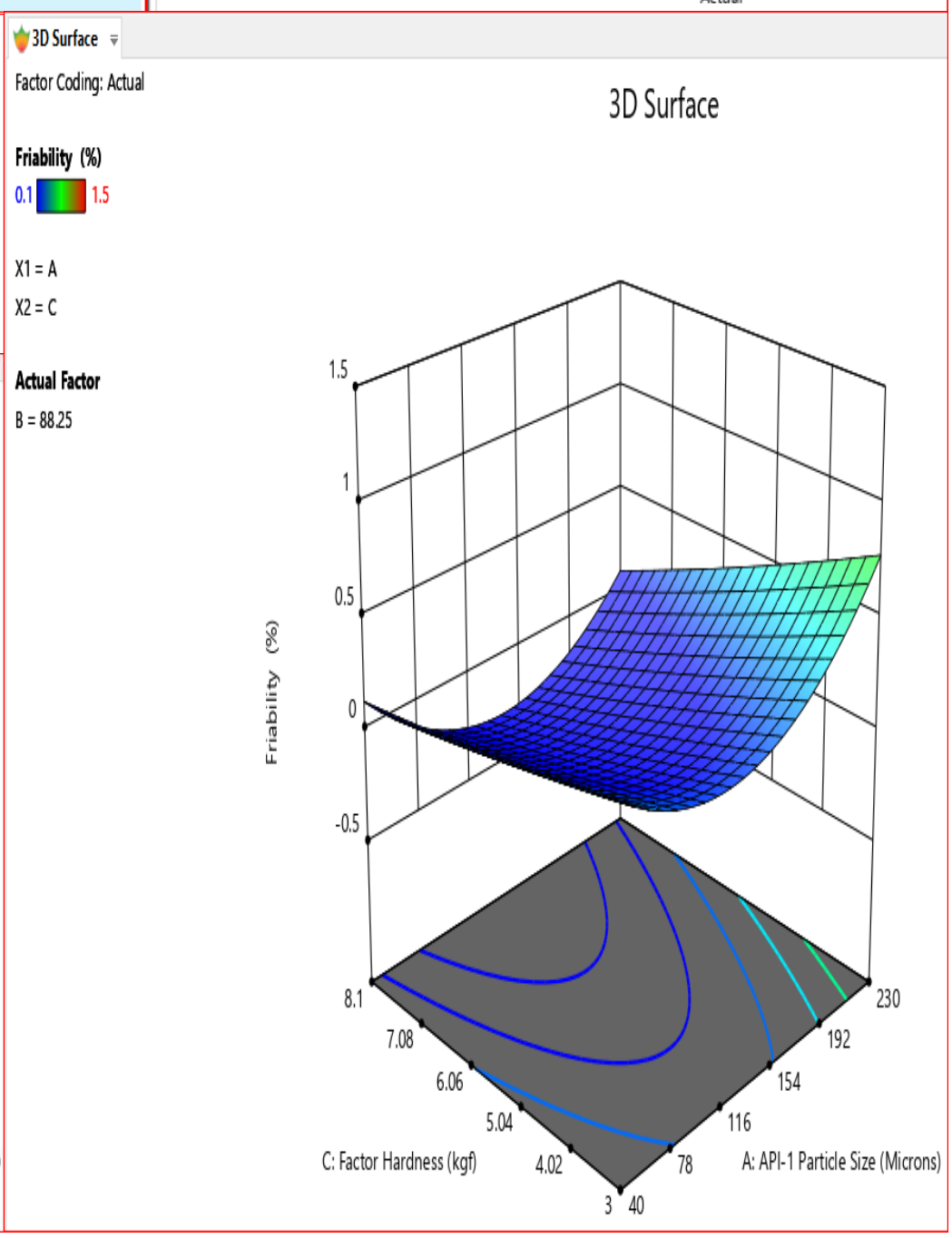


Figure 15: Granulation to compression Surface Design for the response Friability

For the response friability, the sample size is 31 actual production batches. There are three factors with two levels for each factor. The factor interaction was given by Design Expert 13, as depicted in Table 14.

Table 14: Factor interaction for the response Friability.

m	Intercept	⚠	AB^3	⚠	$A^2B^2C^2$
m	A-API-1 Particle Size		AC^3	⚠	A^2B^3
m	B-API-1 Content	⚠	B^3C	⚠	A^3B^2C
m	C-Factor Hardness		BC^3	⚠	A^3BC^2
m	AB	⚠	A^4	⚠	A^3C^3
m	AC	⚠	B^4	⚠	A^2B^3C
m	BC		C^4	⚠	A^2BC^3
m	A^2	⚠	A^2B^2C	⚠	AB^3C^2
m	B^2	⚠	A^2BC^2	⚠	AB^2C^3
m	C^2	⚠	AB^2C^2	⚠	B^3C^3
	ABC	⚠	A^3B^2	⚠	A^4B^2
	A^2B	⚠	A^3BC	⚠	A^4BC
⚠	A^2C	⚠	A^3C^2	⚠	A^4C^2
⚠	AB^2	⚠	A^2B^3	⚠	A^2B^4
	AC^2	⚠	A^2C^3	⚠	A^2C^4
⚠	B^2C	⚠	AB^3C	⚠	AB^4C
	BC^2	⚠	ABC^3	⚠	ABC^4
⚠	A^3	⚠	B^3C^2	⚠	B^4C^2
⚠	B^3	⚠	B^2C^3	⚠	B^2C^4
	C^3	⚠	A^4B	⚠	A^5B
⚠	A^2B^2	⚠	A^4C	⚠	A^5C
⚠	A^2BC	⚠	AB^4	⚠	AB^5
⚠	A^2C^2		AC^4		AC^5
⚠	AB^2C	⚠	B^4C	⚠	B^5C
⚠	ABC^2		BC^4	⚠	BC^5
⚠	B^2C^2	⚠	A^5	⚠	A^6
⚠	A^3B	⚠	B^5	⚠	B^6
⚠	A^3C		C^5		C^6
⚠	AB^3	⚠	$A^2B^2C^2$		

m	The term will be included in the model.
⚠	Indicates the term is aliased with another term, or was not estimated in the Fit Summary calculations. Including the term in the model is not recommended.
🔒	A user-forced term. Automatic model selection will always produce a model that includes this term.
🔒	Indicates that the term is required to be in the model by the program.

Design expert 13 gave a fit summary for the suggested Quadratic model based on the p-value, lack of fit and adjusted R^2, as shown in Table 15.

Table 15: Model Fit Summary for the response Friability.

Fit Summary

**Response 1: Friability **

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0094	0.0005	0.2451		
2FI	0.0001	0.0052	0.6000		
Quadratic	**< 0.0001**	**0.6122**	**0.9257**		**Suggested**
Cubic	0.2533	0.6999	0.9320		**Aliased**

R^2 estimates the proportion of variation in the response friability that can be attributed to the model rather than to random error. An R^2 closer to 1 indicates a better fit to the data than does an R^2 closer to 0. An R^2 near 0 indicates that the model is not a much better predictor of the friability than is the friability mean. Figure 15 shows that R^2 is 0.9459, it indicates that 94.59% of the variation in the response dissolution are explained by particle size of API 1, content of API 1 and hardness factors, and the remaining 5.41% of the variability is still unaccounted for. Since R^2 is 0.9459, it indicates a better fit for the Quadratic model. However, R^2 alone does not tell us if the selected model is a good fit. Every time we add a factor, R^2 increases which makes it not a good indicator of a model fit. This is why we also look at R^2 Adjusted which accounts for the number of factors in order to compare models and select the best fit. Table 15 above shows that Quadratic was suggested by Design Expert 13 as the better fit model. Adjusted R^2 is more appropriate when evaluating model fit, meaning in this case study, evaluating the variance in the response friability which is accounted for by API 1 particle size, API 1 content and

hardness while comparing alternative models. Figure 14 shows that R^2 Adjusted value is 0.9257, which suggests a good model fit. On the other hand, R^2 predicted gives an idea of how good our model is and how useful it is in predicting future % friability results. An over-fit model starts to model the random noise which is impossible to predict. For this surface design, we have tried changing the model, removing outliers and optimization through Design expert 13. However, the predicted R^2 came out to be N/A for all selected models and runs which indicates that the prediction power for the response friability using the factors API 1 particle size, API 1 content and hardness could not be determined. Knowing the process, these factors in general should be significant as shown by Figure 15, however, friability analysis seems to be inconsistent which can be either operator error or instrument errors. This should be a future work to be followed up on. Also, it may be possible that none of these factors in reality have an effect on friability even though these factors came out to be statistically significant as shown in Figure 15. As a result, we can't conclude that the quadratic model selected to model the three factors API 1 particle size, API 1 content and hardness for the response friability is a good fit and can be used to predict future % friability for JR tablet product. Figure 15 clearly shows that the ANOVA for Quadratic model for the Response Friability is statistically significant with p-value <0.05. The factors particle size, API-1 % content and hardness highly affects the Friability of JR tablets. The p-value for particle size is <0.05 indicating that particle size statistically significantly affects the response friability before coating tablets. As shown in the contour plot and 3D surface design, the particle size of API 1 should be kept within a range of 40 to 230 Micrometer in order to obtain and guarantee a friability of <1%. The optimum particle size is about 116 Microns as shown in the contour plot. The % content of API 1

should be around 88% while hardness should be kept above 5.5 kgf. As mentioned above in the first Multi Surface Design Space, as the particle size of API 1 goes down, the more the surface area of API-1 to be coated with Tagalin on particles and since Tagalin is a binder the more the binding capabilities and hence the more likely that particles stick together eliminating dustiness leading to lower % Friability. Lower % Friability means less dust generated during tableting operation and less material is lost. Friability is very important since higher friability would indicate that higher powder or tablet fragments are generated. This powder is lost during the de-dusting and coating processes of tablets. Therefore, friability should be kept below 1% which is also a USP pharmacopeia limit before coating. According to both Figure 14 and Figure 15 above, lower API 1 particle size would result in dissolution of more than 75% and Friability of less than 1% if we keep all other factors constant. In addition, the lower the particle size of API 1; most likely the higher the entrapped moisture between the particles and the less Alcohol is added in the granulation stage. However, the drying time of the wet granulated material is not affected since the addition of Alcohol is based on the particle size of API 1 and the moisture content of API 1 active substance from the supplier. Drying of wet granulated material and the final moisture content in the dried granulated materials is critical. Therefore, a third Multi Surface design space was established to study the effect of the degree of drying of the granulated material or LOD% on API 2 distribution or Assay before coating, as shown in Figure 16. This multi-surface design shows the importance of drying the wet granulated intermediate material on API 2 distribution after the final mixing and after the compression stages, just before the coating stage. The reason for building such surface design is that API 2 Assay is a product CQA which historically frequently fails. Failure in API 2 Assay

increases the lead time of JR tablet product, hence, increasing the cycle time because of the additional added time due to reprocessing of batches until API 2 Assay passes. Reprocessing of batches requires samples to be taken to the QC laboratory for analysis which may take four to six hours to complete. This iterative reprocessing and sampling are time consuming and may lead to extensive delays in processing other batches. Figure 16 shows the effect of factors particle size of API 1, Content of API 1, FBD Drying Time and the LOD% on the Response API 2 Assay. This multi-surface design was built for the granulation to before coating stages.

ANOVA for 2FI model

Response 1: API-2 Assay before coating

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Block	162.98	4	40.75			
Model	652.59	10	65.26	127.69	< 0.0001	significant
A-API-1 Particle Size	18.82	1	18.82	36.83	< 0.0001	
B-API-1 Content	3.60	1	3.60	7.04	0.0211	
C-Total Drying Time	34.03	1	34.03	66.58	< 0.0001	
D-FBD: LOD	96.97	1	96.97	189.75	< 0.0001	
AB	52.40	1	52.40	102.53	< 0.0001	
AC	33.08	1	33.08	64.73	< 0.0001	
AD	11.16	1	11.16	21.84	0.0005	
BC	19.90	1	19.90	38.95	< 0.0001	
BD	114.73	1	114.73	224.49	< 0.0001	
CD	7.31	1	7.31	14.30	0.0026	
Residual	6.13	12	0.5111			
Lack of Fit	5.13	10	0.5133	1.03	0.5894	not significant
Pure Error	1.0000	2	0.5000			
Cor Total	821.71	26				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 127.69 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, D, AB, AC, AD, BC, BD, CD are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

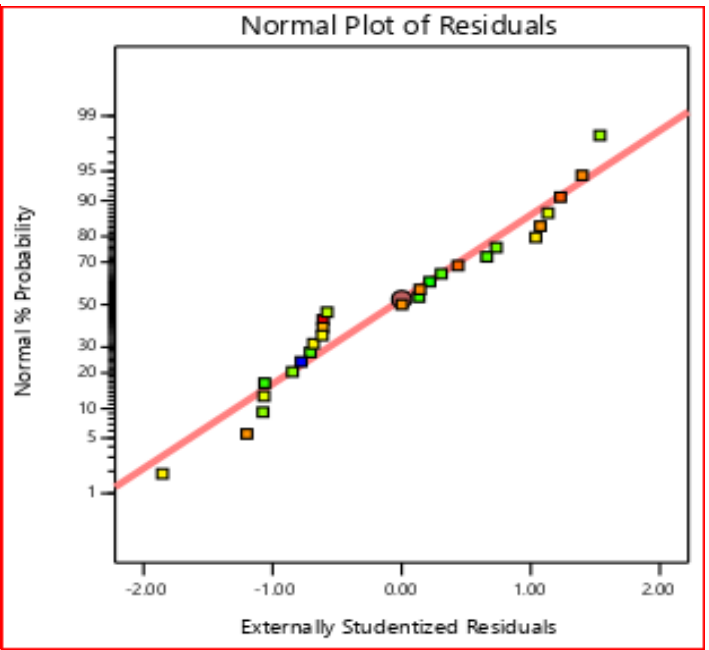
The **Lack of Fit F-value** of 1.03 implies the Lack of Fit is not significant relative to the pure error. There is a 58.94% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	0.7149		**R^2**	0.9907
Mean	100.58		**Adjusted R^2**	0.9829
C.V. %	0.7108		**Predicted R^2**	0.8339
			Adeq Precision	55.0168

The **Predicted R^2** of 0.8339 is in reasonable agreement with the **Adjusted R^2** of 0.9829; i.e. the difference is less than 0.2.

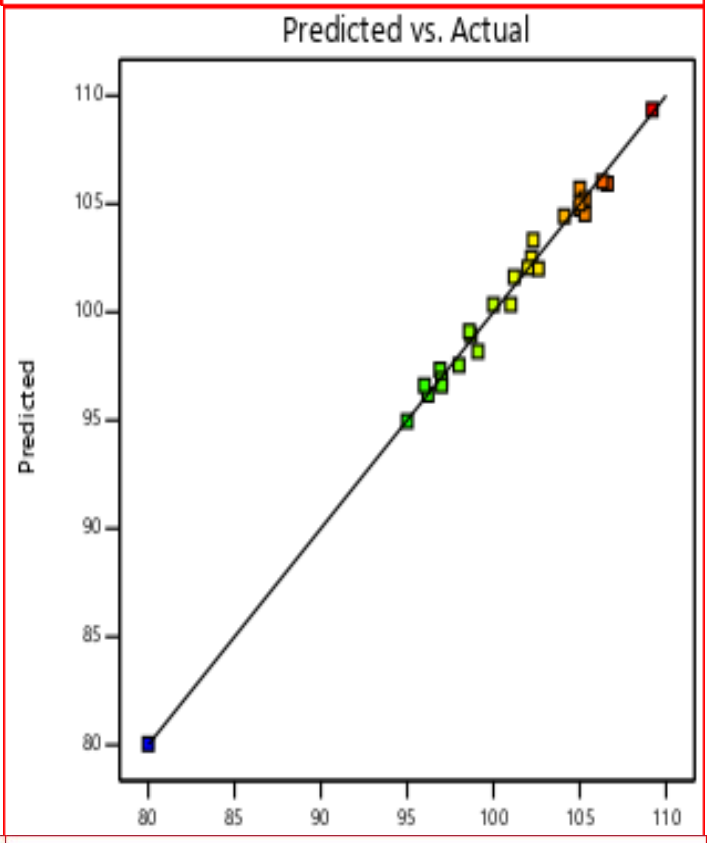
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 55.017 indicates an adequate signal. This model can be used to navigate the design space.



Coefficients in Terms of Coded Factors

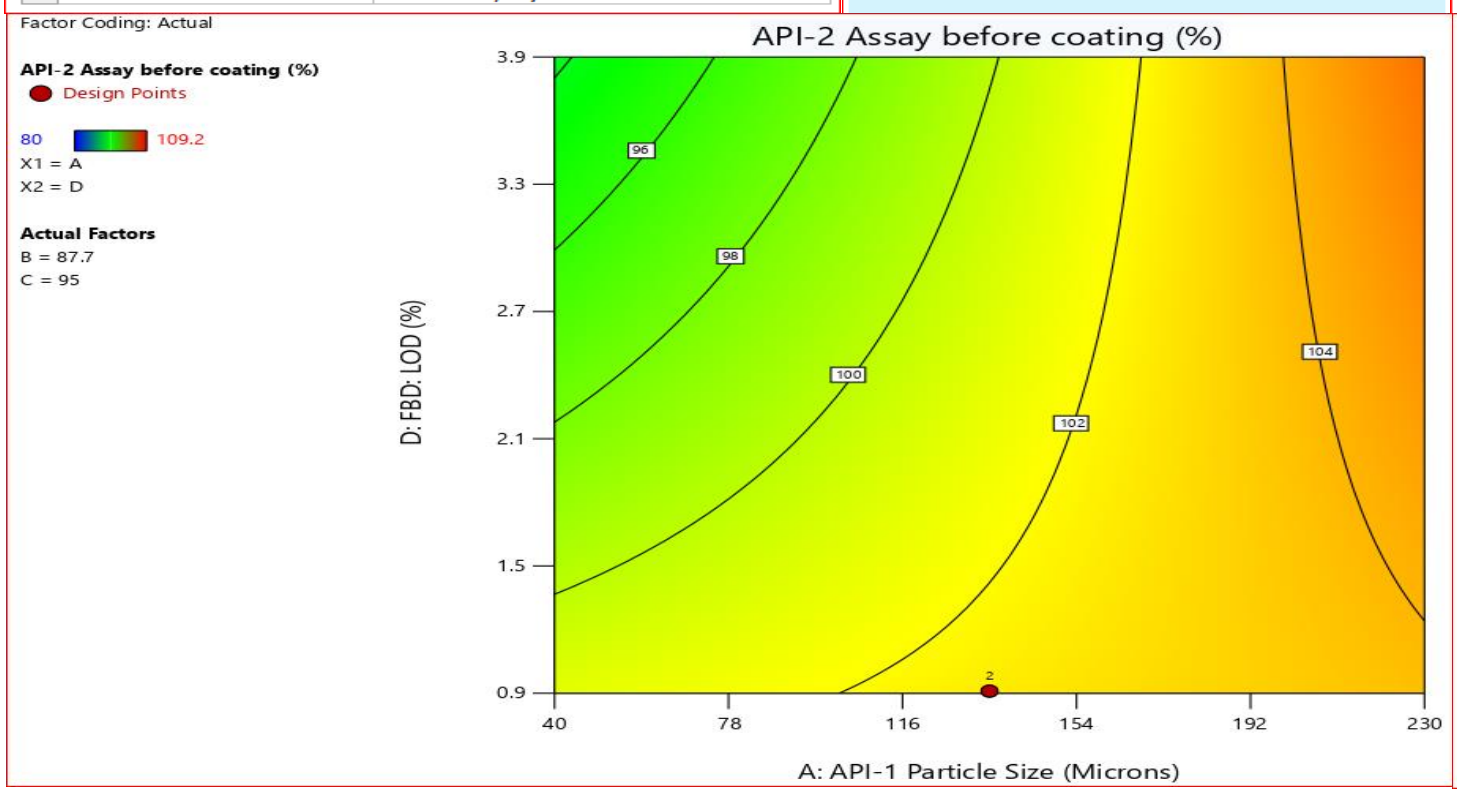
Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	101.18	1	0.3895	100.35	102.01	
2017	2.89	4				
2018	-1.70					
2019	1.95					
2020	1.40					
Block 5	-4.55					
A-API-1 Particle Size	-7.84	1	1.17	-10.34	-5.35	13.40
B-API-1 Content	-0.5953	1	0.5758	-1.82	0.6321	2.55
C-Total Drying Time	4.26	1	0.7739	2.61	5.91	3.15
D-FBD: LOD	-13.25	1	1.15	-15.69	-10.81	9.40
AB	-19.50	1	2.87	-25.63	-13.37	26.90
AC	-4.22	1	1.07	-6.50	-1.94	3.96
AD	2.30	1	0.8700	0.4428	4.15	4.10
BC	5.45	1	1.06	3.20	7.70	3.60
BD	-18.67	1	2.11	-23.16	-14.17	17.53
CD	1.85	1	1.27	-0.8517	4.56	4.65

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.



Final Equation in Terms of Actual Factors

API-2 Assay before coating	=
-3866.94200	
+15.40048	* API-1 Particle Size
+45.18597	* API-1 Content
-5.72045	* Total Drying Time
+1048.10419	* FBD: LOD
-0.174593	* API-1 Particle Size * API-1 Content
-0.000950	* API-1 Particle Size * Total Drying Time
+0.016897	* API-1 Particle Size * FBD: LOD
+0.066135	* API-1 Content * Total Drying Time
-12.01921	* API-1 Content * FBD: LOD
+0.029893	* Total Drying Time * FBD: LOD



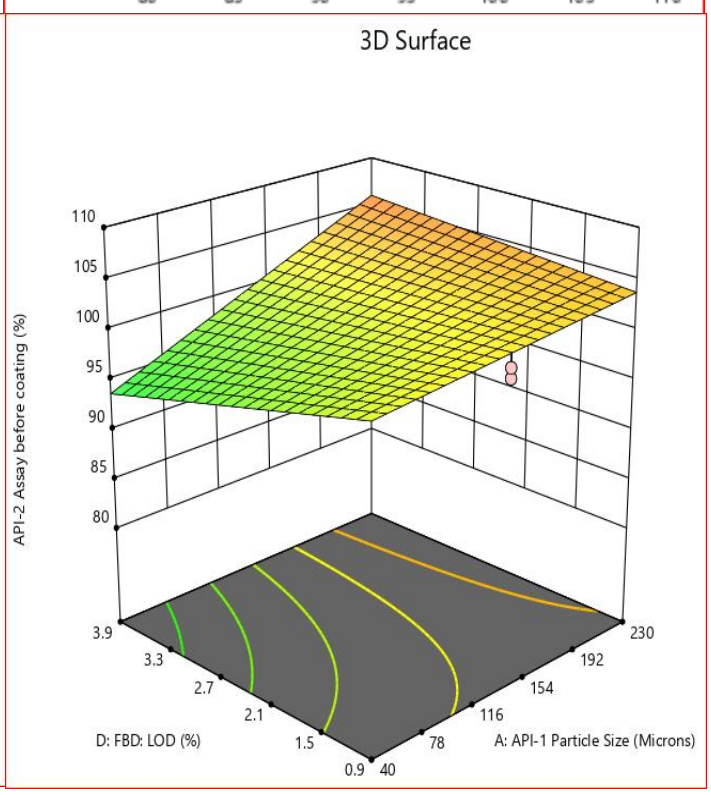
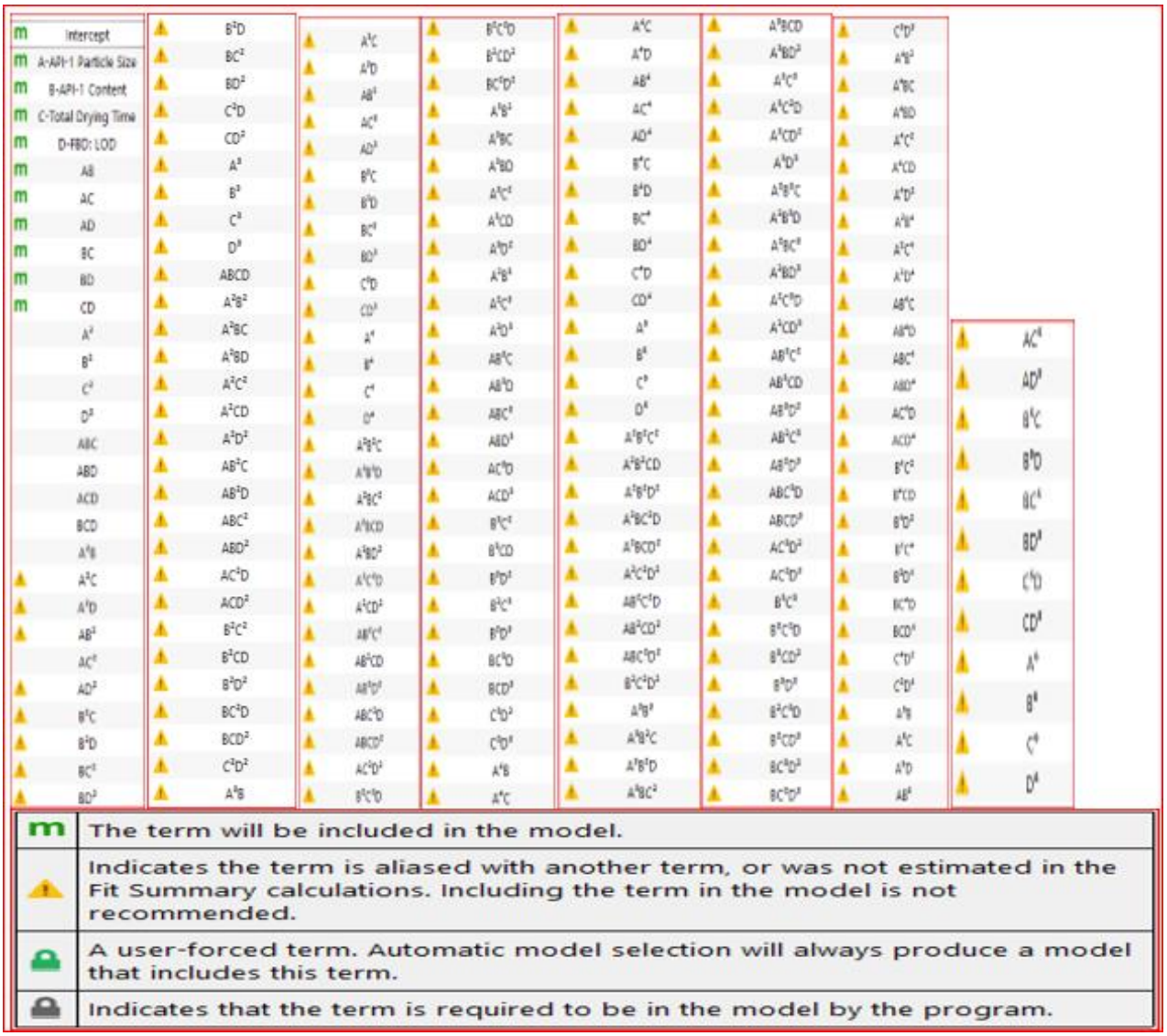


Figure 16: granulation to after compression API-2 Assay

The sample size is 27 actual production batches. Four factors API 1 particle size, API 1 content, total drying time and % LOD were used to study their effect on the response API 2 % Assay with two levels for each factor. The factor interaction was given by Design Expert 13, as depicted in Table 16.

Table 16: Factors interaction for API 2 % Assay response.



Design expert 13 gives a fit summary for the suggested model based on the p-value, lack of fit, adjusted R^2 and predicted R^2, as shown in Table 17.

Table 17: API 2 % Assay response Model Fit Summary.

Fit Summary

Response 1: API-2 Assay before coating

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0028	0.0283	0.4815	-0.6407	
2FI	**< 0.0001**	**0.5894**	**0.9829**	**0.8339**	**Suggested**
Quadratic	0.9253	0.4491	0.9768	-3.5513	
Cubic	0.4491		0.9833		**Aliased**

R^2 estimates the proportion of variation in the response API 2 % Assay that can be attributed to the model rather than to random error. An R^2 closer to 1 indicates a better fit to the data than does an R^2 closer to 0. An R^2 near 0 indicates that the model is not a much better predictor of API 2 % Assay than is API 2 % Assay mean. Initially, Design Expert 13 suggested a Quadratic model resulting in R^2 = 0.9669, Adjusted R^2 = 0.9449 and Predicted R^2 = 0.3181. Then, I have removed outliers while Design Expert 13 replaced the Quadratic model with a new suggested two factor interaction (2FI) model. This new model as shown in Figure 16 shows that R^2 is 0.9907, it indicates that 99% of the variation in the response API 2 % Assay are explained by particle size of API 1, content of API 1, total drying time and % LOD factors, and the remaining 1% of the variability is still unaccounted for. Since R^2 is 0.99, it indicates a better fit for the 2FI model rather than the Quadratic model. However, R^2 alone does not tell us if the selected 2FI model is a good fit. R^2 Adjusted is employed which accounts for the number of factors in order to compare models

and select the best fit. Table 17 above shows that 2FI model was suggested by Design Expert 13 as the better fit model. Figure 16 shows that R^2 Adjusted value is 0.9829, which suggests a good model fit with high predictive power. On the other hand, R^2 predicted gives an idea of how good our model is and how useful in predicting future API 2 % Assay results. Figure 16 shows that the predicted R^2 is 0.834 indicating that the 2FI model has an 83% prediction power for the response API 2 %Assay using the factors API 1 particle size, API 1 content, total drying time and % LOD. As a result of evaluating R^2, adjusted R^2 and predicted R^2, we conclude that the 2FI model selected to model the four factors API 1 particle size, API 1 content, total drying time and % LOD for the response API 2 % Assay is a good fit and can be used to predict future API 2 % Assay before coating for JR tablet product. From the ANOVA results, the p-value for API 1 particle size, Drying Time and LOD% is <0.05 which indicates that these factors are statistically significant affecting the Response API 2 Assay before coating. The Contour plot and the 3D Surface Design clearly shows that as the Drying Time is higher meaning that the LOD% is lower say below 1.5% LOD, API 2 Assay distribution efficiency or Assay is higher while keeping API 1 particle size within a range of (40 to 200) Microns instead of <250 Microns. Scientifically, the results in Figure 16 from Design Expert 13 clearly shows that as we dry the granulated material longer in the FBD, the %LOD (Moisture in the dried granulated materials) becomes lower which means less moisture between the granules giving more chances that API 2 particles are efficiently and homogenously distributed after the final mixing and compression stages while ensuring that the dried granulated materials is geometrically mixed with MCC and an equivalent amount of the dried granulated materials before the final mixing stage. when the particle size of API 1 goes down, we use less Alcohol in the

granulation solution, hence, we need less drying time to evaporate the excess solvent in the Fluid Bed dryer. Therefore, the more we dry the granulated material, the less the % LOD and the more that API 2 in the mixing stage is able to be distributed, hence, contributing to the elimination of the possibility of API 2 Assay % failure. It is expected that as the LOD% is higher meaning that the moisture entrapped between the granules is higher, the distribution of API 2 in the final mixture would be most likely lower, and moisture may lead to API 2 degradation overtime. During the thirteen batches trial, the LOD% was changed from a specification limit of 2% to 3% to a specification limit of <1.5% according to the Multi Surface Design Space. These results will help resolve API 2 Assay failure which we have been experiencing for the past several years. As a result of the three Multi Surface Design Spaces, QRM and scientific background and experiences; the control strategy of JR manufacturing was established as mentioned in the control phase of the DMAIC in section 4.2.5.

4.2.4 DMAIC-improve phase

Additional thirteen (13) production batches of JR tablets, each batch size is 600,000 tablets, were produced. In the first two batches, the existing MPR was used to validate the existing system and have an infield manufacturing experience of how operators execute the MPR for JR. After that, gradual and single changes to the MPR based on the Design Spaces and QRM was completed to identify wastes related to delays and unnecessary implemented steps in the JR tablet manufacturing. As a result, the MPR was modified, as depicted in Figure 17, reflecting all of the improvement changes which led to the reduction of the manufacturing cycle time.

These improvement changes to JR tablet represented by the MPR can be summarized as follows:

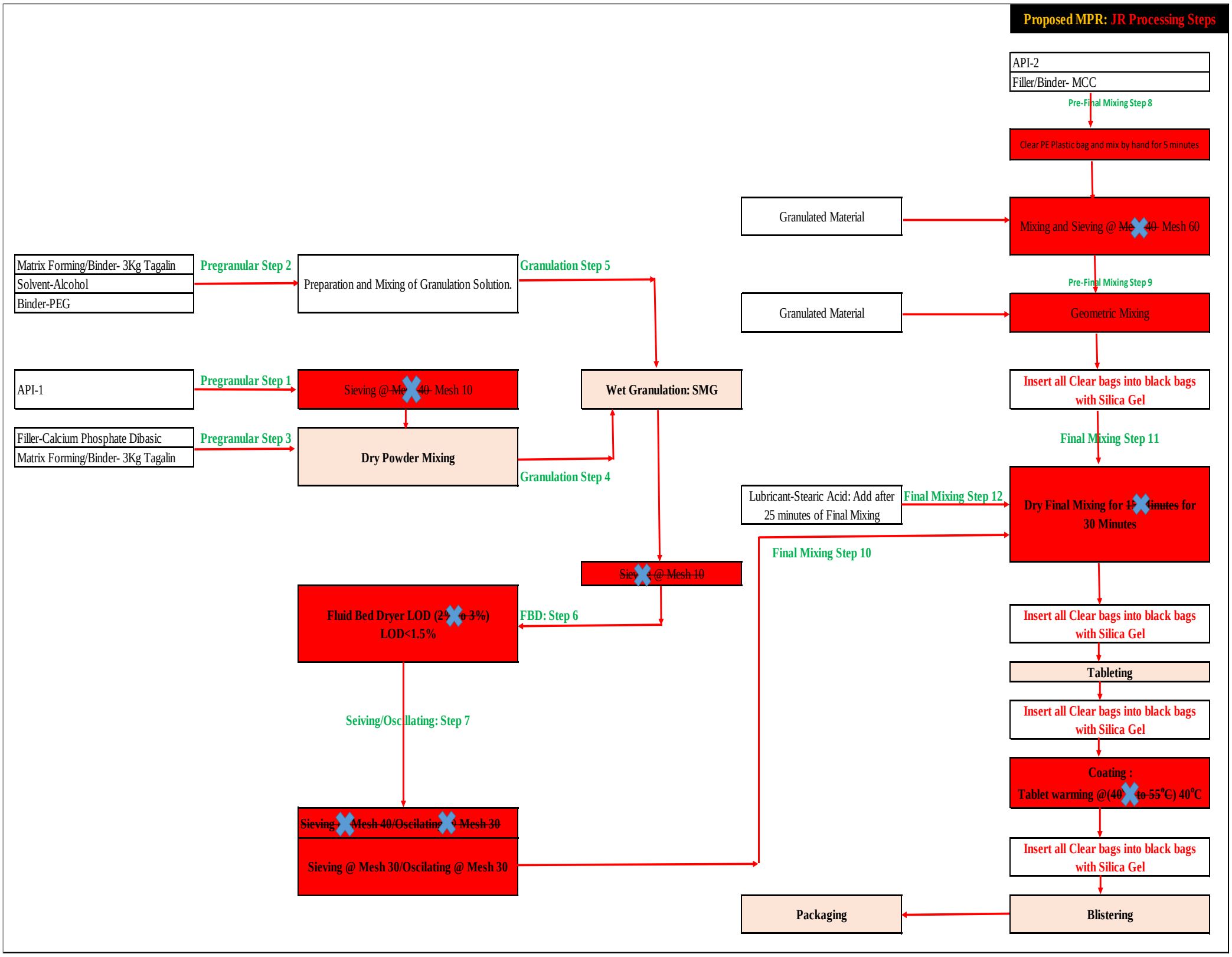


Figure 17: Manufacturing procedure record for JR tablet after improvements.

- **API 1 Sieving:**

API 1 Sieving is the first step of the MPR. API 1 particle size ranges from 40 Micron to a maximum of 230 Micron for some lots. The data were taken for years 2017, 2018, and 2019. As indicated in the MPR, the operator uses 60 mesh screen which can pass particles 250 Micron and less. This sieving operation takes about 2 hours to complete. As a result of this evaluation, this step of the process was found to be not necessary which reduces the cycle time by 2 hours. Therefore, I had the operator use 10 mesh screen which took 15 minutes. The purpose

of sieving is to break up clumps and to ensure that all particles pass is less than 250 Micron where in fact all particles are less than 250 Micron meters. In addition, API 1 is dry mixed in the Super Mixer which operates at 1720 RPM milling speed and 3440 RPM chopper speed before granulation. Therefore, sieving is not necessary if lumps of API 1 are found inside the raw material bags and that mesh 10 can help break any lumps.

- **Granulation Step:**

Granulation time should be 30 minutes based on using 100% of Alcohol to prepare the granulation solution while taking into consideration API-1 particles size. The lower the particle size, the less Alcohol is required, as indicated in Table 18.

Table 18: Particle size versus alcohol usage.

API 1 Particle Size (Micrometer)	Alcohol Usage (Liters)
40-100	10-14
100-150	14-18
150-250	18-20

Table 18 was validated during this research study since the Alcohol % quantity was found to be very critical during the granulation step. API 1 at smaller particle size contains more moisture trapped between the particles to keep them lumped together than larger particle size, hence, adding more Alcohol to smaller API 1 particles builds no granules resulting in failure of the granulation step if the operator was not careful. Table 18 gives a consistent direction for the operator to follow during granulation.

- **Sieving of wet granulated material after granulation:**

The MPR dictates to sieve the wet granulated material at mesh 10 which takes about 30 minutes reducing the cycle time by 30 minutes. This operation was found to be not

necessary since this fluffy wet granulated material is initially suspended and mixed in the Fluid Bed Dryer (FBD) using cold air. Also, this material is processed through an Oscillator or milling machine after drying.

- **Fluid Bed Dryer (FBD) as a drying step:**

The FBD is used to dry the granulated wet material from the granulation step. The existing Loss on Drying LOD as a drying measure is set at LOD of 2% to 3% which is an indication for the operator that the material is dried. However, keeping more moisture in the dried granulated material means that the distribution of API 2 after mixing will most likely be less since the voids between the particles of the granulated material is occupied by moisture. Also, the presence of moisture in the dried granulated materials can lead to API-2 degradation. A Design Space for the dried granulated material and after final mixing step and compression stages was established to understand the effect of higher amount of moisture on API 2 distribution or % Assay after the final mixing and tablet compression stages. The results of the Design Space indicated that there is a direct relationship. Based on the actual data given to Design Expert 13, the Design Space Figure 16 indicated that the LOD should be controlled to <1.5% instead of the existing 2% to 3% LOD. As a result, the distribution of API-2 during the final mixing was improved and the rate of API 2 degradation was highly reduced.

- **Sieving of Dried granulated material after drying:**

The MPR for JR indicates that the dried granulated material to be sieved using 40 mesh and any remaining material above mesh 40 to be oscillated using 30 mesh. This operation almost takes 2 days on average for each JR batch. This processing step was changed to sieving the dried granulated material at mesh 30 and oscillating or milling at mesh 30 which

reduced the cycle time of JR tablets by almost 1 day on average. Also, this helped improve the flow-ability of the overall material after the final mixing and during the tableting or compression step.

- **Final Mixing:**

The existing process as found was that the dried granulated material after oscillating or milling is transferred to the Bin mixer for Final Mixing step. The API-2 concentration in the batch is only 0.22% w/w. The effective distribution of this very small quantity of API 2 is a challenge for JR manufacturing. The existing process is that API 2 is sieved using mesh 40, then MCC component is sieved using the same mesh 40 and both materials are added to the Bin mixer. After 10 minutes of mixing, lubricant (Stearic Acid) is added to the Bin mixer and mixed for another 5 minutes. A sample is collected by the QC inspector for analysis. The critical material attribute in this step is the Assay of API 2 after the Final Mixing step. The acceptable range for API 2 Assay is between 95% to 110%. Frequently, API 2 after the Final Mixing step fails the Assay test and the reason was not known. Therefore, operation kept on remixing again and again until the Assay of API 2 passes the test and the Assay is between 95% to 110% acceptable range. Addition of more API 2 practice is against the label claim for JR tablet as registered and remixing is time-consuming which affects JR manufacturing cycle time. After the manufacture of the first two batches, it was determined that the reason for API 2 Assay failure was that since API 2 is sieved at mesh 40, lumps of API 2 sticks together which affected the distribution effectiveness of API 2 in the Final mixture. Therefore, a pre-mixing step was added prior to the Final Mixing step. In the pre-mixing step, MCC is added to the API 2 Polyethylene bag and mixed by hand for 5 minutes. MCC in this case is used as a carrier. Then, MCC

/API 2 are sieved using 60 mesh which is much smaller than mesh 40 to prevent lumping of API 2. Three kilograms of the oscillated dried granulated material are sieved using the same mesh 60 to remove any remaining API 2 material on the screen of the sieve. After ensuring that the mesh 60 screen does not contain remains of the yellow-coloured API 2, the resulting material is geometrically-mixed twice three kilograms each time with the oscillated dried granulated material. These improvements to the Final Mixing step helped eliminate the lumps of API 2, effectively distribute API 2 in the Final Mixing step and most importantly the API 2 Assay test results were within the acceptance specification limits of 95% to 110%. As a pre-caution, mixing time was changed from 15 minutes to at least 25 minutes giving more time for homogenous mixing of API 2 in the final mixture since its quantity in the batch is very small and no baffles are present in the bin mixer.

- **Coating:**

In addition to the above improvements, the coating stage was evaluated. Initially, the coating stage was not part of this research study. After 12 batches of the 13 batches, the Quality Control lab (QC) indicated that API 2 Assay was out of control in all batches after coating. Therefore, the coating stage was included as part of this research study and the last batch was supervised. The API 2 Assay analysed for this last batch by the QC lab before coating was 109.2% while after coating it was 86.3%. This batch was supervised to understand the coating process and to try to uncover possible issues of why API 2 Assay drops after coating. Several issues were concluded from the coating step as follows:

1) The MPR indicates to heat the tablets in the coating machine by introducing hot compressed air at 40^{o}C to 55^{o}C. However, the operator set the inlet hot air temperature at 58^{o}C while the control panel read as high as 63^{o}C.

2) Initially when heating of tablets started, the vacuum pressure during the heating process was fluctuating between 200 to 300 Pascal, then the operator dropped the vacuum pressure to about 80 Pascal. This decrease in vacuum pressure led to raising the tablets temperature from 36^{o}C to as high as 48^{o}C. At this elevated temperature, API 2 decomposes and degrades.
3) After 4 hours of coating, the coating solution was finished indicating the end of the coating process. The operator switched the coating machine in a jog mode, introduced cold compressed air and increased the vacuum pressure to 400 Pascal and opened the coating machine door. This practice is considered unacceptable since rapid cooling of tablets or quenching uncovered the reason of found fractured tablets after the coating of some JR tablets which eventually are considered as defects.

While supervising the coating process, as shown in Appendix 16, the MPR dictates to warm the tablets before coating using hot compressed air at temperatures between 40^{o}C to 55^{o}C. The setup inlet air temperature was placed at 58^{o}C, not following the 40^{o}C to 55^{o}C specification range, while the coating machine PLC control panel indicated or read a temperature as high as 63^{o}C indicating a 5^{o}C increase from the set up incoming air temperature which is considered as a critical process parameter. The tablets inside the coating machine read a temperature, bed temperature, of as high as 48^{o}C using a hand temperature indicator. This led to further investigation and complete a three variables one level DOE to understand the effect of humidity, light and temperature on API 2 Assay. However, we were at the end of this campaign of the 13 JR batches and only one batch was left without coating. A sample was collected after compression and before coating from

this batch and completed a DOE in the QC laboratory, as shown in Table 19 in order to understand the effect of humidity, temperature and light on API 2.

Table 19: Coating stage DOE results.

Tablets After Compression from the last Batch of the Thirteen Batches					
RunOrder	Exposed to outside Humidity	Light for (3 days)	Temperature °C (Direct Heat for 1 hour)	API-2 Assay %	Comments
Initial Sample (Before Heating)	NO	NO	25	109.2	Sample before heating tablets @ room Temperature
Sample 1	NO	NO	40	98.9	First sample heated @ 40C for 1 hour
Sample 2	Yes	Yes	40	98.6	2nd sample heated @ 40C for 1 hour
Sample 3	Yes	Yes	60	93.3	3rd sample heated @ 60C for 1 hour
Sample 4	NO	NO	60	86.3	Fourth sample heated @ 60C for 1 hour
Pure API-2 Material used in the Thirteen Batches Trial					
RunOrder	Exposed to outside Humidity	Light for (3 days)	Temperature °C (Direct Heat for 1 hour)	API-2 Assay %	Comments
Initial Sample	NO	NO	25	101.1	Sample before heating pure API 2 @ room Temperature
Sample 1	Yes	Yes	40	96.6	First sample heated @ 40C for 1 hour
Sample 2	NO	NO	40	96	2nd sample heated @ 40C for 1 hour
Sample 3	Yes	Yes	60	97	3rd sample heated @ 60C for 1 hour
Sample 4	NO	NO	60	95	Fourth sample heated @ 60C for 1 hour
Note: Water content is the same as when we analyzed the raw material at receiving to be 8.5%					

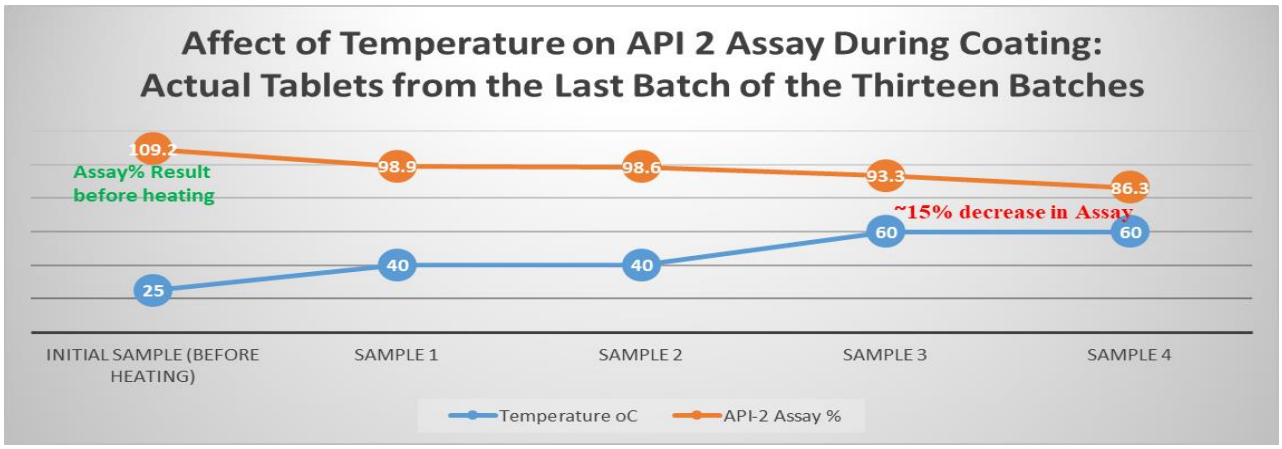


Figure 18: Effect of temperature on JR tablet.

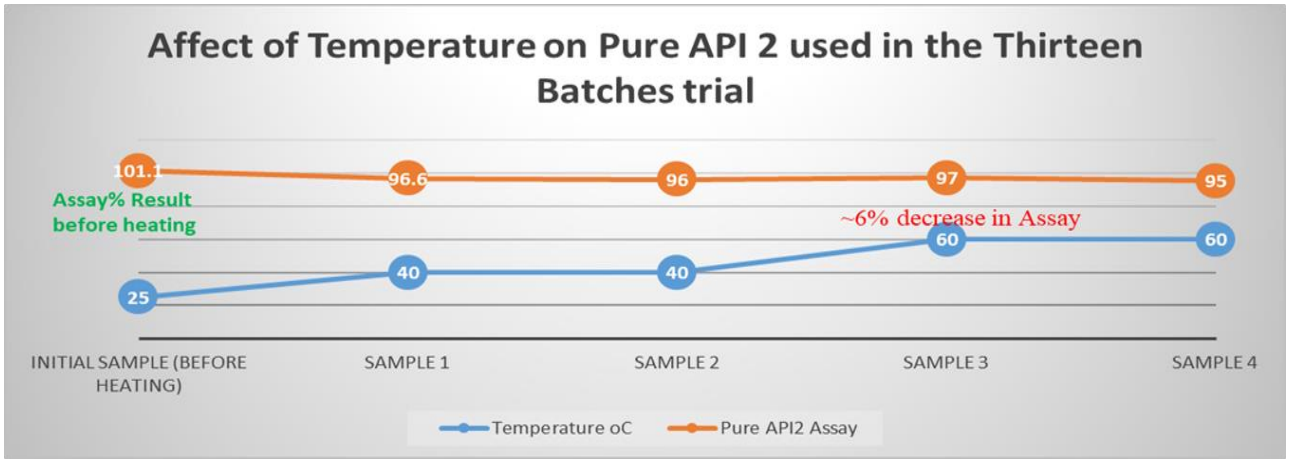


Figure 19: Effect of temperature on pure API 2.

The DOE study was expanded and a sample of tablets and pure API 2 were collected. These samples were initially placed on a table under room conditions for 3 days with the office light kept on in August 2020. Then after three days, some of the tablets and some of the API 2 samples were exposed to heat at 40^{o}C and 60^{o}C in a heating oven in the lab as indicated in Table 19, Figure 18 and Figure 19. The factor B in Design expert 13 "light" was initially evaluated using attributable data with Yes or No light exposure to tablets during the DOE. However, if "No" light was used, zero was given to Design Expert 13 and if light was used, then 3 days were given. The results of this DOE shows that API 2 Assay dropped to almost 6% at 40^{o}C and dropped by almost 15% on average at 60^{o}C. A multi surface design was built using Design Expert 13 for the coating stage for the last batch of the thirteen batches of JR tablet, results are shown in Figure 20.

ANOVA for Reduced Quadratic model

Response 1: API-2 Assay %

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	332.51	4	83.13	309.97	0.0426	significant
A-Temperature oC (Direct Heat for 1 hour)	299.29	1	299.29	1116.02	0.0191	
B-Light Exposure	1.82	1	1.82	6.77	0.2336	
AB	32.06	1	32.06	119.53	0.0581	
A^2	1.16	1	1.16	4.32	0.2854	
Residual	0.2682	1	0.2682			
Cor Total	332.78	5				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 309.97 implies the model is significant. There is only a 4.26% chance that an F-value this large could occur due to noise.

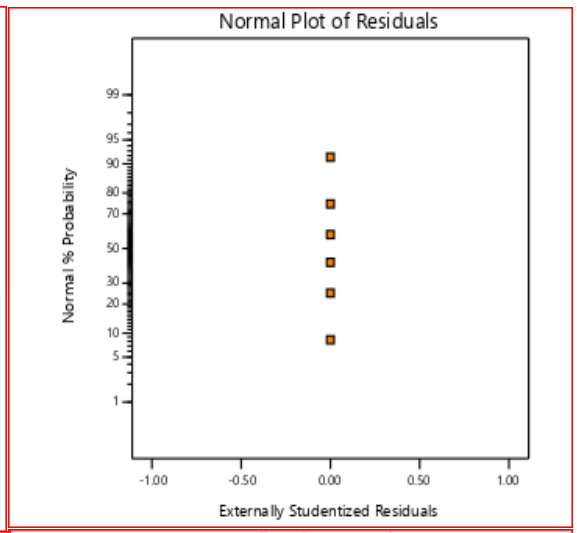
P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.5179	**R^2**	0.9992
Mean	98.55	**Adjusted R^2**	0.9960
C.V. %	0.5255	**Predicted R^2**	0.9537
		Adeq Precision	48.5314

The **Predicted R^2** of 0.9537 is in reasonable agreement with the **Adjusted R^2** of 0.9960; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 48.531 indicates an adequate signal. This model can be used to navigate the design space.



Final Equation in Terms of Actual Factors

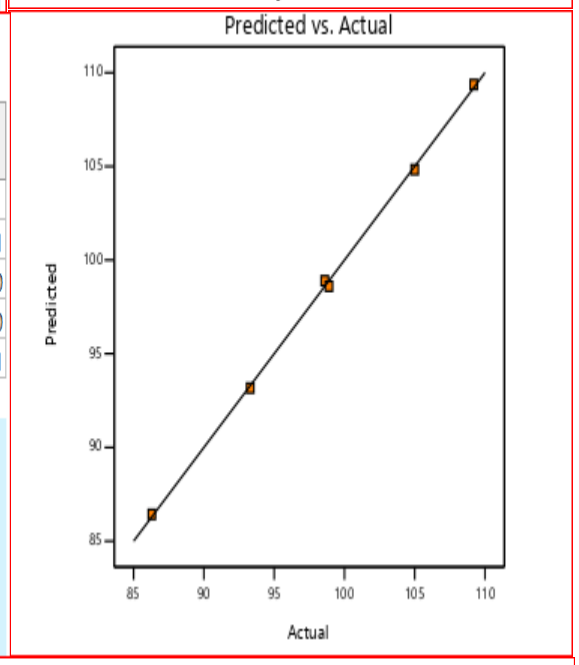
API-2 Assay %	=
+130.43639	
-0.920621	* Temperature oC (Direct Heat for 1 hour)
-4.20045	* Light Exposure
+0.107477	* Temperature oC (Direct Heat for 1 hour) * Light Exposure
+0.003119	* Temperature oC (Direct Heat for 1 hour)^2

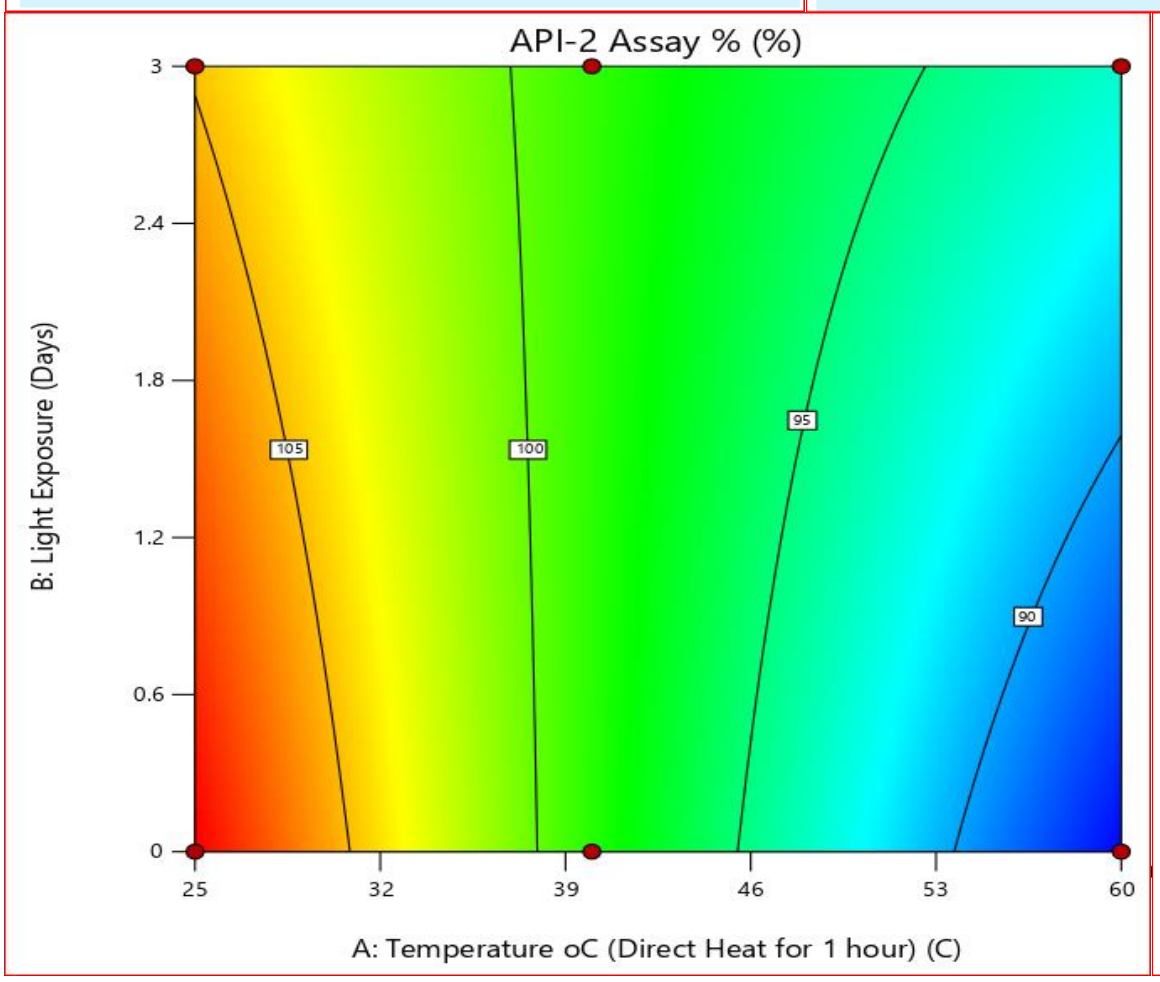
The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	97.49	1	0.3757	92.72	102.27	
A-Temperature oC (Direct Heat for 1 hour)	-8.65	1	0.2589	-11.94	-5.36	1.01
B-Light Exposure	0.5510	1	0.2118	-2.14	3.24	1.00
AB	2.82	1	0.2581	-0.4576	6.10	1.00
A^2	0.9552	1	0.4594	-4.88	6.79	1.01

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.





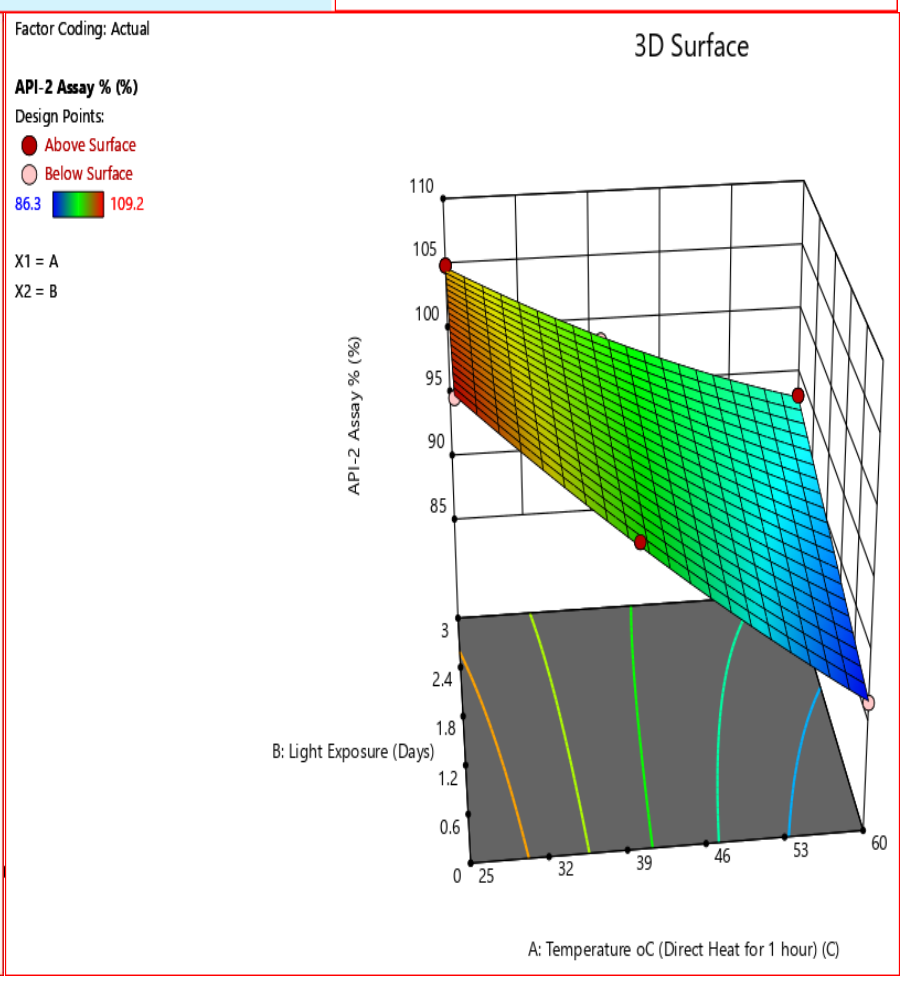


Figure 20: Surface Design for API 2 % Assay response after coating

The sample size is 6 actual production batches. Two factors inlet air temperature and Light were used for the response API 2 % Assay reduction with two levels for each factor. The factor interaction was given by Design Expert 13, as depicted in Table 20.

Table 20: Factor interaction for the response API 2 % Assay after coating

m	Intercept
m	A-Temperatur...t for 1 hour)
m	B-Light Exposure
m	AB
m	A^2
⚠	B^2
	A^2B
⚠	AB^2
⚠	A^3
⚠	B^3
⚠	A^2B^2
⚠	A^3B
⚠	AB^3
⚠	A^4
⚠	B^4
⚠	A^3B^2
⚠	A^2B^3
⚠	A^4B
⚠	AB^4
⚠	A^5
⚠	B^5
⚠	A^3B^3
⚠	A^4B^2
⚠	A^2B^4
⚠	A^5B
⚠	AB^5
⚠	A^6
⚠	B^6

m	The term will be included in the model.
⚠	Indicates the term is aliased with another term, or was not estimated in the Fit Summary calculations. Including the term in the model is not recommended.
🔓	A user-forced term. Automatic model selection will always produce a model that includes this term.
🔒	Indicates that the term is required to be in the model by the program.

Design expert 13 gives a fit summary for the recommended model based on the p-value, lack of fit, adjusted R^2 and predicted R^2, as shown in Table 21.

Table 21: API 2 % Assay response Model Fit Summary

Fit Summary

Response 1: API-2 Assay %

	Source	Model p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
	Design Model	**0.0426**		**0.9960**	**0.9537**	**Recommended**
	Linear	0.0319		0.8323	0.4207	
	2FI	**0.0216**		**0.9893**	**0.9384**	**Suggested**
	Quadratic	0.2854		0.9960	0.9537	**Aliased**

R^2 estimates the proportion of variation in the response API 2 % Assay after coating that can be attributed to the model rather than to random error. An R^2 closer to 1 indicates a better fit to the data than does an R^2 closer to 0. An R^2 near 0 indicates that the model is not a much better predictor of the API 2 % Assay than is API 2 % Assay mean. Initially, Design Expert 13 suggested using 2FI model resulting in R^2 = 0.9994, Adjusted R^2 = 0.9978 and Predicted R^2 = N/A. Then, I have added one more needed data point which is the effect of light at room temperature (25^{o}C) as a result Design Expert 13 replaced the 2FI model with a recommended reduced Quadratic model. This new model as shown in Figure 20 shows that R^2 is 0.9992, it indicates that 99.9% of the variation in the response API 2 % Assay are explained by inlet air temperature and light factors, and the remaining 0.1% of the variability is still unaccounted for. Since R^2 is 0.999, it indicates a better fit for the recommended reduced Quadratic model rather than the 2FI model. However, R^2 alone does not tell us if the recommended reduced Quadratic model is a good fit. R^2 Adjusted is employed which accounts for the number of factors in order to compare models and select the best fit. Table 21 above shows that the reduced Quadratic model is recommended by Design Expert 13 as the better fit model. Figure 20 shows that R^2 Adjusted value is 0.9960, which suggests a good model fit with high predictive power. On the other hand, R^2

predicted gives an idea of how good our model is and how useful in predicting future API 2 % Assay results. Figure 20 shows that the predicted R^2 is 0.9537 indicating that the reduced Quadratic model has an 95% prediction power for the response API 2 %Assay using the factors inlet air temperature and light. As a result of evaluating R^2, adjusted R^2 and predicted R^2, we conclude that the reduced Quadratic model selected to model the two factors inlet air temperature and light for the response API 2 % Assay after coating is a good fit and can be used to predict future API 2 % Assay after coating for JR tablet product. Figure 20 above shows that API 2 % Assay of JR tablets is highly affected by temperature. The P-value for the factor temperature is <0.05 indicating that it is a statistically significant factor while light in this case study is not statistically significant factor affecting API 2 % Assay. There is a fine-line here where we can't just preheat the tablets at room temperature which is 25^{o}C to prepare the tablets for coating to obtain the maximum API 2 %Assay. As a result, the coating stage in the MPR of JR tablets was modified and a new set point for compressed air inlet temperature was changed from (40^{o}C-55^{o}C) to (40^{o}C) while ensuring that the coating machine bed or tablets temperature to be kept between 35^{o}C to 38^{o}C before starting the spray coating process. My DOE exposed tablets for three days in my office to outside humidity and office light over the weekend. As a precaution, we will keep what we have in our MPR to have all in process material inside black plastic bags with silica gel for light and humidity protection. All improvements mentioned above have been validated, except the coating stage because one last JR tablet batch was supervised during the coating stage. Coating was completed for the batch before the last one while the DOE was in progress and operation did not want to wait the results of the DOE since the QC lab took almost two weeks to complete the required analysis for the DOE samples. In order to

validate the effect of heat on API 2 degradation, four batches of JR tablet were manufactured taking into consideration all mentioned improvements. However, because of COVID 19, materials were delayed and the coating stage was validated at the end of July 2021, as shown in Appendix 17. As a result of the improvement changes, the Value Stream Map was re-established for the case after making changes in the process. The VSM after improvement and its calculations, depicted in Appendix 18, shows that the manufacturing cycle time was reduced from 16.74 days on average before improvement to 9.11 days on average after improvements. The coating step normally takes on average five hours to complete by following the existing MPR. So, the VSM for the coating step for the before and after case did not change yet. However, using the newly-changed MPR, the coating step cycle time is expected to increase from five hours to seven hours since the heating process will be done using a set point of 40ºC of the inlet air instead of as high as 63ºC. This lower temperature set point of the inlet air will take longer to heat the tablets than the 63ºC, but will ensure that API 2 Assay is within the required specification limit of 95% to 110%.

4.2.5 DMAIC-control phase

During the control phase, several documents were updated in order to provide consistent instructions to operators so that JR tablets are produced each time and every time with the same required quality as a finished pharmaceutical drug product with the required characteristics including safety, efficacy, quality, purity, identity and strength. The control strategy for JR tablet process performance and quality was developed. All of the process parameters, material attributes, CQAs and control methods were specified and tabulated.

The modifications made to the MPR and operating procedures including operator training, materials attributes and process parameters specification limits are as follows:

- **Manufacturing Procedure Record (MPR) including operating ranges:**

The existing MPR or step by step procedure to produce JR tablets was modified to include all improvement changes made during this research study. The new MPR, shown in Appendix 19, reflects best practices, optimum process parameters and control strategy in order to consistently produce JR tablets with the required quality attributes. The MPR includes operating ranges, some initially obtained from the Design Spaces established, which are critical for the manufacturing of JR tablets ensuring stability and validity in obtaining a finished JR drug product with the required characteristics such as safety, quality, efficacy, purity, identity and strength. This step-by-step procedure is clear and detailed enough to prevent deviations when operators are changed. Also, if this MPR is followed as written, it is most likely to prevent fluctuation in cycle time. The calculated theoretical cycle time is 2.54 days as seen in the MPR while the actual average cycle time after improvement is 9.11 days which includes lead time between manufacturing stages or steps. Finally, the QC analysis and testing at every critical stage will not be necessary but will be required after the coating stage which still needs to be validated. As mentioned in the Guidance for Industry Process Validation in the General Principles and Practices (FDA, 2011), continued process verification (CPV) is defined as providing assurance that during routine commercial production the process remains in a state of control**.** The entire process of JR product has been validated with excellent results up to the compression stage. However, since the coating stage was added at the end of the thirteen-batches trial; validation of changes proposed to the coating stage has not been validated yet.

- **Operating Procedures:**

The operating procedures for all machines and equipment were modified to provide operation consistency during machines startups, shutdown and emergency. The critical process parameters were identified and listed in the MPR and these parameters were verified during the 13 batches trial. The maximum, minimum and optimum operating conditions of machines and equipment were also verified with operating limits given in the MPR. As a result, Stable Operation of all unit operations including granulation, drying, mixing, compression and coating was achieved to provide continuous operation of JR tablets according to a manufacturing plan. This new manufacturing plan covers 5 batches campaign instead of 13 batches campaign since production fully cleans the manufacturing rooms after 5 batches as a result of cleaning validation. The 5 batches campaign will take one week or 5 working days to complete until the coating stage with cleaning. Therefore, as a result of this research study, it is not recommended to start the granulation of other batches and have these batches set in the Work in Process (WIP store) 5 days waiting for further processing which increases the cycle time of these batches.

- **Control Strategy:**

As defined in ICH Q10, “a control strategy is a planned set of controls derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control” (ICH, 2008). In order to effectively internally control the control strategy, the MPR, Operating Ranges within the MPR based on the Design Spaces and

operating procedures of machines and equipment were modified. In addition to the control strategy, good manufacturing practices of operators, machines and premises used during all manufacturing steps can be of help to provide consistency for future performance monitoring and implementation of the control strategy during the execution of JR batches. What is required according to Thomson *et al.* (2014) have summarized ICH Q11 control strategy in the general development of drug substance as a series of bullet points:

- Controls on material attributes (including raw materials, starting materials, reagents and primary packaging for drug substance).
- Controls implicit in the design of the manufacturing process (e.g., order of addition of reagents).
- IPCs, including in process tests and process parameters.
- Controls on the drug substance (e.g., release testing).

In this research study, the control strategy will include modifications made in the MPR, IPC operating ranges specification limits and operating procedures; and end product testing while tightly constrain material and process attributes by continuous monitoring by the operators and QAI. The control strategy for JR tablets was established based on the results of the Design Expert 13 software and risk assessments. The selected few factors of CMAs and CPP with their effect on the selected few response CQAs are tabulated in Table 22.

Table 22: JR tablet Control Strategy

JR Tablet Overall Control strategy										
Criteria		**Existing Control**			**Design Space Proposed Control**			**Proposed Operating Ranges**		
Criticals	**Type**	**LSL**	**Target**	**USL**	**LSL**	**Target**	**USL**	**LSL**	**Target**	**USL**
API 1 Particle Size	CMA	N/A	N/A	250 Microns	40	116	230	40	120	220
API 1 Content	CMA	86%	N/A	90%	87%	88%	90%	87%	88%	90%
Granulation Time	CPP	10 min	N/A	22 min	15	30	40	25	30	35
LOD%	CPP	2%	N/A	3%	N/A	N/A	1.5%	N/A	N/A	1.2%
Dry granulated material-Sieving	CPP	Sieve@mesh 40/Mill@mesh30			Sieve@mesh 30/Mill@mesh30			Sieve@mesh 30/Mill@mesh30		
Pre-Final Mixing-Geometric	CPP	N/A	N/A	N/A	Steps provided in new MPR			Steps provided in new MPR		
Final Mixing Time	CPP	10 min	15 min	15 min	25 min	30 min	40	25 min	30 min	35
API 1 Assay-After Final Mixing	CQA	98%	N/A	108%	98%	N/A	108%	99%	N/A	105%
API 2 Assay-After Final Mixing	CQA	95%	N/A	110%	96%	N/A	110%	97%	N/A	110%
API 2 Assay-After Compression	CQA	95%	N/A	110%	95%	N/A	110%	97%	N/A	110%
Dissolution-1st hour	CQA	40%	N/A	60%	40%	N/A	60%	40%	N/A	60%
Dissolution-3rd hour	CQA	75%	N/A	N/A	75%	N/A	N/A	75%	N/A	N/A
Hardness	CQA	4 kgf	N/A	N/A	5 kgf	5.5 kgf	7 kgf	5 kgf	5.5 kgf	6 kgf
API 2 Assay-After Coating	CQA	95%	N/A	110%	96%	N/A	110%	96%	N/A	110%
Inlet Air temperature	CPP	55^{o}C	58^{o}C	63^{o}C	32^{o}C	35^{o}C	40^{o}C	28^{o}C	30^{o}C	35^{o}C
Environment	CPP	Mixing, Tableting and coating with Light			Mixing, Tableting and coating with NO Light			Mixing, Tableting and coating with NO Light		

If we only control the CMAs and CPPs shown in Table 22 leaving all other factors studied constant, unchanged and as practiced, we will be able to manufacture JR tablets without in process testing and only complete the final after coating analysis. The existing control is the LSL and USL of in process and finished product of JR tablet during and after some of the manufacturing stages which were found to be critical. As a result of the Design Spaces and risk assessments, new LSL and USL for the Design Space proposed controls were tabulated in Table 22 indicating that any of the parameters or attributes which comes out of these specification limit will most likely lead to JR tablet product failure. This will require a deviation, an investigation and the PMOH must be informed. Therefore, the NOR defining its LSL and USL were established as a safe limit of operation so that if we come out of the NOR, we will still be in the Design Space specification limits which does not require informing the PMOH since we are still in the registered Design Space specification limits. These specification limits are ranges where the target is not defined in some cases since it will be difficult to achieve. Sometimes, N/A value is given for targets which indicate that as long as we are within the specification limits, we will be able to produce JR tablets consistently with quality and safety characteristics with N/A is not required since it will be difficult to achieve as indicated above. Table 22 can be used in conjunction with Figure 22 by the operators and QAI to control and monitor the manufacturing process of JR tablet. The flow diagram for the control strategy shows what unit operations, attributes and controls required and important to ensure that JR tablet product is consistently produced with the required Quality, Efficacy, Safety, Purity, Identity and Strength Characteristics.

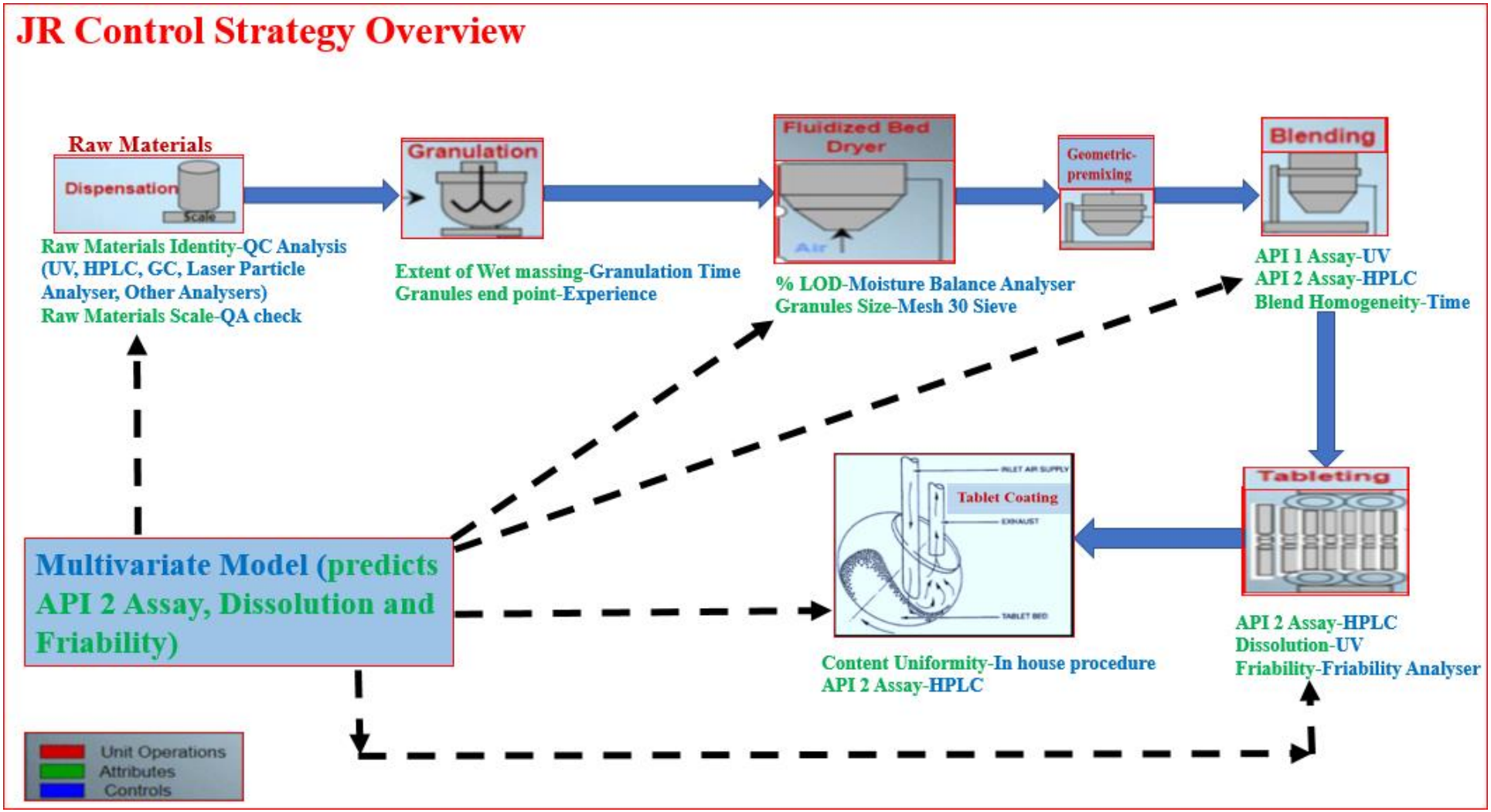


FIGURE 22: JR tablet control strategy overview flow diagram.

4.3 Palestinian Ministry of Health (PMOH) and Jepharm regarding QbD

Palestinian GMP guidelines are mostly emanated from the (FDA) and EMA guidelines as mentioned by PMOH technical experts. However, not all pharmaceutical companies in the world uses QbD to get approval for the marketing authorization. For example, Qi et al. (2015) said that "Pharmaceutical Technology's annual manufacturing and equipment survey found that while 28% of respondents stated they fully use QbD in process development/optimization for solid dosage manufacturing and 56% apply QbD to some extent, 16% said they do not use QbD. Respondents indicated that a lack of knowledge, training and clarification from regulators contributed to their reluctance to use QbD. Cost and time also factored into the decision to not incorporate QbD into their processes". QbD is one of the most scientifically assembled documentation to be submitted to regulators within the Common Technical Document (CTD). With all of the benefits mentioned in this case study about QbD and the hesitation of companies in implementing QbD especially in Palestine, QbD is unknown now which must be investigated and developed to be known and common practice in the coming centuries. As highlighted in the book "Advances in Pharmaceutical Technology" by (Schlindwein & Gibson, 2018, P. 293) a source from the FDA indicated that QbD may not be mandatory now, but it will be in the coming future. Pharmaceutical companies' reluctance in using QbD has to do with their concern of losing their intellectual properties. "One strong reason for not providing the full set of knowledge in a complete QbD submission is fear of loss of intellectual property (IP)" (Schlindwein & Gibson, 2018, P. 321). Most pharmaceutical companies adhere to all documentation requests by the FDA, but QbD is not mandatory. Palestinian regulators are engineers and pharmaceutical doctors who know and understand QbD and design space requirements

according to ICH. Palestinian regulators should encourage QbD similar to the FDA since implementing QbD is in their benefit, also. ICH guidelines were used into my approach referring to ICHQ8 (R2), ICH Q9 and ICH Q10 to establish a design space for the control and manufacturing of an existing JR drug product. Jepharm has accepted the results of the Design Spaces established and their implementation during the thirteen-batch trial campaign. References to ICH, FDA and EMA guidelines were shared with Jepharm upper management. As a result, Jepharm implemented a change control to eliminate the in process testing and only tests JR after compression and coating. Also, Jepharm has accepted the recommendations of this research study. This is a calculated risk which was based on the trials' and the FMEA's results. Keeping all of the guidelines in check, the trials' finished JR required TQPP final results indicated that we were able to manufacture a JR tablet dosage form product with the required quality, efficacy, safety, strength, purity and identity characteristics meeting the acceptance criteria. According to ICH Q8 (R2), the QTTP is a summary of the drug product's quality characteristics which should be achieved to ensure that the required Quality, Safety, Efficacy, Purity, Identity and Strength characteristics of the product is obtained. In this research study, ICHQ8/Q9/Q10 guidelines were followed utilizing QbDvision software to effectively manage the study and implement it according to ICH guidelines. Therefore, the study results can be submitted to the Palestinian MOH for approval. Finally, Jepharm should follow up on the FDA, EMA and or ICH guidelines, regulations and requirements for updates regarding QbD and Design Space since there may be yearly updates. "Recently, the US Food and Drug Administration (FDA) has approved some new drug applications (NDAs) with regulatory flexibility for QbD-based analytical approaches" (Chatterjee, 2013). This FDA approach can be an

encouragement to pharmaceutical companies to use QbD to develop and manufacture their products with advantages of regulatory flexibility allowing for improvements to the product life cycle. Therefore, “Products that have been developed by a QbD approach can follow a continuous process verification approach as an alternative to traditional PV. A hybrid approach using a mixture of the traditional approach and continuous process verification for different production steps can also be used” (Schlindwein & Gibson, 2018, P. 293). Finally, PMOH has been contacted and they have no problems with implementing QbD. PMOH said that as of today, no pharmaceutical company submitted products using QbD. PMOH mentioned that to request an approval for a QbD-based product, ICHQ8R2, ICH Q9 and ICHQ10, similar to FDA, guidelines should be followed. As far as Jepharm is concerned, they have approved the use of QbD. Jepharm is in the process of purchasing QbDvision software to implement QbD for all of their existing and new products.

Chapter Five: Discussion

5.1 Overview

The purpose of this chapter is to discuss the outcome results of this study by comparing the actual results of the thirteen batches actual trial results to the retrospective 2018 and 2019 data. As a result, recommendations have been suggested in order to improve the overall cycle time and the manufacturing efficiency of JR product. Also, this chapter lists the limitations, obstacles and delays experienced and gives a brief comparison between other research studies related to this study. Finally, the chapter lists the benefits of this research study to Jepharm as a company.

5.2 Discussion

This research study covered an existing JR product where PAT technology is not used at this factory. Utilizing prior experience and knowledge, Quality Risk Management, Design of Experiment coupled by using Design Expert 13 software and QbDvision software were used to understand and define the links, relationship and interactions of multiple variables and perform empirical tests to define and map out appropriate and selected Design Space(s) and normal operating ranges for an efficient manufacturing of JR tablet dosage form product to reduce the overall cycle time. The manufacturing Cycle Time of JR product was improved by 45% due to the improvements made as a result of this research study. The results of the QRM and DOE studies utilizing Design Expert 13 indicated that JR manufacturing process is contributing to the excessive high Cycle Time of the JR tablet

product life cycle at the general facility. The life cycle starts from receiving of raw and packaging materials to storing the finished product in the finished product warehouse ready for shipment. The QRM identified unnecessary processing steps, an incomplete homogenization API 2 in the final mixture and an occurrence of degradation of API 2 in the coating stage which all were considered the most significant issues leading to this excessive high manufacturing Cycle Time of JR product. As a result of these manufacturing process issues, operation completes reprocessing of batches after the mixing stage to ensure that API 2 Assay is within the acceptable range of 95% to 110%. Sometimes, this reprocessing takes days to complete including QC lab analysis and QA inspector reviews and approval. API 2 Assay is considered the most critical Quality attribute (CQA) for JR product which is measured after the final mixing, after the compression and after the Coating stages. In order to ensure that this CQA is met, pre-mixing including Geometric mixing was introduced as a new processing step before the Final Mixing stage to ensure API 2 distribution. In addition, a surface design was built for the after mixing and compression stages to understand the reasons for API 2 %Assay frequent failure. The results of the surface design indicated that there is a significant relationship between %LOD and API 2 distribution in the final mixture, hence, also in the tablet after compression. With the addition of geometric mixing, and at smaller API 1 particle size and lower % LOD, API 2 % Assay tends to be within acceptable range of 95% to 110% with no failure which was validated by executing four batches in July 2021. The surface design for friability after the compression stage results came out to be inconclusive since the predicted R^2 was not defined with the results being N/A. George Box, one of the great industrial statisticians of the 20th century, said that all models are wrong, but some

are useful. “The defining characteristic of a *statistical model* is that the noise variables have an important rather than a minor influence on the outputs, and such models have a particular utility for the study of technological and biological systems in which we rarely have the chance to fully understand all of the details” (Schlindwein & Gibson, 2018, P.185). In this study, these nuisance variables or noise variables could be related to other things such as operator errors in measuring friability, errors in using the friability meter and or instrument errors. Friability measurement is also related to % Tagalin coated on API 1 particles. The higher the % of Tagalin coated on API 1 particles during granulation, the higher the bonding force between API 1 particles, hence, the stronger the granule resulting in less dust generation leading to lower % friability. However, after a thorough analysis of the response friability data, it was concluded that most of the friability results are between 0.1% and 0.3% while the limit is <1%. As a result, this will be a future work that should be investigated to define the reasons. The factor hardness for the response dissolution after compression came out to be statistically insignificant with p-value >0.05. Hardness is a mechanical strength of a tablet, how much brittle or fragile a tablet is on impact. For most tableting operations, the tablet machine’s compression force is used to increase or decrease the hardness of a tablet. In general, the higher the hardness, the harder it is to break the tablet, hence, the slower the tablet will dissolve in a human stomach. It was found that for JR tablet, granule bonding is the factor affecting the hardness and not the compression force of the machine. In a wet granulation manufacturing process for Brivanib Alaninate tablets, Badawy and Narang mentioned that “Tablet in which dissolution was also found to be independent of tablet hardness, and the rate limiting step of tablet dissolution is granule disintegration rather than tablet disintegration” (Badawy & Narang, 2018, P. 679).

For JR tablet, granule disintegration strength is based on the % of Tagalin coated on the surface of API 1 particles. The higher the % of Tagalin coated on the surface of API 1 particles, the higher the hardness, hence, the slower the dissolution rate or the slower the tablet will dissolve in a human stomach. As a result of the surface design for the coating stage, temperature does have an effect on API 2 degradation while light and humidity don't. While this DOE did not show an effect of light nor humidity on API 2 degradation or decomposition, a research study "Stability of Folic Acid under several parameters", "Folic Acid was found to be degraded very readily and it is highly sensitive to several environmental factors such as heat, UV light and oxygen." (Gazzali, et al., 2016). However, the coating stage DOE study concluded that API 2 is not affected by light or outside humidity in August 2020 outside environmental conditions. In this research study, JR tablet is a coated tablet so it is possible that the coating thin layer protected API 2 from the outside environment, however, when the tablets were exposed to temperatures above 40^{o}C, this thin coating layer could not protect these tablets from heat. As a result of the DOE, the heating step in the coating stage was modified from heating using an inlet air temperature as high as 63^{o}C to using an inlet air temperature of 40^{o}C. As a result of the coating temperature process parameter changes, the coating step cycle time increased from an average of 5 hours to 7 hours. The overall manufacturing cycle Time is still a lot lower, but this lower temperature set point of 40^{o}C of the inlet air slowly heats the tablets to ensure that API 2 Assay is still within the required specification limit of 95% to 110% while ensuring that the tablets are heated to the required temperature of up to 38^{o}C. On the other hand, while preparing for the thirteen-batches trial and after drawing the Value Stream Mapping for the existing manufacturing process, two bottle necks in the JR manufacturing

process have been identified, one being the Oscillating/Milling stage which took on average of 50 hours to complete and the other is the compression stage which took on average of 38 hours to complete. A recommendation was given to top management to purchase these two machines prior to the thirteen-batches trial. Purchase orders were written and a new Oscillator and a new tablet machine were purchased and are qualified to operate during future JR batches. These two machines were not used during the thirteen-batches trial since they arrived at the end of the trial. They are almost replicate of an existing Oscillator and tablet machines which is why a Design for Six Sigma (DFSS) was not completed during the improve phase of the DMAIC process. The new Oscillator or Milling machine will cut the milling cycle time in half and so as the tablet machine since two machines will operate at the same time with no delays expected. As a result of the above findings and changes, the Manufacturing Procedure Record (MPR) and all other documentations in the batch manufacturing file were modified. The in-process testing was reduced to minimum, as indicated in the new modified MPR and control strategy. “QbD doesn’t essentially mean less analytical testing, rather it means that proper analysis at the right time, and is based on science and risk assessment” (Darkunde, 2020). The CMA, CPP and the CQA of the finished product were all added to the MPR so that they are monitored by the operator, the supervisor, the QC laboratory and the Quality Assurance Inspector (QAI) prior to giving a line clearance to proceed to the next manufacturing stage. The operator, the supervisor and the QAI signatures must be completed for each completed manufacturing stage before going to the next manufacturing stage. These signatures indicate that the completed manufacturing stage’s material attributes have been met and are within the acceptable ranges as indicated in the control strategy. “The output of QbD

development takes the form of a process and product quality control strategy which ensures that the final product consistently meets pre-established acceptance criteria for the critical quality attributes (CQAs)" (Yu, 2008; Yu et al., 2014). The control strategy for JR manufacturing was developed ensuring that the final finished product is consistently produced with the required CQAs appropriate to ensure that the TQPPs are met, hence, achieving the TPPs of the final product. "A well-developed control strategy will reduce risk but does not change the criticality of attributes. It plays a key role in ensuring that the CQAs are met, and hence that the QTTP is realized" (ICH, 2011). ICH emphasizes on continuously improving the control strategy during the lifecycle of the product since more knowledge and data is obtained and gained which can be analysed through trend analysis studies to modify and improve the manufacturing process. The new changes as a result of this study were also reflected on the operating procedures. Operators, the supervisor, the Quality Control Inspector and the QAI were all trained on the new changes and their training records were documented.

5.3 Thesis limitations

1. This research study covered the manufacturing stages of JR tablet including raw materials preparations such as sieving operations, granulation, drying, intermediate material sieving, final fixing, compression or tableting and coating stages.
2. The thirteen batches trial were supervised by the researcher, but time management of batches was supervised by the tablet section supervisor. This was to ensure that all intermediate materials stay within the Hold Time criteria covered by an approved procedure.

3. Final decisions during the trials were made by the tablet section supervisor and the production manager while I was given limited authority.
4. During the DOE study, Quality Control Lab could not complete all of the requested analysis, so only eight analyses were completed while the requested was 16 analyses. So, I had to remove moisture or humidity factor effect on API 2 degradation from the DOE study.
5. The new Oscillator or milling equipment which is a replicate of the existing equipment was not used during the trial since it was fairly new and required qualification before usage. Also, the new granulation liquid solution's feed pumping system was not used because it was not qualified and had operating issues.
6. Traveling was limited during the trial because of the closure of cities by the Palestinian government so Zoom and Team online meetings were completed instead of face to face meetings with my mentors.

5.4 Obstacles and delays

1. COVID-19 pandemic was the main obstacle which led to too many delays during the thirteen batches trial. The Tableting section was closed twice while the Quality Control unit was closed once with a total of almost 1.5 months of delays.
2. Raw materials shipping delay was another factor which led to delays in the research study specially after completing the thirteen batches trial. Since five batches were requested for validation of all changes made for the JR manufacturing process, raw materials were not available. Raw materials for JR are purchased from Germany and a request was given in December of 2020, but the materials have not arrived until the end

of February. The delays in shipping were attributed to the restrictions which were put by countries on international shipments because of COVID-19 pandemic.

3. In order to make quick changes as a result of establishing a Design Space, pharmaceutical companies require Process Analytical Technology (PAT) to easily implement them. However, Jepharm does not have PAT. Therefore, this research study used prior knowledge and experience, Quality Risk Management, DOE through Design Space through Design Expert to define relationships between selected critical input variables, critical process parameters and critical product quality attributes. The output of the Design Space model's recommended changes was made on a batch and we had to wait to validate the results of these changes on another or next batch. This is a manual work and took a lot of time and effort.
4. In order to provide stable and continuous operation during campaign manufacturing of the thirteen batches of JR, an Oscillator and an additional tablet machine is required since these stages are found to be a bottle neck in the manufacturing process which is highlighted by the Value Stream Mapping. Therefore, batches after the final mixing stage were stored in the Work in Process room waiting Oscillation or compression. A new tablet machine was purchased but was not used in this trial since it was not qualified.

5.5 Managerial implications

Quality management methods and tools were introduced for the first time at Jepharm including Quality by Design to establish a Design Space, SS DMAIC and LSS VSM. These methods and tools were successfully used leading to improvement opportunities of JR tablet manufacturing. In order to help in better distribution of API 2 in the final mixture,

granulated material was dried to LOD <1.5%, the application of geometric mixing prior to the final mixing stage was instituted and the final mixing time was doubled to provide a homogenous mixing of API 2 in the final mixture since its quantity in the batch is very small and no baffles are present in the Bin mixer. In addition, it was found that API 2 is affected by Temperature in the coating stage's tablet warming step with the temperature reaching a maximum of 63^{o}C leading to an out of specification API 2 Assay limit with 15% reduction in Assay between the before coating and after coating stage. All of the improvements made reduced the manufacturing cycle time of JR by 45% and ensured that API 2 assay is within 95% to 110% limit which frequently failed this limit. The manufacturing process of JR tablet became much simple and not the nightmare that operators have been experiencing. In process QC testing were eliminated and the focus of operators and QA inspector is on the established control strategy which contains very few parameters, material attributes and CQAs which can be managed and controlled effectively. Finally, a new Oscillating/Milling machine and a new Tablet machine were purchased as recommended by this research study to help reduce identified bottlenecks in JR tablet manufacturing process which was showed by the VSMs.

Chapter Six: Conclusions and recommendations

6.1 Overview

The purpose of this chapter is to provide a conclusive outcome of the study and to give recommendations for future researchers with a similar study. Effectively planning trials and obtaining the required power to make changes during the trials are found to be very important. Actively communicating with senior management may be required at some instances. The conclusion started with a brief thesis statement and provided an overall summary of the results including the most significant results with their significance to the community.

6.2 Conclusion

Quality by Design (QbD) principle guidelines were used to establish Design Space (s) with control strategies and safe operating limits in order to ensure that the produced existing JR tablets have the required finished product attributes' Target Quality Product Profile (TQPP) to achieve the required TPPs. Achieving the required TPPs which are safe and effective for the patient at an affordable price without in process Quality Control (QC) testing while improving the manufacturing processes to reduce JR manufacturing cycle time leads to customer satisfaction internally and externally. Patient satisfaction was the focus since a patient is the most important customer who requires the highest quality affordable medicinal product with drug characteristics including safety, quality, efficacy, purity, strength and identity. Even when removing the in-process QC testing, the final finished product was fully tested after the coating stage and was within the required specification limits of the TQPP. Initially, all of the critical material attributes and critical process parameters with their relationship to the Target Quality Product Profile were identified and

tabulated. Utilizing Six Sigma and Lean Six Sigma with related tools and ICH Q8R2, Q9 and Q10 guidelines for QbD using QbDvision helped in giving me guidance to effectively manage this research study while using scientific background and knowledge of pharmaceutical manufacturing to identify many improvement opportunities for the manufacturing process of JR tablets. A Quality Risk Management (QRM) and DOE were completed taking into account all of the critical and noncritical attributes and parameters which gave an indication where Design Space(s) may be needed. As a result, Design Space models were established for selected critical process manufacturing stages which affect API 2 distribution and content uniformity in the final tablet dosage form. One Design Space for the granulation stage to the Final mixing and after compression stages for the response API 2 % Assay and the second for the granulation stage to the compression stage for the response dissolution. The third design space was established for the response friability while the fourth design space was established for the coating stage to study the effect of temperature, humidity and light factors on the response API 2 assay. These Design Space models covered the critical material attributes for raw, intermediate and finished product materials and critical process parameters affecting these attributes. Design Expert 13 software was used to build these four Design Spaces which provided directional process improvement changes which were made during and after the thirteen batches trial. As a result, API 2 particle distribution in the final mixture was improved to ensuring that API 2 Assay was within the acceptable range of 95% to 110% after the final mixing and compression stages. Using smaller mesh screen to sieve API 1 helped in reducing the cycle time by two hours. While using slightly larger mesh screen to sieve the dried granulated material shortened the manufacturing cycle time by one day and improved powder flow-

ability during compression which eliminated capping and chipping of tablets. Also, in order to improve homogeneity of the final mixture, mixing time was increased because the Bin mixer which is used to complete the final mixing process does not contain baffles. Since it was found that API 2 Assay was affected by temperature in the coating stage during the tablets warming step, a DOE was completed and a fourth Design Space was established. As a result of the fourth design space, it was found that API 2 decomposes exponentially at temperatures above 40^{o}C while humidity and light statistically had no effects. The rate of decomposition of API 2 in JR tablets increases as temperature increases. The results of the DOE study indicated that API 2 Assay decreases by 6% when JR tablets are heated for 60 minutes at 40^{o}C while it decreases by 15% when JR tablets are heated for 60 minutes at 60^{o}C. The 15% API 2 Assay in JR tablet reduction is what operation has been experiencing for many years. These results are very significant since the issues of JR were always attributed to API 2 Assay failure after the final mixing and after the coating stages. These failures tremendously affected the cycle time of JR manufacturing due to the frequent reprocessing of batches. The overall cycle time of JR tablet is highly affected by the manufacturing cycle time while the manufacturing cycle time is highly affected by the final mixing and coating unit operations due to reprocessing. A Value Stream Map (VSM) for the before and another for the after improvements were established to show the difference in the manufacturing cycle time of JR tablets indicating a reduction of 45% of which about 40% was attributed to reprocessing. A control strategy for JR manufacturing was established and in order to institute these improvement opportunities, a change control for JR was written to modify the Manufacturing Procedure Record (MPR), the operating procedures, some of the in-process control parameters and tests, and machines and

equipment and tools lists. Training of the Tablet Section operators, supervisors, Quality Assurance Inspector and Quality Control Inspector was completed covering all modified Quality Management System documentations. All of the JR manufacturing processes were validated during the thirteen-batches trial except for the coating stage because the coating stage was not initially part of this research study. The validation of the coating stage with the new operating acceptable ranges is recommended. All of the established Design Spaces, if accepted by the Palestinian Ministry of Health, may or may not be accepted by other Ministry of Health of other countries. Accepted QbD product in a submission by an agency such as EMA may or may not be accepted by other agencies such as the FDA. Therefore, QbD implementation has many benefits as mentioned in this case study and has concerns. However, building trust between both pharmaceutical companies and regulatory agencies and being able to work together for the sake of technological and developmental improvements to help suffice quality and quality management in the pharmaceutical industry can lead to knowledge development and more understanding of products and processes leading to quality building for the sake of the patient and for the good of the next generations of people and pharmaceutical manufacturing.

6.3Thesis contributions

This research study is to establish a design space and utilize quality management tools to help improve the manufacturing process efficiency and reduce the overall manufacturing cycle time using actual manufacturing data. This study bridged the gap of Design Space, Six Sigma, Lean Six Sigma and QRM. The contributions of this thesis can be summarized as follows:

- Established Design Spaces to improve the manufacturing of JR tablet. These improvements can be summarized as follows:
    - Helping in better distribute API 2 in the final mixture and reducing API 2 degradation due to moisture.
    - Eliminated API 2 degradation during the coating stage.
    - Introduced geometric mixing prior to the final mixing stage.
    - Reduced manufacturing cycle time.
- Applied the procedure of QRM principles to quantify, mitigate and reduce the risks of an existing JR tablet manufacturing. Quality Risk Management was never completed for JR tablet; initially completing QRM led to recommended actions which were investigated during the thirteen-batch trial.
- Applied Lean Six Sigma VSM to assess the manufacturing process of JR tablet and reduced non-value-added activities to enhance the manufacturability of JR tablet and identify two bottlenecks in the process.
- Used QbDvision software as a management tool to assess the degree of implementation of the ICH guidelines at JEPHARM. As a result, templates were filled and uploaded as requested by the software. Links between attributes and parameters were established and risk assessments were completed in the software. The software gave reports for JR tablet according to ICH guidelines.

Moreover, this study is the first in the Palestinian context to cover QbD to establish a Design Space for an existing pharmaceutical tablet dosage form manufacturing process with actual manufacturing batches.

6.4 Research recommendations

1. The thirteen-batches trial of JR should have been split into a campaign of five batches, five batches and three batches. The Design Spaces results can be reflected during the first five batches. Then, taking a one week off to modify all related JR documentations so that the second five batches could be produced using the modified documents with few changes to be made in order to finalize all limits and collect new data to be used back into the Design Space(s). Finally, the last three batches will be used for validation.
2. Jepharm should work 24 hours, 7 days a week for two weeks to complete a campaign of fifteen-batches of JR with no stop. They should line up the two milling machines, two tablet machines and one blister machine back-to-back until all fifteen-batches are completed.
3. The QC lab should line up only one lab technician to complete all of the lab analysis for JR, this is so to eliminate variability in analysis.
4. API 1 should be tested for moisture at receiving since Alcohol quantity addition depends on the moisture content besides particle size.
5. Installing Baffles in the Bin Mixer to provide a more homogenous mix of the final mixture.
6. Ensuring that raw materials are available to complete the trials needed to finalize the study. In this case, API 2 active material took 5 months to arrive from Germany because of COVID-19.
7. Ensuring that there is a plan for the Quality Control Laboratory during the month of executing the trials and that the QC lab is able to support all of the tests or analysis required without delays.

8. Jepharm should install PAT and utilize QbD as a future improvement for the company in order to be a global successful competitor. PAT technology allows us to view, manipulate, track and trend data online which provides up with the opportunity to quickly respond to variability or out of limit measurements.
9. In addition, Jepharm should look into converting their manufacturing processes from batch-type process to continuous process since continuous pharmaceutical manufacturing process is much leaner with better quality products. A continuous process is generally more effective and efficient than a traditional batch process since we will be able to process materials with no interruption. Also in a continuous process variability can be followed on immediately which eventually leads to reduce the quality cost. Therefore, Jepharm should install PAT technology in their processing units and adopt QbD as a future improvement opportunity to improve their processes with an online and inline analysis and release of their products to tremendously reduce the manufacturing cycle time.

6.5 Future work

Future researchers in similar studies within the context of Palestine should keep in mind that even the best plan may change during the implementation of trails. They should ensure that holding time for intermediates shall be reduced to minimum especially after the final mixing stage in order to reduce API 2 degradation since API 2 is affected by light, humidity and temperature. Adopting QbD and PAT approach to process control has been proven more successful than the traditional method of relying on human to make the necessary adjustments to process parameters to stabilize the process to the desired specification limit

which can be less efficient and may take longer than an automated process. The newly established Design Spaces and control strategy were validated at the end of July 2021. Four batches were completed with excellent results, as depicted in Appendix 19, validating the Design Spaces and control strategy. For the response friability, more work is required to gather data for the reliability of the friability measurements evaluating the analyst and the measuring instrument. This was one improvement cycle. Future work should start the improvement cycle of JR tablet over again in order to continously improve the product since QbD is based on the principle of continous improvement.

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الجامعة العربية الامريكية

كلية الدراسات العليا

إنشاء مساحة تصميم لمنتج دوائي قائم على شكل أقرص من أجل فعالية التصنيع وتأكيد الجودة في فلسطين.

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قدمت هذه الاطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في ادارة الجودة بكلية الدراسات العليا في الجامعة العربية الامريكية

2021

Appendixes

1) Appendix 01: FMEA.
2) Appendix 02: Study Charter.
3) Appendix 03: SIPOC.
4) Appendix 04: Process Flow Diagram.
5) Appendix 05: Processing Flow Map.
6) Appendix 06: Value stream map and its calculations before improvement.
7) Appendix 07: Materials attributes.
8) Appendix 08: Intermediate Quality Attributes (IQAs).
9) Appendix 09: Control Methods.
10) Appendix 10: Unit Operations.
11) Appendix 11: Process Component (Equipment) used.
12) Appendix 12: Process Parameters.
13) Appendix 13: Risk Assessment and TQPP evaluation.
14) Appendix 14: Risk Assessment for CQAs.
15) Appendix 15: Thirteen batches processing data.
16) Appendix 16: Coating stage one batch supervision results.
17) Appendix 17: Value Stream Map and its calculations after improvements.
18) Appendix 18: Manufacturing Procedure Record (MPR) after improvements.
19) Appendix 19: Four batches trial to validate the Design Spaces and Control strategy.

الملخص

يتضمن هذا البحث النهج الجديد لأدارة الجودة عن طريق تصميم الجودة والتخطيط الممنهج لها لكي نضمن أنتاج مستحضرات أمنة وبجودة عالية للمريض وبأسعار منافسة. في هذا البحث تم تصميم الجودة من خلال بناء مساحات تصاميم لبعض العوامل المهمه والتي تم فرزها على أنها ضرورية والتي أذا خرجت عن الحدود يحصل تأثير على نتائج المستحضر النهائي وهو ج ر على شكل أقراص. فقد تم أختيار مستحضر ج ر في هذة الدراسة وهو مستحضر مهم جدا كمصدر حديد لنساء الحوامل. وهذا المستحضر ليس بجديد فقد تم البدء بصناعتة قبل 30 سنة تقريبا. فهذا المستحضر له أعلى دورة صناعية من بين جميع المستحضرات المصنعة في شركة القدس للمستحضرات الطبية. للحصول على الجودة المطلوبة للمستحضر فيتم أعادة تصنيع بعض المراحل مثل أعادة الخلط النهائي في كثير من التشغيلات مما يؤثر على أرتفاع الدورة الصناعية. القصد من هذه الدراسة البحثية هو الاستفادة من QbD لإنشاء مساحة التصميم والاستفادة من الخلفية العلمية والمعرفة، ستة سيغما وليين ستة سيغما وأدواتهما، وإدارة مخاطر الجودة، وDOE والمبادئ التوجيهية ل ICH للجودة حسب التصميم في تقليل وقت دورة التصنيع للمنتج الحالي ج ر أقراص صيدلانية مع التركيز في نهاية المطاف على المريض الذي يستحق أعلى جودة أدوية بأسعار معقولة. تم جمع بيانات تجريبية بأثر رجعي لعامي 2018 و2019 عن وقت دورة التصنيع لجميع المنتجات المصنعة في شركة القدس للأدوية وتم تحديد ج ر على أن له أسوأ دورة زمنية تصنيعية. تم تحديد العلاقة بين سمات المواد الخام وضوابط العمليات الأنتاجية وذلك بأستخدام بيانات من ع2017 2018 و2019 وبذلك تم معرفة الحرجة منها من خلال دراسة المخاطر وكذلك من خلال دراسة ملف تعريف المنتج ل ج ر . تم استخدام برنامج Design Expert 13 لبناء نماذج مساحة التصميم. وبعد أن تم التحقق من صحة مساحات التصميم المنشأة ، قمنا بعمل تعديلات على الملف التصنيعي. فمن التعديلات التي تم تعديلها من خلال هذة الدراسة ألغاء غربلة المواد وتغيير عملية غربلة الخليط الحبيبي المجفف لأنه تبين أنها غير مجدية. API 2 Assay هو أعلى سمة جودة حرجة لعملية تصنيع ج ر من أجل المساعدة في توزيع أفضل ل API 2 في الخليط النهائي وبذلك تم تجفيف المواد الحبيبية إلى LOD <1.5٪، وكذلك تم خلط API 2 Geometrically وMCC بعد الغربلة من خلال شبكة 60 مع حوالي 3 كجم من المواد الحبيبية المجففة. تم زيادة وقت الخلط النهائي إلى ما لا يقل عن 30 دقيقة بدلا من 15 دقيقة مما يعطي المزيد من الوقت للخلط المتجانس. من خلال هذا البحث تبين أن API 2 يتأثر بدرجة الحرارة في خطوة التدفئة في مرحلة التلبيس عند وصول درجة

حرارةالهواء الداخل الى ماكينة التلبيس الى 63 درجة مئوية كحد أقصى مما يؤدي إلى تدني نسبة API 2 خارج المواصفات المعتمدة وذلك بانخفاض بنسبة 15٪. فلقد تم خفض درجة حرارة الهواء الداخل الى ماكينة التلبيس الى أقل من 32 درجه مئويه لمنع أنخفاض نسبةAPI2 في المستحضر النهائي. هذه النتائج مهمة جدا لأن التحسينات التي أدخلت خفضت وقت دورة التصنيع ل ج ر بنسبة 45٪ وضمنت أن Assay API2 هو ضمن حدود 95٪ إلى 110٪ والذي كان يفشل في كثير من الأحيان في خلطات سابقة. لقد تم عمل التعديلات اللازمة لضبط جميع العمليات الصناعية لمستحضر ج ر وذلك عن طريق وضع Control Strategy والتي تتمثل بوضع الضوابط في طريقة التصنيع التي يتبعها منفذ العمل لتصنيع مستحضر ج ر. هذة التعديلات كانت لازمة لتأكيد أنتاجية ج ر بدون عمل فحوصات مخبرية خلال العمليات الصناعية والأكتفاء بفحص المستحضر بعد عملية الكبس والتلبيس فقط. وبذلك تم وضع ضوابط على العمليات من خلال تعديل الإجراءات ووضع حدود لمواصفات العمليات واستكمال التدريب وفقا لذلك لضمن التقيد بالمواصفات والضوابط المتمثلة ب TQPPs للمستحضر والتي ستمكننا من ضمان الحصول على TPPs لمستحضرج ر .

Summary

This research includes the new approach to quality management through quality by design and systematic planning in order to ensure the production of safe and high quality products for the patient at competitive prices. In this research, the quality was designed by building design spaces for some important factors, which were sorted as necessary, and which if they go out of specification limit, have an impact on the results of the final tablet dosage form product. JR tablet product was chosen in this study which is a very important product as an iron source for pregnant women. This product is not new, product manufacturing started nearly 30 years ago. This product has the highest manufacturing cycle time among all the products manufactured at Jerusalem Pharmaceuticals Company. To obtain the required quality of the product, some stages are re-processed, such as the final re-mixing in many batches leading to this high manufacturing cycle time. The intent of this research study is to utilize QbD to establish a design space(s) and to utilize scientific background and knowledge, Six Sigma and Lean Six Sigma and their tools, Quality Risk Management, DOE and ICH Quality by Design guidelines to reduce the manufacturing cycle time of an existing JR pharmaceutical tablets product with the ultimate focus on the patient who deserves the highest quality medicinal products at an affordable price. Quantitative empirical 2018 and 2019 overall cycle time retrospective data for all products at Jepharm were collected and JR tablet was identified with the worst overall cycle time. Also, 2017 to 2019 retrospective data for the manufacturing of JR tablet were collected. The relationship between Critical Material Attributes, Critical Process Parameters and Critical Quality Attributes was identified for JR tablet. Design Expert 13 software was used to build the Design Space models. After validating the design spaces through actual JR tablet

batches, it was found that the manufacturing cycle time is the main and most critical process factor affecting the overall cycle time of JR tablet. Final mixing and coating stages are the most critical unit operations affecting the manufacturing cycle time. Oscillating and sieving unit operations were modified to remove none value added activities. API 2 assay was found to be the most Critical Quality Attribute of JR tablet manufacturing process. In order to help better distribute API 2 in the final mixture and eliminate degradation of API 2, granulated material was dried to LOD <1.5% and geometric mixing was introduced before the final mixing stage. Mixing time was increased from 15 minutes to 30 minutes giving more time for homogenous mixing of API 2 since its concentration in the batch is about 0.3% and no baffles are present in the Bin Mixer. In addition, API 2 was found to be affected by temperature in the coating stage's warming step with the inlet air temperature reaching a maximum of 63^{o}C leading to an out-of-specification of API 2 assay with 15% reduction. The inlet air temperature to the coating machine was reduced to <32^{o}C eliminating product degradation. These results are very important because the improvements made reduced the manufacturing cycle time by 45% and ensured that API 2 assay stays within (95% - 110%) limit which frequently failed this limit leading to reprocessing of batches. The necessary adjustments have been made to control all manufacturing processes of JR tablet product by establishing the Control Strategy. These modifications were necessary to ensure the manufacturing of JR tablets without performing in-process laboratory tests and only testing the product after the compression and coating stages. Thus, controls were placed in the MPR, and procedures and in-process specification limits were updated while training was completed accordingly to ensure adherence to the

specifications and controls represented by the TQPPs of the product, which will enable us to ensure obtaining the TPPs for the JR tablet product.